40th Annual Winter Conference on Brain Research 2007

40th Annual

Winter Conference on Brain Research

January 27–February 2, 2007
Snowmass Village, Colorado

Office of Continuing Education
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Welcome to the Fortieth Annual Winter Conference on Brain Research

This is our 40th anniversary. The first "WCBR" (which wasn't called that) was organized by neuroscientists from UCLA and was held at the University of California conference center near Lake Tahoe in 1968. There were ~60 attendees, and the meeting was oriented mostly towards behavioral neuroscience and electrophysiological recording. Now our meeting includes ~500 neuroscientists from all over the world who work in a wide variety of fields. The format includes over 80 posters and 90 panels and workshops. The aim of panels is for experts in a specific field to provide a broad overview for a general audience. Workshops are more focused and are aimed at discussing specific issues in a given field. Posters represent an individual's scientific contributions. Taken together, the meeting provides a unique opportunity for all of us to catch up on new developments in fields outside our own, meet and interact with long-time colleagues, and develop new collaborations in a casual setting.

The week begins on Saturday night with the opening reception. The opening breakfast on Sunday will feature our Keynote speaker, Barbara Forrest, Ph.D., Professor of History and Political Science at Southern Louisiana College of Arts and Sciences. She is a leading opponent of attempts to teach creationism in our schools. Her talk is entitled: "What Is Intelligent Design? Why We Should Care and What We Can Do."

Other special events will include: 1) the school outreach program, run by Karen Greif, which includes ~20 WCBR participants who bring neuroscience to the local elementary, middle, and high schools; 2) a town meeting organized by Kristin Anstrom, which will feature a talk entitled, "Obesity and Your Brain: Perfect Together!" for Aspen area residents; 3) the Mountain lunch and the Smitty Stevens Memorial (NASTAR) ski race, organized by Tom Swanson, will both be held on Tuesday this year (not the usual Wednesday slot); 4) the 40th annual banquet featuring live music, awards and some wild and crazy neuroscientist dancers; and 5) the WCBR business meeting on Wednesday at 6:30PM, immediately following the afternoon sessions. Please attend to elect new Board members and a conference chair-elect and to provide your thoughts on the program, overall organization and future meeting sites. Because Board members play a vital role in the governance of WCBR, we ask all of you to consider nominating yourself (or nominating a "friend") for open positions in the categories of cell/molecular, clinical or systems/behavioral neurosciences.

Finally, this is an all-volunteer organization. We have an especially dedicated group of officers, board of directors, and committee chairs. Kristen Keefe has done a wonderful job as facilities chair working with the University of Illinois at Urbana-Champaign conference planners to make this a successful meeting. Wendy Macklin, program chair, and her committee have worked successfully to increase the number of proposal submissions. The result is an exceptionally broad and interesting program this year. Jakie McGinty begins her first year as treasurer, taking over our books from Suzanne Haber, who served us diligently for five years. Jill Becker and her committee have screened many applicants and identified 19 pre- and post-doctoral students and junior faculty travel fellows, as well as a comparable number of mentors for those fellows at the meeting. Steve Levison, exhibits chair, is our liaison with the exhibitors who provide important financial support for the meeting. They sponsor the afternoon breaks during which you can visit their booths and the scientific posters.

So, please enjoy the meeting, your colleagues, and the snow.

Barry Levin
Conference Chair

Don't forget to visit the exhibits

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Kimberly Topp
Doug Weber

Town Meeting

Kristen Anstrom

2007 Fellowship Awardees

Mara Balda
Jonah Chan
Elena Chartoff
François Georges
Paul J. Kenny
Thomas Klausberger
David Kline
Vedran Lovic
Peter Magill
Nicholas Mallet
Sarah McCallum
Samuel McClure
Courtney Miller

Wayne Pratt
Jason Radley
Ghazaleh Sadri-Vakili
Michael Sutton
Jacquie Van Hoomissen
Anne West

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Elizabeth Abercrombie
Gary Aston-Jones
Jill Becker
Jonathon Cohen
Christine Colvis
William Freed
William Greenough
Johannes Hell
Barry Levin
Michael Levine
David Mendelowitz
Cella Olmstead
Elior Peles
Nick Spitzer
Kuei Tseng
George Uhl
Derek van der Kooy
Dan Weinberger
Roy Wise

Fellowship Sponsors

We thank the individuals and organizations that have generously supported the travel fellowship program.

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Conference Arrangements

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Exhibitors

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General Information

Headquarters is the Snowmass Conference Center. All scientific activities will be held there.

WCBR Information Desk and Message Center are in the Registration Booth. The desk hours are as follows:

	Morning	*Afternoon*	*Evening*
Saturday 1/27	9:00–11:00 AM	3:30–5:30 PM	6:30–10:00 PM
Sunday 1/28	7:00–8:00 AM	3:30–6:30 PM	
Monday 1/29–Friday 2/2	7:00–8:00 AM	3:30–4:30 PM	

The telephone number for messages is 217-714-9479.

Registration packets containing a conference badge, registration receipt, tickets for breakfasts, mountain lunch and closing banquet, and program book should be picked up at the WCBR Information Desk. Attendance at this conference is strictly limited to PREREGISTERED participants. On-site registration is not available.

Posters will be available for viewing in three different sessions during the week in the Anderson Room: Poster Session 1, Sunday–Monday; Poster Session 2, Monday–Tuesday; and Poster Session 3, Tuesday–Thursday. Poster presenters will be by their posters for discussion from 3:30–4:30 PM according to the schedule listed on pages 23–29. Presenters may put up their posters after 8:30 PM on the day their session starts. Presenters should take down their posters by 8:30 PM on the final day of their session. Please see Poster Sessions section in program for titles and names of presenters.

Exhibits and Lounge are in the Anderson Room. Coffee is available there from 9:30–10:30 AM Monday through Friday. Refreshments are provided 3:30–4:30 PM, Sunday through Thursday. Exhibits close after 10:30 AM on Friday. Friday's afternoon break will be in the ballroom lobby.

Breakfast is served to all registrants on Sunday 7:30–8:30 AM, in the Anderson Ballroom, and on Monday through Friday, 6:30–7:30 AM, in Hoaglund. Social guests ONLY will have breakfast in Hoaglund from 9:00–10:00 AM Monday through Friday. The tickets in your registration packet are required for admission.

Ski Lift Tickets will be available from the WCBR Information Desk. Daily tickets can be purchased or prepaid tickets can be picked up during desk hours.

Special Events

Saturday, January 27

Welcome Wine and Cheese Reception • 6:00–7:30 PM, Anderson Ballroom. Newcomers, fellows, and mentors only from 6:00–6:30 PM, all attendees from 6:30–7:30 PM.

Sunday, January 28

Conference Breakfast and Opening Address • 7:30 AM, Anderson Ballroom

(Your required ticket is in your registration packet.) The plenary keynote speaker will be **Dr. Barbara Forrest**, Endowed Professor, Department of History and Political Science, College of Arts and Sciences at Southeastern Louisiana University.

"What Is Intelligent Design? Why We Should Care and What We Can Do"

"Intelligent design" (ID) is the belief that God created the world according to a divine design for life and that his intelligent activity is empirically detectable. Promoted by the Discovery Institute's Center for Science and Culture in Seattle, ID is the most recent variant of American creationism. Pursuing the goals of their "Wedge Strategy," ID creationists seek to alter the public understanding of science to include the supernatural, to convince educational policy-makers that ID is a scientific theory, and thereby to gain entry for ID in public school science classes. Most essentially, the ID movement is an integral part of the Religious Right's effort to control public education and government by controlling policy-making processes. It thus poses a threat to public science education—and therefore ultimately to science itself—and to the separation of church and state. Scientists, acting as both professionals and citizens, must play a major role in counteracting ID. They can do this by working with pro-science activists at the local, state, and national levels to explain science to the public and by assuming the civic responsibility of educating elected officials and other policy-makers about the importance of proper science education.

Meeting of Panel and Workshop Organizers • 9:30–10:30 AM, Anderson Ballroom, immediately after breakfast. The meeting will be brief but important. Session organizers and WCBR staff should attend.

Monday, January 29

First Meeting of the Board of Directors • 6:30–8:30 AM, Max Park Room of the Wildwood Hotel

Tuesday, January 30

Breakfast for Travel Fellows and Mentors • 6:30-7:30 AM, Hoaglund

Look for reserved tables.

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 AM, Spider Sabich Race Arena

NASTAR registration cards to be completed no later than Monday, January 29, 8:00 AM at WCBR Information Desk.

Mountain Lunch • 11:30 AM–2:00 PM, Spider Sabich Picnic Palace

Required lunch ticket is in your registration packet. Non-skiers requiring transportation should sign up by Monday, January 29, 8:00 AM at WCBR Information Desk.

Travel Fellows Meeting • 3:15-4:15 PM, Snobble

Meet with Dr. Kathie Olsen, Deputy Director of the National Science Foundation

Town Meeting • 7:00 PM, Aspen High School, Aspen, CO

Wednesday, January 31

Travel Fellows Meeting • 3:15-4:15 PM, Snobble

Meet with NIH Program Officers

Business Meeting • 6:30 PM, Kearns

Election of Conference Chair-elect and three members of the Board of Directors, presentation of budget, and discussion of future meeting sites.

Friday, February 2

Second Meeting of the Board of Directors • 6:30–7:30 AM, Max Park Room of the Wildwood Hotel

Travel Fellow Meeting • 6:30 PM, WCBR Information Desk

Meet with Dr. Jacqueline McGinty to collect reimbursement checks.

Banquet and Dance • 7:30 PM, Anderson Ballroom

Required ticket is in your registration packet. Cash bar opens at 6:30 PM in the Ballroom Lobby.

Preamble to the Program

The 2007 WCBR Program consists of panels, workshops, and posters. Please consult the program booklet and posted announcements for details regarding the scientific presentations as well as information regarding the School Outreach program and the Town Meeting.

Sunday, January 28

7:30 AM

Plenary Breakfast • Anderson Ballroom

What Is Intelligent Design? Why We Should Care and What We Can Do

Dr. Barbara Forrest, Endowed Professor, Department of History and Political Science, College of Arts and Sciences at Southeastern Louisiana University

3:30–4:30 PM

Exhibits and Posters • Anderson

4:30–6:30 PM

1. Panel • Carroll

Epigenetics of Cocaine Addiction

Christine Colvis, Anne West, Chris Pierce, Ghazaleh Sadri-Vakili, Craig Ferris

2. Panel • Erickson

Guidance and Regeneration in the Nervous System

Marie T. Filbin, Alex L. Kolodkin, Yimin Zou, Zhigang He

3. Panel • Janss

Post-Transcriptional Control of the Circadian Network

Joseph Takahashi, David Virshup, Carla Green, Martha Gillette

4. Panel • Kearns

Neuronal Dysfunction in Huntington's Disease: The Cortex and the Striatum

Michael Levine, Ilya Bezprozvanny, Austen Milnerwood, Carlos Cepeda, Kerry Murphy

5. Panel • Sinclair

Axon-Glia Interaction in Myelination

Elior Peles, Wendy Macklin, Tim Kennedy, Jonah Chan

6. Panel • Snobble

Operation Head-Start: Early Life Nutrition, Stress, and Bonding Influences on Adult Brain Function

Amy Naleid, Mary Olmstead, Vedran Lovic, Barry Levin

8:30–10:00 PM

7. Panel • Carroll

Craving from the Dark Side of the Brain

George Koob, Paul Kenny, Yavin Shaham, Subhash Pandey

8. Panel • Erickson

Parsing the Clinical Heterogeneity of Schizophrenia: Effects of Schizophrenia Susceptibility Loci

Anil K. Malhotra, Richard Keefe, Joseph Callicott, Katherine Burdick

9. Panel • Janss

The Role of the NR2 Subunit in NMDA Receptor Function

Stephen Traynelis, Jon Johnson, Stefano Vicini, Johannes Hell

10. Panel • Kearns

Parkinson's Genes and their Role in Mitochondrial Function

David Park, Heidi McBride, Edward Fon, Anurag Tandon, Mark Cookson

11. Panel • Sinclair

Molecular Control of Migration in the Postnatal Subventricular Zone

Francis Szele, Harold Cremer, Angelique Bordey, Eva Anton

12. Panel • Snobble

Sleep, Memory, and Brain Plasticity

Matthew Walker, Richard Ivry, Robert Strecker, Giulio Tononi

Monday, January 29

7:30–9:30 AM

13. Panel • Carroll

Co-morbid Pain and Addiction: Mechanisms and Risk Factors

Jon-Kar Zubieta, Charles O'Brien, Richard Harris, Mark Greenwald

14. Panel • Erickson

The Glass Ski Boot: Fitting Thalamic Afferents into Striatal Anatomy and Function

Kristen Keefe, Yoland Smith, Peter Magill, Elizabeth Abercrombie

15. Panel • Janss

Molecular Mechanisms in Autism Spectrum Disorders

Joseph Coyle, Randy Blakely, Joseph Piven, William Greenough

16. Panel • Kearns

Killer or Good Samaritan? Role of Nitric Oxide in the Pathophysiology of Brain Disorders

Margie Ariano, David A Wink, Carol A. Colton, Christopher J Schmidt, Tony West

Monday, January 29, continued

17. Panel • Sinclair

Nanotechnology and Neuroscience

Vladimir Parpura, Gabriel Silva, Laura Ballerini, Mario Romero

18. Panel • Snobble

New Ideas About Electrical and Chemical Synaptic Transmission in the Retina

Stewart Bloomfield, Stephen Massey, Maureen McCall, Jeffrey Diamond

3:30–4:30 PM

Exhibits and Posters • Anderson

4:30–6:30 PM

19. Panel • Carroll

Progressive Pursuits to Prevent Professional Paresis (or Fostering the Phantasmagorical Future of Neuroscience)

Kathie L. Olsen, Gwen Jacobs, Elliott Albers, Connie Atwell

20. Panel • Erickson

Genetic and Environmental Factors in Complex Neuropsychiatric Disorders: Schizophrenia and Autism

Thomas Hyde, Daniel Weinberger, Joel Kleinman, Daniel Geschwind, Tyrone Cannon

21. Panel • Janss

Adrenocortical Steroids in Stress and Stress Adaptation

Greti Aguilera, Stoney Simons, Stafford Lightman, Pier Vincenzo Piazza, Joe Herbert

22. Panel • Kearns

Beyond Dopamine Depletion: Neuronal Adaptations from Dopaminergic to Non-Dopaminergic Systems

Kuei-Yuan Tseng, Sarah McCallum, Michelle Day, Nicolas Mallet, Gustavo Murer

23. Panel • Sinclair

The Endosomal-Lysosomal System in Neurodegenerative Diseases

Lian Li, Bruce Horazdovsky, Peter Lobel, Ralph Nixon

24. Panel • Snobble

GPR55: A Novel Cannabinoid Receptor

Ken Mackie, Nephi Stella, Hui-Chen Lu, Andy Irving

8:30–10:00 PM

25. Workshop • Carroll

Microglial Activation: Just What the Neuron Ordered!

Monica Carson, Jean Harry, Benoit Melchior, Jake Streit

26. Workshop • Erickson

Transport and Local Translational Regulation of mRNAs in Neurons

William Greenough, Suzanne Zukin, Gary Bassell, David G Wells, Oswald Steward

27. Panel • Janss

Exercise Neuroscience

Jacquie Van Hoomissen, Amelia Russo-Neustadt, Fernando Gomez-Pinilla, Benjamin Greenwood

28. Workshop • Kearns

Dopaminergic Burst Firing and Behavior: Are You and I Talking about the Same Thing?

Kristin Anstrom-Kelly, Anthony West, Paul Phillips, Michela Marinelli

29. Panel • Sinclair

Postsynaptic Structural and Functional Dynamics in Hippocampal Neurons

Mark DellAcqua, Alaa El-Husseini, Reed Carroll, K. Ulrich Bayer

30. Workshop • Snobble

Taking Control with Neural Prosthetic Interfaces

Gerald Loeb, Andrew Schwartz, Jiping He, Gregory Clark, Douglas Weber

Tuesday, January 30

7:30–9:30 AM

31. Panel • Carroll

Schizophrenia and Bipolar Disorder: Different Clinical Facades Arising from the Same Genetic Architecture?

Daniel Weinberger, Paul Harrison, Barbara Lipska, John Kelsoe, Amanda Law

32. Panel • Erickson

Another Way to Die: Caspase-Independent Mechanisms in Excitotoxic Neuronal Death

Denson Fujikawa, Shaida Andrabi, Klas Blomgren, Alan Faden

33. Panel • Janss

Photoreceptors, Mechanosensory Hair Cells, Ribbon Synapses, and Deafblindness

Monte Westerfield, Teresa Nicolson, Stephan Neuhauss, Bronya Keats

34. Panel • Kearns

Functional Interactions between Striatal D1 and D2 Dopamine and Ionotropic Glutamate Receptors in Cocaine Addiction

David Self, Anthony Grace, Marina Wolf, Richard Palmiter, Ryan Bachtell

Tuesday, January 30, continued

35. Panel • Sinclair

Dopaminergic Neurons Derived from Human Embryonic Stem Cells and Application to Parkinson's Disease

William Freed, Catherine Schwartz, Su-Chun Zhang, Curt Freed

36. Panel • Snobble

Emerging and Re-emerging Viral Infections of the Human Nervous System: What We Know from the Past and What We Need to Know for the Future

Michael Nunn, Kenneth Tyler, Glenn Telling, Christine Zink, Eugene Major

3:30–4:30 PM

Exhibits and Posters • Anderson

4:30–6:30 PM

37. Panel • Carroll

Skating on Thin "Ice": Neurobiological and Behavioral Consequences of High Dose Methamphetamine

Ronald See, Bryan Yamamoto, Kristen Keefe, John Marshall

38. Panel • Erickson

Protein Misfolding—A Common Theme in Neurodegenerative Diseases

Menelas Pangalos, Charles Glabe, Peter Reinhart, Daniel Otzen, Donald Lo

39. Panel • Janss

Are Supplements a Panacea for the Brain?

Mary Ann Ottinger, Jean Harry, James Joseph, Nigel Greig, Michael Forster, Sherry Ferguson

40. Panel • Kearns

Dopamine, Stress, and Plasticity in the Prefrontal Cortex

Yukiori Goto, Graham Williams, Satoru Otani, Jason Radley

41. Panel • Sinclair

Prospects for Repair and Neuroprotection in Multiple Sclerosis

Ian D. Duncan, Alastair Compston, Joel Black, Charles ffrench-Constant

42. Panel • Snobble

Modulating Memory and Consciousness: Relating Anesthetic Effects on Molecules, Synapses, Networks, and Brain Function

Robert Pearce, Hugh Hemmings, M. Bruce MacIver, Matthew Banks, Robert Veselis

7:00 PM

Town Meeting • Aspen High School

8:30–10:00 PM

43. Panel • Carroll

Cytokines, Brain, and Behavior

Allan Siegel, Steven Zalcman, William Banks, John Petitto

44. Workshop • Erickson

Progenitor Cells: Basic Science to Translation

Charles Ribak, Derek van der Kooy, Lee Shapiro, Hans Keirstead, Mark Jacquin

45. Workshop • Janss

'Inhibitoxic' Cell Death in the Immature Brain: Basic Mechanisms and Clinical Realities

Karen Gale, Christopher Turner, Daniel Herrera, Bruce Ransom

46. Panel • Kearns

Functional Impact of Drug Dependence on the Mesolimbic Dopamine System and Reward

Elena Chartoff, Steven Laviolette, Roy Wise, John Williams

47. Panel • Sinclair

Cortical Interneurons: Implications of Diversity and Molecular Determinants

Mark Cunningham, Thomas Klausberger, Lindsey Glickfeld, Ken Pelkey

48. Panel • Snobble

Global Warming...and Cooling.... and Heating...and Freezing

Clifford Woolf, Alan Basbaum, Ardem Patapoutian

Wednesday, January 31

7:30–9:30 AM

49. Panel • Carroll

STOP Gene in Schizophrenia: Stop Here or Keep Going?

Barbara Lipska, Didier Job, Annie Andrieux, Sharon Eastwood

50. Panel • Erickson

PPARs in Neurological Conditions: A Current Update

Doug Feinstein, Tammy Kielian, Jarek Aronowski, Raghu Vemuganti, Christian Grommes

51. Panel • Janss

Neurotoxic Consequences of Misfolded Proteins

Steve Richardson, Avi Chakrabartty, Charles Glabe, Witold Surewicz, Neil Cashman

52. Panel • Kearns

Cellular Mechanisms of Dopamine-Neuron-Bursting

Carlos Paladini, Steven Johnson, Mark Teagarden, Hitoshi Morikawa, Michael Beckstead

Wednesday, January 31, continued

53. Panel • Sinclair

Cell Adhesion Molecules and Addiction

George Uhl, Thomas Biederer, Shernaz Bamji, Michael Charness

54. Panel • Snobble

Biomaterials for Neuronal Regeneration

Herbert M. Geller, Ravi V. Bellamkonda, Patrick A. Tresco, Donna J. Osterhout

3:30–4:30 PM

Exhibits and Posters • Anderson

4:30–6:30 PM

55. Panel • Carroll

Signaling in Neuronal Development and Plasticity

Thomas Soderling, Andrew Matus, Michael Sutton, Nicholas Spitzer

56. Panel • Erickson

A Stem Cell Is a Stem Cell Is an NG2 Cell?

Joel Levine, Akiko Nishiyama, Steven Goldman, Toru Kondo

57. Panel • Janss

Eyes Are Not just for Seeing

Samer Hattar, Michael Iuvone, Satchindananda Panda, Susan Doyle, Steven Lockley

58. Panel • Kearns

Parkinson's Disease: Advances, Insights, and Challenges from Genetic and Toxin Models

Richard Nass, Kalpana Merchant, Leo Pallanck, Michael Aschner

59. Panel • Sinclair

Designing Modulators of AMPA Receptor Activity for Therapeutic Use: Implications of Studies from Molecules to Monkeys

Kathy Partin, Gary Lynch, Eric Nisenbaum, Frank Menniti, Samuel Deadwyler

60. Panel • Snobble

It's Bedtime! Journey to the Center of the Brain: The Bed Nucleus of the Stria Terminalis

Francois Georges, Danny Winder, Eric Dumont, Heidi Day, Gary Aston-Jones

6:30–7:30 PM

Business Meeting and Elections • Kearns

Thursday, February 1

7:30–9:30 AM

61. Panel • Carroll

Nutrition, Lifestyle, Brain Aging, and Neurodegenerative Diseases: Making It to your 60th WCBR

Part 1: Oxidative Stress and Inflammation (The Villains)

Kimberly Topp, Susanna Rosi, David Cook, Fulton Crews, Donald Ingram

62. Panel • Erickson

Genetic Manipulation of Astrocytes for Functional Studies

Michael Brenner, Philip Haydon, Flora Vaccarino, Milos Pekny, Harald Sontheimer

63. Panel • Janss

Outer Retina Circuitry and Signaling

Ron Gregg, Catherine Morgans, Maarten Kamermans, Laura Frishman

64. Panel • Kearns

Stem Cells as Tools for Experimental Therapeutics in the Nervous System

Vassilis Koliatsos, Igor Nasonkin, Brian Cummings, Hongjun Song

65. Panel • Sinclair

Progesterone and Estrogen for the Treatment of Brain Injury: Taking Research from the Bench to the Bedside

Donald Stein, Douglas Covey, Stephanie Murphy, Jacob VanLandingham

66. Panel • Snobble

A Vocal Minority: Interpreting the Function of Striatal Cholinergic Interneurons

Wayne Pratt, Paola Bonsi, Paul Apicella, Michael Ragozzino

3:30–4:30 PM

Exhibits and Posters • Anderson

4:30–6:30 PM

67. Panel • Carroll

Nutrition, Lifestyle, Brain Aging, and Neurodegenerative Diseases: Making It to your 60th WCBR

Part 2: Quenching the Fires of Aging

James Joseph, Stephane Bastianetto, Gregory Cole, Elizabeth Head

68. Panel • Erickson

Monitoring CNS Gene Therapies with Neuroimaging

William Bunney, Howard Federoff, Krystof Bankiewicz, Mark Tuszynski, Steven Potkin

Thursday, February 1, continued

69. Panel • Janss

Inflammation after Spinal Cord Injury: What Are its Negative Consequences and How Can We Alter Them?

Lynne Weaver, Phillip Popovich, Gregory Dekaban, Dana McTigue

70. Panel • Kearns

The Yin to the Dopaminergic Yang: Cholinergic Mechanisms in Cocaine Addiction

Bryon Adinoff, Bartley Hoebel, James E. Smith, Deborah Mash

71. Panel • Sinclair

What Is Critical about the Critical Period?

Elizabeth Quinlan, Kevin Fox, Hey-Kyoung Lee, Peter Hickmott

72. Panel • Snobble

Novel Regulators of Glucose and Energy Balance: Use of Old and New Mouse Models in the Discovery Process

Stephen Salton, John Pintar, Iris Lindberg, Lloyd Fricker

8:30–10:00 PM

73. Panel • Carroll

The Role of the 5-HT Transporter (5-HTT) in Emotion/Stress Regulation, Impulse Control, and Anxiety: A Developmental and Psychopathologic Perspective

Larry Siever, Andrew Holmes, Christina Barr, David Goldman

74. Panel • Erickson

Microglia in Neurodegenerative Disease

Thomas Moeller, Nephi Stella, Paul Muchowski

75. Panel • Janss

Anesthesia and Consciousness

Anthony Hudetz, Giulio Tononi, Michael Alkire, Misha Perouansky

76. Panel • Kearns

Glutamate Transporters: Structural Dynamics, Synaptic Mechanisms, and Therapeutic Potential

Jeffrey Diamond, Peter Larsson, Jacques Wadiche, David Poulsen

77. Panel • Sinclair

Autonomic Responses to Hypoxia and Hypercapnia: Is it Sheer Bliss?

David Mendelowitz, Patrice Guyenet, David Kline, Gordon Mitchell

78. Panel • Snobble

Rethinking Functional Subdivisions in the Striatum

Paul Clarke, Pieter Voorn, Satoshi Ikemoto, Ann Kelley

Friday, February 2

7:30–9:30 AM

79. Panel • Carroll

Plasticity as a Mechanism for Recovery Following Damage to the Nervous System

James Fawcett, Karim Fouad, Mark Tuszynski, Corinna Darian-Smith

80. Panel • Erickson

Neural Substrates of Appetitive Associative Learning: New Perspectives on Drug Seeking

Gloria Meredith, David Rademacher, Fei Shen, Taco De Vries

81. Panel • Janss

Control Your Inhibitions: Local Circuit Processing in the Striatum

Aaron Gruber, Paul Bolam, James Tepper, Francois Gonon

82. Panel • Kearns

The Role of Nitric Oxide in Drug Abuse

Stephen Sammut, John Wang, Mara Balda, Luigi Pulvirenti

83. Panel • Sinclair

hESC-Derived Neural Stem Cells

Xianmin Zeng, Mahendra Rao, Steven Goldman, Thomas Schulz

84. Panel • Snobble

AMPA Receptor Trafficking in Synaptic Plasticity and Neuronal Death

John Isaac, Hey-Kyoung Lee, **R. Suzanne Zukin**, June Liu

4:30–6:30 PM

85. Panel • Carroll

RNA-Mediated Toxicity in Neurological Disorders

Peng Jin, Laura Ranum, William Yang, Charles Thornton

86. Panel • Erickson

Regulation of Ionotropic Glutamate Receptor Trafficking and Clustering

Andres Maricq, Roger Nicoll, Katherine Roche, David Bredt

87. Panel • Janss

GABAA Receptor-mediated Damage in the Developing Brain

Joseph Nuñez, Fernando Valenzuela, Kevin Staley, Vesna Jevtovic-Todorovic

88. Panel • Kearns

Recent Advances in Understanding the System Level Functions of Dopamine and Norepinephrine and their Interaction

Jonathan Cohen, Read Montague, Gary Aston-Jones, Samuel McClure, Kimberlee D'Ardenne

Friday, February 2, continued

89. Panel • Sinclair

Making Connections: Factors Influencing Axon Outgrowth

Karen Greif, Gianluca Gallo, Lorene Lanier, Paul Letourneau

90. Panel • Snobble

Individual versus Environmental Determinants of Daily Behaviour in Humans

Rémi Quirion, Kenneth Wright, Julie Carrier, Diane B. Boivin, Jonathan Emens

Don't forget to visit the exhibits

Poster Session 1

Sunday–Monday • Anderson

Posters will be available for viewing after 8:30 PM Sunday through 6:30 PM Monday. Presenters will be with posters on Monday from 3:30–4:30 PM.

P1. Sleep Disturbance in Withdrawing Marijuana Users

Karen Bolla

P2. Anatomical and Functional Analysis of the "Slouchy" Mouse

Martin Hanson

P3. Partial Restoration of Postischemic Pial Artery Dilation to ADP after Global Ischemia Is Mediated by eNOS, But Does Not Involve the Adenosine 2b Receptor

Min Li

P4. Brain Reorganization in Tinnitus

Josef P. Rauschecker

P5. Investigation of Brain Remodeling after Neural Progenitor Cell Treatment of Stroke, Using MRI

Zhenggang Zhang

P6. A Novel Mechanism by which Clozapine Induces ERK1/2 Activation in Cortical Neurons

George Fink

P7. NGF-promoted Differentiation of PC12 Cells Alters Nucleotide-stimulated Catecholamine Release and P2 Receptor Expression

David B. Arthur

P8. Anticonvulsant Effects of 1,3-Butanediol, A Metabolic Precursor of Ketone Bodies

Maciej Gasior

P9. Pharmacological Inactivation of L-type (Cav 1.3) Ca 2+ Channels Strongly Attenuates Rotenone Toxicity on Dopaminergic Neurons of the Substantia Nigra

Ema Ilijic

P10. Pharmacologic Analysis of Transgenic Rats Expressing the Human Bradykinin B1 Receptor in the Central Nervous System

Duane Reiss

P11. Animal Models of Usher Type IC

Jennifer Lentz

P12. Reversal of Memory Deficits in APP Transgenic Mice through Inhibition of Calcineurin

Giulio Taglialatela

P13. Neuregulin-1 Regulates Cell Adhesion through an erbB2/phosphoinositide-3 kinase/Akt-Dependent Pathway: Implications for Schizophrenia

Christopher G. Kanakry

P14. DNA Methyltransferase Activity Regulates Memory Formation and Synaptic Plasticity

Courtney A. Miller

P15. Transgenic Mice Deficient in Alanine-serine-cysteine-1 Transporter Reveal an Important Role for Regulating D-serine Levels in Brain

Christian Thomsen

P16. Ethanol Modulation of D1 Dopamine Receptor Signaling May Be Mediated by Protein Kinase C in an Isozyme-specific Fashion

David R. Sibley

P17. Longitudinal Behavioral Evaluation of a Knock-in Mouse Model of Huntington's Disease

Mary Y. Heng

P18. TNFα Impairs Growth Cone Motility by a Rac1-mediated Oxidative Damage to the Neuronal Actin Cytoskeleton

Thomas Kuhn

P19. Arrestin-binding Determinants on D2-like Dopamine Receptors

Kim Neve

P20. GRIF1, A Novel Regulator of Endosomal Trafficking

Elizabeth A. Kirk

P21. SynGAP Is Associated with the Cytoskeleton and Regulates the Dynamic Turnover of Actin in Dendritic Spines

Gavin Rumbaugh

P22. Adapting to Fast Rotation in Artificial Gravity

Laurence R. Young

P23. Regulation of Neuronal Pentraxin 1 Expression Is Associated with Synaptic Damage in Alzheimer's Disease

Ramon Trullas

P24. Diabetes-induced Allodynia: Correlation between Behavioral Intensity, Duration of Diabetes, and Periaqueductal Gray (PAG) Activation

Thomas J. Morrow

P25. Tracing Tracts in Down Syndrome Mice with μMRI

Russell Jacobs

P26. Human Cognitive Decline Associates with Cortical Synapse Loss

Stephen Scheff

P27. Potassium Trafficking by Satellite Glial Cells in the Trigeminal Ganglion as a Determinant of Orofacial Neuropathic Pain

Luc Jasmin

Poster Session 2

Monday–Tuesday • Anderson

Posters will be available for viewing after 8:30 PM Monday through 6:30 PM Tuesday. Presenters will be with posters on Tuesday from 3:30–4:30 PM.

P28. Voluntary Running Attenuates Age-Associated Deficits Following SCI

Monica M. Siegenthaler

P29. Neural Mechanisms Involved in Saccadic Eye Movement Fragmentation

Edward Keller

P30. Inhibition of Peroxynitrite-mediated Oxidative Damage after Spinal Cord Contusion Injury in Rats by the Nitroxide Antioxidant Tempol

Edward Hall

P31. Donepezil Reverses Scopolamine-induced Amnesia in Rats: Relation with Hippocampal EEG?

Arjan Blokland

P32. Deficient Activity-dependent mRNA Transport in a Mouse Model of Fragile X Syndrome

Jason B. Dictenberg

P33. A Role for Abnormal Sensory Input in Restless Legs Syndrome

Douglas Wright

P34. Differential Contributions of the Basolateral and Central Nucleus of the Amygdala in Mediating Intra-Accumbens Opioid-induced Approach and Consummatory Phases of High-Fat Feeding

Matthew Will

P35. Navigating Drug Development Moguls for Potential Biotechnology Moguls

Eric W. Harris

P36. The Role of Brainstem Reorganization in the Expression of Hindlimb Receptive Fields in the Forelimb-Stump Representation of the Somatosensory Cortex in Neonatally Amputated Rats

Richard Lane

P37. Expression Profiling of Microglia in situ after a CNS Insult. A Combination of Immunohistochemistry, Laser Capture Microdissection and Microarrays

Fredrik Kamme

P38. A PPARdelta Agonist Promotes Differentiation of Oligodendrocytes from Oligospheres

Anne Boullerne

P39. Diverse Classes of Antidepressant Produce Dopaminergic Sensitization in BALB/cByJ Mice

Douglas Marsteller

P40. Kalirin-7 Controls Activity-Dependent Structural and Functional Plasticity of Dendritic Spines

Peter Penzes

P41. Unraveling the Mystery of Human Trace Amine Receptors

Anita H. Lewin

P42. eNOS Phosphorylation Modulates Vascular Reactivity and Stroke Outcome in S1179D and S1179A Knockin Mice

Dmitriy Atochin

P43. The Endogenous Role of NMNAT1 in the Developing Mouse Brain

Chia-Ling Chang

P44. Disruption of NMDA Receptor Signaling in Dopamine Neurons Impairs Contextual Reward Association

Larry S. Zweifel

P45. Dopamine D3-Receptor Ligands as Tools for In Vivo Investigation in Models of Drug Abuse

Amy Hauck Newman

P46. Melatonin 1/2 Receptor Agonist Properties May Be Sufficient for the Anxiolytic-Like Activity of Agomelatine

Chad J. Swanson

P47. NMDA Receptors at Glutamatergic Synapses on Striatopallidal and Striatonigral Medium Spiny Neurons

John Partridge

P48. Working-Memory Deficits in Adult Rats Previously Sustaining Partial Loss of Mesoprefrontal Dopamine Early in Development: Effects of Reboxetine

Janet M. Finlay

P49. A Novel Endocannabinoid-Dependent Potentiation of Excitatory Synaptic Transmission in Hippocampus

Michael P. Kavanaugh

P50. Transcriptional Regulation of PINK1

Kelly Jean Thomas

P51. RNA-Binding Targets of the Recessive Parkinsonism Protein DJ-1 Reveals Involvement in Mitochondrial, Oxidative Stress and PTEN/Akt Survival Pathways

Marcel van der Brug

P52. Regulation of Proopiomelanocortin Neurons by Endocannabinoid-Sensitive Terminals at Distal Dendrites

Shane T. Hentges

P53. Expression of mRNA Transcripts Associated with DJ-1, Implicated in Parkinson's Disease, in Wild Type and DJ-1 Knockout Mice

Jeff Blackinton

P54. The Effect of Catecholamine Depletion by Alpha-Methyl-Para-Tyrosine on Measures of Cognitive Performance and Sleep in Abstinent MDMA Users

Una McCann

P55. Phase and Power of Hippocampal Theta Modulates Responsiveness of Nucleus Accumbens Neurons in the Awake Behaving Rat

John Wolf

Don't forget to visit the exhibits

Poster Session 3

Tuesday-Thursday • Anderson

Posters will be available for viewing after 8:30 PM Tuesday through 6:30 PM Thursday. Presenters will be with posters on Thursday from 3:30–4:30 PM.

P56. Kappa Opioid Inhibition of Somatodendritic Dopamine IPSCs

Christopher Ford

P57. Regulation of Alpha-Synuclein Phosphorylation in Mammalian Cells

David Miller

P58. The Influence of Acetaldehyde on Nicotine-Induced Neurotransmitter Changes in the Brain

Erin Shearman

P59. Inactivation of Prefrontal Cortex Abolishes Sensory-Evoked Acetylcholine Release from Sensory Cortices

Douglas Rasmusson

P60. Genetic Association and Expression of STOP (MAP6) in Schizophrenia

Andrew Joseph

P61. Insulin-Sensitive Neuropeptide Secretory Granules May Provide their own Calcium for Exocytosis

Timothy Eisen

P62. Morphological and Molecular Features of Early and Late Onset CMT1B

Michael Shy

P63. Modulation of Neural Stem Cell Proliferation and Differentiation by Arginase I

Sara Becker-Catania

P64. IGF-I Mediated Signaling Pathways and Downstream Targets in Oligodendrocyte Progenitors

Teresa Wood

P65. Differential μ-Opioid Receptor Regulation Following Chronic Treatment with Morphine or Methadone

Michael Virk

P66. Pharmacological Studies of mGlu2/3 Drugs on Glutamate Release Utilizing Ceramic-Based Microelectrode Arrays

Peter Huettl

P67. BLOC-1 Complex Components Dysbindin (DTNBP1) and MUTED Modulate Dopamine D2 Receptor Endocytosis in Human Neuroblastoma Cells and Lymphoblasts

Yukihiko Iizuka

P68. EAE-induced CNS Inflammation Accelerates ALS-like Disease in the hmSOD Transgenic Rat Model

Brent Harris

P69. Short-Term Limb Immobilization Produces Behavioral and Cortical Plastic Changes in Normal Subjects

M. Felice Ghilardi

P70. Spinal Cord Injury Is Followed by Gene Expression Changes in the Rat Hippocampus

Nicole Berchtold

P71. PTEN-induced Protein Kinase, PINK1: Cellular and Subcellular Localization, its Interacting Molecules and Possible Function

Mika Shimoji

P72. GABA Spillover to Extrasynaptic GABAA Receptors: A Major Component of Inhibition during Conditions of Synchronous Transmitter Release

David Naylor

P73. There Is No Spoon—The Misrepresentations of Association Cortex

Ralph Siegel

P74. Ventral Hippocampal Inputs to the Amygdala and the Prefrontal Cortex Have Dissociable Roles in Emotional Learning

Witold Lipski

P75. Nucleus Accumbens Injection of MT-II in Mice Decreases Food Intake

Amanda Sharpe

P76. Ketone Bodies Decrease Hyperexcitability in Acute Hippocampal Slices from Kcna1-null Mice

Timothy Simeone

P77. The Ketogenic Diet Is Neuroprotective and Reduces Mitochondrial Oxidative Damage in Mouse Models of Acute and Chronic Seizures

Heather Milligan

P78. A Multi-Electrode Array Investigation of Intrinsically Epileptic Human Hypothalamic Hamartoma Tissue

Kristina Fenoglio

P79. The Equlibruim of GAT1 Helps to Determine the Level of Tonic Inhibition

George Richerson

P80. Encoding of "Value" by Mesolimbic Dopamine Reflects Benefits but not Costs of Future Rewards

Jerylin Gan

P81. Modulation of Anterior Cingulate Cortical Activity Associated with Sacral Nerve Root Stimulation for Treating Urogenital Distress

Dan Silverman

Session Abstracts

Panel • Sunday 4:30–6:30 PM • Carroll

1. Epigenetics of Cocaine Addiction

Christine Colvis, Anne West, Chris Pierce, Ghazaleh Sadri-Vakili, Craig Ferris

Epigenetics encompasses persistent changes in gene expression that occur without alterations in DNA sequence. For example, enzymatic modifications to DNA and histones, the main protein component of chromatin, regulate transcription factor access to gene promoter regions. This panel will focus on recent evidence using animal models indicating that chromatin remodeling contributes to cocaine-induced functional changes in the brain. Anne West will discuss how phosphorylation regulates activity of the methyl-DNA binding protein MeCP2, which represses gene transcription by recruiting histone deactylases and histone methyltransferases onto its target genes. Dr. West will show that both acute and chronic treatment of mice with cocaine induce MeCP2 phosphorylation in striatal neurons. Chris Pierce will outline evidence that the histone deacetylase inhibitor, sodium butyrate, impairs the acquisition of cocaine self-administration by rats. In addition, Dr. Pierce will present data indicating that increased CaM-KII mRNA expression in the medial prefrontal cortex (mPFC) is required for the acquisition of cocaine self-administration. Ghazaleh Sadri-Vakili will summarize recent results demonstrating that cocaine self-administration increases BDNF mRNA levels the mPFC. Moreover, ChIP combined with qPCR analyses demonstrated an increase in acetylated histones associated with the BDNF gene in the mPFC following cocaine self-administration. Craig Ferris has used functional magnetic resonance imaging in awake animals to identify cocaine responsive areas of the brain, such as the mPFC, hippocampus and insular cortex, that are sensitive to chromatin modifying drugs. Dr. Ferris will present results showing that functional changes in brain activity following cocaine exposure are altered by inhibiting histone deacetylase.

Panel • Sunday 4:30–6:30 PM • Erickson

2. Guidance and Regeneration in the Nervous System

Marie T. Filbin, Alex L. Kolodkin, Yimin Zou, Zhigang He

The adult CNS does not spontaneously regenerate after injury. This is largely due to the presence of an inhibitory environment composed of inhibitors expressed by glial cells. In recent years it has become apparent that many guidance cues that give axons direction during development are up-regulated after trauma or injury and are likely to contribute to the lack of spontaneous regeneration in the adult. It is key that we understand how these guidance cues function during development in order to predict whether they may also play a role during regeneration in the adult. Through genetic studies Alex Kolodkin will describe the role of the repulsive guidance cues, the Semas, and their various receptors in the fly and in the mouse. Yimin Zou will report on the bifunctional mode of action of the Wnt family of guidance cues in spinal axon development. Zhigang He will describe the work he has carried out on the signaling of inhibitors of axonal regeneration in the adult CNS. Marie Filbin will speak about overcoming inhibitors of axonal regeneration.

Panel • Sunday 4:30–6:30 PM • Janss

3. Post-Transcriptional Control of the Circadian Network

Joseph Takahashi, David Virshup, Carla Green, Martha Gillette

Tremendous progress has been made in our understanding of the molecular mechanisms of circadian clocks in mammals. Circadian oscillations are generated by a set of genes that form a transcriptional autoregulatory feedback loop. Recently, the post-transcriptional regulation of this pathway has come into prominence. The speakers in this panel will discuss four novel aspects of post-transcriptional regulation of the circadian clock. Dr. David Virship will discuss the role of Casein kinase I epsilon (CKIe) and beta-TRCP in the proteasomal degradation of circadian clock proteins. Dr. Joseph Takahashi will present data on tissue-specific regulation of CKIe and elucidation of novel circadian mutants in the ubiquitin proteosome pathway. Dr. Carla Green will provide data on the role of mRNA deadenylation in control of circadian output pathways. Dr. Martha Gillette will discuss the role of actin-based cytoskeletal

reorganization in the modulation of the light and glutamate signaling pathway in the suprachiasmatic nucleus. The participants are engaging speakers and discussion of each presentation in the context of the others will be encouraged.

Panel • Sunday 4:30–6:30 PM • Kearns

4. Neuronal Dysfunction in Huntington's Disease: The Cortex and the Striatum

Michael Levine, Ilya Bezprozvanny, Austen Milnerwood, Carlos Cepeda, Kerry Murphy

Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by progressive disturbances in movement, cognition and mood. In HD there is a progressive and selective degeneration of striatal medium-sized spiny neurons as well as of neurons in the cortex and hippocampus. Mouse models of HD permit the study of mechanisms of neuronal dysfunction that ultimately lead to neurodegeneration. This panel will describe new findings in different mouse models involving changes in striatal neurons that make them more susceptible to degeneration as well as alterations in the cortex and the interplay between cortical outputs to the striatum and neuronal responses that can induce dysfunctions in striatal cells. Michael Levine will introduce the topic. Ilya Bezprozvanny will discuss calcium signaling and neurodegeneration of striatal neurons in the YAC128 mouse model of HD. The main focus will be on connections between glutamate and dopamine-induced calcium signals and apoptosis of medium-spiny striatal neurons in this mouse model. Austen Milnerwood will discuss NMDA receptor function in the YAC mouse models of HD. He will concentrate on current data examining alterations in receptor signaling, localization, trafficking and their roles in excitotoxicity. Carlos Cepeda will provide evidence for alterations in synaptic activity in the corticostriatal pathway, primarily in the R6/2 model of HD, and how these alterations may predispose striatal medium-sized spiny neurons to degeneration. Finally, Kerry Murphy will discuss abnormal synaptic plasticity in the cortex of the R6/1 mouse model of HD. He will focus on the non-generic nature of synaptic deficits in the perirhinal and medial prefrontal cortex of this mouse model and on the emerging role of dopamine as an early mediator of cortical dysfunction.

Panel • Sunday 4:30–6:30 PM • Sinclair

5. Axon-Glia Interaction in Myelination

Elior Peles, Wendy Macklin, Tim Kennedy, Jonah Chan

The panel will present recent data about the molecular mechanisms of myelination in the peripheral and central nervous system. Wendy Macklin will talk about the signaling pathways that regulate myelination in the CNS, with a focus on Akt. In mice overexpressing constitutively active Akt, oligodendrocytes increase myelination throughout their life and all white matter areas increase in size. Early during development, the interaction between Akt-overexpressing oligodendrocytes and developing axons leads to premature and inappropriate organization of Nodes of Ranvier. Tim Kennedy will speak about the roles for Netrin-1 in oligodendrocyte. Netrin-1 is a required chemorepellent guidance cue that directs migrating oligodendrocyte precursor (OP) cells in the embryonic CNS. Netrin-1 and its receptors DCC and UNC5H1 are also expressed in the adult mammalian CNS, where they contribute to oligodendroctye maturation and myelination. Jonah Chan will present newly exciting data about the establishment of cell polarity and the initiation of myelination in the PNS. The Par polarity complex consisting of Par-3, Par-6, and atypical PKC is localizes asymmetrically in Schwann cells at the axon-glial junction when co-cultured with dorsal root ganglion neurons. Disruption of the Par complex, by over-expression and RNAi knockdown, dramatically inhibits myelination, suggesting that Par-3 acts by recruiting molecules essential for the initiation of myelination to the axon-glia interface. Elior Peles will discuss the roles of cell adhesion molecules in myelination. Axon-glial contact along the internodes is mediated by several members of the Nectin-like (Necl/SynCAM/IgSF4) CAMs, which are located at the axon-glial interface. The interaction between different Necls is required for cell contact and myelination.

Panel • Sunday 4:30–6:30 PM • Snobble

6. Operation Head-Start: Early Life Nutrition, Stress, and Bonding Influences on Adult Brain Function

Amy Naleid, Mary Olmstead, Vedran Lovic, Barry Levin

The rapidly changing modern environment offers increased access to highly palatable foods and to technology that may limit direct human interaction. These lifestyle changes no doubt affect an organism's

physiology and may be particularly detrimental to children and adolescents as they undergo dramatic developmental changes. Animal studies can address this issue by manipulating early environmental experience and measuring neural, hormonal and behavioral changes in adulthood. This panel will present data showing how perinatal and post-weaning changes in nutrition or maternal care alter responses to palatable food, the ability to process information, and homeostatic mechanisms in adult rats. Naleid will describe the effects of a high-fat diet in post-weaning on responding for a highly palatable treat in adulthood. Olmstead will present data on the interaction between maternal care and stress-induced binge eating in adolescent female rats. Lovic will show that artificial rearing (no maternal contact) increases adult locomotor activity, behavioral disinhibition, and impulsiveness, while reducing sensorimotor gating and the ability to shift attention, all suggestive of changes in the prefrontal cortex. Finally, Levin will describe the interaction of genetic predisposition with perinatal maternal diet and metabolic state as well as post-weaning exercise on the development of obesity and the neural pathways that regulate energy homeostasis. These talks demonstrate the validity of animal models to study the impact of modern conditions on development, highlighting the interaction between variables such as diet, stress, and parental contact. The findings may provide insight into the potential outcomes of raising children in this environment.

Panel • Sunday 8:30–10:00 PM • Carroll

7. Craving from the Dark Side of the Brain

George Koob, Paul Kenny, Yavin Shaham, Subhash Pandey

Compulsive drug- and food-taking behaviors in humans derive from several sources, including the positive reinforcing effects of the rewards, the aversive states associated with reward withdrawal, and stress. The goal of our session is to present recent data on the mechanisms underlying reward craving induced by withdrawal states and stress, i.e., the "dark side" of craving. George Koob (The Scripps Research Institute, La Jolla) will provide a conceptual framework for the panel and show evidence for the role of the amygdala and corticotropin-releasing factor (CRF) in conditioned withdrawal from opioid drugs. Paul Kenny (Scripps Florida) will describe the role of conditioned withdrawal in nicotine and opioid dependence, with an emphasis on how withdrawal-associated conditioned stimuli can produce anti-reward effects through Pavlovian processes and thereby increase drug self-administration. Yavin Shaham (Intramural Research Program, National Institute on Drug Abuse) will discuss data on the role of CRF1 receptors in stress-induced

relapse to palatable food-seeking during dieting, as measured in a reinstatement model (commonly used to study relapse to abused drugs). Subhash Pandey (University of Illinois) will discuss a molecular cascade of events in the amgydala that drives the negative affective states of alcohol withdrawal, with a focus on changes in CREB and neuropeptide Y. Our panel will discuss novel animal models, neurocircuitry, and molecular mechanisms underlying reward craving induced by both withdrawal and conditioned withdrawal states, and by stress.

Panel • Sunday 8:30–10:00 PM • Erickson

8. Parsing the Clinical Heterogeneity of Schizophrenia: Effects of Schizophrenia Susceptibility Loci

Anil K. Malhotra, Richard Keefe, Joseph Callicott, Katherine Burdick

This panel will discuss recent advancements in data linking clinical assessment, neurocognitive methodology, and fMRI imaging with the underlying genetic etiology of the complex phenotype of schizophrenia. Dr. Richard Keefe will present data from the CATIE trial and introduce the clinical correlates that contribute to the heterogeneity of treatment outcome and neurocognitive function in patients with schizophrenia. He will discuss how comprehensive and careful phenotyping can enhance the power to detect genetic loci for schizophrenia. Dr. Anil Malhotra, who will be chairing the session, will discuss the partitioning of the clinical phenotype in genetic studies of schizophrenia. He will present data on a number of schizophrenia loci, including DRD2, COMT and DTNBP1, which are associated with specific aspects of the disease such as treatment response, negative symptoms, and comorbid affective symptomatology. Dr. Katherine Burdick will review work suggesting differential effects of several schizophrenia susceptibility genes on neurocognitive performance in patients with schizophrenia. She will present data from dysbindin (DTNBP1), catechol-o-methyltransferase (COMT), and disrupted in schizophrenia 1 (DISC1) and discuss the relationship between each of these genes and both general and specific functional neurocognitive assays in schizophrenia. Finally, Dr. Joseph Callicott will examine the relationship between several candidate genes, schizophrenia, and fMRI imaging. He will present work showing that genetic variation is related to differential patterns of brain activation that are associated with the disease and neurocognitive dysfunction. The session will leave time for audience-based discussion about the multiple scientific issues raised during this symposium.

Panel • Sunday 8:30–10:00 PM • Janss

9. The Role of the NR2 Subunit in NMDA Receptor Function

Stephen Traynelis, Jon Johnson, Stefano Vicini, Johannes Hell

This symposium will provide information on four different aspects of NMDA receptor signaling. First, Dr. Stephen Traynelis will describe recent advances in molecular dynamics modeling of agonist binding domain for the NR2D subunit, and discuss differences in the NR2 subunits that are relevant for function. Second, Dr. Jon Johnson will provide an updated perspective on how NR2 subunits control perhaps the most important regulatory feature of NMDA receptors, their voltage-dependent block by extracellular Mg2+. Third, Dr. Stefano Vicini will describe the importance of the NR2 subunit in controlling single channel and EPSC properties in autaptic NMDA-EPSCs in cultured cerebellar neurons from mice lacking NR2A or NR2C subunits. Finally, Dr. Johannes Hell will describe the role of NMDA receptors in regulation of CaMKII, Pyk2, and Src. These four presentations touch on all aspects of NMDA receptors: structure, biophysical function, synaptic function, and regulation, and should provide a coherent and up to date view of some of the key issues surrounding this critically important class of receptors.

Panel • Sunday 8:30–10:00 PM • Kearns

10. Parkinson's Genes and their Role in Mitochondrial Function

David Park, Heidi McBride, Edward Fon, Anurag Tandon, Mark Cookson

Increasing evidence suggests the central nature of the mitochondria in degeneration of dopamine neurons in PD. Mitochondria are central regulators of ATP production, important source of reactive oxygen species, relay stations for signals related to death, and important in synaptic transmission. Intriguingly, all the above mentioned processes play potentially pathogenic roles in neuronal dysfunction. However, there is a tremendous deficit in our molecular understanding of mitochondrial regulation and how it relates to neuronal injury, function, and recovery. Recently several genes linked to familial PD have been identified. Importantly, many of these genes have been shown to either localized to or impact mitochondrial function. These genes include Parkin, DJ-1, Pink1 and LRRK2. In this panel, we will discuss evidence of whether/how these genes may impact mitochondrial function. Dr. McBride will first provide an overview of mitochondrial function and dynamics and how

they may be linked to PD. Dr. Fon will then talk about Parkin and its role in cellular signaling/trafficking and how it may impact the mitochondria. Drs. Tandon and Cookson will discuss the demonstrated role of Pink1 in the mitochondria as well as how DJ-1 may fit into this picture.

Panel • Sunday 8:30–10:00 PM • Sinclair

11. Molecular Control of Migration in the Postnatal Subventricular Zone

Francis Szele, Harold Cremer, Angelique Bordey, Eva Anton

The molecular regulation of cell migration is being elucidated at a remarkable rate in a variety of systems including embryonic cerebral cortex development. The genes that produce chemotropic gradients, growth cone directionality, and nuclear translocation are being discovered. The adult subventricualr zone generates thousands of neurons every day that migrate long distances to the olfactory bulbs and become functional interneurons. Many questions remain about how postnatal subventricular zone cells migrate to the the olfactory bulbs and elsewhere. Do only neuroblasts or also stem cells migrate? What mechanisms cause glioblasts to migrate out of the SVZ whereas neuroblasts remain within the rostral migratory stream? Are there molecular barriers in adult periventricular parenchyma that prevent emigration? How different or similar are embryonic cortical migration and postnatal subventricular zone migration? This panel will explore these and other issues concerning subventricular zone migration. We will discuss the basic regulation of migration as well as emigration in the context of brain disease/injury and therapeutics.

Panel • Sunday 8:30–10:00 PM • Snobble

12. Sleep, Memory, and Brain Plasticity

Matthew Walker, Richard Ivry, Robert Strecker, Giulio Tononi

While the functions of sleep remain the subject of considerable debate, there has been a resurgence of interest in the hypothesis that sleep is critical for learning and plasticity. This session will offer an overview of recent developments in the study of sleep-dependent memory, spanning a range of analysis from molecules to neural systems to behavior. Matthew P. Walker will discuss behavioral and functional neuroimaging data in humans, demonstrating the essential need for sleep both before and after learning for the effective encoding and consolidation of memory, respectively. He will conclude with a theoretical framework of

how sleep may modify, reorganizes and enhance our memories. Richard Ivry will discuss data-driven hypotheses concerning the relationship of sleep dependent consolidation to hippocampal function. One hypothesis focuses on the distinction between explicit and implicit memory. A second focuses on learning mechanisms that integrate multidimensional information, akin to contextual learning associated with the hippocampus. Robert Strecker will describe the cognitive and associated neurobiological changes produced by sleep fragmentation in rats. Sleep fragmentation impairs hippocampal dependent learning & memory via alterations in synaptic plasticity. Sleepiness, changes in sustained attention, and executive function will also be discussed in the context of the underlying neural mechanisms. Giulio Tononi will describe molecular/genetic approaches, including genome-wide expression across phylogeny, identifying genes whose expression change as a function of wake, sleep and sleep-deprivation. The presentation will converged on a synaptic framework hypothesis, which claims that that sleep subserves synaptic homeostasis.

Panel • Monday 7:30–9:30 AM • Carroll

13. Co-morbid Pain and Addiction: Mechanisms and Risk Factors

Jon-Kar Zubieta, Charles O'Brien, Richard Harris, Mark Greenwald

Both pain and addiction are unique entities involving the nervous system, with significant contribution from central opioid mechanisms. Research and clinical practice show that addictive responses can be affected by pain where as pain responses can be changed by the presence of addiction. The complexity of treatment approaches as well as the rising concern with prescription opioid abuse in the US population urges scientists to seek a more complete understanding of the mechanisms of interaction between pain and drugs of abuse, particularly the opiates.

Dr. Charles OBrien will introduce the subject of individual differences in opioid system function in various substance use disorders and their influence by common genetic polymorphisms. Dr. Richard Harris will present new data as to the effect of chronic, clinical pain on opioid receptor concentrations and their relationship with clinical pain characteristics. Dr. Mark Greenwald will present data and discuss individual variations in the concentration and function of opioid receptors in non-treatment seeking opiate dependent volunteers. Dr. Jon-Kar Zubieta will present data on the function of the endogenous opioid system in pain,

individual variations in the response of this and other neurotransmitter transmitter systems (i.e., dopamine) at the interface between pain and the effects of drugs of abuse. The panel will then synthesize this information to provide with clearer perspectives on the points of interaction between chronic pain, opiates and other drugs of abuse, and how they influence each other modulating the risk for the developemnt of substance abuse.

Panel • Monday 7:30–9:30 AM • Erickson

14. The Glass Ski Boot: Fitting Thalamic Afferents into Striatal Anatomy and Function

Kristen Keefe, Yoland Smith, Peter Magill, Elizabeth Abercrombie

The thalamus has historically been a lowly stepsister to the cortex with respect to regulation of striatal neurons. However, appreciation of the important role that thalamostriatal afferents play in regulating striatal neurons in particular and cognitive function in general is growing rapidly. This panel will review current findings related to synaptic organization of thalamostriatal afferents and the functional impact of this pathway on striatal function. Yoland Smith will compare the synaptic organization of thalamostriatal afferents from intralaminar and non-intralaminar nuclei, the differential organization of these synapses in patch-matrix compartments of striatum, and the impact of MPTP-induced dopamine loss on this synaptic connectivity in primates. His presentation will be followed by Pete Magill who will discuss the in vivo physiological properties and synaptic connections of individual, identified thalamostriatal neurons, with a view to highlighting functional differences between thalamostriatal neuron types. Elizabeth Abercrombie will then discuss the effects of manipulations of thalamostriatal afferents arising from parafascicular nucleus on acetycholine efflux in striatum and how these dynamics are influenced by striatal dopamine depletion. Finally, Kristen Keefe will discuss the characteristics of excitatory transmission mediated by thalamostriatal afferents with an emphasis on subtypes of NMDA receptors mediating this input and regulation of gene expression in striatal efferent neurons by thalamostriatal afferents. It is the goal of this panel to provide an overview on current knowledge of the thalamostriatal projection and to stimulate discussion regarding the functions of this beautiful, but oft neglected, afferent. Corticostriatophiles will be welcomed!

Panel • Monday 7:30–9:30 AM • Janss

15. Molecular Mechanisms in Autism Spectrum Disorders

Joseph Coyle, Randy Blakely, Joseph Piven, William Greenough

Recent epidemiologic studies indicate that autism spectrum disorders (ASDs) are much more common than previously thought with a prevalence of 5 per thousand. Risk genes responsible for ASD or related disorders including Fragile X Syndrome (FgX) and Rett Syndrome have been identified, thereby permitting the elucidation of their mechanisms in mice. This panel will review the clinical features of ASDs and discuss the molecular and behavioral implications of three mutations associated with ASDs.

Piven will provide an overview of ASDs, putative risk genes and brain structural abnormalities. Blakely will discuss the association of the serotonin transporter gene (5HTT) with risk for autism and describe coding mutations of the 5HTT that he has identified. Greenough will discuss the phenotypic characteristics of the mouse model for FgX in which the Fmr1 gene has been inactivated. He will address the role of the Fmr1 protein in regulating mRNA translation in dendrites and the impact of its loss on spine formation. Coyle will describe the phenotypic features of a mouse in which one of the most common mutations (R168X) of the gene responsible for Rett Syndrome, MeCPII, has been inserted into the mouse gene. He will distinguish the behavioral phenotype of the R168X mutant from the more commonly used null mutation.

Panel • Monday 7:30–9:30 AM • Kearns

16. Killer or Good Samaritan? Role of Nitric Oxide in the Pathophysiology of Brain Disorders

Margie Ariano, David A. Wink, Carol A. Colton, Christopher J. Schmidt, Anthony West

Nitric oxide (NO) producing cells are critically involved in regulating neuronal function in diverse brain regions. NO production occurs under normal conditions and may function as a neurotransmitter. In pathological conditions, NO has been implicated in both neuroprotective and neurodegenerative processes. NO is generated by NO synthases (NOS): neuronal (nNOS), inducible (iNOS) and endothelial (eNOS). Recent studies indicate that NOS activity is regulated by multiple neuromodulators and intracellular signaling cascades. NO signaling plays a major role in the pathophysiology of many brain disorders including schizophre-

nia, Alzheimer's disease (AD), and Parkinson's disease (PD). This panel will present recent advances to our understanding of NOS regulation and monitoring, and discuss signaling mechanisms involved in nitrergic neurotransmission in brain regions associated with specific neuropsychiatric disorders. David Wink will give an overview of novel techniques for measuring NO production using cellular indicators. Their utility for assessing protective actions of NO in peripheral and central neurons will be shown. Carol Colton will present evidence for a neuroprotective role of NO in chronic neurodegeneration generated from a new mouse model of AD where removal of NO by genetically deleting iNOS exacerbates the observed pathophysiology. Chris Schmidt will report on genetic deletions of nNOS and cyclic nucleotide phosphodiesterases on striatal functioning and responsiveness to dopaminergic modulation by antipsychotic drugs. Tony West will discuss glutamate and dopamine modulation of striatal nNOS activity and NO signaling in normal and parkinsonian animals. Together these presentations will extend our knowledge of how regulation of nNOS activity and nitrergic signaling occurs in normal and pathological conditions.

Panel • Monday 7:30–9:30 AM • Sinclair

17. Nanotechnology and Neuroscience

Vladimir Parpura, Gabriel Silva, Laura Ballerini, Mario Romero

Nanotechnology is a branch of engineering that deals with materials and devices of nanometer scale. Nanodevices and nanomaterials are increasing being used in many research areas, most notably, in electronics. Applications of nanotechnology in neuroscience, however, are only at the early stages of development. While there are many challenges in this area, there has been significant progress in the use of nanotechnology in neurosciences.

In the proposed panel, speakers will explore the applications of nanotechnology in different aspects of neuroscience. Our exploration will start with quantum dots, where Dr. Silva will discuss their use as a tool for probing neurons and astrocytes. Dr. Silva will also discuss selective differentiation of neural progenitor cells by high-epitope density nanofibers. Next, Dr. Parpura will discuss the use of carbon nanotubes (CNTs) as a scaffold or substrate for neuronal growth; modifications of CNTs can be employed to modulate the branching of neurites and their outgrowth. Additionally, Dr. Parpura will discuss the use of a nanofabricated carbon-based detector for studying single secretory granules. Dr. Ballerini will discuss the use of CNTs as potential devices for improving synaptic

transmission. Dr. Romero will discuss the use of CNTs, nanoyarns and nanosheets to support cellular growth.

Together, these speakers will provide a fertile ground for discussions regarding applications of nanotechnology in neuroscience.

Panel • Monday 7:30–9:30 AM • Snobble

18. New Ideas about Electrical and Chemical Synaptic Transmission in the Retina

Stewart Bloomfield, Stephen Massey, Maureen McCall, Jeffrey Diamond

The vertebrate retina has served for many years as a model system for studying CNS structure and function. The retina offers several advances over other CNS loci in that it is a relatively simple and accessible portion of the brain that can be isolated, yet still stimulated physiologically with light. As the subtypes of retinal neurons and their connections have been well documented, we are now able, at the single cell level, to determine the circuitry involved in the extraction and encoding of different visual cues. This panel will detail recent advances in our understanding of how specific retinal circuits, using electrical or chemical transmission, compute and propagate visual signals. Stewart Bloomfield will discuss how light modifies the conductance of gap junctions in the retina and their role in encoding visual signals sent to the brain. Steve Massey will discuss the expression of the different connexins in the retina. His work indicates that while multiple connexins are found in the retina, they are expressed by specific neuronal cell types. Maurren McCall will talk about the role of inhibitory feedback circuitry in modifying the responses of ganglion cells under different adaptational states. She will also discuss the role of the unique GABAc receptors in mediating this inhibition. Jeffrey Diamond will discuss recent results on the different synaptic mechanisms underlying feedback inhibition onto rod bipolar cells. He will also focus on the diversity of mechanisms, including roles for voltage-gated sodium and calcium channels, and NMDA receptors in modifying GABAergic and glycinergic feedback.

Panel • Monday 4:30–6:30 PM • Carroll

19. Progressive Pursuits to Prevent Professional Paresis (or Fostering the Phantasmagorical Future of Neuroscience)

Kathie L. Olsen, Gwen Jacobs, Elliott Albers, Connie Atwell

Science today is driven by large, complex questions that frequently reside at the intersections of traditional disciplines. The field of neuroscience has been, since its beginning, an example of the interconnectedness of the disciplines—integrating and synthesizing biology and chemistry with medical science and psychology, all aided by tools and technologies dependent upon advances in engineering and the physical sciences. Yet, the grand challenges in neuroscience on tomorrows horizon will be significantly more complex and will require highly-collaborative approaches that incorporate an even broader diversity of disciplines. The possibilities for exciting and important new discoveries are boundless, but are we designing optimal pathways for future success? The panel, moderated by Kathie L. Olsen, NSF, will take a far-reaching view of the future of neuroscience and explore how we might best adapt our institutions and approaches to enable the tools, techniques, and the interdisciplinary, geographically dispersed teams required. Panelists (Gwen Jacobs, Montana State University; Connie Atwell, NIH (retired); and Elliott Albers, Georgia State Universitys Center for Behavioral Neuroscience) will address international, university, federal agency, and multi-institutional center perspectives on structure, practices, and reward systems that either facilitate or inhibit advances in interdisciplinary and collaborative neuroscience. Going beyond general concepts, the panelists will raise specific issues and discuss related strategies that are now being identified and implemented to encourage and enable collaborative, interdisciplinary research (e.g., recognizing multiple PIs). Ample time will be provided for discussion and debate between participants and panelists.

Panel • Monday 4:30–6:30 PM • Erickson

20. Genetic and Environmental Factors in Complex Neuropsychiatric Disorders: Schizophrenia and Autism

Thomas Hyde, Daniel Weinberger, Joel Kleinman, Daniel Geschwind, Tyrone Cannon

The interplay between genetic and environmental factors that increase the risk for neuropsychiatric disorders has become the subject of intense interest. As we learn more about the genetic basis of disorders such as schizophrenia and autism, the interaction of susceptibility genes with environmental risk factors has come under greater scrutiny. Dr. Daniel Geschwind will highlight the challenges faced by studies of complex neuropsychiatric disease and the approach he has employed based on identifying converging lines of evidence and biological pathway analysis to identify autism genes. Dr. Tyrone Cannon will present new data implicating differential expression of inflammatory and neurotrophic factors in maternal serum and cord blood samples following obstetrical stressors among individuals who subsequently developed schizophrenia as adults, and the role of schizophrenia susceptibility genes in mediating this dysregulation. Dr. Joel Kleinman will discuss changes in the expression of putative schizophrenia susceptibility genes over the normal lifespan, and the implications of these changes in the genesis of psychotic behavior. Dr. Weinberger will conclude the session by presenting new evidence that obstetrical complications interact with genes related to the risk for schizophrenia and susceptibility to hypoxic-ischemic brain injury. The focus of this session is to present an integrated approach to the investigation of the etiology of schizophrenia and autism, as paradigms for research into complex neuropsychiatric disorders.

Panel • Monday 4:30–6:30 PM • Janss

21. Adrenocortical Steroids in Stress and Stress Adaptation

Greti Aguilera, Stoney Simons, Stafford Lightman, Pier Vincenzo Piazza, Joe Herbert

Adequate regulation of adrenocortical steroid secretion in basal and stress conditions is essential for homeostasis. Glucocorticoids mediate metabolic adaptation to stress and in the brain they influence learning, memory and behavior, as well as regulating their own secretion through negative feedback actions. This panel will address the mechanisms

underlying the effects of glucocorticoids in the brain. After a brief introduction by Greti Aguilera, Stoney Simons will present an overview of the molecular basis for positive and negative regulatory actions of glucocorticoids and will show novel data suggesting malleability of the genomic actions of steroids. Stafford Lightman will follow by illustrating circadian and ultradian patterns of corticosterone secretion in rats. Using a model of pulsatile corticosterone secretion he will demonstrate that individual glucocorticoid pulses are associated with discrete activation of both glucocorticoid and mineralocorticoid receptors in a tissue-specific manner. Piervi Piazza will show evidence for region specific nuclear translocation of glucocorticoid receptors during the dark phase of the circadian rhythm, and show that glucocorticoid receptor mediated activation of the MAP kinase pathway has a role on the behavioral effects of glucocorticoids. Finally, Joe Herbert will discuss how an interaction between inhibitory effects of glucocorticoids and the stimulatory effect of serotonin on neurogenesis in the hippocampus could be part of the mechanisms underlying hippocampal plasticity during depression and SSREIs administration. Discussion of these topics will open new perspectives for future studies on the role of adrenocortical steroids in the pathogenesis and treatment of stress related disorders.

Panel • Monday 4:30–6:30 PM • Kearns

22. Beyond Dopamine Depletion: Neuronal Adaptations from Dopaminergic to Non-Dopaminergic Systems

Kuei-Yuan Tseng, Sarah McCallum, Michelle Day, Nicolas Mallet, Gustavo Murer

Clinical manifestations in Parkinson's disease (PD) do not emerge until the progressive loss of dopamine (DA) neurons reach to a critical level concurrent with at least 70% reduction of striatal DA. Consequently, several non-DA systems become altered, particularly within the cortico-basal ganglia circuitry. Although it remains to be determined how the non-DA synaptic changes are initiated and maintained, it is clear that these factors are tightly linked and are relevant to PD. Sarah McCallum will present data indicative of a pre-synaptic compensation of DA function despite decreases in striatal dopamine levels. For example, nearly intact nicotine- and K+-evoked [3H]dopamine release from striatum of primates lesioned with the neurotoxin MPTP was observed concurrent with >50% declines in local DA. Michelle Day will present two-photon imaging data showing differences in excitability in the spines and dendrites of D1-expressing striatonigral and D2-expressing striatopallidal

neurons and how these differences are impacted in mouse models of PD. Nicolas Mallet will highlight how striatal fast-spiking interneurons shape the imbalance of striatal projections neurons in chronic DA-depleted rats. Finally, Gustavo Murer will summarize recent findings establishing a link between trans-striatal pathways imbalance and the abnormal oscillations that take place downstream in the parkinsonian basal ganglia. A proper analysis of the input-output transformations within the cortico-basal ganglia circuitry could contribute to unveil important dynamic aspects of information processing in the PD brain. These presentations will provide several novel interpretations on how disruptions of these non-DA interactions could lead to the functional alterations observed in PD.

Panel • Monday 4:30–6:30 PM • Sinclair

23. The Endosomal–Lysosomal System in Neurodegenerative Diseases

Lian Li, Bruce Horazdovsky, Peter Lobel, Ralph Nixon

The endosomal-lysosomal system consists of a dynamic network of membrane-bound organelles, including early endosome, multivesicular body (MVB)/late endosome, and lysosome. It is becoming increasingly clear that this system not only controls protein degradation, but also regulates neuronal signaling and synaptic transmission. Moreover, emerging evidence has begun to implicate endosomal–lysosomal dysfunction as a common pathogenic mechanism in a number of neurodegenerative diseases, including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and Niemann-Pick Type C disease and other lysosomal storage disorders.

This panel will provide an informative overview of recent advances in our understanding of the molecular mechanisms governing protein trafficking along the endosomal-lysosomal pathway, and discuss the genetic, pathological, and molecular evidence linking endosomal-lysosomal dysfunction to the pathogenesis of neurodegenerative diseases. Bruce Horazdovsky will address the importance of Rab5 guanine nucleotide exchange factors in regulation of receptor trafficking and endosome-dependent signaling, and discuss how genetic mutation in one such factor, alsin, leads to neurodegeneration in ALS. Peter Lobel will discuss the Niemann-Pick Type C disease proteins (NPC1 and NPC2) and their role in the control of lipid transport from the lysosome and neuronal survival. Ralph Nixon will present findings that disturbances in the endosomal-lysosomal system occur at early stages of Alzheimer's disease and contribute to the disease pathogenesis. Lian Li will describe the

molecular machinery controlling endosome-to-lysosome trafficking and its link to Huntingtons disease and frontotemporal dementia. We expect that this panel will foster extensive discussion of endosomal-lysosomal function and dysfunction in the nervous system.

Panel • Monday 4:30–6:30 PM • Snobble

24. GPR55: A Novel Cannabinoid Receptor

Ken Mackie, Nephi Stella, Hui-Chen Lu, Andy Irving

While the effects of cannabis and endogenous cannabinoids (endocannabinoids) are, in part, mediated via the CB1 and CB2 cannabinoids receptors, substantial evidence supports the presence of additional cannabinoid receptors. It is likely that these receptor(s) mediate some of the effects of cannabinoids and must be considered when interpreting the behavioral effects of both endocannabinoids and phytocannabinoids. For this panel Nephi Stella will introduce the concept of additional cannabinoid receptors and review the evidence. This introduction will serve to place the next three talks into context. Ken Mackie will present work dissecting the signaling pathways activated by GPR55. This presentation will focus on how these pathways differ from the well-characterized signaling pathways of the CB1 and CB2 receptors and what this might mean for GPR55 function. Hui-Chen Lu will report on studies examining the distribution of GPR55 during development using in situ hybridization and immunocytochemistry. This work will emphasize the dynamic regulation of GPR55 during cortical barrel map formation. Andy Irving will discuss the use of fluorescent GPR55 fusion proteins to help identify ligands that interact with the receptor and to study agonist-induced receptor trafficking. These three talks will provide a thorough overview of our current understanding of the distribution, signaling, and function of this novel cannabinoid receptor.

Workshop • Monday 8:30–10:00 PM • Carroll

25. Microglial Activation: Just What the Neuron Ordered!

Monica Carson, Jean Harry, Benoit Melchior, Jake Streit

Microglia are now recognized to actively monitor neuronal activity in the healthy CNS. Recent evidence now suggests that they have the potential to promote either neurorepair or neurodestruction. As yet, it is unclear to what extent neurons actively drive these microglial choice points. It is also unclear to what extent the failure to choose neuro-

repair is the fault of the microglia in their interpretation of neuronal instructions or the fault of the neurons for providing improper instructions. Here we propose to discuss how age, injury, development and environment alters specific receptor:ligand interactions between microglia and neurons.

The speakers will raise the following issues for an open discussion with session attendees:

1) Monica Carson: identification of novel receptor pathways regulating neuroprotective microglial function in vivo

2) Jean Harry: Interactions between microglia and progenitor cells of the hippocampal subgranular zone: developmental versus inflammatory influences

3) Benoit Melchior: Nasu-Hakola disease: an example of how microglial dysfunction may directly lead to cognitive dementia in humans

4) Jake Streit: Is microglial aging and degeneration the underlying reason for the lack of neuroprotection and neurorepair in neurodegenerative diseases (both AD and ALS)?

Workshop • Monday 8:30–10:00 PM • Erickson

26. Transport and Local Translational Regulation of mRNAs in Neurons

William Greenough, Suzanne Zukin, Gary Bassell, David G Wells, Oswald Steward

In the style of "old fashioned" WCBR workshops, where formal presentations are brief and audience participation in the discussion is encouraged, this session will host a wide-ranging and speculative WCBR workshop on local protein synthesis in dendrites. Zukin will discuss evidence that mRNAs encoding AMPAR subunits GluR1 and GluR2 are localized to dendrites of hippocampal neurons and are bidirectionally regulated by glutamatergic signaling. Wells will discuss progress on the functional consequences of inhibiting the function of the mRNA-binding protein CPEB in neurons. He will specifically discuss how inhibiting this mechanism only in Purkinje neurons produces a loss of the late-phase of cerebellar LTD and produces ataxic mice. Contrasting the differences between FMRP loss and CPEB dysfunction in Purkinje neurons will highlight the differences between these two mechanisms for dendritic mRNA translation. Bassell will discuss the role of FMRP in activity-dependent mRNA transport and synaptic protein synthesis. He will specifically discuss trafficking of FMRP in mRNA granules in

dendrites and synapses in response to glutamatergic signaling and the apparent dual role for FMRP in activity-dependent mRNA transport and synaptic protein synthesis. In cultured neurons from FMR1 knockout mice, the activity-dependent transport of specific mRNAs into dendrites was impaired. Analysis of glutamate-regulated protein synthesis in synaptoneurosomes revealed dysregulation of the synthesis of glutamate receptor subunits and associated proteins. Steward will focus on focus on the apparent rate-limiting nature of the protein synthetic machinery, and what this implies in terms of translational regulation.

Panel • Monday 8:30–10:00 PM • Janss

27. Exercise Neuroscience

Jacquie Van Hoomissen, Amelia Russo-Neustadt, Fernando Gomez-Pinilla, Benjamin Greenwood

Evidence from animal experiments revels that physical activity alters nervous system function in a number of ways ranging from changes in the function of specific neurotransmitter systems, to increasing neurogenesis and neurotrophic factor levels in the brain, to alterations in behavior. These results provide potential neurobiological mechanisms for clinical findings regarding the beneficial effects of exercise on mental health. This panel will discuss the history of research into the effects of physical activity on brain function and highlight some of the current areas of interest, including exercise effects on the central norepinephrine system, neurotrophic factors in the central nervous system and stress response systems. The overall goal of the session is to provide an opportunity to highlight the importance of physical activity in promoting brain health and the beneficial consequences of promoting exercise as a way to improve mental health.

Workshop • Monday 8:30–10:00 PM • Kearns

28. Dopaminergic Burst Firing and Behavior: Are You and I Talking about the Same Thing?

Kristin Anstrom-Kelly, Anthony West, Paul Phillips, Michela Marinelli

Although it is well-known that midbrain dopamine neurons have slow, irregular firing patterns that are punctuated by periodic bursts, the role of burst firing in the regulation of tonic dopamine levels and behavioral control has been debated. In general, dopaminergic burst firing can be defined as a transient rapid firing of dopaminergic cell bodies that produces an enhanced release of intrasynaptic dopamine

and is dependent on afferent input. Salient, predictive stimuli can elicit time-locked dopaminergic bursts that produce extrasynaptic dopamine efflux; however, dopaminergic burst firing also occurs in the absence of environmental stimuli in both awake and anesthetized animals. Burst activity is hypothesized to be critical to reward, learning and synaptic plasticity, but can increased or decreased levels of burst firing account for hyper- or hypodopaminergic tone associated with biobehavioral disorders? Is it appropriate to assign the same role to stimulus-evoked and inherent burst firing in circuit mechanisms that underlie behavioral control? What is the role of phasic inhibitory responses? The purpose of this workshop is to compare and contrast the possible roles of stimulus-evoked versus inherent burst firing in the regulation of tonic and phasic levels of extracellular dopamine and how this regulation may influence behavior and/or disorders such as addiction and schizophrenia. Panelists include Drs. Anthony West (systems electrophysiology), Michela Marinelli (systems electrophysiology), Paul Phillips (cyclic voltammetry) and Kristin Anstrom (multiunit recording).

Panel • Monday 8:30–10:00 PM • Sinclair

29. Postsynaptic Structural and Functional Dynamics in Hippocampal Neurons

Mark DellAcqua, Alaa El-Husseini, Reed Carroll, K. Ulrich Bayer

Recent studies point to cell-cell contact via cell adhesion molecules on axons and dendrites as providing the signals that trigger synapse formation. Adhesion molecule engagement initiates signalling pathways that coordinate recruitment of specialized pre- and postsynaptic protein assemblies to the site of contact. A key event in excitatory postsynaptic development is the recruitment of glutamate receptors and signalling proteins by scaffold proteins. The goal of this session is to provide an overview of our current knowledge and highlight emerging mechanisms by which excitatory synapse formation and function are modulated by adhesion molecules, scaffolding proteins, and kinases and phosphatases. Exciting new results will be presented from the laboratories of four relatively junior experts. Dr. El-Husseini will provide an overview of synapse formation and present new findings on PSD-95 scaffold complexes and Neuroligin adhesion molecules in regulating synapse formation. Dr. Carroll will present an overview of AMPA receptor trafficking in plasticity and present new findings exploring PICK1 as a sensor for NMDA receptor Ca2+ signals regulating AMPA receptor trafficking

between synapses and endosomes. Dr. Dell'Acqua will present an overview of AMPA receptor phosphorylation in plasticity and present new findings demonstrating regulation of postsynaptic AKAP79/150 scaffold-PKA targeting by NMDA receptors during LTD. Dr. Bayer will present an overview of CaMKII signaling in plasticity and present new findings on CaMKII targeting to NMDA receptors and F-actin in synapse development and LTP. In particular, this panel will emphasize use of fluorescence microscopy to image dynamics of receptor trafficking, postsynaptic structure, and signalling in hippocampal neurons.

Workshop • Monday 8:30–10:00 PM • Snobble

30. Taking Control with Neural Prosthetic Interfaces

Gerald Loeb, Andrew Schwartz, Jiping He, Gregory Clark, Douglas Weber

"There is nothing like an imminent hanging to concentrate the mind upon a single idea" (Sam Johnson). After years of developing electronic interfaces with various parts of the neuraxis and using data from them to propound theories of sensorimotor control, our brave (perhaps foolhardy) band of discussants is trying to apply them to control paralyzed and prosthetic arms and hands. Which signals are actually useful for what purposes? Can we extract command signals for everyday reach and grasp activities from motor cortical unit activity (Schwartz, He) or from motoneurons in peripheral nerve (Clark) or from residual movement and EMG (Loeb)? Can we obtain somatosensory feedback signals from dorsal root ganglia (Weber), peripheral nerve (Clark) or injectable transducers (Loeb)? Do we use it for closed loop control (He, Loeb) or to stimulate artificial sensation (Weber, Clark, Schwartz)? Can we adequately control muscles by stimulating intramuscular motor axons (Loeb), peripheral nerves (Clark), or spinal cord (Weber, He)? What clinical disabilities and prosthetic performance will justify these invasive approaches to rehabilitation? Invited participants will introduce their technologies, current results and aspirations in three slides each, then the free-for-all begins.

Panel • Tuesday 7:30–9:30 AM • Carroll

31. Schizophrenia and Bipolar Disorder: Different Clinical Facades Arising from the Same Genetic Architecture?

Daniel Weinberger, Paul Harrison, Barbara Lipska, John Kelsoe, Amanda Law

Schizophrenia and bipolar disorders, both highly heritable, are considered nosologically and etiologically separate disease entities. Recent studies have challenged this notion by providing evidence of overlap of genetic susceptibility loci between these two diseases. Both linkage disequilibrium analysis and SNP association as well as post mortem gene expression studies show that schizophrenia and bipolar disorder share genetic susceptibility for a number of genes, including DISC1, DTNB1, G72, RGS4, COMT, and NRG1. In this panel, we will present data showing that some genes may predispose to a variety of phenotypes, ranging from schizophrenia through schizoaffective disorder to bipolar illness and depression. We will also discuss the role of gene-gene interactions in illness risk and severity, and in phenotypic expression. Paul Harrison will talk about similarities and differences in neuropathological findings and brain gene expression between patients with schizophrenia and bipolar disorder. Barbara Lipska will show that RGS4 expression in schizophrenia and bipolar patients is associated with COMT Val/Met genotype, and SNPs in DISC1, a susceptibility gene for schizophrenia and affective disorders, predict expression of other developmentally important molecules. John Kelsoe will present data on the genetic basis of the bipolar spectrum, focus on GRK3 and stargazing genes, and argue that the data best fit a model in which different sets of genes predispose to overlapping phenotypes. Amanda Law will describe molecular pathways involved in neuregulin and erbB4 signaling that have been implicated in schizophrenia and bipolar psychosis, and illustrate how genetic variation related to risk for schizophrenia and bipolar psychosis modulates activity in this signaling system.

Panel • Tuesday 7:30–9:30 AM • Erickson

32. Another Way to Die: Caspase-independent Mechanisms in Excitotoxic Neuronal Death

Denson Fujikawa, Shaida Andrabi, Klas Blomgren, Alan Faden

In the adult mammalian brain, excessive presynaptic and astrocytic glutamate release results in postsynaptic activation of NMDA receptors

and excessive calcium influx into neurons, which triggers a cascade of biochemical processes that result in neuronal death. This excitotoxic event is produced by pathological insults such as cerebral ischemia, traumatic CNS injury, and prolonged seizures (status epilepticus, or SE). Although the neuronal death produced is not apoptotic morphologically, programmed cell death mechanisms are activated. Activation of caspase pathways is important in apoptotic neuronal death in the immature brain, but it is probably substantially less important in the adult brain. Instead, in the adult brain, caspase-independent programmed mechanisms play a major role. Andrabi will discuss in vitro evidence that activation of a DNA repair enzyme, (polyADP-ribose) polymerase-1 (PARP-1), results in translocation of the mitochondrial flavoprotein apoptosis-inducing factor (AIF) to the nucleus, where it contributes to nuclear chromatin condensation and cell death. Blomgren will show that under ischemic conditions, PARP-1 and Bid trigger AIF translocation to neuronal nuclei, where it contributes to DNA fragmentation and chromatin condensation, and he will also show the age-dependency of ischemic caspase activation. Faden will discuss additional programmed mechanisms important in traumatic CNS injury, including calpain I activation and cell cycle up-regulation. Fujikawa will conclude with evidence that in SE translocation of lysosomal cathepsins and DNase II, as well as mitochondrial AIF and endonuclease G, may be involved in producing nuclear pyknosis, chromatin condensation and internucleosomal DNA cleavage (DNA laddering), all of which occur in excitotoxic neuronal death.

Panel • Tuesday 7:30–9:30 AM • Janss

33. Photoreceptors, Mechanosensory Hair Cells, Ribbon Synapses, and Deafblindness

Monte Westerfield, Teresa Nicolson, Stephan Neuhauss, Bronya Keats

Both photoreceptors and mechanosensory hair cells form ribbon synapses, highly specialized for sustained high frequency release of synaptic vesicles. Both neuron types also degenerate in Usher syndrome, the most frequent cause of deafblindness. Usher patients develop retinal degeneration due to photoreceptor loss and deafness due to sensory hair cells loss. This panel will discuss new information about ribbon synapses and Usher syndrome from studies of zebrafish. Nicolson will present analysis of hair cell ribbon synapses that implicates the L-type calcium channel, Cav1.3, and Synaptojanin as proteins specifically required for hearing and balance. Mutations in cav1.3 and synaptojanin affect synaptic transmission, causing defects in hair-cell ribbon synapse exo-

and endocytosis. Neuhauss will present analysis of zebrafish mariner mutants, mutations in myosin VIIA (Ush1b). Characterization of retinal morphology and visual function suggests a defect in light adaptation and higher vulnerability to light damage. Immunohistochemistry and ultrastructural analyses reveal defects in the outer retina, including synapses. Keats will focus on HARMONIN, the gene associated with Usher syndrome 1C, found mostly in the Acadian population of southwestern Louisiana. Morpholino knockdown of Ush1c in zebrafish results in significant reduction in the number of functional sensory hair cells in neuromasts, balance abnormalities, and possible visual defects. Westerfield will present analysis of ush2a and ush2c genes. Knockdown produces impaired vision and balance and early degeneration of photoreceptors and hair cells. The presentations will provide novel evidence that Usher syndrome is a developmental disease affecting ribbon synapses.

Panel • Tuesday 7:30–9:30 AM • Kearns

34. Functional Interactions between Striatal D1 and D2 Dopamine and Ionotropic Glutamate Receptors in Cocaine Addiction

David Self, Anthony Grace, Marina Wolf, Richard Palmiter, Ryan Bachtell

The medium spiny neurons of the nucleus accumbens (NAc) receive dense glutamatergic and dopaminergic input that interacts to regulate addictive behavior. The panel will present emerging evidence that cocaine addiction involves changes in ionotropic glutamatergic input to the NAc through specific and differential interactions in neurons containing D1 or D2 dopamine receptors. Tony Grace will show differential modulation of prefrontal cortex and hippocampal input to the NAc by D1 and D2 receptors, a functional competition between these inputs with tetanization, and differential neuroplasticity with cocaine sensitization. Marina Wolf will describe alterations in AMPA receptor levels and surface expression that occur as a result of behavioral sensitization to cocaine or cocaine self-administration leading to "incubation" of craving. She will also discuss underlying signaling mechanisms and potential effects on surface expression of NMDA and DA receptors. Richard Palmiter will show that mice with reduced NMDA receptor activity specifically in D1R-containing cells have attenuated sensitization and conditioned place preference to cocaine. He will also present new data in mice lacking NMDA receptors specifically in dopamine neurons. Finally, Ryan Bachtell will show that down-regulating AMPA receptor

input to NAc neurons with a dominant-negative GluR1 induces cocaine sensitization and facilitates cocaine seeking through a specific enhancement of D2 receptor responses, whereas wild type GluR1 reverses these changes. Together, these studies suggest that bi-directional interactions exist between ionotropic glutamate and D1 and D2 receptors that influence the induction and expression of sensitization processes in cocaine addiction.

Panel • Tuesday 7:30–9:30 AM • Sinclair

35. Dopaminergic Neurons Derived from Human Embryonic Stem Cells and Application to Parkinson's Disease

William Freed, Catherine Schwartz, Su-Chun Zhang, Curt Freed

The potential clinical application of human embryonic stem cells (hESC) for transplantation in Parkinson's disease has attracted a great deal of interest. Although hESC have great potential, there also are a number of unique obstacles ranging from possible adverse events to difficulties in obtaining pure populations of desired neuronal phenotypes. The topic of this panel will be differentiation of dopaminergic neurons from hESC, and the possibility that such cells can be employed for clinical transplantation. William Freed will discuss biological processes which must be addressed for successful transplantation, and dopaminergic differentiation of hESC. Catharine Schwartz will describe her studies using the Ntera2 cell line as a model to facilitate studies of hESC differentiation, as well as gene expression patterns in differentiating Ntera2 cells, hESC, and normal dopaminergic neurons. Su Chun Zhang will discuss differentiation protocols for hESC which can allow for specification of specific subtypes of dopaminergic neurons, and the properties of hESC-derived dopaminergic neurons produced by different techniques. Curt Freed will describe experiments aimed at developing neurons which are phenotypically identical to the A9 dopaminergic neurons, and will conclude with a brief summary of the clinical results of fetal brain tissue in PD, including clinical results and cell survival achieved with fetal dopamine cell transplants up to 14 years after transplantation. Overall, this panel will describe derivation of dopamine neurons from hESC, properties that these cells share with fetal-derived dopaminergic neurons, and both opportunities and obstacles which are unique to dopaminergic neurons derived from hESC.

Panel • Tuesday 7:30–9:30 AM • Snobble

36. Emerging and Re-emerging Viral Infections of the Human Nervous System: What We Know from the Past and What We Need to Know for the Future

Michael Nunn, Kenneth Tyler, Glenn Telling, Christine Zink, Eugene Major

The panel will describe four human infectious agents, the pathology they cause in the brain and the reasons these agents are emerging as serious challenges to public health. Mike Nunn will introduce the panel and highlight the importance of recognizing the brain as a target for infectious agents and the vulnerability of the nervous system to acute and persistent infections. Ken Tyler will describe the characteristics of the West Nile Virus and its neuroinvasive and neurovirulent properties. Glenn Telling will discuss the transmission and pathogenic properties of prion proteins in CJD, vCJD (BSE), and CWD (chronic wasting disease). Chris Zink will explain the use of non-human primate models to understand human lentivirus infections of the brain and why HIV-1 remains in the brain of AIDS patients for decades. Last, Gene Major will detail the reactivation of widespread human polyomaviruses that traffic to the brain at times of immune modulation and the presence of infected neural stem cells in brain tissue. The panel will focus on the brain as a primary target for these agents and emphasize that multiple factors in the brain contribute to neuropathogenesis.

Panel • Tuesday 4:30–6:30 PM • Carroll

37. Skating on Thin "Ice": Neurobiological and Behavioral Consequences of High Dose Methamphetamine

Ronald See, Bryan Yamamoto, Kristen Keefe, John Marshall

Recent research supports the notion that methamphetamine (METH) is among the most addictive of abused substances, by some measures surpassing cocaine or heroin in terms of persistent drug-seeking behavior and impairments in quality of life. Nevertheless, our understanding of the neurobiology of METH addiction and its consequences has lagged behind other drugs of abuse, inhibiting development of treatment strategies. This panel brings together four interrelated areas of research focusing on critical neurobiological substrates affected by METH and the relationship of these changes to behavioral endpoints. Yamamoto

will describe mechanisms whereby METH causes long-term toxicity to dopamine and serotonin nerve terminals in the brain via excitotoxic, bioenergetic, and oxidative stress mechanisms. Keefe will present on METH-induced learning impairments and the relationship of these impairments to striatal monoamine loss and synaptic plasticity molecules. Marshall will discuss how repeated METH produces neocortical cell injury as well as impairments in a novelty preference task of object recognition without affecting monoamine transporter binding. See will show the characteristics of conditioned-cued and drug-induced reinstatement of METH-seeking behavior in a rat model of relapse, including evidence for resistance to extinction and highly robust reinstatement of METH-seeking behavior. Furthermore, changes in cognitive performance and their relationship to drug-seeking will be examined. The panel will provide an integrated perspective on the neuropathology produced by METH and the relationship of these pathologies to disrupted cognitive function.

Panel • Tuesday 4:30–6:30 PM • Erickson

38. Protein Misfolding—A Common Theme in Neurodegenerative Diseases

Menelas Pangalos, Charles Glabe, Peter Reinhart, Daniel Otzen, Donald Lo

There is a growing body of evidence that an increased propensity for proteins to misfold can give rise to neuronal dysfunction and neurodegeneration. Protein misfolding can give rise to protein aggregation in the form of oligomeric, fibrillar, and even higher-order molecular species. The commonalities of protein misfolding as a key step in the pathogenesis of neurodgenerative disorders such as Alzheimer's disease and Parkinson's disease will be discussed in a series of presentations. Dr. Daniel Otzen (Aalborg University, Denmark) will discuss the earliest steps of alpha-synuclein aggregation and discuss the therapeutic potential of novel anti-aggregation approaches. Dr. Charlie Glabe (UCAL, USA) will discuss a common structure and toxic function of amyloid oligomers and how these imply a common mechanism of pathogenesis. Dr. Don Lo (Duke, USA) will discuss the role of pathologically aggregated tau and enhanced neurofibrillary tangle formation giving rise to cerebral atrophy and cognitive deficits, and Dr. Peter Reinhart (Wyeth Research, USA) will discuss preclinical experiments targeting oligomeric amyloid peptides and alpha-synuclein aggregates as disease-modifying therapies for the treatment of Alzheimer's and Parkinson's disease. The session will be introduced and chaired by Dr. Menelas Pangalos (Wyeth Research, USA).

Panel • Tuesday 4:30–6:30 PM • Janss

39. Are Supplements a Panacea for the Brain?

Jean Harry, Jim Joseph, Mary Ann Ottinger, Nigel Greig, Michael Forster, Sherry Ferguson

Survey results indicate that about 40% of the U.S population use dietary supplements. However, the effects of many of these uncontrolled substances on the brain, behavior, and cognition are unclear and confounded by gender, age, and overall health. The topic of this session will be to examine experimental data on selected nutritional supplements generally regarded as healthy and beneficial with few side effects. Current data on the mechanisms of action, efficacy, and scope of action will be considered as well as available information on the use of these supplements. Nigel Greig will introduce the pharmacology of supplements that are neurally active. Michael Forster will consider effects of vitamin E and other supplements on brain aging and motor, cognitive, and sensory function. Mary Ann Ottinger will talk about the actions of lutein and soy phytoestrogens in comparative animal model systems. Sherry Ferguson will discuss phytoestrogen and their effects, including cognitive behavior and neural systems.

Panel • Tuesday 4:30–6:30 PM • Kearns

40. Dopamine, Stress, and Plasticity in the Prefrontal Cortex

Yukiori Goto, Graham Williams, Satoru Otani, Jason Radley

Dopamine (DA) plays a critical role in modulating prefrontal cortical (PFC) circuitry and function. Increasing evidence suggests that stress may disrupt PFC function through alterations in DA transmission. This panel will discuss how stress affects DA regulation in the PFC, with particular attention paid to how stress-induced changes in DA signaling alter structural and functional plasticity in this region. Dr. Williams will summarize how DA transmission and PFC functions exhibit an inverted U-shaped relationship, accounting for how either excessive or deficient DA release could produce PFC dysfunction. Dr. Otani will describe the role of tonic DA tone in regulating synaptic plasticity in PFC. Specifically, a reduction in background DA signaling, as is known to result from chronic stress, may promote abnormal LTD. Dr. Radley will continue with a description of how chronic stress impacts dendritic and synaptic morphology in PFC. Dr. Goto will describe the impact of acute stress on

LTP in normal and schizophrenia model animals. He will describe LTP facilitation with short, but impairment with longer, durations of acute stress in normal animals, whereas in the schizophrenia model, all stress durations impair LTP, suggesting greater vulnerability to stress. These presentations will provide a novel perspective on how stress impacts DA signaling in the PFC. In the panel discussion, emphasis will be placed on understanding these advancements in the context of psychiatric disorders where DA signaling in the PFC may play a prominent role, such as in schizophrenia and depression.

Panel • Tuesday 4:30–6:30 PM • Sinclair

41. Prospects for Repair and Neuroprotection in Multiple Sclerosis

Ian D. Duncan, Alastair Compston, Joel Black, Charles ffrench-Constant

Considerable attention is being directed toward therapies in Multiple Sclerosis (MS) that will lessen inflammation, promote remyelination and protect nerve fibers against acute and chronic degeneration. The recent upsurge in interest in axon loss and its relevance to chronic disability has focused attention on the need for early therapy, and therapy that can repair areas of demyelination before they become targets for axon degeneration. This panel will discuss the new opportunities that exist toward these goals. To set the scene, Alastair Compston will present clinical aspects of the disease that bear relevance to patient selection, time of treatments and target sites for repair where inflammatory or non-inflammatory axon loss may occur. Joel Black will discuss the evidence and potential mechanisms for both inflammatory and non-inflammatory mediated neural degeneration in MS. Strategies for assessing the outcomes of new neuroprotective drugs and their trial design will be discussed. Charles ffrench-Constant will discuss the possibility that endogenous remyelination is the most likely therapy for remyelination and why it eventually fails in chronic disease. Oligodendrocyte progenitors are likely present in some chronic lesions yet they seen incapable of repair. The role that integrins and the extracellular matrix play in myelination and remyelination as well as molecular differences in progenitor maturation during remyelination, will be discussed, and how the basic science may be translatable to clinical trials. Finally, Ian Duncan will compare exogenous repair with endogenous remyelination and identify specific targets where such therapy could be applied focally or to treat more generalized disease.

Panel • Tuesday 4:30–6:30 PM • Snobble

42. Modulating Memory and Consciousness: Relating Anesthetic Effects on Molecules, Synapses, Networks, and Brain Function

Robert Pearce, Hugh Hemmings, M. Bruce MacIver, Matthew Banks, Robert Veselis

Among the many behavioral effects of anesthetics, their ability to produce a reversible state of unconsciousness accompanied by anterograde amnesia is the one that is most desired by patients and wondered at by clinicians and scientists. How does this come about? The past two decades have seen dramatic shifts in our thinking about possible answers to this question at multiple levels, including the molecular nature of anesthetic targets, how changes in cellular function lead to altered network activity patterns, and which brain regions are associated with specific endpoints. This symposium will bring together investigators whose research at these different levels has contributed substantially to our current understanding. Hugh Hemmings will discuss the molecular nature of anesthetic targets, focusing on presynaptic mechanisms that have attracted much recent attention. Bruce MacIver will address how modulation of specific proteins alters synaptic transmission and cellular function. Matthew Banks will discuss the mechanisms by which synchrony in interneuronal networks is modulated in frequency and coherence by anesthetic agents that prolong inhibition, using physiological recordings, dynamic clamp and network simulations. Bob Veselis will describe neuroimaging and behavioral studies which reveal that amnesia is related to two effects—sedation and drug induced amnesia. Possible electrophysiologic/molecular mechanisms underlying drug induced amnesia will be explored as a demonstration of "bridging the gap" between bench and clinical research. Together these speakers will synthesize information spanning a number of levels that has begun to reveal answers to the longstanding mystery of anesthesia.

Panel • Tuesday 8:30–10:00 PM • Carroll

43. Cytokines, Brain, and Behavior

Allan Siegel, Steven Zalcman, William Banks, John Petitto

Immune-and brain-derived inflammatory cytokines potently modulate central neurotransmitter activity and behavior. The neurobehavioral profile of interleukin (IL)-2 differs from that associated with the classically defined proinflammatory cytokines. This panel will discuss: (1) how

peripheral IL-2 affects centrally mediated behaviors; (2) mechanisms by which IL-2 is transported across the blood-brain barrier; (3) how developmental abnormalities in cytokine gene expression affect brain and behavior; and (4) how IL-2 selectively interacts with neurotransmitter-receptors in specific regions of brain to modulate behavior. Zalcman will discuss how peripherally administered IL-2 influences repetitive behaviors and enhances neuronal activation in striatum. The immune-to-brain signaling pathways mediating these effects will be discussed. Inflammatory cytokines may influence brain function via the blood-brain barrier (BBB). Banks will discuss transport of IL-2 across the BBB. He will provide evidence for a saturable efflux system, which constitutes the first such mechanism involving a cytokine. Petitto will discuss the relationship between IL-2 and brain development, focussing upon the septal-hippocampal pathway. He will further show that alterations in the cytoarchitecture of the hippocampus occur in mice lacking the IL-2 gene, indicating that the absence of that gene is linked to dysregulation of cytokines produced by CNS. Siegel will present data demonstrating that modulating effects of IL-2 upon feline defensive rage are specific to medial hypothalamus and PAG, which are regions associated with rage behavior, and that the modulating effects are further linked to specific neurotransmitter-receptors. Information resulting from this panel may generate novel approaches for treatment of psychiatric disorders in which cytokines are implicated.

Workshop • Tuesday 8:30–10:00 PM • Erickson

44. Progenitor Cells: Basic Science to Translation

Charles Ribak, Derek van der Kooy, Lee Shapiro, Hans Keirstead, Mark Jacquin

Stem cell research carries great therapeutic promise. However, functional application of this science has yet to be realized in the human central nervous system. This workshop will highlight recent basic science pertaining to endogenous progenitor cells and the use of endogenous and implanted stem cells in varied translational paradigms. Dr. Ribak will present a brief introductory overview of the state of the art and facilitate discussion. van der Kooy will present new data on a population of stem cells in the postnatal mouse brain that migrate from the cerebral cortex into the striatal subependyma. These cells generate neurons that remain in the striatum or migrate to the olfactory bulbs. Shapiro will show a novel region of neurogenesis in the adult rat cerebral cortex. The data from van der Kooy and Shapiro both present separate challenges to the prevailing views on adult ventricular subependymal zone neurogenesis. The second half of the workshop will focus on the use of transplanted

embryonic stem cells to repair the injured spinal cord. Keirstead will present positive and negative data on the use of human embryonic stem cell derivatives to treat spinal cord injury in rodents. Jacquin will then offer a brief cautionary stance in the face of his laboratory's negative results using murine bcl-2 overexpressing embryonic stem cells transplanted into the contusion-injured spinal cord of the adult rat. The juxtaposition of positive and negative results in this paradigm is sure to generate lively discussion and suggestions for future research.

Workshop • Tuesday 8:30–10:00 PM • Janss

45. 'Inhibitoxic' Cell Death in the Immature Brain: Basic Mechanisms and Clinical Realities

Karen Gale, Christopher Turner, Daniel Herrera, Bruce Ransom

Because the immature brain reacts to injury very differently than the adult brain, we desperately need to understand the rules governing neuronal survival during development if we want to safely treat neurological conditions in pregnancy and infancy. Paradoxically, agents that protect neurons from injury in adult brains can promote injury in the neonatal brain, even after acute exposure. Alcohol, sedatives, anxiolytics, anaesthetics, and antiepileptic drugs all have been shown to cause a striking increase in neuronal apoptosis during the early postnatal period (corresponding to the brain 'growth spurt') in the rodent, but the mechanisms responsible for this remain elusive. In this workshop, participants and audience members will debate possible answers to questions such as: Why is this effect restricted to a specific critical period and to certain brain regions? Are "new" neurons in the adult brain vulnerable? Can we extrapolate across species? What are the functional consequences in terms of behavioral outcomes? Can we prevent the deleterious effects without interfering with naturally occurring developmental programmed cell death? We will also discuss novel findings that nicotinamide can prevent ethanol-induced apoptosis and long-term behavioral impairments (Herrera), and that secondary synaptic reorganization occurs following brief MK-801 exposure (Turner). A crucial role for calcium binding proteins (Turner) and the importance of oxidative and nitrosative stress (Herrera) will be considered. Special problems with drug combinations and unique challenges for treating epilepsy will be raised (Gale), and we will brainstorm about clinical applications and realistic concerns for a variety of therapeutic interventions in pregnancy, preterm and full-term infants (Ransom).

Panel • Tuesday 8:30–10:00 PM • Kearns

46. Functional Impact of Drug Dependence on the Mesolimbic Dopamine System and Reward

Elena Chartoff, Steven Laviolette, Roy Wise, John Williams

The idea that drug addiction is a disease is not new, but recent advances in neuroscience show just how dramatic the corresponding pathological changes in brain function are. The ventral tegmental area (VTA) and nucleus accumbens (NAc) comprise the mesolimbic dopamine system, which is a primary player in the initiation, development, and expression of addiction. Continued drug use leads to physiological changes in this system such that normal function is compromised. In this session the speakers will describe molecular, physiological, and behavioral studies on newly identified forms of drug-induced plasticity within the VTA and NAc. Elena Chartoff (McLean Hospital/ Harvard Medical School) will provide a brief overview and will discuss how morphine dependence alters the behavioral and molecular effects of dopamine D1 receptor activation in the NAc. Steve Laviolette (U. of Western Ontario) will present evidence of a discrete, opiate addiction switching mechanism that involves GABAA receptors within the VTA transitioning from inhibitory to excitatory signaling modes. Roy Wise (IRP/NIDA) will discuss how, in cocaine-experienced but not cocaine-naive animals, cocaine and stress cause VTA glutamate release, which leads to increased dopamine release and can trigger relapse to cocaine seeking. John Williams (OHSU) will discuss how chronic cocaine exposure changes the electrophysiological response of VTA dopamine neurons to cocaine: dopamine-mediated inhibitory currents in the VTA desensitize faster and to a greater extent. The goal of these presentations is to foster cross-disciplinary discussion on drug dependence-induced pathological changes in reward circuitry.

Panel • Tuesday 8:30–10:00 PM • Sinclair

47. Cortical Interneurons: Implications of Diversity and Molecular Determinants

Mark Cunningham, Thomas Klausberger, Lindsey Glickfeld, Ken Pelkey

Cortical networks are endowed with a rich diversity of cortical interneurons. Recent work has begun to shed light on the functional significance of such heterogeneity at both the network and behavioural level. The aim of this symposium will be to present more recent developments in this area to the general neuroscience community. Thomas Klausberger will begin this symposium with an overview of current information on

interneuronal diversity in the hippocampus. He will in addition show new data from in vivo studies on the firing patterns of cholecystokinin-expressing interneurons that express the CB1 receptor and relate this to formation of cell assemblies and representations in the hippocampus. Following on from this Lindsey Glickfeld will present work on the modulation of the temporal output of two subclasses of inhibitory interneurones by endocannabinoids. Lindsey will demonstrate that the spike timing of CB1R-expressing basket cells, a major target for cannabinoids in the rat hippocampus, is distinct from the other main group of basket cells, the CB1R-negative. Mark Cunningham will talk about his use of gene-targeted mice to study the contribution of synaptic excitation onto interneurons in the generation and maintenance of network oscillations in the hippocampus. He will then relate this to biophysical results and the behavioural performance of the mice in various spatial working memory and control tasks. Finally, Ken Pelkey will discuss the plastic nature of excitatory transmission onto interneurons. Specifically, Ken will demonstrate that presynaptic mGluR7 activation and trafficking critically control bidirectional plasticity of excitatory drive onto interneurons in a strong feedforward inhibitory circuit. The presentations by four young scientists will give the audience an introduction to the established as well as hot new work on this population of neurons that are increasingly appreciated as fundamental cellular elements in network function and CNS function.

Panel • Tuesday 8:30–10:00 PM • Snobble

48. Global Warming...and Cooling...and Heating... and Freezing

Clifford Woolf, Alan Basbaum, Ardem Patapoutian

How do we differentiate the ice cold of Snowmass from the warmth of an après ski Jacuzzi? Why do we feel pain in response to excessive heat, and why after sunburn is a warm shower intensely painful? Why does extreme cold feel burning, not cool? What is the relationship between chilis, raw garlic, mustard, wasabi, menthol, camphor, tear gas and thermo sensation?

The answer to all these questions will be revealed in this Panel to be the transient receptor potential (TRP) family of ion channels.

Sensation begins with the conversion of external stimuli into a flux of ions across the membrane of the peripheral terminals of primary sensory neurons. Several TRP channels act as specific thermo sensitive transdu-

cers, exquisitely tuned to respond to different ranges of temperature, but are responsive also to other ligands like capsaicin, endocannabinoids, protons, bradykinin and maybe even mechanical force! The threshold of the channels is plastic, subject to post-translational change, and their expression alters dynamically, making them key players in pain hypersensitivity and culinary ecstacy.

Ardem Patapoutian will discuss the molecular and cell biology of the thermo sensitive TRP channels, how they work, Allan Basbaum their expression, regulation, and what the phenotype of TRP knockouts reveal, what they do. Clifford Woolf will discuss the pro and cons of TRP channels as targets for reducing the aches and pains of skiing, and other conditions.

Panel • Wednesday 7:30–9:30 AM • Carroll

49. STOP Gene in Schizophrenia: Stop Here or Keep Going?

Barbara Lipska, Didier Job, Annie Andrieux, Sharon Eastwood

Stable tubule-only polypeptide (STOP) proteins are a family of microtubule associated proteins (MAPs) important in microtubule stabilization. STOP (MAP6) null mice exhibit synaptic deficits and a variety of behavioural changes indicative of a hyperdopaminergic state. Some of these abnormal behaviors are alleviated by antipsychotic treatment. These findings suggested that STOP mutant mice may be useful in studies of synaptic function, and could be especially relevant to schizophrenia, postulated to be a disorder of the synapse. Moreover, a genetic association between SNPs in a STOP gene and schizophrenia has been recently reported. Didier Job will introduce microtubule physiology and present data concerning STOP structure and function. Annie Andrieux will talk about STOP KO mice, their phenotypes and their potential use as models for the search of new antipsychotic agents. Sharon Eastwood will present mRNA expression data from STOP KO mice providing evidence for a role of STOP in synaptic function, and suggesting that STOP, and possibly other microtubule proteins, may contribute to the synaptic pathology of schizophrenia. Barbara Lipska will present genetic association data from studies on STOP in schizophrenia, and the data from postmortem studies showing that expression of STOP is not different between patients with schizophrenia and controls. We will discuss these contradictory lines of evidence in relationship to the potential involvement of the STOP gene in the pathopysiology of schizophrenia.

Panel • Wednesday 7:30–9:30 AM • Erickson

50. PPARs in Neurological Conditions: A Current Update

Doug Feinstein, Tammy Kielian, Jarek Aronowski, Raghu Vemuganti, Christian Grommes

In the past few years, increasing interest has emerged in the ability of agonists of peroxisome proliferator activated receptors (PPARs) to reduce inflammation and neuronal damage in a variety of neurological diseases and conditions. Most interest has focused on the PPARgamma isotype, since there are several agonists already FDA approved, and the drugs have good safety profiles. These drugs, including members of the insulin sensitizing thiazodinedione (TZD) class, have already been shown to be effective in animal models of MS, AD, and PD; and clinical trials for these diseases are in progress or nearly completed. More recently, PPARg agonists have begun to show promise in several other neurological conditions. Dr. Kielian will present data showing that PPARg drugs are effective in reducing brain inflammatory responses in response to bacterial infections and in brain abscess models. Dr. Aronowski will present data indicating that PPARg agonists directly provide neuroprotection independent of their ability to reduce inflammation, in oxygen-glucose deprivation, excitotoxicity, and MCAO models. Dr. Vemuganti will present data that PPARg agonists have potential in reducing inflammation and injury after spinal cord injury. Finally, Dr. Grommes will present data describing the efficacy of PPARg drugs in reducing growth of gliomas. The question arises whether the effects of PPARg agonists in these distinct conditions are mediated by the same pathways, or indeed if they require activation of the receptor or can occur in receptor-independent manners. An understanding of their effects in these models will help address these issues, and hopefully provide further justification for moving these agents into clinical testing.

Panel • Wednesday 7:30–9:30 AM • Janss

51. Neurotoxic Consequences of Misfolded Proteins

Steve Richardson, Avi Chakrabartty, Charles Glabe, Witold Surewicz, Neil Cashman

The biological activity of a protein depends on its 3 dimensional structure, i.e., the pattern in which a sequence of amino acids is folded determines what the protein is able to do. This panel will discuss the contributions of misfolded proteins to neurodegenation in amyotrophic

lateral sclerosis (ALS), amyloid-related disorders, and prion diseases. Chakrabartty will show that misfolded Cu/Zn-superoxide dismutase (SOD1) is localized almost exclusively to mitochondria in degenerating motor neurons in an ALS patient with the A4V-SOD1 mutation, and in 4 rodent models of ALS. Glabe will discuss evidence that the primary pathogenic species in Alzheimer's and other amyloid-related diseases, are not the deposits of insoluble amyloid fibrils, but rather are abnormal soluble amyloid oligomers that are formed before the deposits. These amyloid oligomers have the ability to propagate indefinitely, and to damage cells by permeabilizing cell membranes. Vaccination against the amyloid epitope may prevent degeneration in Alzheimer's, Parkinson's, and Huntington's diseases, and in type II diabetes. The self-perpetuating misfolding of prion protein is the pathogenic factor in transmissible spongiform encephalopathies, a group of diseases that includes Creutzfeld-Jacob and kuru in humans, scrapie in sheep, bovine spongiform encephalopathy in cows, and chronic wasting disease in elk and deer. Surewicz will present data concerning the molecular basis of the conversion of normal prion protein to the misfolded prion protein, of the molecular characteristics of prion strains, and of barriers to prion transmission between species. Cashman will discuss prion protein misfolding in the disease process and the implications of this to the pathogenesis and management of prion diseases.

Panel • Wednesday 7:30–9:30 AM • Kearns

52. Cellular Mechanisms of Dopamine-Neuron Bursting

Carlos Paladini, Steven Johnson, Mark Teagarden, Hitoshi Morikawa, Michael Beckstead

The firing pattern of dopamine neurons encodes reward prediction error, which is essential for reinforcement learning. Uncovering the mechanisms responsible for generating the reward prediction signal in dopamine neurons is a major challenge for neurophysiologists studying motivation and reward and associated disorders. The encoding of this signal is relatively simple. These neurons normally fire constantly at a low rate, and speed up, firing a phasic burst when reward exceeds prediction. Nonetheless, the cellular mechanism underlying burst production remains undetermined, largely due to the difficulty in reproducing burst firing in vitro. However, recent technical advances have allowed researchers to overcome this experimental obstacle and directly address the cellular mechanisms of burst generation. Dr. Steven Johnson will discuss how in vitro activation of NMDA-gated channels or blockade

of SK channels by apamin can induce burst firing in dopamine neurons via both Ca2+-dependent and Ca2+-independent mechanisms. Dr. Mark Teagarden will address how responses to glutamatergic inputs are modulated by intrinsic cellular properties of dopamine neurons to induce bursting. Dr. Hitoshi Morikawa will talk about the role of Ca2+ store-dependent activation of SK channels in shaping the integration of NMDA-mediated excitatory and GABAergic inhibitory inputs. Finally, Dr. Michael Beckstead will describe a novel stimulus-dependent long-term depression of inhibitory currents mediated by dopamine that is dependent on intracellular Ca2+ and could result in disinhibition of firing.

Panel • Wednesday 7:30–9:30 AM • Sinclair

53. Cell Adhesion Molecules and Addiction

George Uhl, Thomas Biederer, Shernaz Bamji, Michael Charness

While cell adhesion molecules (CAMs) and mechanisms have been implicated in memory systems for some time, it is only recently that data from human genome scanning, studies of actions of alcohol, studies of gene regulation and other approaches have implicated CAM and extracellular matrix mechanims in addiction. Uhl will introduce the topic and review that large amount of data from human genome scanning studies that support roles for human variants in GPI-anchored, single TM and seven-TM domain CAMs in addiction vulnerability and confirmatory evidence from studies in postmortem human brains and transgenic mouse models. Biederer will update current information on the role of SynCAM adhesion molecules as a trans-synaptic code for synapse formation. Bamji will present recent work on cadherins. Charness will present new data on the ways in which alcohol interacts specifically with CAMs in ways that might contribute to its actions and its developmental toxicities.

Panel • Wednesday 7:30–9:30 AM • Snobble

54. Biomaterials for Neuronal Regeneration

Herbert M. Geller, Ravi V. Bellamkonda, Patrick A. Tresco, Donna J. Osterhout

A major challenge in neural regeneration research is the ability to stimulate directed axonal outgrowth across damaged nerve tissue and local control over delivery of factors that may influence the extent of growth. Failure of axonal growth is attributed to lack of factors that trigger

regeneration as well as the expression of growth-inhibitory molecules at the lesion site. Biomaterials are being developed as delivery systems for agents that can neutralize inhibitory molecules and promote directed axonal regrowth. This session will highlight recent advances in the use of several types of biomaterials to achieve these goals. Dr. Herbert Geller will present an overview of the problems and potential solutions. Dr. Donna Osterhout will present data on the use of of biodegradable nanospheres that release chondroitinase to promote regeneration in spinal cord injury. Dr. Bellamkonda will present data on the use of nanofibers for promoting peripheral neurve regeneration. Finally, Dr. Tresco will present data on engineered guidance channels that incorporate extracellular matrix molecules.

Panel • Wednesday 4:30–6:30 PM • Carroll

55. Signaling in Neuronal Development and Plasticity

Thomas Soderling, Andrew Matus, Michael Sutton, Nicholas Spitzer

Signaling in Neuronal Development and Plasticity. Neurons are highly polarized cells comprised of a cell body, an axon and multiple dendrites. Complex signaling pathways are requisite to achieve appropriate development and plasticity of the exquisite connections (i.e., synapses) necessary for neuronal communications. This panel discussion will focus on several newly discovered signaling mechanisms that dictate proper synaptic functionality. Tom Soderling (Vollum Institute) will describe how neuronal activity, through NMDAR-mediated Ca2+ influx, triggers sequential activation of CaM-kinase I and, through cross-talk with Ras/MEK/ERK, stimulate CREB-dependent transcription of Wnt-2 to enhance dendritic outgrowth and branching. Andrew Matus (Friedrich Miescher Institute) will present evidence that NMDAR stimulation promotes the actin-binding protein profilin to stabilize dendritic spines and to accumulate in the nucleus. This may serve as a mechanism to "tag" activated synapses and simultaneously regulate gene transcription through p442pop. Michael Sutton (Univ. Michigan) will demonstrate that tonic neuronal activity, through NMDARs, suppresses dendritic protein synthesis and regulates postsynaptic AMPAR abundance and subunit composition at synaptic sites, critical for long-term potentiation. Nick Spitzer (U.C. San Diego) will reveal how in early development activity-dependent, Ca2+-mediated modulation of presynaptic neurotransmitters (glutamate, GABA, glycine) induces a corresponding change in expression of postsynaptic receptor type. In summary, multiple signaling mechanisms that regulate diverse neuronal functions will be discussed.

Panel • Wednesday 4:30–6:30 PM • Erickson

56. A Stem Cell Is a Stem Cell Is an NG2 Cell?

Joel Levine, Akiko Nishiyama, Steven Goldman, Toru Kondo

The NG2 proteoglycan antigen marks a population of cells in the adult CNS that have been termed oligodendrocyte precursor cells (OPCs), synaptocytes, and polydendrocytes. These unusual cells act as oligodendrocyte precursor cells during development and after experimentally induced demyelination. Their abundance in the adult CNS, however, suggests that they may have other functions and properties. Although the nature of these functions remains unknown, they can act as postsynaptic targets and they have the potential to become multipotential stem-like cells. This panel will explore recent observations concerning the phenotypic plasticity of NG2+ cells and the transcriptional mechanisms that may regulate their plasticity and stem-cell like properties. Joel Levine will briefly introduce NG2+ cells and recount some of the early attempts to identify and understand these cells. Akiko Nishiyama will then present data from the analysis of new strains of transgenic NG2-reporter mice showing the phenotypic plasticity of developing NG2+ cells. Steven Goldman will discuss the relationships of NG2+ cells to white matter multipotential precursor cells. Toru Kondo will discuss mechanisms of sox2 gene expression during the conversion of NG2+ cells to neural stem-like cells and Joel Levine will present data concerning the expression and functions of REST/NRSF during the differentiation of NG2+ cells. This panel will also seek to provide a forum for further discussion about the nature of these enigmatic cells.

Panel • Wednesday 4:30–6:30 PM • Janss

57. Eyes Are Not just for Seeing

Samer Hattar, Michael Iuvone, Satchindananda Panda, Susan Doyle, Steven Lockley

The eyes are well known for their role in spatial vision, which allows us to form images of the world around us. However, eyes also have subconscious functions, independent of image formation, that are important for the physiology and function of organisms. For example, the eyes allow us to adjust our internal biological rhythms to the outside solar day. This adjustment affects many functions such as general activity and sleep wake cycles. Therefore, it is imperative to understand how the eyes regulate internal biological rhythms.

This session addresses this question through four different presentations. Michael Iuvone will present how retinal clocks and retinal sensitivity to light are regulated. He will discuss the role of regulatory neurotransmitters such as dopamine in these abovementioned functions. Satchidananda Panda will elucidate the role of the new photoreceptors, melanopsin-containing retinal ganglion cells, in signaling light information to the brain and address their phototransduction pathway. Susan Doyle will present her intriguing discovery concerning the role of the retina in switching the niche of rodents from nocturnal to diurnal. She will discuss whether this switch is due to changes in the central clock or in downstream effectors that bypass clock function. Finally, Steven Lockley will present data on human circadian rhythms indicating that blue light, which predominantly activates melanopsin cells, affects the biological clocks and other light dependent functions much more efficiently than other colors of light. In conclusion, this session will present a comprehensive overview of non-visual light reception in mammals.

Panel • Wednesday 4:30–6:30 PM • Kearns

58. Parkinson's Disease: Advances, Insights, and Challenges from Genetic and Toxin Models

Richard Nass, Kalpana Merchant, Leo Pallanck, Michael Aschner

Parkinson's disease is the second most prevalent neurodegenerative disease and is characterized by the irreversible loss of dopamine neurons. Despite its high prevalence and many decades of research, the origin of the pathogenesis and the molecular determinants involved in the disorder has remained elusive. Confounding this issue is the lack of experimental models that completely recapitulate the disease state. The identification of a number of genes thought to play a role in the cell death, as well as the development of both toxin and genetic models to explore the function of the genes both in unaffected and diseased cells, are now providing new insights into the neurodegeneration. In this session, we will describe the advances and advantages, as well as the challenges that invertebrates, cell culture, and rodents provide in the identification of the molecular mechanisms involved in the cell death, and putative drug targets that can be used to combat the disorder. Dr. Richard Nass will describe his toxin and genetic PD studies involving the genetically tractable nematode C. elegans, Dr. Leo Pallank will describe his PD studies using the fruit fly D. melanogastor, Dr. Michael Achner will describe his PD-associated neurotoxicity studies using rodents and cell culture, and Dr. Kalpana Merchant will describe her MPTP mouse

studies, as well as giving an industry perspective on the opportunities and challenges that model systems provide in drug discovery.

Panel • Wednesday 4:30–6:30 PM • Sinclair

59. Designing Modulators of AMPA-Receptor Activity for Therapeutic Use: Implications of Studies from Molecules to Monkeys

Kathy Partin, Gary Lynch, Eric Nisenbaum, Frank Menniti, Samuel Deadwyler

Emerging evidence suggests that a novel therapeutic approach to neurological and psychiatric diseases may be the regulation of glutamatergic synaptic transmission using allosteric modulators of ionotropic glutamate AMPA receptors. Gary Lynch will review evidence that subclasses of ampakines differ with regard to (1) the cell types and brain regions on which they exert their strongest effects, (2) the manner in which they affect synaptic plasticity, and (3) their potency in up-regulating production of neurotrophic factors. New strategies for using the compounds to reverse age- and disease-related losses in memory will be discussed. Eric Nisenbaum will present data from functional and crystallographic structural analyses elucidating the common and unique molecular determinants responsible for selective allosteric regulation of AMPA receptor isoforms by distinct classes of compounds. The application of this new information to rationally designed novel molecules will be considered. Frank Menniti will describe the identification of a class of non-competitive AMPA receptor antagonists that inhibit AMPA receptors through a binding site located at the interface between the ligand binding domain and the channel pore. The use of these compounds in investigating the role of AMPA receptor overactivation in glutamate excitotoxicity will be discussed. Sam Deadwyler will describe how ampakines facilitate cognitive performance in nonhuman primates as revealed by PET-imaged activity in different brain regions and in complementary recordings from single neurons in these same areas. The role of ampakines in alleviating sleep disorders will be compared to other agents in terms of brain regions that are susceptible to ampakine regulation.

Panel • Wednesday 4:30–6:30 PM • Snobble

60. It's Bedtime! Journey to the Center of the Brain: The Bed Nucleus of the Stria Terminalis

Francois Georges, Danny Winder, Eric Dumont, Heidi Day, Gary Aston-Jones

The bed nucleus of the stria terminalis (BNST) is a limbic forebrain structure part of the 'extended amygdala'. It has a high content of CRF, NPY and enkephalin and receives dense noradrenergic inputs. It is innervated by glutamatergic connections from the prefrontal cortex and the hippocampus as well as GABAergic inputs from the amygdala. Efferents include the paraventricular nucleus of the hypothalamus and the ventral tegmental area. These anatomical data suggest that the BNST is uniquely positioned to integrate responses to stress, pain and drugs of abuse. The focus of this panel is on the neuronal mechanisms underlying integration of stress and reward-related processes, and the science discussed will be highly interdisciplinary, encompassing behavioral, anatomical and electrophysiological approaches. Danny Winder will present work on opposing roles of NPY and CRF in regulation of GABAergic transmission in the BNST and its implication in regulation of alcohol intake. Eric Dumont will present recent evidence suggesting nuclei-specific response to pain-induced autonomic, neuroendocrine and somato-motor responses in the BNST. François Georges will present work on the synaptic regulation of BNST neurons during acute stimulation of CB1 receptor with specific attention to the role of glutamatergic mechanisms. Heidi Day will discuss recent evidence suggesting that cells of the dorsolateral BNST containing enkephalin are inhibited under conditions of acute psychological stress. Gary Aston-Jones will present recent behavioral experiments showing that the activity in the ventral BNST is strongly elevated during expression of preference for a morphine or cocaine-associated environment with specific attention to noradrenergic system.

Panel • Thursday 7:30–9:30 AM • Carroll

61. Nutrition, Lifestyle, Brain Aging, and Neurodegenerative Diseases: Making It to your 60th WCBR

Part 1: Oxidative Stress and Inflammation (The Villains)

Kimberly Topp, Susanna Rosi, David Cook, Fulton Crews, Donald Ingram

It has been postulated that behavioral and neuronal deficits in aging may result from an increasing inability to inactivate free radicals or inflammation impinging upon the organism, and an increasing vulnerability to these insults, thus creating a "fertile environment" for the subsequent development of age-related, neurodegenerative diseases. In this first of two panels of this set, we will discuss sources of oxidative stress and inflammation that could occur throughout life that could result in functional neuronal deficits in aging. Kimberly Topp will introduce the panel and provide a short introduction to the field by summarizing the literature showing that oxidative stress producing injuries early in life may predict later decrements in cognitive function. Susanna Rosi will talk about how chronic neuroinflammation can modify features of neural network activation that may underlie learning and memory impairments associated with several neurological diseases such Alzheimer's disease. David Cook will describe recent studies examining the relationship between Alzheimer's disease and dysfunction of glutamate transporters, a family of molecules that are important for limiting oxidative damage in the brain. Fulton Crews will discuss inflammatory and oxidative stress-mediated neurodegeneration and describe the role of systemic cytokines and microglia in this process. Don Ingram will provide a transition to Panel II by describing the role of diet and caloric intake in providing protection against the deleterious effects of inflammatory and oxidative stresses.

Panel • Thursday 7:30–9:30 AM • Erickson

62. Genetic Manipulation of Astrocytes for Functional Studies

Michael Brenner, Philip Haydon, Flora Vaccarino, Milos Pekny, Harald Sontheimer

Interest in astrocytes has been burgeoning as these cells become implicated in multiple novel roles in CNS function. To facilitate investiga-

tion of these roles, several approaches are being used for their genetic manipulation. Several of these will be illustrated by the talks in this panel. In addition, each of these presentations represents a significant advance in understanding astrocyte function. Mike Brenner will provide a brief introduction and summary of the capabilities of several GFAP promoters. Phil Haydon will describe use of a GFAP-based astrocyte-specific tetracycline-inducible system to show that adenosine released from astrocytes causes a presynaptic inhibition of synaptic transmission at CA3-CA1 synapses, thereby coordinating synaptic networks by mediating heterosynaptic depression. Flora Vaccarino will describe use of a GFAP promoter-driven tamoxifen-inducible cre to study genetic fate mapping. Her results indicate that postnatal GFAP-positive cells generate proliferating progenitors that produce neurons, astrocytes and oligodendrocytes in several different brain regions. Milos Pekny will describe use of GFAP KO mice to show that reactive astrocytes support neuroprotection and wound healing but inhibit subsequent synaptic and axonal regeneration. He will also show that modulation of reactive gliosis by genetic ablation of intermediate filaments improves the integration of CNS transplants. Harry Sontheimer will conclude the session by describing the mechanism used by glioma cells to undergo coordinated volume changes as they invade the normal brain. The contribution of different ion and water channels to these volume channels has been evaluated by modulating their expression through inhibition with siRNA or enhancement by transfection with expression vectors.

Panel • Thursday 7:30–9:30 AM • Janss

63. Outer Retina Circuitry and Signaling

Ron Gregg, Catherine Morgans, Maarten Kamermans, Laura Frishman

In the outer retina visual information is initially transferred from photoreceptors at a specialized synaptic complex, known as the photoreceptor synaptic triad. This synaptic triad consists of a photoreceptor terminal, bipolar cell dendrites and horizontal cell processes. The photoreceptor terminal is highly specialized and contains a synaptic ribbon and a unique set of ribbon, vesicular and synaptic proteins that mediate a graded release of the neurotransmitter glutamate. The complexity of the synapse provides multiple ways that signals can be processed depending on the light conditions. The interplay of signals from these three processes are critical for signaling to retinal ganglion cells that are the output neurons of the retina.

The presenters will discuss new findings regarding the functional organization of outer retinal circuitry. Morgans will discuss the various

mechanisms and molecules (calcium channels and internal stores) that control active zone calcium concentration and thereby control glutamate release from photoreceptors. Kamermans will discuss how horizontal cell feedback can produce novel gain control mechanisms, which have important implications for retinal ganglion cell function. Frishman will discuss how signaling through newly discovered rod signaling pathways are of major importance to vision under intermediate light conditions. Gregg will discuss how pre and post-synaptic proteins that when mutated disrupt signaling at the triad and have varying effects on morphology and function of bipolar and retinal ganglion cells.

Panel • Thursday 7:30–9:30 AM • Kearns

64. Stem Cells as Tools for Experimental Therapeutics in the Nervous System

Vassilis Koliatsos, Igor Nasonkin, Brian Cummings, Hongjun Song

Recent developments in our ability to isolate, propagate and differentiate human embryonic stem cells (HESC) have raised great hopes for cell replacement therapies for traumatic and degenerative diseases of the nervous system. The proposed panel will examine key concepts and developments related to the potential clinical applications of HESCs in neurological diseases. Vassilis will give a historical overview of experimental therapeutics for the nervous system and place HESC applications in the general context of regenerative therapies. He will particularly emphasize similarities and differences with trophic factor approaches and review some of the problems encountered with clinical applications of trophic factors of significance to HESC applications. Igor will review present approaches and technologies in culturing HESC and open up issues related to limitations and problems, as well as discuss potential solutions prior to the onset of clinical trials. Hongjun will summarize exciting research on the innate neurogenic capacity of the mammalian forebrain and present insights on the largely unexplored clinical significance of dentate and olfactory neurogenesis. Brian will make the contrast to spinal cord, i.e. a region with limited or no neurogenic potential in adult subjects but in which clinical applications have been already explored and actively pursued at the present time. Together, these summaries will give a clinically relevant presentation of a hot and at times controversial subject for which the degree of clinical excitement is often unrelated to the nature or definitiveness of scientific discoveries.

Panel • Thursday 7:30–9:30 AM • Sinclair

65. Progesterone and Estrogen for the Treatment of Brain Injury: Taking Research from the Bench to the Bedside

Donald Stein, Douglas Covey, Stephanie Murphy, Jacob VanLandingham

At present, there are no pharmacological treatments proven successful in the treatment of traumatic brain injury (TBI), and much the same can be said for ischemic stroke, where the only available post-stroke agent is tPA. TPA is used in only about 5% of stroke victims because of its potentially devastating side effects and risk of converting an ischemic stroke to one that is hemorrhagic. In contrast, progesterone and estrogen have been shown to be safe and effective in the treatment of both TBI and stroke in animal models, and progesterone has been successful in reducing mortality and enhancing functional outcomes in a Phase II clinical trial for TBI. Despite the apparent benefits, the underlying mechanisms of these hormones are not completely understood. This workshop will review the progress that has been made in understanding both the receptor- and non-receptor-mediated effects of estrogen and progesterone on stroke and TBI. D. Covey will speak on the use of steroid enantiomeric structures as probes for neuroprotective steroid mechanisms of action, and their relationship to the development of therapeutic agents. S. Murphy will speak on the role of sex steroids in ischemic stroke outcomes. The effects of estrogen and progesterone, alone or in combination, on experimental ischemic stroke will be discussed. J. VanLandingham will discuss how progesterone and its metabolites improve molecular and functional outcomes after TBI and ischemic stroke.

Panel • Thursday 7:30–9:30 AM • Snobble

66. A Vocal Minority: Interpreting the Function of Striatal Cholinergic Interneurons

Wayne Pratt, Paola Bonsi, Paul Apicella, Michael Ragozzino

Despite the fact that cholinergic interneurons constitute a small proportion of neurons within the striatum, recent evidence suggests that they play an important role in striatal function. These tonically-active neurons respond to biologically significant events and the cues that predict them, and pharmacological manipulations of striatal cholinergic receptors affect both goal-directed behaviors and the cellular plasticity of the output neurons of the striatum. This panel will provide an overview of recent work examining the functions of striatal acetylcholine.

Paola Bonsi will introduce the striatal cholinergic interneurons and their unique electrophysiological properties, as well as their modulation of other neuronal populations of the striatum. Paul Apicella will summarize evidence from neuronal recordings in behaving monkeys implicating striatal cholinergic interneurons (TANs) in building stimulus-reward associations and encoding temporal relationships between task stimuli and rewards. Dr. Apicella will also highlight how the modulation of TAN activity by motivationally relevant events is highly dependent on the context of the associated movement, suggesting that these local interneurons could contribute to different computations used in learning and action functions of the striatum. Michael Ragozzino will present a series of experiments utilizing microdialysis and pharmacological techniques that have investigated whether cholinergic activity in the dorsomedial striatum supports learning when conditions require a shift in strategies. Current findings suggest the muscarinic cholinergic receptors, but not nicotinic cholinergic receptors in the striatum are critical for facilitating strategy shifting. Wayne Pratt will summarize recent evidence supporting a role for nucleus accumbens acetylcholine in food intake, learning, and motivational state.

Panel • Thursday 4:30–6:30 PM • Carroll

67. Nutrition, Lifestyle, Brain Aging, and Neurodegenerative Diseases: Making It to your 60th WCBR

Part 2: Quenching the Fires of Aging

James Joseph, Stephane Bastianetto, Gregory Cole, Elizabeth Head

The evidence is becoming increasing clear that diet plays an important role in increasing "health span". However, questions of which foods might be the most beneficial in preventing cognitive and motor behavioral deficits in aging remain. It has been shown that the inclusion of vegetables (e.g., spinach) and fruits (e.g., berryfruit) and beverages (e.g. tea, red wine) that contain high amounts of polyphenolic compounds with antioxidant/anti-inflammatory properties are likely to promote healthy brain aging. This panel will discuss how the benefits of diets containing these polyphenols may prevent or forestall age-related behavioral and neuronal deficits. Stephane Bastianetto will describe the mechanisms involved in the protective effects of red wine and green tea polyphenols in aging and provide evidence showing these extracts may reduce the incidence of age-related neurological disorders (e.g., dementia). Greg

Cole will discuss the effects of curcumin in reducing pathogenesis in Alzheimer disease. Elizabeth Head will provide evidence showing food enriched with supplemental antioxidants and mitochondrial cofactors can improve and maintain cognitive function in aging dogs and the effects by behavioral enrichment. Jim Joseph will discuss the putative signaling mechanisms involved in the beneficial effects of high antioxidant fruits (e.g, blueberries) on behavioral and motor deficits in aging, and will suggest a "Nutritional GPS" as a guide in the selection of these and other fruits and vegetables in the diet.

Panel • Thursday 4:30–6:30 PM • Erickson

68. Monitoring CNS Gene Therapies with Neuroimaging

William Bunney, Howard Federoff, Krystof Bankiewicz, Mark Tuszynski, Steven Potkin

The promise of gene therapy for Alzheimer's disease (AD) and Parkinson's disease (PD) faces many challenges including the heterogeneous nature of brain tissue, the blood brain barrier and limited access to specific brain systems. There is a compelling need to develop in vivo monitoring systems to longitudinally determine where the gene is, where the gene product exerts its effect and whether activity is continuing. This is essential as 1) brain cells are not equivalent in their capacity to express a therapeutic gene and to promote a therapeutic action, 2) Genes and gene products can be transported from the sites of vector instillation and expression. Current progress using brain imaging as a surrogate measure of gene expression following genetic therapies for PD and AD in animal models and in human trials will be presented.

William Bunney will moderate the panel. Howard Federoff will review the complexities in monitoring gene therapies and present the ideal characteristics of in vivo monitoring systems. Krys Bankiewicz will present non-human primate data and results from a clinical trial where the successful transfer of the AADC gene has been imaged serially. Steven Potkin will review reporter gene techniques linking a therapeutic gene to a reporter gene whose product can be imaged with applications from oncology and their application to CNS diseases. Mark Tuszynski will discuss how FDG PET has been used to monitor NGF gene therapy in phase 1 and 2 human AD trials, and the correlation of imaging with behavioral and cognitive outcomes.

Panel • Thursday 4:30–6:30 PM • Janss

69. Inflammation after Spinal Cord Injury: What Are its Negative Consequences and How Can We Alter Them?

Lynne Weaver, Phillip Popovich, Gregory Dekaban, Dana McTigue

Inflammation after spinal cord injury (SCI) can be destructive, mediating secondary tissue damage, neuronal cell death and neurological decline. This panel will discuss effects of inflammation on the injured rodent spinal cord and novel strategies to reduce, selectively, the pathogenic consequences of the inflammatory response. Dr. Phil Popovich will present data illustrating the acute destructive potential of the innate and adaptive immune response triggered by SCI, including a potential role for toll-like receptors in regulating the pathological potential of microglia/macrophages after SCI and triggering of B cell synthesis of IgG2a antibodies have pathogenic potential. The next two panelists will focus on the role of integrins in mediating the inflammatory response and ensuing secondary damage after SCI. Dr. Greg Dekaban will describe data showing that the CD11d/CD18 and alpha4 beta1 integrins are key to SCI-induced inflammation. He will elucidate some of their roles in the trafficking of neutrophils and monocyte/macrophages into the injured cord using CD11d knockout mice. Dr. Lynne Weaver will show that anti-integrin antibodies and small molecules that block integrin binding greatly reduce oxidative damage to the injured cord, leading to tissue sparing and improved neurological outcomes. Dr. Dana McTigue will describe another novel neuroprotective strategy. Agonists of the peroxisome proliferator-activator receptors (PPAR), that are widely expressed nuclear receptors, reduce pro-inflammatory cascades in several CNS disorders. She will show that the PPAR? agonist Pioglitazone leads to significant tissue sparing and improved motor function. The panelists will demonstrate why inflammation is an excellent target for developing neuroprotective treatments for SCI.

Panel • Thursday 4:30–6:30 PM • Kearns

70. The Yin to the Dopaminergic Yang: Cholinergic Mechanisms in Cocaine Addiction

Bryon Adinoff, Bartley Hoebel, James E. Smith, Deborah Mash

Reinforcement behaviors depend upon a balance between nucleus accumbens dopamine and acetylcholine (ACh), and reinforcement

learning involves both muscarinic and nicotinic cholinergic receptor subtypes in the storage of drug-related information. Disruptions in cholinergic discharge and receptor systems may therefore play a key role in the addictive process. The panelists will describe alterations in cholinergic functioning that may be involved in continued drug use, using an array of both preclinical and clinical models of chronic cocaine self-administration. Bartley Hoebel will present a series of studies that describe the interaction between nucleus accumbens dopaminergic and cholinergic systems in the modulation of withdrawal. James Smith will describe the region-specific turnover of acetylcholine in rodents following the intravenous self-administering cocaine, relative to yoked vehicle-infused controls. Alterations in muscarinic and nicotinic receptor systems in abstinent cocaine-addicted subjects, as assessed with SPECT imaging techniques following physostigmine and scopolamine challenges, will be discussed by Bryon Adinoff. Deborah Mash assessed the distribution of muscarinic and nicotinic receptors in postmortem brain specimens from cocaine-related sudden deaths and drug-free control subjects using microarray, radioligand ligand, and quantitative autoradiography techniques. In toto, these findings describe a disruption in cholinergic systems following chronic cocaine self-administration in both animal and human studies, and suggest that cholinergic mechanisms may afford a novel target for drug development in the treatment of cocaine addiction.

Panel • Thursday 4:30–6:30 PM • Sinclair

71. What Is Critical about the Critical Period?

Elizabeth Quinlan, Kevin Fox, Hey-Kyoung Lee, Peter Hickmott

Sensory deprivation in juveniles results in rapid reorganization in cortical receptive fields. Accumulating evidence demonstrates that the adult brain is also capable of significant reorganization at multiple levels: synaptic, morphological and the regulation intrinsic excitability. However, juvenile and adult receptive field plasticity may differ in many ways, including the duration of the deprivation required to reveal a maximal change, and the biochemical, physiological and anatomical pathways recruited by the deprivation. Together we will present several novel aspects of experience-dependent plasticity that provide an opportunity to compare receptive field plasticity in juveniles and adult sensory cortex to ask: what is critical about the critical period?

Kevin Fox (University of Cardiff) will provide evidence that deprivation-induced depression depends on signaling through the GluR1 subunit of the AMPAR, while recovery from depression, which is developmentally

constrained, involves PKA-dependent potentiation. Hey Kyoung Lee (University of Maryland) will provide evidence that visual deprivation in adults can induce cross-modal changes, evident by a scaling up of AMPAR-dependent synaptic strength in the visual cortex, and a compensatory scaling down of AMPAR-mediated synaptic strength in the somatosensory cortex. Peter Hickmott (University of California, Riverside) will present data demonstrating changes in dendritic morphology and intrinsic excitability in response to denervation in the adult rat somatosensory cortex. Elizabeth Quinlan (University of Maryland) will present data that visual deprivation in adults, reactivates juvenile-like ocular dominance plasticity in the adult visual cortex, and promotes the recovery of function in an eye deprived of vision from birth.

Panel • Thursday 4:30–6:30 PM • Snobble

72. Novel Regulators of Glucose and Energy Balance: Use of Old and New Mouse Models in the Discovery Process

Stephen Salton, John Pintar, Iris Lindberg, Lloyd Fricker

Obesity and diabetes are major world-wide health problems. Control of glucose balance and energy homeostasis largely relies on CNS neuropeptide regulators (e.g. NPY and AGRP) and a number of peripheral circulating hormones (e.g. leptin and insulin). The goal of this session will be to discuss the impact that old and new mouse models are having in this field, both to increase our understanding of energy balance control, and as a source of novel neuropeptide regulators of feeding and body weight. Steve Salton will introduce some of the basic aspects of central and peripheral control of energy and glucose homeostasis, and discuss insights into these processes that have been gleaned from the study of VGF knockout and transgenic mice. John Pintar will then describe the major impact that combinatorial gene targeting of three insulin-like growth factor binding proteins (IGF-BPs) in mice has on body weight control and glucose balance. Iris Lindberg will introduce the role that prohormone convertases (PCs) play in the control of neuropeptide processing and secretion, then discuss how the PC2 helper protein 7B2 might function to control body weight. Lastly Lloyd Fricker will talk about peptidomics and the use of mouse models with processing enzyme mutations to discover novel hypothalamic neuropeptide regulators of feeding and energy balance. Ample time will be provided to discuss these approaches, the novel gene products and peptides that have been identified as a result, and their impact on our understanding of energy and glucose regulation, and behavior.

Panel • Thursday 8:30–10:00 PM • Carroll

73. The Role of the 5-HT Transporter (5-HTT) in Emotion/Stress Regulation, Impulse Control, and Anxiety: A Developmental and Psychopathologic Perspective

Larry Siever, Andrew Holmes, Christina Barr, David Goldman

In this panel both preclinical data from rodents and primates, as well as clinical studies in humans point to a critical role of the 5-HTT in the vulnerability to environmental stress and trauma in interaction with genetic susceptibilities. Andrew Holmes will present data in rodent studies that suggest lower expression of the 5-HTT gene as is associated with increased anxiety and vulnerability to trauma linked to functional changes in prefrontal cortex (PFC) and amygdala. Knockout mice for 5-HTT have increased "behavioral despair" and morphologic abnormalities in pyrimidal neurons. Christina Barr will discuss interactive effects between exposure to early adversity in a functional variant in the regulatory region for the serotonin transporter gene (rh5-HTTLPR) in predicting stress reactivity, HPA Axis output, and gene expression in the brain. David Goldman will discuss genetic and environmental interactions on child emotional symptoms and anxiety with a triallelic polymorphism of the HTTLPR in a very large data set from the Avon longitudinal child/parent study. Larry Siever will discuss genetic associations of the 5-HTTLPR and other serotonin receptor genes in interaction with environment as well as reduced binding of the 5-HTT with [11C] DASB in PET imaging in relation to impulsive aggression in personality disordered patients and their implications for response to treatment.

Panel • Thursday 8:30–10:00 PM • Erickson

74. Microglia in Neurodegenerative Disease

Thomas Moeller, Nephi Stella, Paul Muchowski

Microglia are the resident immune cells of the central nervous system (CNS). They resemble peripheral tissue macrophages and are the primary mediators of neuroinflammation. Upon CNS injury, these cells are rapidly activated and participate in the pathogenesis of many neurological disorders. Studies in the last two decades have demonstrated the involvement of microglia in many acute and chronic neurological diseases such as stroke and Alzheimer's Disease. In this panel T. Moeller will give an introduction into microglial biology and will present data on the involvement of these cells in amyotrophic lateral sclerosis (ALS). In

mutant SOD1-mediated ALS, the expression of mutated protein might lead to new, neurotoxic properties of microglia. N. Stella will elucidate the role of microglial cells in multiple sclerosis (MS) and how microglial activation can be modulated by endocannabinoids. Finally, P. Muchowski will discuss the role of microglial cells in Huntington's disease (HD). He recently showed, that huntingtin interacts with kynurenine 3-monooxygenase, an enzyme, which in the CNS is mainly restricted to microglial cells. The presentations will provide novel insights into to role of microglial cells and emphasize the concept of non-cell autonomy in neurodegeneration.

Panel • Thursday 8:30–10:00 PM • Janss

75. Anesthesia and Consciousness

Anthony Hudetz, Giulio Tononi, Michael Alkire, Misha Perouansky

The mechanism by which anesthetic agents ablate sensation, consciousness and memory has been of interest for well over a century. Elucidating how anesthetics produce unconsciousness has been particularly elusive. This is due in part to our lack of understanding of the neurobiological basis for consciousness itself. From this point of view, anesthetic agents can be used as tools to probe the neural correlates of consciousness. One emerging hypothesis that is now gaining support is that general anesthetic agents disrupt the functional complexity of long-range corticocortical and thalamocortical networks required for conscious information processing. This panel will provide an overview of our current state of knowledge of the problem and will present evidence from molecular to system levels to support an integrative theory of anesthetic-induced unconsciousness. Giulio Tononi will present a theoretical framework for consciousness emphasizing the importance of information integration within the thalamocortical system that serves as the foundation for a systems level view of anesthetic mechanisms. Michael Alkire will present a theory of anesthetic-induced unconsciousness based on data from human functional brain imaging performed with various general anesthetic agents. Misha Perouansky will talk about the differential effects of nonimmobilizers, the observation that there are anesthetic-like drugs that cause amnesia without apparently causing alterations in consciousness. Anthony Hudetz will present experimental data supporting the hypothesis that general anesthetic agents disrupt long-range functional connectivity in the cerebral cortex at anesthetic concentrations that produce unconsciousness.

Panel • Thursday 8:30–10:00 PM • Kearns

76. Glutamate Transporters: Structural Dynamics, Synaptic Mechanisms, and Therapeutic Potential

Jeffrey Diamond, Peter Larsson, Jacques Wadiche, David Poulsen

By clearing synaptically released glutamate from the extracellular space, high-affinity glutamate transporters play crucial roles in maintaining normal synaptic transmission, limiting glutamate excitotoxicity, and counteracting the development of several neurological disorders. Recent x-ray crystallographic work shows that glutamate transporters have a richly complex structure. To understand more how these transporters function and to evaluate their potential as a therapeutic target, it is essential to determine how transporters operate at the molecular level, how they contribute to normal excitatory and inhibitory synaptic transmission in different brain regions, and how transporter overexpression might confer resistance to neuropathological insults. Dr. Peter Larsson will present new work using FRET, voltage clamp fluorometry and cysteine modifications to characterize molecular conformational changes induced by ligand binding and glutamate transport, leading to a dynamic structural model of glutamate transport. Dr. Jacques Wadiche will show how transporter dynamics contribute to transmitter clearance at cerebellar synapses and how regional differences in glutamate transporter expression within the cerebellum affect extrasynaptic receptor activation and the consequent regulation of synaptic plasticity. Dr. Jeff Diamond will compare the roles of glial and neuronal transporters in preserving synapse specificity in the CA1 region of the hippocampus. Finally, Dr. David Poulsen will explore the therapeutic potential of glutamate transporters by presenting new work showing that viral-mediated overexpression of glutamate transporters in inhibitory neurons reduces susceptibility to epileptogenesis.

Panel • Thursday 8:30–10:00 PM • Sinclair

77. Autonomic Responses to Hypoxia and Hypercapnia: Is it Sheer Bliss?

David Mendelowitz, Patrice Guyenet, David Kline, Gordon Mitchell

Cardiorespiratory responses to hypoxia and hypercapnia are among the most powerful homeostatic reflex responses, yet the cellular basis for these reflexes have remained poorly understood. This panel will discuss recent work which is providing a foundation for understanding

the cellular mechanisms that mediate these responses. Patrice Guyenet will begin the panel by discussing the recent identification of chemosensitive neurons which have extensive dendrites that extend along the ventral surface of the medulla, and the cellular mechanisms by which these brainstem neurons likely initiate the cardiorespiratory responses to hypoxia. David Kline will discuss the role of the potassium channel gene Kv1.1 in regulating the excitability of peripheral sensory neurons that mediate reflex cardiovascular and respiratory responses to hypoxia. David Mendelowitz will then present evidence reactive oxygen species generation in the brainstem is necessary to recruit a glutamatergic pathway to parasympathetic cardioinhibitory neurons in response to intermittent hypoxia, and discuss the evidence that this pathway is responsible for the bradycardia that is evoked by hypoxia. Gordon Mitchell will end the panel by presenting his work that focuses on the plasticity and long term changes in the respiratory system after hypercapnia and hypoxia. This panel will address many complementary aspects of chemosensitivity in sensory neurons and neurons within the brainstem, as well as hypoxia/hypercapnia evoked changes in the neuronal pattern and function of cardiorespiratory networks in the brainstem.

Panel • Thursday 8:30–10:00 PM • Snobble

78. Rethinking Functional Subdivisions in the Striatum

Paul Clarke, Pieter Voorn, Satoshi Ikemoto, Ann Kelley

The striatum is commonly conceived in terms of a dorsal part (caudate-putamen) related to sensorimotor functions and "habits", and a ventral part (mainly nucleus accumbens) mediating motivational processes. Panel members will contend that this dorsal-ventral distinction is outmoded, by presenting anatomical and behavioral evidence that the striatum comprises functionally distinct domains that do not obey dorsal-ventral dividing lines. Pieter Voorn (Vrije University) will review anatomical connections and argue that a ventromedial-laterodorsal reorientation is needed to unveil anatomical coherence in functional data. Satoshi Ikemoto (NIDA) will discuss behavioral evidence suggesting that the ventromedial portion of the striatum including medial accumbens shell and medial olfactory tubercle plays a dominant role in psychomotor stimulant reward. He will also report that dopaminergic afferents to the ventromedial striatum come from distinct zones of the ventral midbrain, and argue that this medial path mediates the rewarding effects of various drugs of abuse. Paul Clarke (McGill University) will report

that the locomotor stimulant and rewarding effects of several drugs are segregated between accumbens core, shell and olfactory tubercle in rats. He will also show that rewarding and aversive effects of nicotine depend on DA transmission in separate striatal locations. Lastly, Ann Kelley (University of Wisconsin) will present evidence that dorsal striatum has limbic properties, and that the learning of motor skills depends importantly on ventral as well as dorsal striatum We will stress the notion that the continued dorsal-ventral conceptualization is misleading, and should be refined to reflect the extant data.

Panel • Friday 7:30–9:30 AM • Carroll

79. Plasticity as a Mechanism for Recovery Following Damage to the Nervous System

James Fawcett, Karim Fouad, Mark Tuszynski, Corinna Darian-Smith

When the nervous system is damaged by trauma, stroke or neurodegeneration some degree of lost function can be restored through re-arrangements in connections within the CNS, a process known as plasticity. Thus, following a stroke functional imaging of the brain may reveal that the tasks that used to be performed by the damaged region have migrated to the perilesional area or more widely. The infant CNS has greater plasticity than that of adults, which is associated with a greater ability to compensate for injury. The panel will address functional recovery through plasticity in various systems, mechanisms that control plasticity and treatments that can enhance it.

James Fawcett will talk about the ways in which the extracellular matrix is involved in the control of plasticity, how it can be manipulated to enhance plasticity and the mechanisms that reduce plasticity after childhood. Karim Fouad will discuss rearrangements of connections after spinal cord injury, including changes in cortical maps and sprouting of spared reticulospinal and corticospinal tract fibers, and treatments that might be used to increase these forms of plasticity. Corinna Darian-Smith will show examples of her work on sensory plasticity in primates. After selected sensory inputs are lesioned in the dorsal roots, there is functional compensation accompanied by sprouting of intact sensory inputs in the cord and changes in cortical maps. Mark Tuszynski will describe the existence of complex movement representations in the rat motor cortex that exhibit plasticity after injury and rehabilitation, serving as a relevant predictor of functional recovery.

Panel • Friday 7:30–9:30 AM • Erickson

80. Neural Substrates of Appetitive Associative Learning: New Perspectives on Drug Seeking

Gloria Meredith, David Rademacher, Fei Shen, Taco De Vries

Associative learning is important for acquisition and maintenance of drug taking behavior as well as drug seeking after abstinence. The members of this panel will shed light on the neural substrates mediating this learning. Meredith (Chicago Med School) will introduce the topic by providing an overview on how different brain substrates subserve different conditioned responses. Rademacher (Chicago Med School) will present the differential effects on amphetamine conditioned place preference and conditioned motor sensitization on markers of neuronal activity, synaptogenesis, and neurotrophic factor receptor (tyrosine kinase B receptor (TrkB)) that mediates synaptic plasticity. The implications of these data to the association of context with reward and motor behaviors in amygdalar and hippocampal circuitry will be discussed. Shen (Loyola University Medical Center) will discuss the effect of amphetamine conditioned place preference and context-dependent motor sensitization on TrkB receptor expression and will demonstrate that hippocampal TrkB receptors are critical mediators of both behaviors. De Vries (Netherlands VU Medical Center) will speak on different neuronal activation patterns in prefrontal cortical subregions following a cue-induced reinstatement test in rats with a history of sucrose or heroin self-administration. Pharmacological challenges with amphetamine confirm an important role of the infralimbic cortex in conditioned sucrose but not heroin seeking. The implications of these important findings to the neuroadaptations that underlie compulsive drug seeking will be discussed.

Panel • Friday 7:30–9:30 AM • Janss

81. Control Your Inhibitions: Local Circuit Processing in the Striatum

Aaron Gruber, Paul Bolam, James Tepper, Francois Gonon

Neural processing in cortico-striatal circuits, and its regulation by neuromodulation, is critically important for normal behavior. Although the integration of inputs by striatal spiny neurons has been extensively explored, many open questions remain. Particularly contentious has been the role of GABAergic inputs from neighboring spiny neurons and from a small number of interneurons for the regulation of activity.

This panel explores important recent advances in our knowledge of the anatomical and electrophysiological aspects of inhibition from local striatal sources, and seeks to address how local circuit processing in the striatum contributes to shaping striatal activity. Paul Bolam will give an overview of the connectivity and molecular organization of the striatum. Jim Tepper will present data from in vitro experiments that examine the influence of inhibition from neighboring spiny neurons and from interneurons on spike generation in target spiny neurons, and the regulation of this process by acetylcholine. Francois Gonon will present in vivo data showing that feedforward inhibition from interneurons filters the spike response of spiny neurons to cortical input and narrows the time window of this response, which becomes imbalanced in dopamine depleted animals. Aaron Gruber will present in vivo intracellular data characterizing the temporal and spatial aspects of spiny neuron integration of cortical activity, which features a prominent role for inhibition that is sensitive to the spatial location of cortical stimulation. The ability of intrastriatal inhibition to shape striatal responses, as described by panelists, provides an important context in which to interpret input integration and neuromodulation in the striatum.

Panel • Friday 7:30–9:30 AM • Kearns

82. The Role of Nitric Oxide in Drug Abuse

Stephen Sammut, John Wang, Mara Balda, Luigi Pulvirenti

Nitric oxide (NO) is a ubiquitous neuromodulator synthesized from a reaction catalyzed by nitric oxide synthase (NOS). In both the striatum and cortex, neuronal NOS (nNOS) activity is found in a subclass of medium aspiny interneurons believed to play critical roles in modulating synaptic activity. Current studies indicate that alterations in the mesocorticolimbic dopamine (DA) system and its interaction with glutamate (Glu) afferents in the cortex and striatum may be critical for the neuroadaptations and resultant behavioral changes associated with drug abuse. Furthermore both DA and GLU have been shown to modulate NO efflux. NO, in turn, also modulates the activity of these two neurotransmitters. The aim of this panel is to discuss recent advances in our understanding of the regulation of NO signaling as it pertains to drug abuse. J.Q. Wang will present insights into the expression of NMDA receptors on NOS interneurons in the striatum in amphetamine treated rats. S. Sammut will discuss electrochemical data related to NO release in the cortex and striatum following the administration of cocaine. M.A. Balda will report on the role of the nNOS gene in differences in adolescent and adult responsiveness to the incentive value of cocaine reward in mice. L. Pulvirenti will discuss the role of NO synthesis in the behavioral expression

of drug addiction in the rat. It is anticipated that together, these reports will enhance our knowledge of the role that nNOS and nitrergic signaling play in drug abuse.

Panel • Friday 7:30–9:30 AM • Sinclair

83. hESC-Derived Neural Stem Cells

Xianmin Zeng, Mahendra Rao, Steven Goldman, Thomas Schulz

Regenerative medicine and cell therapy are based on the premise that large numbers of normal cells will be available from adult, fetal or embryonic sources. Human embryonic stem cells (hESCs) can be propagated as undifferentiated cells over multiple passages, and thus offer a renewable source of a wide range of cell types including cells of neural lineages. Therefore, there has been significant interest in using hESC-derived cells for neural transplantation. The topic of this panel will be phenotype-specific and neural differentiation of neural stem cells derived from hESC, and their potential applications in neural transplantation. Xianmin Zeng will discuss approaches of generating neural and neuronal precursor cells from hESCs, and gene expression profiles of hESCs at different stages of neural differentiation. Mahendra Rao will present data on the properties of neural stem cells harvested from hESC cultures and comparisons with fetal tissue derived neural stem cells. Steve Goldman will address the potentiation of phenotype-specific motor neuronal differentiation from hESCs by modeling the normal cellular environment in vitro, and the molecular agents that control this process, as revealed by subtractive microarrays. Thomas Schulz will describe experiments on controlled and scaled expansion of undifferentiated hESCs, and uniform differentiation of hESCs to neural progenitors and terminal cell types. Overall, this panel will discuss the properties of hESC-derived neural stem cells and the possibility of using these cells for neural transplantation.

Panel • Friday 7:30–9:30 AM • Snobble

84. AMPA Receptor Trafficking in Synaptic Plasticity and Neuronal Death

John Isaac, Hey-Kyoung Lee, R. Suzanne Zukin, June Liu

Regulated AMPA receptor (AMPAR) trafficking at excitatory synapses is a mechanism critical to activity-dependent alterations in synaptic efficacy. Glutamate receptors are constitutively and acutely internalized via clathrin-mediated receptor endocytosis. Recent findings suggest

an additional role for regulated AMPAR trafficking in insult-induced synaptic remodeling and cell death. Isaac will present recent data that long-term potentiation in CA1 hippocampal pyramidal neurons causes rapid incorporation of GluR2-lacking calcium-permeable-AMPARs at synaptic sites. Calcium permeable AMPARs are present transiently, and within minutes after LTP induction, are replaced by GluR2-containing AMPARs. Lee will discuss exciting new evidence that visual deprivation produces opposite changes in synaptic function in primary visual and somatosensory cortices in rats, and that the changes are rapidly reversed by visual experience. This type of bidirectional cross-modal plasticity is associated with targeting of GluR2-lacking AMPA receptors to synapses of the visual cortex. Zukin will present evidence ischemia promotes redistribution of AMPARs at synapses of hippocampal neurons, leading to a switch in AMPAR subunit composition and that AMPARs at synapses of insulted neurons exhibit functional properties of GluR2-lacking AMPARs. Liu will present data that repetitive synaptic activation of calcium-permeable AMPA receptors causes a rapid reduction in Ca2+ permeability and a change in the amplitude of excitatory postsynaptic currents, owing to the incorporation of GluR2-containing AMPARs. This molecular switch in AMPAR subtype requires the synaptic scaffolding proteins GRIP and PICK1. Thus, neuronal activity and insults promote targeting of calcium-permeable, GluR2-lacking AMPARs to synapses of hippocampal neurons, and their removal, mechanisms relevant to synaptic plasticity and remodeling.

Panel • Friday 4:30–6:30 PM • Carroll

85. RNA-Mediated Toxicity in Neurological Disorders

Peng Jin, Laura Ranum, William Yang, Charles Thornton

The most widely accepted view on mechanisms leading to neuronal cell death in neurodegenerative disease is that the main culprits are proteins abnormally modified as the result of mutations, aberrant processing or post-translational modifications. However, over the past few years, new evidence has emerged for the involvement of RNA-mediated mechanisms in a number of degenerative pathologies of the central nervous system (CNS). The studies in myotonic dystrophy type 1 (DM1) and type 2 (DM2) have led to the recognition of a new pathogenic pathway in which the mutations exert their deleterious effects at the RNA level. An RNA gain of function mechanism has also been implicated in fragile X tremor ataxia syndrome (FXTAS). Studies in fly, mouse and neuro-

nal cultures have demonstrated that riboCGG repeats themselves are toxic, and can induce the formation of inclusions and cause neuronal cell death. The similar RNA gain of function mechanism may also play a role in the pathogenesis of other non-coding repeat expansion disorders, including spinocerebellar ataxia type 8 (SCA8), SCA10, SCA12 and Huntington disease-like 2. The main objective of this session is to review the most recent advances on the ground-breaking concept of RNA neurotoxicity and to provide a thought-provoking forum from which working models with a wide implication for human diseases will emerge. This panel will particularly focus on DM1, DM2, HDL2, SCA8 and FXTAS, in which the toxicity of noncoding RNAs has been demonstrated in different animal models.

Panel • Friday 4:30–6:30 PM • Erickson

86. Regulation of Ionotropic Glutamate Receptor Trafficking and Clustering

Andres Maricq, Roger Nicoll, Katherine Roche, David Bredt

The strength of excitatory neurotransmission depends in part on the regulated trafficking of ionotropic glutamate receptors and their subsequent clustering at synapses. Most synapses contain receptors preferentially gated by the agonists NMDA (NMDARs) and AMPA (AMPARs). How these different classes of receptors are delivered to the membrane, and localized and clustered at synaptic sites, is the focus of the presentations in this panel. Roger Nicoll will discuss the role of PSD-95-like membrane associated guanylate kinases (PSD-MAGUK) in synaptic targeting. Roger will focus on the relative roles of PSD-95, PSD-93 and SAP-102 in promoting the clustering of AMPARs and discuss how these proteins contribute to glutamatergic transmission. Katherine Roche will discuss the trafficking of NMDARs. Endogenous NMDARs are complexes of NR1 and NR2 subunits (NR2A-D). Katherine will present data showing that molecular determinants encoded within the NR2A, NR2B, and NR2C subunits regulate trafficking and surface expression of NMDARs. David Bredt will discuss the roles of transmembrane AMPAR regulatory proteins (TARPs) in the nervous system. These auxiliary subunits promote the surface delivery, synaptic localization and function of AMPARs. David will present data on the differential roles of TARP family members in promoting the trafficking and function of AMPARs. Villu Maricq will discuss a genetic analysis of stargazin-like proteins in C. elegans. These proteins are required for the reconstitution of C. elegans AMPAR-mediated currents; however, their in vivo functions have not been defined. Villu will present data showing how stargazin-

like proteins contribute to behavior and their effects on glutamatergic neurotransmission.

Panel • Friday 4:30–6:30 PM • Janss

87. GABAA Receptor-mediated Damage in the Developing Brain

Joseph Nuñez, Fernando Valenzuela, Kevin Staley, Vesna Jevtovic-Todorovic

GABA is the predominant inhibitory neurotransmitter in the adult central nervous system. Activation of the GABAA receptor is crucial for synaptic inhibition in the adult, and has been used as an effective means of attenuating over-excitation. In stark contrast, GABA action via the GABAA receptor results in neuronal excitation in the developing central nervous system. By virtue of the elevated intracellular chloride concentration and depolarized equilibrium potential for chloride, GABAA receptor activation in immature neurons results in membrane depolarization and opening of voltage sensitive calcium channels. Therefore, the response to GABAergic drugs in the developing brain may have quite unexpected and devastating effects compared to their action in the adult. To shed more light on the deleterious actions of GABAergic agents in the neonatal brain, Joseph Nuñez will discuss how genetic sex and developmental steroid hormones influence the response to GABAA receptor activation. This will be followed by recent data from Fernando Valenzuela on the effects of fetal alcohol exposure on GABAergic transmission in the immature hippocampus, where alcohol acts as a potent stimulant of neuronal network activity. Kevin Staley will discuss exciting evidence for depolarizing GABA action in seizures, and the role of chloride co-transporter expression. Finally, Vesna Jevtovic-Todorovic will present data on the damaging effects of anesthetics that act on the GABAA receptor in the immature brain.

Panel • Friday 4:30–6:30 PM • Kearns

88. Recent Advances in Understanding the System Level Functions of Dopamine and Norepinephrine and their Interaction

Jonathan Cohen, Read Montague, Gary Aston-Jones, Samuel McClure, Kimberlee D'Ardenne

Over the past decade, there has been a dramatic evolution in our understanding of dopamine (DA) function, from the view that it signals reward

to the view that it signals a reward prediction error that mediates reinforcement learning. A similar evolution has occurred in thinking about norepinephrine (NE) function, from the view that it mediates arousal to more sophisticated hypotheses about its role in regulating attention and cognitive control. However, these developments have focused almost exclusively on the independent functions of DA and NE, ignoring the close and dynamic interactions between these systems involved in normal function, and the importance of disturbances in these interactions in psychiatric disorders. This panel will review advances both in our understanding of DA and NE function and their interaction. Read Montague will begin by providing an update regarding hypotheses concerning DA function, including recent work examining the dynamics of DA release and it role in reinforcement learning. Gary Aston-Jones will provide a parallel review of advances in our understanding of NE function, including monkey neurophysiology and modeling studies concering the role of the locus coeruleus system and NE in attention and cognitive control. Sam McClure will then describe a novel hypothesis concerning DA-NE interactions in regulating the trade-off between exploiting known sources of reward and exploring the environment for new, potentially more valuable ones. Finally, Kimberlee D'Ardenne will report on recent developments in the use of fMRI to image the activity of DA and NE brainstem nuclei, and test hypotheses regarding the function of these systems and their interaction.

Panel • Friday 4:30–6:30 PM • Sinclair

89. Making Connections: Factors Influencing Axon Outgrowth

Karen Greif, Gianluca Gallo, Lorene Lanier, Paul Letourneau

During development, neurons elaborate processes in order to build functional networks. Some aspects of the cell biology of axon outgrowth and patterning are well understood, but many others remain elusive. This panel will explore recent findings regarding the factors that influence axon outgrowth. Extension of processes requires a dynamic balance between the actin and microtubule cytoskeletons, as well as selective insertion of new membrane. We will address how external factors might influence cytoskeletal organization and how such signals might be translated into axon development. Dr. Greif will present a brief overview of current hypotheses on mechanisms of axon development and present data suggesting that transported synaptic proteins themselves influence process development. Dr. Gallo will discuss the regulation of sensory

axon collateral formation by endogenous developmental changes and by the extracellular matrix, with an emphasis on the dynamics of the actin cytoskeleton and the functions of myosin II. Dr. Lanier will discuss the role of actin-binding proteins such as Arp2/3 in regulating the actin-microtubule cross-talk that drives growth cone dynamics. Dr. Letourneau will discuss the signaling pathways activated by neurotrophins that regulate actin dynamics in nerve growth cones. Ample time will be permitted for questions and discussion.

Panel • Friday 4:30–6:30 PM • Snobble

90. Individual versus Environmental Determinants of Daily Behaviour in Humans

Rémi Quirion, Kenneth Wright, Julie Carrier, Diane B. Boivin, Jonathan Emens

There is evidence that individual characteristics modulate the quality of the rest-activity cycle and its relationship to environmental synchronizers. The panel will discuss the impact of individual versus environmental determinants of daily behaviour in humans. Ken Wright will demonstrate that fundamental individual characteristics, such as the length of the endogenous circadian period, can affect the phase relationship between the rest-activity cycle and circadian markers. According to models of sleep-wake cycle regulation, a precise interaction between homeostatic and circadian processes ensure optimal quality of sleep and vigilance. Julie Carrier will show evidences that between the ages of 20 and 60 years, changes in this interaction occur, since increasing age is associated with less time spent asleep, more wakefulness during sleep, and less slow-wave sleep. Diane Boivin will explore this interaction in psychiatric populations, using protocols such as the forced desynchrony and ultrarapid sleep-wake cycle procedures. These experiments revealed that the circadian regulation of sleep is disturbed in chronic schizophrenia such that REM sleep is increased at all circadian phases and the circadian variation of sleep propensity is phase advance, akin that observed in older subjects. Jonathan Emens will discuss the particular case of blind patients, who often suffer from a lack of entrainment to their environment. He will present data on the variable effects of photic and non-photic environmental time cues on the circadian system of blind individuals. Altogether, these presentations will provide evidence for an interaction between endogenous and exogenous factors and their clinical significance for physical and mental health.

Poster Abstracts

Poster Session 1

Sunday–Monday • Anderson Ballroom

Posters will be available for viewing after 8:30 PM Sunday through 6:30 PM Monday. Presenters will be with posters on Monday from 3:30–4:30 PM.

P1. Sleep Disturbance in Withdrawing Marijuana Users

K. Bolla*, S. Lesage, C. Gamaldo, D. Neubauer, F.R. Funderburk, P. David, J.L. Cadet

Marijuana (MJ) is the most widely used illicit drug in the United States. In 2002, an estimated 75% of America's 14.8 million illicit drug users utilized MJ alone or in conjunction with other illicit drugs. In withdrawing MJ users, 76% reported sleep disturbance (insomnia, restlessness, vivid dreams). Despite reports by recently abstinent MJ users of sleep difficulties, no published studies have used objective polysomnographic (PSG) measures to characterize these self-reported sleep disturbances. We studied 12 heavy MJ users and 16 drug-free controls. The MJ group resided at the NIDA-IRP research unit for 14 days. PSG measurements were recorded on nights 1, 2, 7, 8, and 13 of withdrawal. Subjective measures of sleep disturbance and other symptoms of withdrawal were also assessed with daily questionnaires (e.g., Sleep Diary, Behavioral Checklist). The control group stayed for 3 nights in the GCRC, and PSG studies were recorded on nights 1 and 2. Our preliminary data showed PSG abnormalities in MJ users compared to controls (e.g., longer initial sleep latency, less slow wave sleep, more periodic leg movements). During 14 days of withdrawal, most of these abnormalities persisted. One possible neurobiological mechanism to explain some of these findings includes reports that insomniacs and abstinent MJ users both show decreased metabolism in the orbitofrontal cortex. Since sleep is essential for good quality of life, we believe that sleep disturbance may significantly hinder treatment of cannabis abuse disorders and could help explain why 93% of treatment seekers report that they are unable to stop smoking MJ.

P2. Anatomical and Functional Analysis of the "Slouchy" Mouse

M. Gartz Hanson, Lee Niswander*

Locomotion requires the proper connectivity and communication between motoneurons within the spinal cord and their target muscle. Although some of the genes required for development of the locomotion system are known, there is still a considerable gap in our knowledge of the molecular mechanisms that integrate the development, differentiation, maturation and behavior of this intricate system.

To provide direct insight into this process, we have undertaken a genetic screen in mice to specifically identify mutations that disrupt normal locomotion. Using a streamlined physiological and behavioral assay as the screen, one mutagenized mouse model was identified with specific deficits in locomotion. This line, called "slouchy", displayed kyphosis (hunchback) and carpoptosis (wrist drop). Furthermore, slouchy embryos are completely non-motile during reflex and spinal cord stimulation. These phenotypes are suggestive of a lack of synaptic communication and/or lack of muscle contraction. Further functional and anatomical analysis of this line suggests a gene with novel functions in axonal branching and distribution of neuromuscular junctions. Our aims of this study are to identify all functional and anatomical defects in the slouchy mouse line as well as the responsible gene that is critically required in the control of locomotion.

P3. Partial Restoration of Postischemic Pial Artery Dilation to ADP after Global Ischemia Is Mediated by eNOS, But Does Not Involve the Adenosine 2b Receptor

Min Li, Raymond C. Koehler, Marguerite T. Littleton-Kearney*

Previously, we found that estrogen (E) partially restores postischemic pial artery dilation to ADP in ovariectomized rats. Using a closed cranial window, we sought to determine if restoration of postischemic pial artery vasodilatory capacity to ADP in E-replaced rats involves the adenosine A2b receptor. In a separate cohort we ascertained if estrogen treatment alters microvascular eNOS expression. Sexually mature female rats were randomly divided into two groups (n=5-6), ovariectomized females (OVX) or OVX plus 17β-estradiol replaced females (OVXE), and subjected to 15-min reversible forebrain ischemia (4-vessel occlusion) followed by reperfusion. All rats were anesthetized and ventilated throughout the experiments. Pial artery responses to ADP (10

mM) were assessed prior to ischemia. At 1-hr of reperfusion dilation to ADP was re-tested; alone, in the presence of alloxazine (Allo; 10 mM), an adenosine A2b receptor antagonist, or Allo plus L-NNA. Estrogen depletion markedly reduced postischemic pial dilation to ADP. However, estrogen repletion restored postischemic responses to ADP (22±6% of baseline; preischemia vs. 17±4% of baseline; postischemia). Allo had no effect on the postischemic pial response to ADP (14±3% of baseline), but Allo plus L-NNA caused further depression of postischemic response to ADP (8±3% of baseline; $P<0.05$). Compared to OVX, estrogen treatment resulted in a 7-fold increase in cerebral microvascular eNOS expression (measured by western blot) ($P<0.05$). We conclude that postischemic restoration of pial artery dilatory response to ADP is associated with estrogen-induced increases in eNOS production, but does not involve the A2b receptor.

P4. Brain Reorganization in Tinnitus

Josef P. Rauschecker*, Amber Leaver, Mark Mühlau, Laurent Renier, Susan Morgan, Hung Jeffrey Kim

Tinnitus is one of the most common ailments of the auditory system, with total numbers of patients going into the millions, but little is known about its mechanisms of origin. The chronic ringing in the ears associated with tinnitus is usually triggered by low-level damage to the inner ear and loss of hair cells, which seems to be followed by a profound reorganization in the central auditory system. Our studies provide direct evidence, using high-resolution functional magnetic resonance imaging (MRI), of auditory cortical involvement in tinnitus patients and, more specifically, of a reorganization in the tonotopic map of primary auditory cortex. We monitored changes in brain activity while participants listened to band-passed noise bursts with different center frequencies. Each tinnitus patient was matched with one control subject that heard the same range of frequencies. Our results indicate hyperactivity in the auditory cortex of tinnitus patients and a distortion within its tonotopic map. In addition, we present evidence from high-resolution structural MRI (voxel-based morphometry) that tinnitus also involves brain centers outside the auditory system. The grey-matter volume of the nucleus accumbens (NAc) in the ventral striatum is significantly reduced in tinnitus patients. Cells in the NAc being serotonergic and receiving input from the amygdala and raphe nuclei, this finding may help to explain why tinnitus is often exacerbated by stress or sleep deprivation and is sometimes co-morbid with mild depression.

P5. Investigation of Brain Remodeling after Neural Progenitor Cell Treatment of Stroke Using MRI

Q. Jiang, Z.G. Zhang, G.L. Ding, L. Wang, M. Chopp*

We evaluated the effects of neural progenitor cell (NPC) treatment of stroke on white matter reorganization (WMR) using MRI. Male Wistar rats were subjected to 3 h of middle cerebral artery occlusion without (n=7) and with labeled NPC treatment (n=11) at 48 h after ischemia. MRI measurements of T1, T1sat, T2, 3D, and FA were performed one day, and weekly for 5-7 consecutive weeks after stroke. Prussian blue, Bielshowsky, and Luxol fast blue staining were performed to detect labeled NPCs, axons, and myelination. MRI measurements revealed that WMR was coincident with increases of FA ($p < 0.05$) and coincident with decreases of relative T1, T2, T1sat ($p < 0.05$) in the ischemic recovery regions compared to that in the ischemic core region in both groups. The treated group appears early and large increase in FA ($p<0.01$) in the ischemic recovery regions compared with control group at 5 weeks after stroke. Our data suggest that FA differentiated white matter reorganized brain tissue from other ischemic damaged tissues. T1, T2, and T1sat provide complementary information to characterize status of ischemic tissue with and without brain remodeling. Of these MRI methods, DTI related parameters appear to be the most useful MR measurements which identify the location and area of WMR.

P6. A Novel Mechanism by which Clozapine Induces ERK1/2 Activation in Cortical Neurons

Avril Pereira, George Fink, Suresh Sundram*

Clozapine is more effective in the treatment of refractory schizophrenia than other atypical antipsychotic drugs (McEvoy et al 2006 Am J Psychiatry 163:600-610). This cannot be explained simply by differences in receptor binding and occupancy alone. Rather, it could reflect the fact that clozapine may initiate signalling pathways such as the mitogen activated protein kinase-extracellular signal regulated kinase (MAPK-ERK) cascade in a unique manner to affect synaptic plasticity and connectivity, processes impaired in schizophrenia. We investigated this possibility by measuring phosphorylation of the MAPK isoforms, ERK1/2 by antipsychotic drugs in primary murine cortical cultures using Western immunoblotting. Clozapine alone stimulated ERK1/2 after 60 min exposure. This delayed ERK increase was not abolished by pertussis toxin, serotonin (DOI, 8-OH-DPAT) and muscarinic (carbachol) agonists or by the PKA or phospholipase C inhibitors H89 and U73122, respectively. Con-

sequently, we investigated the effect of clozapine on transactivation of the ERK pathway. The EGFR inhibitor, AG1478 0.5 mM, caused marked inhibition of clozapine induced ERK1/2 activation (pERK1, 29±13%; pERK2, 24±5%) whereas the PDGFR inhibitor tyrphostin A9 did not (pERK1, 93±21%; pERK2, 105±9%). Whether clozapine exerts these effects via a pathway mediated by Src-family kinases, matrix metalloproteinase or b-arrestin endocytosis is still to be determined. Notably, clozapine transactivation of EGFR to phosphorylate ERK1/2 differs from olanzapine regulation of ERK (Lu & Dwyer 2005 J Mol Neurosci 27:43-64) and this may implicate the EGF system as a molecular substrate for treatment resistant schizophrenia.

P7. NGF-promoted Differentiation of PC12 Cells Alters Nucleotide-stimulated Catecholamine Release and P2 Receptor Expression

David B. Arthur, Laurent Taupenot, Paul A. Insel*

Molecules that regulate synaptic transmission are important modulators of neuronal communication. One such class of modulators, extracellular nucleotides, signals via activation of P2 receptors. This study examined the regulation by nucleotides and P2 receptors of another well-defined class of neurotransmitters, catecholamines, in the setting of neurotrophin-promoted neuronal differentiation. Nerve growth factor (NGF)-induced differentiation of the sympathoadrenal cell line, PC12, enhanced the stimulation of norepinephrine (NE) release by a nonhydrolyzable ATP analog, ATPγS. This enhancement was not due to changes in NE uptake or in levels of the NE transporter or chromagranin A mRNA. ATPγS, αβMeATP, and 2-MeSATP, agonists selective for P2X receptors, stimulated greater NE release from NGF-differentiated compared to undifferentiated PC12 cells. Nucleotides stimulated NE release from a distinct, barium-insensitive pool. NGF-mediated differentiation of PC12 cells altered mRNA expression of multiple P2Y and P2X receptor subtypes but protein expression was only increased for P2X, in particular $P2X_{1\text{-}4}$. In parallel, P2X, but not P2Y, receptor inhibitors significantly reduced the NGF-mediated increase in NE release in response to nucleotide stimulation. These results in PC12 cells indicate that NGF-stimulated sympathetic neuronal differentiation elevates expression of distinct P2X receptor sub-types and increases nucleotide-mediated regulation of catecholamine release without affecting uptake. Neurotrophin-promoted increase in expression of particular P2X receptors thus appears to be a physiologically important response in the development of sympathetic neurons. (Supported by grants from NIH).

P8. Anticonvulsant Effects of 1,3-Butanediol, A Metabolic Precursor of Ketone Bodies

M. Gasior, J. Yankura, A. French, A. Hartman*, M.A. Rogawski*

(R,S)-1,3-Butanediol (1,3-BD) is a common food additive that has a long history of safety in various species. 1,3-BD is metabolized by alcohol and aldehyde dehydrogenases in the liver to form β-hydroxybutyrate, acetoacetate, and acetone, which are the same ketone bodies whose levels are elevated in the ketogenic diet1. Here we sought to determine if 1,3-BD has anticonvulsant effects and could potentially be a replacement for the ketogenic diet.

The anticonvulsant activity of 1,3-BD was assessed in several in vitro and in vivo models. Acute toxicity was determined in the inverted-screen test. To determine the contribution of ketosis to the anticonvulsant efficacy of 1,3-BD, animals were pretreated with the alcohol dehydrogenase inhibitor 4-methylpyrazole. In addition, we used the R- and S-enantiomers of 1,3-BD since only the R-enantiomer can be directly converted to acetone.

1,3-BD attenuated epileptiform activity induced by 4-aminopyridine (55 μM) in rat hippocampal slices in a concentration-dependent manner (10-100 mM). Furthermore, 1,3-BD (1-32 mmol/kg, IP) demonstrated a broad anticonvulsant profile in a variety of seizure tests in mice (iv PTZ test, electroconvulsive threshold, 6-Hz seizure model) and rats (amygdala-kindled seizures). The anticonvulsant effects of 1,3-BD occurred at doses devoid of acute toxicity. After the administration of an anticonvulsant dose of 1,3-BD, levels of the ketone body, β-hydroxybutyrate, were comparable to those seen in mice exposed to the ketogenic diet for several weeks. Inhibition of 1,3-BD conversion to ketone bodies by 4-methylpyrazole (25 mg/kg) augmented the anticonvulsant effects of 1,3-BD, indicating that 1,3-BD itself has anticonvulsant activity. Like the racemic form of 1,3-BD, the R- and S-enantiomers individually demonstrated robust anticonvulsant properties, demonstrating that conversion to ketone bodies is not required for seizure protection. However, the R-enantiomer was modestly more potent suggesting that ketone bodies could contribute to the anticonvulsant activity.

Conclusions: 1,3-BD and its enantiomers are protective in a broad range of seizure models. Conversion to ketone bodies is not required for efficacy, but could augment the activity of the parent. Further studies are required to assess the potential of 1,3-BD or its enantiomers in the treatment of epilepsy.

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P9. Pharmacological Inactivation of L-type (Cav 1.3) Ca 2+ Channels Strongly Attenuates Rotenone Toxicity on Dopaminergic Neurons of the Substantia Nigra

E. Ilijic*, C. S. Chan, D. J. Surmeier

Prominent characteristic of Parkinson's disease (PD) is selective degeneration of nigral dopaminergic (DA) neurons. Our previous work has shown that DA neurons of adult substantia nigra (SN) have peculiar physiology; that is, these neurons are Ca 2+ -dependent autonomous pacemakers so their basal activity relies on special class of voltage-dependent Cav 1.3 Ca 2+ channels. Juvenile DA neurons (<P21) and great majority of pacemaking brain neurons, on the other hand, are Na+ and HCN channels dependent pacemakers. We hypothesize that susceptibility of adult SN DA neurons to rotenone, mitochondrial toxin, is due to load of Ca2+ into SN DA neurons and that pharmacological inactivation of Cav 1.3 channels with L-type channel antagonist, isradipine, can suppress rotenone toxic effect. To test this hypothesis, 270 μM thick coronal midbrain slices were cut from mice brain and exposed to ACSF solution for 2 hrs with or without isradipine (20 μM) following incubation with rotenone (100 nM, 300nM, 1 μM) for 1 hour. After fixation, slices were cut into 30 μM thick sections used for immunohistochemistry. We utilized tyrosine hydroxylase (TH) immunolabeling to detect SN DA neurons and therefore to visualize morphological changes of SN DA due to exposure to rotenone. We observed that dendritic fragmentation induced by rotenone was strongly reduced with isradipine treatment.

This work was supported by Picower Foundation.

P10. Pharmacologic Analysis of Transgenic Rats Expressing the Human Bradykinin B1 Receptor in the Central Nervous System

Duane R. Reiss, Meacham Harrell, Fred Hess, Dennis Dean, Dai-Shi Su, Scott Kuduk, Christina Di Marco, Kristi Hoffman, Bang-Lin Wan, Zhizhen Zeng*

The discovery of novel pain medications relies on the development of new methods to assess therapeutic efficacy in the central and peripheral nervous systems. Bradykinin B1 receptor mechanisms of the CNS and periphery are activated during the chronic phase of inflammation to elicit pain responses. Under normal conditions, B1 receptors are expressed at very low levels, but are rapidly induced in response to tissue trauma or inflammatory conditions. Even when induced, the expression level of the B1 receptor is low. Standard binding methods are not sufficiently sensitive to quantify such low receptor density. Furthermore, because B1 receptor pharmacology is markedly different across species, animal pain models have limited utility in evaluating efficacy or receptor occupancy of selective human B1-antagonist compounds. To overcome these obstacles, a CNS receptor occupancy assay was developed using a novel transgenic rat expressing the human B1 receptor in the brain and spinal cord. The assay involves i.v. administration of the test compound followed by CNS dissection and determination of the rate of association of the radioligand. The rapid timeframe of the assay and high dilution of tissue virtually eliminates any potential for association/dissociation artifacts. This study capitalized on the transgenic rat model to establish a method for identifying novel Bradykinin B1 antagonists for treating chronic pain.

P11. Animal Models of Usher Type IC

J. Lentz, F. Pan, J. Phillips, K. Owens, S. Ng, P. Deininger, E. Rubel, M. Westerfield, D. Raible, B. Keats*

Usher syndrome is the leading cause of combined deaf-blindness. A cryptic splice site mutation (216G→A) in exon 3 of the USH1C gene, encoding the protein harmonin, was found in Acadian Usher type IC families in south Louisiana. In vitro analysis with mutant 216A constructs and subsequent analysis of patient cells lines revealed a 35 base deletion. To analyze the impact of this frame-shift mutation, we created a knock-in mouse model using Cre/loxP recombination containing the human 216G→A mutation cloned from an Acadian patient. All homozygous Ush1c216A (216AA) mice are hyperactive, display circling

and head tossing behavior, and do not have a Preyer reflex at 21-25 days old. Heterozygous mice show no behavioral phenotype. RT-PCR analysis of the cochlea and retina from 216AA mice shows the same 35 base pair deletion characteristic of Usher IC patients. No auditory brainstem response was evoked from the 216AA mice at 30 days, indicating that they are deaf. Retinal degeneration is not expected until the mice are several months old. In parallel, we isolated a full length zebrafish ush1c cDNA that encodes a protein with 76% identity to the N-terminus of human and a nearly identical hydrophobicity profile throughout its length. In-situ hybridization shows expression in both the developing otic vesicle and retina. Morpholino knock-down of zebrafish ush1c results in circling, impaired righting behavior and reduced optokinetic response. Extending our work on Usher type IC to zebrafish will complement and enhance our ongoing mouse and human studies.

P12. Reversal of Memory Deficits in APP Transgenic Mice through Inhibition of Calcineurin

Giulio Taglialatela, WenRu Zhang, Dale Hogan, Kelly Dineley*

Alzheimer's Disease (AD) is an age-associated dementia characterized by memory deficits, loss of CNS neurons, and eventually death. A prominent neurotoxic event in the AD brain is the presence of excess amyloid beta (Ab) peptide, the result of abnormal processing of the larger precursor protein (APP). Thus, preventing Ab toxicity would be a significant advance toward developing an effective cure for AD. However, the cellular mechanisms mediating Ab βtoxicity are still unclear. The protein phosphatase calcineurin (CaN) has been reported to be a crucial signaling element capable of decreasing synaptic plasticity and memory function and modulating neuronal death, all events that characterize the impact of Ab in the CNS. On this basis, we hypothesize that aberrant activation of CaN is one mechanism mediating the cognitive and neurotoxic effects of Aβ. Here we show that Tg2576 mice, which accumulate Ab in their brain and display memory deficits reminiscent of AD, exhibit a significant increase in CNS CaN activity. Treatment with the CaN inhibitor FK506 decreased CaN activity to normal levels and restored memory function. Collectively, these results indicate that CaN may be an important component mediating Ab-promoted cognitive impairments and suggest that CaN inhibitors should be further explored as pharmacological tools in AD.

Supported by NINDS grant 1R21NS053986 to GT.

P13. Neuregulin-1 Regulates Cell Adhesion through an erbB2/phosphoinositide-3 kinase/Akt-Dependent Pathway: Implications for Schizophrenia

Christopher G. Kanakry, Zhen Li, Yoshitatsu Sei, Daniel R. Weinberger*

Neuregulin-1 (NRG1) is a putative schizophrenia susceptibility gene involved in neuronal differentiation and migration, synaptic modulation, and oligodendrocyte development. The mechanism by which it relates to schizophrenia pathogenesis is unknown. Using a B lymphoblast cell model, we have previously demonstrated impairment in NRG1α-mediated migration in cells from schizophrenic subjects as well as effects of an NRG1 and COMT risk alleles. Here, we examine cell adhesion, which is associated with cell motility, using an integrin-mediated cell adhesion assay based on the interaction between ICAM-1 and the CD11a/CD18 integrin heterodimer receptor expressed on lymphoblasts.

In our assay, NRG1α induces lymphoblasts to assume varying adhesive states characterized by time-dependent fluctuations in the firmness of attachment. The range or "amplitude" of this varying adhesion correlates strongly with NRG1α-induced migration (r^2=0.6065). This NRG1α-induced varying adhesion state is specifically blocked by erbB2, PI3K, and Akt inhibitors, but not by PLC, ROCK, MLCK, or MEK inhibitors, implicating the erbB2/PI3K/Akt1 signaling pathway in integrin-mediated cell adhesion. In cell lines from 20 patients with schizophrenia and 20 controls, cells from patients show a significant deficiency in the amplitude of variation in NRG1α-induced adhesion (p=0.0002). In contrast, the response of patient-derived cells to phorbol myristate acetate is unimpaired. Single nucleotide polymorphisms in the putative schizophrenia susceptibility genes, catechol-O-methyl transferase (COMT) and NRG1, are associated with differences in the amplitude of varying cell adhesion even in normal subjects and they interact epistatically in conferring this phenotype. Our findings suggest that the mechanism of the NRG1 genetic association with schizophrenia involves the molecular biology of cell adhesion.

P14. DNA Methyltransferase Activity Regulates Memory Formation and Synaptic Plasticity

Courtney A. Miller, Susan L. Campbell, J. David Sweatt*

Long-term memory formation depends on an entire cascade of events. The steps for hippocampus-dependent memory include NMDA receptor activation, calcium influx, signaling pathway activation, and gene transcription. Histone acetylation, a post-translational modification

and epigenetic mechanism that regulates gene transcription, has been found to be an additional, necessary step. Recently, our laboratory has found a role for another epigenetic mechanism, DNA methylation, in hippocampal synaptic plasticity in vitro. DNA methylation, a covalent modification of DNA catalyzed by DNA (cytosine-5) methyltransferases (DNMTs), has been studied extensively as a molecular information storage mechanism in development. Here we report that memory consolidation decreases methylation of reelin, a gene important for memory and synaptic plasticity, and increases DNMT3A and 3B gene expression in the adult rat hippocampus. Inhibition of DNMT activity in Area CA1 blocks memory consolidation, along with the concomitant histone 3 acetylation. Memory consolidation, along with long-term potentiation, can be preserved by artificially increasing levels of histone acetylation prior to DNMT inhibition. These observations demonstrate that DNA methylation is acutely regulated during memory formation in the adult nervous system and suggest that DNMT activity may regulate chromatin structure.

P15. Transgenic Mice Deficient in Alanine-serine-cysteine-1 Transporter Reveal an Important Role for Regulating D-serine Levels in Brain

Christian Thomsen*, Pekka Kalunki, Claus Christoffersen, Henriette Bak Husum, Nils Ole Dalby, Lone Helboe, Kenneth Vilsted, Niels Plath, Jan Egebjerg, Garrick Smith, Arne Mørk

Alanine-serine-cysteine transporter-1 (asc-1) is a Na+-independent transporter which transport small neutral amino acids. Asc-1 is widely distributed in the central nervous system and confined to neuronal cell populations but its physiological roles remain elusive. Using transgenic mice deficient in asc-1 we have studied the functional consequences of deletion of this gene. In cortical synaptosomes prepared from asc-1 (–/–) mice, no specific uptake of [3H]D-serine was observed in Na+-free buffer whereas ~50% uptake remained in Na+-containing buffer. When measuring D-serine levels in vivo using microdialysis in the ventral hippocampus, the basal levels of D-Serine in wild type (+/+) mice were significantly increased by ~80% in (–/–) mice as well as in heterozygous mice (+/–). Extracellular recordings in hippocampal slices, measuring NMDA currents showed significantly increased currents in response to D-serine in (–/–) mice as compared to (+/+) mice. The relative expression levels of RNA isolated from (–/–) mice were compared to expression levels in corresponding age-matched wildtype samples on the 22K Agilent mouse microarray. P-values for changes in relative gene

expression level were calculated for each gene of the 22,000 genes on the microarray and 906 genes were changed (P-value < 0.05). Among the 25 glutamate receptors and subunits investigated, five genes including NMDA-2A and 2C were regulated but the most robust change was for mGluR3 (P=0.004, 2.3 fold down). Thus, asc-1 has a profound role in regulating D-serine levels in brain and due to D-serine's functional regulation of the NMDA receptor, this may have physiological implications in e.g., schizophrenia. Currently, the behavioural consequences of asc-1 deletion is being explored in asc-1 (+/–) mice using models with relevance for this disease.

P16. Ethanol Modulation of D1 Dopamine Receptor Signaling May Be Mediated by Protein Kinase C in an Isozyme-specific Fashion

*Elizabeth B. Rex, Michele L. Rankin, David M. Cabrera, David R. Sibley**

Ethanol consumption is known to modulate dopaminergic signaling and this is partially mediated by the D1 dopamine receptor (DAR), although the underlying mechanism has been unclear. We have now found that ethanol pretreatment of D1 DAR-transfected cells potentiates DA-stimulated cAMP accumulation and decreases D1 DAR phosphorylation without altering receptor expression. We hypothesized that ethanol decreases D1 DAR phosphorylation and enhances signaling by either activating a protein phosphatase or inhibiting a protein kinase. To examine the involvement of phosphatases or kinases, we pretreated cells with several phosphatase or protein kinase C (PKC) inhibitors prior to DA-stimulation. Pretreatment with phosphatase inhibitors did not abolish the ethanol potentiation of DA-stimulated cAMP levels or the decrease in D1 DAR phosphorylation. However, pretreatment with PKC inhibitors mimicked the effects of ethanol on both DA-stimulated cAMP levels and D1 DAR phosphorylation, suggesting that ethanol functions to inhibit PKC activity. In cells cotransfected with the D1 DAR and the PKC isozymes γ or δ, the ethanol-dependent decrease of D1 DAR phosphorylation appears to be augmented suggesting that the effects of ethanol may be mediated by these PKC isozymes. Based on in vitro kinase assays, using immunoprecipitated PKC isozymes, ethanol treatment attenuated PKCγ kinase activity in crude membrane preparations. Preliminary data suggests that ethanol treatment also attenuates the kinase activity of PKCδ. Taken together, these results suggest that the ethanol modulation of D1 DAR signaling does not appear to directly involve phosphatases, but instead is mediated by inhibiting specific PKC isozymes, such as PKCγ and PKCδ.

P17. Longitudinal Behavioral Evaluation of a Knock-in Mouse Model of Huntington's Disease

Mary Y. Heng, Roger L. Albin*

We established age-dependent late onset behavioral phenotype and biochemical evidence of striatal pathology in HdhCAG(150) knock-in mice. 70 and 100 week old HdhCAG(150) mutants exhibited motor deficits and reduced striatal neurotransmitter receptors. Longitudinal behavioral and anatomical characterization of the HdhCAG(150) knock-in mice is a necessary prelude to the use of this model to study HD pathogenesis.

P18. TNFα Impairs Growth Cone Motility by a Rac1-mediated Oxidative Damage to the Neuronal Actin Cytoskeleton

*S. Steward, B. M. Barth, D. L. LaVictoire, D. Cabrie, T. B. Kuhn**

Inflammation and its many mediators play a crucial role in the progression of acute, chronic, and psychiatric CNS disorders. Persistent high level-expression of TNFα is typical for the ailing CNS and suspected to be a key factor in the failure of axons to regenerate after injury. Although underlying mechanisms are poorly understood, we focused on Rac1 and reactive oxygen species (ROS) production based on findings in non-neuronal cells and since growth cone motility and thus actin filament dynamics is Rac1-dependent and highly susceptible to oxidative damage. In vitro studies on spinal cord neurons (laminin substrate) demonstrated that a presence of TNFα (100 μg/ml) severely compromised growth cone motility and morphology (>90% collapsed growth cones) through a preceding production of ROS as determined by ratiometric fluorescence analysis. These responses were mitigated by antioxidants, NADPH oxidase inhibition, or downregulation of Rac1 activity. Enhanced Rac1 activity per se generated ROS and impaired neurite outgrowth in a redox-sensitive manner. Similarly in SH-SY5Y neuroblastoma cells, TNFα elicited a transient rearrangement of the actin cytoskeleton, which strictly dependent on Rac1 activity and ROS formation. Translocation of p67phox into the plasma membrane and p40 phosphorylation suggested a NADPH oxidase activation as the ROS-generating source. Moreover, SH-SY5Y cells exposed to TNFα exhibited severe oxidative damage (carbonylation) to the actin cytoskeleton as revealed 2,4-DNP modification. Our findings suggest a Rac1-dependent redox signal accounting for the adverse effect of TNFα on neurite outgrowth and support the benefits of antioxidant therapies to improve axon regeneration.

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P19. Arrestin-binding Determinants on D2-like Dopamine Receptors

Kim Neve, Hongxiang Lan*

Non-visual arrestins (arrestin-2 and -3) serve as adaptors linking agonist-activated G protein-coupled receptors (GPCRs) to the endocytotic machinery and as scaffolds for other signaling proteins, but the molecular determinants of arrestin binding to GPCRs are still being elucidated. The dopamine D2 and D3 receptors have similar structures, but distinct characteristics of interaction with arrestins. The ability of purified arrestins to bind to glutathione S-transferase (GST) fusion proteins containing the second or third intracellular loops (GST-IC2 and GST-IC3) of D2-like receptors was assessed. Arrestin-3 bound to GST-IC3 and GST-IC2 of both receptors, with the order of affinity being D2-IC3 = D3-IC3 > D2-IC2 > D3-IC2. In IC2, D2 residue K149 was particularly important for the preferential binding of arrestin. We also identified a determinant of arrestin binding in the N-terminal region of GST-D2-IC3. Mutation of a stretch of 4 amino acids (IYIV212-215) in this region of the full-length D2 receptor disrupted receptor-mediated arrestin-3 translocation to the membrane and agonist-induced internalization of the receptor, without affecting ligand binding or G-protein coupling. These results imply that the differential effects of D2 and D3 receptor activation on receptor internalization and translocation of arrestin-3 to the cell membrane are in part due to the different binding affinities of D2- and D3-IC2 for arrestin-3, and that the sequence IYIV212-215 at the N-terminus of IC3 of the D2 receptor is required to form a binding site for arrestin.

(MH045372 and VA Merit Review)

P20. GRIF1, A Novel Regulator of Endosomal Trafficking

Elizabeth A. Kirk, Lih-Shen Chin, Lian Li*

Internalized cell surface receptors are delivered to early endosomes, where receptors are rapidly and specifically sorted between recycling and lysosomal degradation pathways. In neurons, the fate of internalized cell surface receptors can have profound effects on both signaling and survival. Here we report the identification of GABAA receptor interacting factor-1 (GRIF1), a recently discovered protein of unknown function, as a novel regulator of endosome-to-lysosome trafficking. Yeast two-hybrid screen and co-immunoprecipitation analysis reveal that GRIF1 interacts with hepatocyte growth factor-regulated tyrosine kinase substrate (Hrs), an essential component of the endosomal sorting machinery. We have mapped the binding domains of GRIF1 and Hrs that mediate

their association and shown the colocalization of GRIF1 with Hrs on early endosomes. Like Hrs, both overexpression and siRNA-mediated depletion of GRIF1 inhibit the degradation of internalized epidermal growth factor receptors and block the trafficking of the receptors from early endosomes to the lysosomal pathway. Our results indicate, for the first time, a functional role for GRIF1 in the regulation of endosomal trafficking.

P21. SynGAP Is Associated with the Cytoskeleton and Regulates the Dynamic Turnover of Actin in Dendritic Spines

Gavin Rumbaugh, Richard L. Huganir*

SynGAP, a neuron-specific RasGAP, has been functionally associated with deficits in LTP and hippocampus-dependent learning and memory. This protein directly regulates AMPAR trafficking and NMDAR-activated signaling cascades. SynGAP is a major constituent of the PSD and is exclusively localized to excitatory synapses. In an attempt to further understand the function of this protein in neurons, we designed a series of experiments to assess which motifs are responsible for guiding it to synapses. Deletions in the N-terminal region or GAP domain of SynGAP did not significantly disrupt synaptic targeting. In contrast, we identified two regions in the C-terminus (the type I PDZ ligand and a 100 residue coiled-coil motif) that are required for synaptic localization. When both of these regions are disrupted, SynGAP is diffusely distributed throughout neurons. Interestingly, disruption of either domain resulted in a reduced effect of SynGAP on synaptic function. Additional experiments indicated that SynGAP is tethered to the actin cytoskeleton and overexpression of SynGAP altered the dynamics of actin in dendritic spines. These data support the hypothesis that SynGAP is a signaling molecule that acts downstream of NMDA receptors and regulates synaptic function by changing AMPAR trafficking and actin dynamics.

P22. Adapting to Fast Rotation in Artificial Gravity

Laurence R. Young, Thomas Jarchow*

Previous limits to centifuge rotation speed for artificial gravity were thought to be about 6 rpm, constrained by the motion sickngess associated with out-of-place head movements. Our recent studies of incrementatl adaptation show that 30 rpm (180 deg/sec) is easily obtainiable

over a multi-day exposure. The effective stimulus to the neurovestibular system, the intravestibular conflict, has been defined as the product of the centrifuge rotation speed times the sine of the head turn angle. By manipulating centrifuge speed, head angle , and even head velocity, we can enable nearly all subjects to become comfortable to rapid rotation, making artificail gravity a practical countermeasure to long duratin space flight debilitation.

Supported by the National Space Biomedical Reserach Institute, under NASA contract NCC-9-58.

P23. Regulation of Neuronal Pentraxin 1 Expression Is Associated with Synaptic Damage in Alzheimer's Disease

*Maria Alba Abad, Marta Enguita, Isidre Ferrer, Ramon Trullas**

Accumulation of beta-amyloid (A-beta) precedes the synapse loss and the neurite damage that are characteristic in brains affected by Alzheimer's disease. However, the mechanisms responsible for such neurotoxicity remain unclear. Recent studies have shown that A-beta depresses synaptic activity. We investigated whether A-beta neurotoxicity in cortical neurons depends on the expression of Neuronal pentraxin 1 (NP1), a protein involved in excitatory synapse remodeling that has also been shown to mediate neuronal death induced by reduction of neuronal activity. We found that when cortical neurons are exposed to A-beta in culture, the expression of the NP1 protein is markedly increased and that this upregulation of the expression of NP1 precedes apoptotic neurotoxicity. Silencing NP1 gene expression by RNA interference (shRNAi) prevents the synapse damage and rescues cortical neurons from the apoptosis evoked by A-beta. Transgene overexpression of NP1 in cortical cells reproduced the synapse damage and the apoptotic effects of A-beta, which were also blocked by silencing NP1 with shRNAi. Moreover, we found that NP1 was increased in dystrophic neurites of brains from patients with sporadic late onset Alzheimer's disease. These findings suggest that up-regulation of NP1 expression contributes to the pathology of Alzheimer disease. Supported by FIS-PI02055, FIS-PI040376 from Ministerio de Sanidad y Consumo; SAF2005-01167 from Ministerio Educación y Ciencia, and Fundació La Caixa Project No. NE03/49-00.

P24. Diabetes-induced Allodynia: Correlation between Behavioral Intensity, Duration of Diabetes, and Periaqueductal Gray (PAG) Activation

Thomas J. Morrow, Paul Juneau, Pamela E. Paulson*

Peripheral polyneuropathy is a common complication of Type 1 diabetes mellitus and often leads to abnormal pain perception, including mechanical and thermal allodynia or hyperalgesia and severe unremitting spontaneous chronic pain. Unfortunately we know little about the supraspinal mechanisms in painful diabetic neuropathy. Freshwater and Calcutt showed that diabetic rats exhibit a protracted period of flinching behavior in response to a low dose formalin stimulus (formalin-evoked allodynia), which elicits little or no behavioral response in non-diabetic control rats. Accordingly, we used quantitative behavioral testing combined with neuroimaging and immunohistochemistry to identify potential supraspinal mechanisms in low-dose formalin-evoked allodynia using the streptozotocin (STZ) model of Type 1 diabetes mellitus (DM). Four to eight weeks after the onset of diabetes, formalin-evoked behavior was assessed by injecting the left hind paw with 50ul of 0.2% formalin. 35 minutes after formalin injection, we imaged the brain autoradiographically. In addition, we used an in-vivo, fluorescent, polycaspase probe, FlivoTM to determine the level of activated caspases as an indicator of apoptosis in the PAG. Preliminary results show increased activation and greater levels of activated polycaspases in the midbrain PAG of diabetic diabetic rats as compared to controls. These data suggest that neuropathic pain in DM may be due in part to deactivation of the PAG caused by ongoing neuronal apoptosis in the PAG and possibly other structures mediating antinociception.

P25. Tracing Tracts in Down Syndrome Mice with μMRI

R. E. Jacobs, E.L. Bearer, X. Zhang*

Traditionally, connections between neurons are traced by the local delivery of a histologically detectible tracer that is transported within the neuron to distant sites and thereby outlines the communication pathway. These tracers must interact with the intracellular machinery to be delivered along the axon of a neuron and must cross synapses to trace a multi-step pathway. The mechanisms of entry into the neuron, the type of transport used, and retention within the pathway are all important considerations in interpreting the data. For example, whether a tracer only enters at active synapses or can also enter along neuronal processes

influences the analysis of its distribution. Alternatively whether a tracer is transported in the retrograde and/or anterograde direction affects its distribution and the interpretation of the pathway delineated. To trace neuronal circuits in living brains by MRI, a contrast agent must display similar attributes as a histological tracer. We focus on Mn2+, which has recently become a widely used T1 agent. Evidence suggests that it enter neurons through voltage sensitive Ca2+ channels and is transported in the anterograde direction. We have investigated biological mechanisms of Mn2+ transport in hippocampal-basal forebrain network in a Down Syndrome mouse model, Ts65Dn. The hippocampal-basal forebrain system is of importance in neurological disorders. Mn2+ tracttracing following nanoliter injections into the hippocampus clearly outline the hippocampus-fimbria-septal nucleus path. Voxelwise analysis of 3D images warped into the same space allows quantitative statistical assessment of Mn2+ transport.

P26. Human Cognitive Decline Associates with Cortical Synapse Loss

S.W. Scheff*, D.A. Price, F.A. Schmitt, E.J. Mufson, S.T. DeKosky

Synapse loss in key regions of the cortex and hippocampus is a hallmark of Alzheimer's disease (AD). We previously reported declines in total synaptic numbers in the hippocampal dentate gyrus and regio superior in people with early Alzheimer's disease. Individuals with amnestic mild cognitive impairment (MCI) also show a decline in these regions, known for their role in learning and memory functions. It is unclear whether the neocortex of individuals with MCI manifests synaptic alterations similar to that found in the hippocampus. All individuals underwent detailed clinical evaluation within 12 months of death and were categorized as AD (n=7), MCI (n=8) or no cognitive impairment (NCI) (n=8). Unbiased stereological techniques coupled with electron microscopy were used to estimate the total number of synapses in lamina 3 of the inferior temporal gyrus. Individuals with AD lost 45% of the synaptic contacts in lamina 3 while the MCI group lost 38%. Synaptic counts were highly correlated with the subject's mini mental state exam (MMSE). Individuals with high synaptic numbers performed very well while those with low MMSE scores had fewer synapses. This is the first study to estimate the total number of synapses in any region of the human inferior temporal gyrus. These results suggest that the synapse number within the neocortex is significantly reduced in MCI to a degree similar to that found in AD. Synaptic loss appears to be an early manifestation of the disease process and signals a significant target for potential therapeutic intervention.

P27. Potassium Trafficking by Satellite Glial Cells in the Trigeminal Ganglion as a Determinant of Orofacial Neuropathic Pain

Jean Philippe Vit, Luc Jasmin, Aditi Bhargava, Peter T. Ohara*

Satellite glial cells (SGCs) tightly envelop the perikarya of all primary sensory neurons in sensory ganglia. Several lines of evidence highlight the importance of SGCs in potassium ion (K+) buffering. Glial cells in general have high K+ permeability and here we show that proteins involved in K+ homeostasis such as the inwardly rectifying channel Kir4.1, the small-conductance calcium-activated channel SK3 and the connexin 43 (Cx43) subunit of gap junctions are expressed exclusively by SGCs in the trigeminal sensory ganglion. Also found only in SGCs are the metabotropic purinergic P2Y4 receptor, and soluble guanylyl cyclase (sGC), both of which mediate neuron-glia signaling. We tested the behavioral consequences of SGC function by silencing the expression of Cx43 in the rat trigeminal ganglion using in vivo RNA interference (RNAi). Rats treated in this manner developed spontaneous pain behavior identical to that seen after injury to the trigeminal nerve. This observation combined with the finding that SGCs upregulate glial fibrillary acidic protein (GFAP) and incorporate bromodeoxyuridine (BrdU) after nerve injury, further implicates these glial cells in the pathophysiology of neuropathic pain.

Poster Session 2

Monday–Tuesday • Anderson

Posters will be available for viewing after 8:30 PM Monday through 6:30 PM Tuesday. Presenters will be with posters on Tuesday from 3:30–4:30 PM.

P28. Voluntary Running Attenuates Age-Associated Deficits Following SCI

Monica M. Siegenthaler*, Nicole C. Berchtold, Carl W. Cotman, Hans S. Keirstead

There are approximately 11,000 new spinal cord injury (SCI) cases reported every year in the United States, most of which occur in young adults. In the past few decades, the average age at time of SCI and the percentage of injuries in persons over the age of 60 have increased. Studies have shown that there is an age-associated delay in the rate of remyelination following toxin-induced demyelination of the spinal cord, suggesting that there may be an age-associated difference in regenerative efficiency. Here we examine locomotor recovery and myelin pathology in both young and aged adult rats following SCI. Additionally, we examine the effect of voluntary wheel running on the locomotor recovery following SCI in both young and aged adult rats. Our assessment indicates that aged adult rats have a deficit in the rate of locomotor recovery following SCI as compared to young adult rats, and that young adult rats plateau at a greater locomotor ability than that of aged adult rats. Moreover, voluntary running improves locomotor recovery of young adult rats following SCI. Interestingly, the rate of recovery in the aged exercise rats was similar to that of the young sedentary rats early after injury, suggesting that exercise may attenuate the age-associated deficits in locomotor recovery. Examination of myelin pathology reveals that voluntary running results in fewer demyelinated axons following SCI in both young and aged adult rats. Moreover, voluntary running results in a smaller ratio of demyelinated to remyelinated axons in both young and aged adult rats. These data suggest that there is an age-associated decline in the rate and extent of locomotor recovery that can be attenuated with voluntary running, which lessens the amount of demyelination following SCI.

P29. Neural Mechanisms Involved in Saccadic Eye Movement Fragmentation

Edward Keller, Kyoung-Min Lee*

Saccadic eye movements normally reposition the line of sight from the current fixation position to next desired gaze position with a single, smooth, high-velocity step of ocular rotation. A number of disease states have been shown to result in saccadic movements that are fragmented, but still end near the desired target position after a multi-step sequence of movements. Among these disorders are Parkinson's disease and late-onset Tay-Sachs disease (LOTs). We have recently shown that normal human subjects also make two-step saccadic responses in cognitively difficult, visually cued choice response tasks. We have confirmed that monkeys also make a significant percentage of similar two-step saccadic responses in this task when the number of alternative choices for the correct target is large. In monkeys we have been able to record neuronal responses as the animal performs such a choice response task. By comparing the activity of the recorded neurons for the majority of trials that are accomplished with single-step saccades with those producing two-step saccades, we were able to suggest some of the mechanisms that may be involved in the production of the fragmented movements. In particular, we have evidence that neuronal activity in the superior colliculus (both in its rostral fixation zone and its caudal saccade-related zone) and in the cortical frontal eye fields play a role in this behavior.

P30. Inhibition of Peroxynitrite-mediated Oxidative Damage after Spinal Cord Contusion Injury in Rats by the Nitroxide Antioxidant Tempol

E.D. Hall, I.N. Singh, YQ. Xiong*

Traumatic spinal cord injury (SCI) triggers a cascade of secondary pathophysiological insults including oxidative damage, disruption of Ca2+ homeostasis and compromised energy metabolism. The reactive nitrogen species peroxynitrite (PON), formed by nitric oxide synthase generated NO and ″O2-, is believed to be an important mediator of these secondary injury mechanisms because its decomposition products possess potent free radical characteristics. In the present study, we establish that Tempol, a potent scavenger of PON-generated free radicals (″NO2, ″OH, CO3″-), protects against secondary damage in a severe T10 contusion injury model. In untreated animals we documented a significant increase in PON-induced oxidative damage parameters

together with a significant loss of mitochondrial bioenergetics. At 24 hrs after injury, the mean mitochondrial RCR decreased from 6.4 to 2.9 ($p < 0.0001$, n=6). Administration of Tempol (300 mg/kg I.P.) 10 min. after SCI significantly attenuated spinal cord protein nitration and lipid peroxidation and maintained the mean RCR at 4.7 ($p<0.001$). PON-mediated oxidative damage and mitochondrial dysfunction exacerbates intracellular calcium overload, which activates the intracellular protease calpain leading to cytoskeletal protein (e.g. spectrin) degradation. The 145 KD fragment of spectrin, which is specifically generated by calpain, was increased ten-fold at 24 hours post injury compared to the non-injured animals ($p<0.0001$). However, α-spectrin proteolysis was decreased by 65.7% in tempol treated rats compared to the injured vehicle group ($p<0.0001$). These findings strongly support the concept that PON is an important contributor to the pathophysiology of secondary damage after SCI.

P31. Donepezil Reverses Scopolamine-induced Amnesia in Rats: Relation with Hippocampal EEG?

Arjan Blokland, Wim J. Riedel, Anke Sambeth*

Memory is one of the most important cognitive functions and helps us to preserve information of events. In rats, memory functions can be examined using the non-spatial object recognition task (ORT). The present study aimed at examining the role of acetylcholine, by characterizing both the performance and the quantitative EEG of rats during a scopolamine-induced memory impairment (SCOP) and a reversal of this impairment by donepezil (DPZ). A group of 12 rats were first implanted with EEG electrodes into the hippocampus and frontal cortex. The rats were trained in the ORT until they reached a stable discrimination performance. This was followed by drug treatment sessions. All rats were treated with saline, SCOP (0.1 and 0.3 mg/kg), DPZ (3 mg/kg), or a combination of SCOP (0.1 mg/kg) and DPZ (3 mg/kg), on separate days, in a randomized order. Each treatment was given twice. The behavioral results showed a good discrimination performance after saline, DPZ, and SCOP + DPZ, suggesting intact memory processing in these conditions. Discrimination performance, and thus memory processing, was impaired after both dosages of SCOP treatments. Compared to saline, SCOP, DPZ, and SCOP+DPZ affected the EEG more when rats were at rest then when they were active. DPZ did not reverse the effects of SCOP on EEG. Task-related hippocampal EEG did not reveal changes in the theta frequency range, suggesting that object memory leads to changes

in other frequency bands (e.g. gamma) or that hippocampal EEG is not associated with object recognition.

P32. Deficient Activity-dependent mRNA Transport in a Mouse Model of Fragile X Syndrome

Jason B. Dictenberg, Laura N. Antar, Robert H. Singer, Gary J. Bassell*

Fragile X syndrome (FXS) is one of the most prevalent forms of inherited mental retardation in humans resulting from transcriptional silencing of the fragile X mental retardation protein (FMRP) gene. FMRP is an RNA-binding protein that associates with specific mRNAs and regulates their translation at synapses, but it is unclear how these mRNAs are targeted to dendrites. Here we demonstrate that neurons from a mouse model of FXS display impaired mGluR-induced dendritic localization of mRNAs important for neuritogenesis and synaptic plasticity. In wild-type neurons a majority of FMRP is removed from dendritic microtubules by brief application of a small molecule inhibitor of kinesin, and FMRP motility in hippocampal neurons reveals rapid kinesin-dependent anterograde transport as determined quantitatively by fluorescence recovery after photobleaching (FRAP) analysis in living cells. Dendritic transport is linked to the C-terminal domain of FMRP and is enhanced by glutamatergic stimulation, which significantly increases the fraction of FMRP associated with kinesin. In addition, this C-terminal kinesin-binding domain of FMRP causes an increase in both the number and density of dendritic protrusions when overexpressed in hippocampal neurons. Loss of FMRP expression results in the quantitative uncoupling of target mRNAs from kinesin in knockout brains. These data suggest that FMRP functions as a molecular adapter in stimulus-induced dendritic mRNA transport, and highlight a novel mechanism that may contribute to synaptic defects observed in FXS.

P33. A Role for Abnormal Sensory Input in Restless Legs Syndrome

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The mechanisms underlying Restless Legs Syndrome (RLS) remain unclear, but both central and peripheral neural components likely contribute to RLS pathogenesis. Altered dopaminergic modulation of spinal circuitry and iron status appear important in RLS, and rodent models exist to assess the role of each in the disorder. RLS is commonly associated with peripheral neuropathy, suggesting an important role for abnormal peripheral input in the disorder as well. However, the use of animal

models to elucidate the role of peripheral input in RLS is lacking. We propose that an imbalance between incoming peripheral sensory input and descending dopaminergic modulation can lead to RLS symptoms. We have generated transgenic mice that over-express muscle-derived neurotrophin-3, which increases sensory input to the spinal cord from muscle and creates such an imbalance. Behavioral and anatomical analyses are ongoing to determine the candidacy of these transgenic mice as a model of the peripheral mechanisms of RLS. To date, results indicate that these mice demonstrate similarities to RLS patients and existing dopamine-based models, including motor restlessness, abnormal reflex behavior, and increased activation of spinal cord circuitry. Ongoing collaborative efforts to evaluate sleep physiology indicate that these mice also display significantly increased periodic limb movements, a phenomenon closely associated with RLS. Current studies are evaluating the effects of therapeutic pharmacological agents on the above RLS-like characteristics. Thus far, these transgenic mice appear to have the potential to be a valuable model of peripheral abnormalities in RLS.

P34. Differential Contributions of the Basolateral and Central Nucleus of the Amygdala in Mediating Intra-Accumbens Opioid-induced Approach and Consummatory Phases of High-Fat Feeding

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It has previously shown that intra-accumbens administration of the μ-opioid agonist D-Ala2,Nme-Phe4,Glyol5-enkephalin (DAMGO) markedly increases food intake and preferentially enhances the intake of highly palatable substances such as fat, sucrose, and salt (Zhang et al., 2002). More recently, it was shown that bilateral inactivation of the basolateral amygdala (BLA) completely prevented the opioid induced enhancement of fat intake but left baseline intake unchanged; whereas inactivation of the central nucleus of the amygdala (CeA) abolished all food intake (Will et al., 2004). The current experiment was designed to further characterize this phenomenon using a more detailed analysis of multiple feeding related behaviors, including amount of food eaten, duration and number of feeding bouts, and general locomotor activity. Subjects (sprague-dawley rats) were administered the GABAA agonist muscimol or vehicle bilaterally into the BLA or CeA (20 ng/0.25 μl), followed immediately by DAMGO (0.25 μg/0.5 μl/side bilaterally) or vehicle bilateral administration into the nucleus accumbens. Subjects were immediately placed in feeding chambers and allowed ad libitum

access to a high-fat diet for 2 hr. While BLA inactivation prevented the DAMGO-induced increase in fat intake, this treatment led to significantly longer feeding bout-durations compared to all other treatments. Furthermore, CeA inactivation abolished all food intake and feeding bouts. These results suggest that the BLA is specifically involved in mediating the intra-accumbens DAMGO-induced consummatory response, but not the approach or seeking aspects of feeding, and that CeA activation is required for the expression of both behaviors.

P35. Navigating Drug Development Moguls for Potential Biotechnology Moguls

Eric W. Harris*

Academic and clinical scientists are increasingly involved in the development and commercialization of regulated medical products (drugs, biologics and devices, including diagnostics). Examples of such involvement include testing others' proprietary compounds, conducting clinical trials, serving on scientific advisory boards, or joining biotechnology companies. But, even the most seasoned scientists with the most promising technologies more often fail than succeed; this is particularly so for products targeting neurological or psychiatric diseases, for which there are few (e.g., ALS) or no (e.g., neuroprotection after stroke) successful precedents to follow. The more scientists understand the overall terrain (clinical development), the finish line (marketing applications), and the gatekeepers (FDA), the more likely they are to push off in an optimal direction and avoid crashing their projects.

This poster provides a representative overall map (an Integrated Development Plan) that clarifies the major activities required for a new drug approval by 1) organizing activities along four primary tracks (clinical trials, regulatory interactions, preclinical studies, and Chemistry, Manufacturing and Controls, and 2) aligning them on a timeline that illustrates the sequence and interdependence of these activities. Integrated Development Plans tailored to specific projects have proven useful to scientists and entrepreneurs who are new to the pharmaceutical industry, or who are experienced and want to proceed efficiently, or who need to communicate business plans to potential investors. The poster also includes a glossary of common drug development terms, and links to helpful government and industry web sites.

P36. The Role of Brainstem Reorganization in the Expression of Hindlimb Receptive Fields in the Forelimb-Stump Representation of the Somatosensory Cortex in Neonatally Amputated Rats

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Neurons in the cuneate nucleus (CN) of neonatally amputated rats receive inputs from sciatic nerve fibers and express both stump and hindlimb receptive fields. The forelimb-stump region of primary somatosensory cortex (SI) of these rats similarly contains neurons in layer IV that express both stump and hindlimb receptive fields when cortical GABA receptors are blocked. The present study was designed to test whether sprouting of sciatic afferents into the CN is necessary for expression of the ectopic inputs in the SI forelimb-stump field. Sprouting of sciatic afferents into the CN of neonatally amputated rats was inhibites with neurotrophin-3 (NT-3) applied to the cut nerves of the brachial plexus. NT-3 treatment greatly reduced sciatic nerve sprouting into the CN in contrast to the robust sciatic sprouting in the CN of saline-treated neonatally amputated rats. Multi-unit recordings from the CN of six NT-3-treated rats revealed that 6.3 + 1.9% of sites exhibited both stump and hindlimb receptive fields, compared to 30.3 + 4.0% in saline-treated animals. However, the percentage of dual (or split) receptive field sites in the SI stump representation determined during GABA receptor blockade of NT-3-treated amputated rats (34.0 + 3.9%) was not significantly different from that of control animals (31.2 + 1.7%). These results support the theory that reorganization of the brainstem in the form of sprouting of sciatic afferents into the CN is not a prerequisite for the cortical reorganization that produces dual receptive fields in the SI stump representation.

P37. Expression Profiling of Microglia In Situ after a CNS Insult. A Combination of Immunohistochemistry, Laser Capture Microdissection and Microarrays

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Microglia undergo profound morphological changes upon damage to the CNS. These changes imply alterations in the molecular phenotype. Little is known however about microglial molecular phenotypes *in vivo*. For example, it is not known how many molecular phenotypes there are, nor how well the molecular profiles of *in vivo* microglia correspond to data

generated from microglia *in vitro*. Thus applying data generated from microglia *in vitro* to microglia *in vivo* is largely an untested and tenuous extrapolation. We have developed tools to generate expression profiles of microglia *in vivo*, based on laser capture microdissection of immunostained tissue and subsequent microarray analysis. We have applied these techniques to study the microglial reaction at various time points after transient forebrain ischemia in the rat as a first step towards trying to define molecular phenotypes of microglia *in vivo*. The data show transitions between different expression patterns post-ischemia, possibly correlating to different microglial molecular states. Furthermore, some expression changes identified are not found in microglia *in vitro*, suggesting that some microglial states *in vivo* may not be reproduced *in vitro*.

P38. A PPARdelta Agonist Promotes Differentiation of Oligodendrocytes from Oligospheres

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In a method established with assistance from Dr. Wendy Macklin, we isolated oligospheres from E12-13 mouse embryos. Upon plating on poly-lysine, cells immediately started to migrate out of the spheres. After 2 days, most cells had the bipolar morphology of differentiating oligodendrocytes and expressed the oligodendrocyte markers A2B5 and O1. GFAP+ astrocytes represented 12% of the cell population. Cells in spheres remained dividing early progenitors expressing the cell division marker Notch-1 and the neural progenitor marker Nestin. After 2 days, growth factors were removed and Thyroid hormone T3 was added to slow down proliferation and promote further differentiation. After 7 days, cells had developed a network of processes and switched expression of A2B5, Notch-1 and Nestin for O4 and O1. During this period, treatment with the PPARdelta agonist GW0742 resulted in cells with longer processes and a greater number of cells, whereas treatment with the PPARgamma agonist Pioglitazone promoted astrocyte growth. Immunocytochemistry for O4, PLP and MBP showed that the GW0742-treated cells produced larger membrane arborizations than vehicle or Pioglitazone-treated cells. Staining for PPARdelta at later stages showed strong expression in cell clusters in contrast to cells that had migrated out of spheres, with O1 expressed on all cells. This suggests that PPARdelta may be required only at an early stage of bipotential glial progenitor cell differentiation, and therefore its expression is restricted within spheres. Studies of the effects of PPARdelta agonists on factors governing oligodendrocyte differentiation are in progress.

P39. Diverse Classes of Antidepressant Produce Dopaminergic Sensitization in BALB/cByJ Mice

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Chronic (>2 wk) antidepressant (AD) treatment induced locomotor sensitivity to dopamine receptor 2 and 3 (D2/D3) agonists in rats. We hypothesized that a similar AD-induced sensitization to a dopamine agonist could be established in a mouse strain and that SNAP 94847, a melanin concentrating hormone-1 receptor antagonist with AD activity, would also cause sensitivity. We used habituated BALB/cByJ mice to assess the locomotor activity (LMA) response to the D2/D3 agonist quinpirole (10mg/kg) over a 3-hr test period following acute, 1-week, or 3-week administration of SNAP 94847 or fluoxetine. SNAP 94847 (20mg/kg/day) or fluoxetine (18mg/kg/day) were administered by intraperitoneal injection (acute) or given in drinking water (1-and 3-week treatments). Acute fluoxetine or SNAP 94847 had no effect on the LMA response to acute quinpirole given 1-hr later. In mice treated with SNAP 94847 or fluoxetine for 1-week, quinpirole produced a marked increase in LMA that developed during the 90-180 min time block. Following 3-week fluoxetine, the quinpirole-induced sensitivity was apparent, though not further enhanced. However, the hyperlocomotion appeared earlier (30-180 min) in mice treated with 3-week SNAP 94847. To assess the predictive validity of the model, a follow-up study in which BALB/cByJ mice were treated with 1-week of 3 distinct classes of AD (20mg/kg/day): imipramine, duloxetine, or phenylzine resulted in behavioral sensitization to acute quinpirole. This report indicates sensitivity to quinpirole following AD treatment that is not mechanism dependent and also supports the antidepressant potential of MCH-1 receptor antagonists. Furthermore, this dopaminergic phenomenon suggests one common end-point for AD-like action.

P40. Kalirin-7 Controls Activity-Dependent Structural and Functional Plasticity of Dendritic Spines

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Activity-dependent structural and functional modifications of central excitatory synapses contribute to synapse maturation, learning and memory, and neuropsychiatric disorders. However the signaling mechanisms that link glutamate receptor activation to intracellular effectors that maintain plasticity are not well understood. Here we report that NMDA receptor activation in pyramidal neurons causes CaMKII-depen-

dent phosphorylation of the guanine-nucleotide exchange factor kalirin-7, resulting in activation of small GTPase Rac1 and spine enlargement. Kalirin-7 interacts with AMPA receptors, controls their synaptic expression, and is required for activity-dependent enhancement of AMPA-mediated synaptic transmission. Our study identifies a novel signaling pathway that controls structural and functional spine plasticity.

P41. Unraveling the Mystery of Human Trace Amine Receptors

Anita H. Lewin, Hernan A. Navarro, Melissa A. Porter, Brian P. Gilmour, S. Wayne Mascarella*

Two receptors in a recently characterized family of mammalian G-protein -coupled receptors have been found to bind biogenic amines that are usually present in the brain in small amounts (trace amines) and for whom no specific mode of action has been elucidated. This phylogenetic tree for these Trace Amine Associated Receptors (TAARs); includes serotonin, tyramine, and octopamine receptors. The fact that the mRNA for rTAAR 1 and rTAAR 4 receptor proteins is expressed in the substantia nigra/ventral tegmental area, locus coeruleus, and dorsal raphe, which are all areas where cell bodies of the classic biogenic amines are found, suggests that trace amines may act as neuromodulators. The level of hTAAR 1 expression is very low: only 15-100 copies/ng cDNA are expressed in amygdala, and <15-copies/ng cDNA are found in cerebellum, dorsal root ganglia, hippocampus, hypothalamus, medulla and pituitary. To countermand this problem we developed a cell line in which RD-HGA16 cells were stably transfected with hTAAR1 and we used this cell line to develop a high throughput-compatible, homogeneous (no separation steps) functional assay. To study the effect of structural variation(s) on the functional outcome at hTAAR1 a series of analogs of two parent compounds, β-phenethylamine and serotonin, was examined. The results provided the groundwork for development of a hTAAR1 pharmacophore and led to the identification of partial agonists and antagonists at hTAAR1.

P42. eNOS Phosphorylation Modulates Vascular Reactivity and Stroke Outcome in S1179D and S1179A Knockin Mice

Dmitriy Atochin, Annie Wang, James Lapointe, Ryan Godfrey, Salvatore Salomone, Michael Moskowitz, Paul Huang*

Akt phosphorylation of eNOS at serine 1179 (S1179) increases NO production and may modulate vascular reactivity. We introduced the S1179A (unphosphorylatable) or S1179D (phosphomimetic) mutations into exon 26 of the eNOS gene and generated knockin mice. S1179A mice have higher mean arterial blood pressure (110±16 mm Hg, Mean ± SD, n=3) as compared with S1179D mice (90±3, n=3). In S1179D mice isolated, pressurized carotid arteries, maximal endothelium dependent relaxation (67±14 %, n=8) to acetylcholine (ACh, 3×10^{-8}mol/L) was augmented as compared with S1179A (49±22, n=13, $P<0.05$) mice. Using wire myograph, isolated aortas (n=30/group) were challenged with cumulative concentrations of phenylephrine (PE, 10^{-9}–10^{-6}mol/L) with or without L-NAME (3×10^{-4} mol/L), ACh (10^{-9}–10^{-6}mol/L) or sodium nitroprusside (SNP, 10^{-10}–10^{-6} mol/L). L-NAME-treatment increased the PE-induced tone in S1179D (3.43±0.33 vs 4.61±0.20 mN/mm, $P<0.01$) but not in S1179A (3.54±0.25 vs 3.59±0.18), suggesting poor basal NO release in S1179A mice. The relaxation to ACh (10^{-8} mol/L) was more pronounced in S1179D than in S1179A mice (19±3 vs 5±1 %, $P<0.01$). The endothelium-independent SNP (10^{-8} mol/L) relaxation was more pronounced in S1179A (73±4 %) vs S1179D (34±4, $P<0.01$) mice, which may represent a compensatory mechanism to reduced NO availability. S1179D mice show decreased infarct volume (74±27 mm^3, n=6) at 23 hours reperfusion after one hour of middle cerebral artery occlusion by filament as compared with S1179A (113±28, n=5) mice ($P<0.05$). We show that modulation of the eNOS S1179 phosphorylation site directly influences vascular reactivity, as well as outcome in an in vivo mouse model of stroke.

P43. The Endogenous Role of NMNAT1 in the Developing Mouse Brain

Chia-Ling Chang, Huei-Ying Chen, Aisha Ellahi, Jeethy Nair, Hui-Chen Lu*

Neurodegeneration can be triggered by a variety of genetic, epigenetic, or environmental factors. Despite the differences in cause or age of onset, most human neurodegenerative disorders share similar pathological manifestations, such as neuronal loss, memory loss, and cognitive deficits. The loss of nicotinamide mononucleotide adenylytransferase (nmnat) gene in Drosophila causes rapid and severe neurodegeneration similar to Wallerian degeneration in vertebrates, suggesting that the

normal function of nmnat is required to maintain neuronal integrity. More strikingly, over-expression of nmnat in Drosophila not only delays Wallerian-like degeneration but also protects neurons from a variety of degenerative conditions including hyperactivity and Ataxin 1 over-expression-induced neurodegeneration. Interestingly, upon injury or in other neurodegenerative conditions, a spontaneous mutant mouse strain, Wallerian degeneration slow (WldS), shows a much delayed neurodegeneration process compared to wild type. The neuro-protective effects occurring in these mice are attributed to a chimeric gene-Ube4b/Nmnat, which contains the entire coding region of NMNAT, leading to increased NMNAT expression. To explore the roles of NMNATs in mammalian system, we have cloned the full-length of the mouse nmnat 1-3 genes, the orthologs of Drosophila nmnat gene, and examined the expression profiles of these genes in developing brains with in situ hybridization techniques. nmnat1 is highly expressed in the mouse brains during embryonic day 14.5 (E14.5) and post-natal day 7th (P7), while the expression levels of nmnat 2 and 3 are very low. During E14.5, nmnat1 is expressed highly in the cortical plate and ventricular zone, and P7, it is expressed in the cortex, hippocampus, olfactory bulb, and many other areas. To explore the role of nmnat1 in maintaining neuronal health, ShRNA constructs will be designed to knock-down nmnat1 expression. Firstly, the knock-down efficiency will be tested with COS7 cells. Secondly, nmnat1-ShRNA constructs will be introduced to organotypic cultures of hippocampal slices using the gene-gun technology. The morphology of these neurons targeted by the nmnat1-ShRNA will be examined with confocal microscopy. Lastly, in utero electroporation technique will be used to introduce the nmnat1-ShRNA construct to embryonic cortical plate. The morphology of these neurons will then be examined after birth. This will help us to uncover the endogenous role of nmnat1 in the developing mouse brain.

P44. Disruption of NMDA Receptor Signaling in Dopamine Neurons Impairs Contextual Reward Association

Larry S. Zweifel, Emanuela Argilli, Antonello Bonci, Richard D. Palmiter*

The neural basis of addiction is thought to involve stable alterations within the mesocorticolimbic dopamine (DA) circuit. In animal models, repeated exposure to drugs of abuse leads to long-term changes in gene expression and enhanced neural activity within both presynaptic and postsynaptic DA neurons; mediated, in part, by N-methyl-d-aspartate-type glutamate receptor (NMDAR)-dependent mechanisms. To determine if NMDAR-dependent plasticity within DA neurons is necessary

for the behavioral modifications associated with repeated drug exposure, we genetically inactivated NR1, the essential subunit of the NMDAR complex. Cell-specific inactivation of the floxed *NR1* (*Grin1*^{lox}) allele in DA neurons was achieved by Cre recombinase expressed under the transcriptional control of the endogenous DA transporter gene (*Slc6a3*). Inactivation of *NR1* eliminated NMDAR-mediated excitatory post-synaptic currents (EPSCs) and prevented the induction of long-term potentiation (LTP) of excitatory synapses in DA neurons. Surprisingly, a lack of functional NMDAR in DA neurons had no effect on the initial phase of behavioral sensitization to cocaine; however, after long-term withdrawal from cocaine behavioral sensitization was greater in control than KO mice. Intriguingly, NMDAR signaling in DA neurons is critical for contextual reward association. KO mice failed to demonstrate conditioned place preference (CPP) for cocaine or food compared to controls. These findings suggest that NMDAR signaling within DA neurons is critical for reward learning but not behavioral sensitization.

P45. Dopamine D3-Receptor Ligands as Tools for In Vivo Investigation in Models of Drug Abuse

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Dopamine D3 receptor antagonists and partial agonists modulate drug-seeking induced by cocaine and other abused substances. We found that improved dopamine D3 receptor affinity and selectivity was achieved by introducing a trans-butenyl linking chain into the 4-phenylpiperazine class of ligands. In this series, PG01037 showed the best binding profile (Ki (hD3)=0.7 nM; D3/D2=133) and was a D3 antagonist in vitro. PG01037 and its saturated homologue, CJB090, a partial D3 agonist, were chosen for evaluation in animal models of cocaine addiction. In squirrel monkeys, both PG01037 (30 mg/kg) and CJB090 (17.8 mg/kg) attenuated the discriminative stimulus effects of cocaine. PG01037 (30 mg/kg), but not CJB090 (17.8 mg/kg) also attenuated cocaine priming-induced reinstatement of extinguished drug seeking. Neither drug affected motor behavior nor did they induce ataxia or catalepsy at these doses. We have recently prepared a new generation of ligands wherein substitution on the butylamide linking-chain was investigated and these compounds were evaluated in competition binding assays in human D2, D3 or D4 dopamine receptors. In general, these modifications were well tolerated at D3 (Ki=1-5 nM) and several analogues demonstrated >150-fold selectivity over D2 and D4. In addition, efficacy of the compounds was measured by quinpirole-stimulated mitogenesis at hD3 receptor transfected CHO cells. While all the butenyl linked derivatives were ant-

agonists, several of the saturated ligands showed partial agonist activity. Finally, several compounds had lipophilicities (cLogP range= 3-4) that may improve bioavailability profiles for future in vivo investigation into the role of D3 receptors in drug addiction.

P46. Melatonin 1/2 Receptor Agonist Properties May Be Sufficient for the Anxiolytic-Like Activity of Agomelatine

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Agomelatine has recently been reported to possess anxiolytic-like activity in preclinical studies. Here, the anxiolytic-like activity of agomelatine (3, 10 mg/kg, IP) was confirmed in the rat social interaction test. However, the relative contribution of the mixed melatonin receptor 1 and 2 agonist and serotonin 2C receptor (5-HT2C) antagonist activity to the effects of agomelatine is unclear. The present study aimed to assess the functional 5-HT2C antagonist properties of agomelatine in a rat spontaneous locomotor activity (LMA) assay. The 5-HT2C agonist, RO 60-0175 (1, 3, 10 mg/kg, IP), produced a dose-dependent reduction in LMA in a 30-min test. Agomelatine (3, 10, 30 mg/kg, IP) alone had no effect on spontaneous LMA, and was without effect on the 5-HT2C-mediated (10 mg/kg, RO 60-0175) reduction in LMA at doses that were at and above those that enhanced social interaction. In contrast, the 5-HT2C agonist-mediated reduction of LMA was dose-dependently reversed by pretreatment with the selective 5-HT2C antagonist, SB-242084 (0.1, 0.3, 1.0 mg/kg, IP). Complete reversal was achieved at 1.0 mg/kg, while SB-242084 alone had no effect on spontaneous LMA at any dose tested. The present results suggest that the 5-HT2C antagonist properties of agomelatine do not contribute significantly to its in vivo activity in a dose range where anxiolytic efficacy is noted.

P47. NMDA Receptors at Glutamatergic Synapses on Striatopallidal and Striatonigral Medium Spiny Neurons

John Partridge, Stefano Vicini*

The principal targets of excitatory input into the striatum are medium spiny neurons (MSNs) that express AMPA and NMDA receptors. Bacteria artificial chromosome (BAC) transgenic mice in which enhanced green fluorescent protein (EGFP) is selectively driven in neurons that express dopamine D1 or D2 receptors, were used to differentiate striatonigral and striatopallidal pathways. We investigated the properties

of NMDA receptor mediated excitatory postsynaptic currents (NMDA-EPSCs) at striatal synapses. EGFP positive and negative neurons in slices from transgenic mice aged PD13-21 were examined with whole cell patch-clamp recordings. EPSCs from dorsolateral MSNs were elicited by stimulation of glutamatergic afferents and recorded at -70 mV holding potential in the absence of magnesium using a solution containing bicuculline. NMDA-EPSC amplitude and kinetics were assessed by subtraction of the AMPA receptor-mediated EPSC measured in the presence of the NMDA receptor antagonist CPP. Brief trains of presynaptic stimuli doubled the NMDA-EPSCs duration suggesting glutamate spill-over onto extrasynaptic NMDA receptors. The decay time of the NMDA-EPSCs also doubled when the neuron was voltage-clamped at positive holding potentials (+40 mV). The ratio of the NMDA to AMPA receptor mediated synaptic current was determined to be larger in striatopallidal versus striatonigral neurons. Furthermore, we have observed a trend for striatopallidal neurons to express slower NMDA-EPSCs. Together these data support the hypothesis that striatopallidal and striatonigral neurons integrate glutamatergic signals differentially.

P48. Working-Memory Deficits in Adult Rats Previously Sustaining Partial Loss of Mesoprefrontal Dopamine Early in Development: Effects of Reboxetine

Janet M. Finlay, Patricia J. Boyce*

Postmortem anatomical studies have revealed a decreased density of dopamine (DA) nerve terminals in the prefrontal cortex (PFC) of schizophrenic subjects. This may be a neurodevelopmental structural abnormality that subsequently results in dysfunction of the PFC in late adolescence/early adulthood, coincident with the emergence of cognitive deficits associated with the illness. My lab has been examining 1) whether early postnatal loss of DA nerve terminals in the rat medial PFC (mPFC) on postnatal day (PN) 12-14, to an extent similar to that observed in schizophrenia, results in the emergence of cognitive deficits in adult rats (PN90-93) and 2) whether a selective norepinephrine (NE) uptake inhibitor, reboxetine, alleviates cognitive deficits induced by partial loss of mPFC DA. Consistent with our previous research (Boyce & Finlay, 2005, *Developmental Brain Research*, **156**:167-175), local application of 6-hydroxydopamine into the rat mPFC on PN12-14 resulted in a persistent loss of local tissue DA content (control = 0.11 ± 0.01 and lesion = 0.05 ± 0.01, ng/mg tissue) without significantly affecting tissue NE concentration. Working-memory function was assessed using a T-maze delayed-response task. Loss of ~50% of mPFC tissue DA impaired

T-maze delayed-response behavior in adult rats. For example, under a 30 sec delay condition, adult control rats exhibit ~90% correct responses in the T-maze task whereas lesioned rats exhibited ~55% correct responses. Lesioned rats treated chronically with reboxetine (5 mg/kg/day, ip for ~ 2 wks of behavioral training and testing) exhibited ~80% correct responses, indicating that lesion-induced deficits in working-memory are attenuated by a NE transport inhibitor. Following behavioral testing, the effect of an acute reboxetine challenge (5 mg/kg, ip) on extracellular NE and DA in the mPFC of control and lesioned rats was monitored using in vivo microdialysis. Reboxetine evoked similar increases in extracellular NE in the mPFC of lesioned and control rats treated with either chronic saline or reboxetine during behavioral training and testing. In contrast, the reboxetine-evoked increase in extracellular DA was attenuated in lesioned rats previously treated with saline during behavioral training and testing. These data confirm that 1) early partial loss of DA terminals in the mPFC results in working-memory deficits in the adult rat and 2) that these effects are attenuated by chronic administration of a NE uptake inhibitor, perhaps as a result of drug-induced increases in extracellular DA in the mPFC. Supported by the National Alliance for Research on Schizophrenia and Depression.

P49. A Novel Endocannabinoid-Dependent Potentiation of Excitatory Synaptic Transmission in Hippocampus

*Alicia Awes, Katherine Sullivan, Michael P. Kavanaugh**

Modulation of synaptic transmission by endocannabinoids (eCBs) typically involves retrograde signaling resulting in presynaptic inhibition. Here we show that brief trains of moderate frequency (10 Hz) stimulation result in an eCB-dependent long-term potentiation of excitatory synaptic transmission at rat and mouse Schaffer collateral-CA1 pyramidal synapses. This potentiation is distinct from typical high-frequency stimulus induced long-term potentiation (HFS-LTP) in that it is completely abolished by the CB1 antagonist AM251, but not by the NMDA receptor antagonist AP5. This eCB-dependent LTP is further distinguished from HFS/NMDAR-dependent LTP by the involvement of group I mGlu receptors and by marked age-dependence. The eCB-dependent LTP was saturable and reached a maximum of 34 +/– 3.8% after 1–4 bouts of stimulation without occluding HFS/NMDAR-dependent LTP. This potentiation is independent of GABAergic synaptic inhibition, suggesting that it represents a novel form of excitatory synaptic plasticity mediated by the endocannabinoid system in hippocampus.

P50. Transcriptional Regulation of PINK1

Kelly Jean Thomas, Marcel Van der Brug, Kelly Daigle, Alexandra Beilina, Mark R. Cookson*

Early onset Parkinson's disease can be caused by mutations in several genes, including parkin, DJ-1 and PINK1. Prior to mutations being associated with parkinsonism, PINK1 was originally described as one of several genes that are transcriptionally transactivated by the tumor suppressor, PTEN (phosphatase and tensin homologue). PINK1 is a mitochondrial kinase and pathogenic mutations in PINK1 are loss of function mutants. Little is known about the cellular role of this protein but it has been shown to protect neurons against mitochondrial damage. Previous studies have shown that PPARgamma-agonists, such as Troglitazone, can induce PTEN expression in a concentration and time dependent manner by decreasing activity of Casein Kinase 2 (CK2), a negative regulator of PTEN. We hypothesized that PINK1 mRNA could be induced by modulators of PTEN expression and the PI3K/Akt pathway. Using qRT-PCR, we show that PPARgamma-agonists and inhibitors of PI3K, which antagonize the function of PTEN, induce PINK1 mRNA expression levels. No induction was seen in cell lines stably expressing a short hairpin RNA (shRNA) to PINK1. We are currently exploring the functional consequences of this induction, but these data delineate the signaling pathways by which PINK1 expression is controlled. These results suggest that PINK1 may serve as a feedback modulator of the pro-apoptotic activity of PTEN.

P51. RNA-Binding Targets of the Recessive Parkinsonism Protein DJ-1 Reveals Involvement in Mitochondrial, Oxidative Stress and PTEN/Akt Survival Pathways

Marcel P. van der Brug, Jeff Blackinton, Jayanth Chandran, Ling-yang Hao, Ashish Lal, Krystyna Mazan-Mamczarz, Chengsong Xie, Rili Ahmad, Kelly J. Thomas, J. Raphael Gibbs, Jinhui Ding, Amanda J. Myers, Ming Zhan, Huaibin Cai, Nancy M. Bonini, Myriam Gorospe, Mark R. Cookson*

Mutations in DJ-1 (PARK7) are causative for autosomal recessive, early onset PD. While the precise function of DJ-1 is not known, knockout and mutational studies indicate a role in the protective response to oxidative stressors. DJ-1 was originally identified as part of an RNA binding complex of about 400 kDa, but only one subsequent study has investigated this possible activity. In this study, we have identified all mRNA species bound to DJ-1 via immuprecipitation of the DJ-1/RNA complex. DJ-1 bound mRNA was then examined via Illumina whole genome microarrays. We were able to identify approximately 900 transcripts

that could be consistently immunoprecipitated with DJ-1 but not non-specific IgG. These included representatives of a number of transcriptional classes, but prominently included nuclear encoded mitochondrial transcripts, mRNA for selenium-containing proteins, and members of the PI3K/Akt pathway. These were confirmed by qRT-PCR. The basal expression of the same transcripts were not changed in abundance by over expression of DJ-1 or by knockdown using RNAi. However significant changes in the levels of the protein products were confirmed via western blotting. This suggests that DJ-1 plays a role in regulating transcript translation rather than controlling mRNA stability. Identification of the mRNA components of a binding complex including DJ-1, represents a paradigm shift in the role of DJ-1 in Parkinson's disease. It directly associates the observed protective effect of DJ-1 in response to oxidative stress, to a functional mechanism, and presents several targets for potential therapeutic intervention.

P52. Regulation of Proopiomelanocortin Neurons by Endocannabinoid-Sensitive Terminals at Distal Dendrites

Shane T. Hentges

Hypothalamic proopiomelanocortin (POMC) neurons integrate various signals of energy balance and release transmitters to effectively inhibit food intake. The majority of studies examining factors that regulate POMC neuron activity have focused on peptides and rapid neurotransmitters released from terminals in the region of the POMC cell-bodies. However, the majority of afferent inputs to a neuron generally terminate on dendrites. The anatomical distribution of POMC neuron dendrites has not been well characterized nor has the extent to which POMC neuron dendrites can extend beyond the soma. Previous work has demonstrated that arcuate nucleus POMC neurons release endocannabinoids that inhibit presynaptic GABA release onto POMC neurons. Endocannabinoids are released from dendrites where they act in a retrograde manner to inhibit presynaptic transmitter release from nearby terminals. Here, the endocannabinoid inhibition of GABA release was used as a physiological sensor to determine that POMC neuron dendrites extend much farther from the soma than previously recognized. Whole-cell voltage-clamp recordings were made from identified POMC neurons. Endocannabinoids inhibited GABAergic inhibitory postsynaptic currents in POMC neurons only in intact sagittal brain slices, but not coronal, horizontal, or sagittal slices that were truncated rostrally at the level of the optic chiasm. Confocal images demonstrated the presence of putative POMC neuron dendrites extending rostrally beyond the arcuate

nucleus into preoptic hypothalamic regions. Thus, POMC neurons can be regulated by afferent fibers that terminate at sites distant from the POMC cell-body region. The source of these distant inputs remains to be determined, but may provide additional targets for future therapeutics to treat or prevent obesity.

P53. Expression of mRNA Transcripts Associated with DJ-1, Implicated in Parkinson's Disease, in Wild Type and DJ-1 Knockout Mice

Jeff Blackinton, Marcel van der Brug, Dagmar Galter, Lars Olson, Mark Cookson*

Mutations in DJ-1 cause recessive early-onset parkinsonism in familial cases, and it is known that DJ-1 is neuroprotective against oxidative stressors both in human cell lines and in vivo. But for a small, dimeric protein with no clear structural domains, a vast number of additional cellular effects have been suggested, including roles in cancer and spermatogenesis. We noted that rat DJ-1 was identified as a regulatory subunit of an RNA binding complex and a number of proposed interactors are reported nucleic acid binding proteins. In experiments using array technology, we have identified a number of mRNA transcripts that co-immunoprecipitate specifically with DJ-1 in human cell lines and in vivo in mouse brains (see van der Brug). These transcripts include members of the oxidative phosphorylation pathway, the PTEN/Akt cell survival pathway, and the selenoproteins family, including glutathione peroxidases. We have characterized, using in situ hybridization and immunohistochemistry in both wild type and DJ-1 knockout mice, the expression of a number of the target genes. Understanding the localization of expression of these genes and the translational differences resulting from DJ-1 activity, puts into context the effects of DJ-1 on cell survival.

P54. The Effect of Catecholamine Depletion by Alpha-Methyl-Para-Tyrosine on Measures of Cognitive Performance and Sleep in Abstinent MDMA Users

Una D. McCann, Stephen C. Petersen, George A. Ricaurte*

(±) 3, 4-Methylenedioxymethamphetamine (MDMA) is a popular recreational drug of abuse and a brain serotonin (5-HT) neurotoxin in animals. Growing evidence suggests that humans who use MDMA recreationally can also develop 5-HT neurotoxic injury, although func-

tional consequences have been difficult to identify. Twenty-five abstinent MDMA users and twenty-three non-MDMA using controls were studied to determine whether pharmacologic depletion of brain catecholamines by alpha-methyl-para-tyrosine (AMPT) would differentially effect MDMA users on measures of cognition and sleep, two processes dually modulated by brain serotonergic and catecholaminergic neurons. During a 5-day inpatient study, all subjects underwent formal neuropsychiatric testing, repeated computerized cognitive testing, and all-night sleep studies. At baseline, MDMA users had performance deficits on tasks of verbal and visuospatial working memory and displayed increased behavioural impulsivity on several computerized tasks, reflecting a tendency to perform quickly at the expense of accuracy. Baseline sleep architecture was also altered in abstinent MDMA users compared to controls. AMPT produced differential effects in MDMA users compared to controls on several cognitive and sleep measures. Differences in cognitive performance, impulsivity and sleep were significantly correlated with MDMA use. These data extend findings from earlier studies demonstrating cognitive deficits, behavioral impulsivity and sleep alterations in abstinent MDMA users, and suggest that lasting effects of MDMA lead to alterations in the ability to modulate behaviors reciprocally influenced by 5-HT and catecholamines. More research is needed to determine potential relationships between sleep abnormalities, cognitive deficits and impulsive behaviour in abstinent MDMA users.

P55. Phase and Power of Hippocampal Theta Modulates Responsiveness of Nucleus Accumbens Neurons in the Awake Behaving Rat

John A. Wolf, Leif H. Finkel, Diego Contreras*

The nucleus accumbens (NAcb) integrates inputs from the prefrontal cortex (PFC) and hippocampus (HC), as well as the amygdala and thalamus. Abnormal integration of inputs from the HC and PFC in the NAcb has been proposed as a possible factor in schizophrenia. In HC, cells entrain to theta oscillations (4-8Hz) at a phase modulated by the animal's location. Cells in the NAcb and the PFC entrain to these HC oscillations as well. To investigate the relationship between PFC inputs to the NAcb and HC theta in the awake animal, we chronically implanted male Long-Evans rats and examined the response properties of NAcb cells to afferent stimulation from the PFC. Rats were implanted with 12 movable tetrodes in the NAcb, a bipolar recording electrode in ventral HC CA1, and a bipolar stimulating electrode in the PFC. Trains of stimuli were delivered to the PFC while the rat performed a task running around a track for reward. Most recorded NAcb cells responded robustly

to PFC stimulation. A subset of cells (42%) was sensitive to the phase of HC CA1 theta, with a phase-locked increase in response magnitude. Some cells also demonstrated sensitivity to the power of theta in CA1, responding more to PFC stimulation when theta power was high (independent of phase). These results suggest that firing of a subset of cells in the NAcb is modulated by the timing of PFC inputs relative to the phase of CA1 theta oscillations, suggesting a possible mechanism for organizing cell ensembles across these structures.

Poster Session 3

Tuesday–Thursday • Anderson Ballroom

Posters will be available for viewing after 8:30 PM Tuesday through 6:30 PM Thursday. Presenters will be with posters on Thursday from 3:30–4:30 PM.

P56. Kappa Opioid Inhibition of Somatodendritic Dopamine IPSCs

Christopher Ford*, John Williams

In the midbrain, dopamine neurons release dopamine somatodendritically. This results in an inhibitory post-synaptic current (IPSC) within adjacent dopamine cells that occurs via the activation of inhibitory D2 autoreceptors. Kappa, but not mu/delta opioid receptors inhibit this IPSC. Our aim was to determine the mechanism by which κ-opioid receptors inhibit the dopamine IPSC. In both the Ventral Tegmental Area (VTA) and Substantia Nigra Compacta (SNc) the κ-receptor agonist, U69593 inhibited the IPSC, but not the current induced by the exogenous iontophoretic application of dopamine. The endogenous peptide, dynorphin A (1-13) also inhibited IPSCs in the VTA and SNC, but also the dopamine iontophoretic current in the VTA. Although both kappa agonists induced a postsynaptic outward current in the VTA, the current induced by dynorphin was dramatically larger. This suggests that the decrease in iontophoretic dopamine current was the result of occlusion. Occlusion alone could not however completely account for suppression of the IPSC. The kappa opioid inhibition of the IPSC was not affected by global increases or decreases in dopamine cell activity within the slice. These findings suggest that while kappa opioid receptors can hyperpolarize dopamine neurons, they also suppress dopamine release via direct actions at the release site. The results thus demonstrate both pre- and postsynaptic actions of kappa receptor agonists.

P57. Regulation of Alpha-Synuclein Phosphorylation in Mammalian Cells

David W. Miller*, Niraj R. Patel, Jordi Clarimon, Marcel van der Brug, Mark R. Cookson

Phosphorylation of alpha-synuclein at serine 129 (Ser129) is thought to enhance the toxicity of this protein. We have previously shown that this form of alpha-synuclein (Pser129-asyn) is disproportionately elevated in a Lewy body-containing brain region from SNCA triplication cases.

We have also revealed that overexpression of alpha-synuclein drives the phosphorylation of this protein in M17 neuroblastoma cells. The goal of the current study is to determine the serine/threonine kinase responsible for phosphorylating Ser129 of alpha-synuclein in cultured mammalian cell lines. Various kinases, including casein kinase 2 (CK2), have been implicated in phosphorylating alpha-synuclein. To determine if CK2 is the culpable kinase, we treated an alpha-synuclein-overexpressing cell line for 48 hours with a wide concentration range of three different casein kinase inhibitors that have increasing selectivity for CK2 (DRB, TBB, DMAT). Relatively selective inhibition of CK2 resulted in a concentration-dependent decrease in Pser129-asyn as determined via western blot analysis. CK2 inhibition was verified by parallel decreases in phosphorylated p53 (Ser392), a confirmed CK2 substrate. Given the promiscuous actions of most kinase inhibitors, we employed RNA interference to selectively target either CK1 or CK2. Preliminary results reveal that shRNA-mediated knockdown of CK2, but not CK1, partially decreases the level of Pser129-asyn. Since CK2 blockade/knockdown only has a partial effect on Pser129-asyn levels, further studies will also examine the potential role of other previously implicated kinases (GRK2, GRK5) in phosphorylating alpha-synuclein. In conclusion, CK2 activity can mediate alpha-synuclein phosphorylation in mammalian cells and may serve as a therapeutic target for Parkinson's disease.

P58. The Influence of Acetaldehyde on Nicotine-Induced Neurotransmitter Changes in the Brain

S. Fallon, E. Shearman, H. Sershen, A. Lajtha*

The aim of the present study was to examine the role of a low-dose acetaldehyde injection on nicotine-induced neurotransmitter changes in brain areas of cognition and reward. We assayed these effects in the rat brain via microdialysis in conscious freely moving rats. It was reported that low doses of acetaldehyde enhance nicotine self-administration in rats. Since nicotine enhanced learning and reward, while acetaldehyde was reported to inhibit learning, we hoped that examining the effects of acetaldehyde on nicotine-mediated neurotransmitter changes would help to discriminate reward mechanisms less influenced by learning mechanisms. To avoid the aversive effect of acetaldehyde, we used a low dose of acetaldehyde (0.16 mg/kg) administered after systemic nicotine (0.3 mg/kg). We analyzed six brain regions: nucleus accumbens, ventral tegmental area, ventral and dorsal hippocampus, and prefrontal and medial temporal cortex, assaying dopamine, norepinephrine and serotonin. Acetaldehyde lowered dopamine in all areas analyzed and lowered serotonin in the hippocampal and cortical areas. Norepinephrine was

lowered in the accumbens and the cortical areas, but was increased in the ventral tegmental and ventral hippocampal areas. We suggest the possibility that lowering dopamine levels may contribute to the enhancement of nicotine self-administration. Our findings also indicate that compounds affecting reward processes or drug reinforcement alter the activity of several neurotransmitter systems in several brain regions including areas involved in cognitive mechanisms.

P59. Inactivation of Prefrontal Cortex Abolishes Sensory-Evoked Acetylcholine Release from Sensory Cortices

D.D. Rasmusson, S.A. Smith, K. Semba*

Stimulation of different sensory modalities is known to evoke an increase in acetylcholine release from the corresponding cortical area. The pathways by which such sensory information reaches the cholinergic neurons of the basal forebrain that project to the cortical areas and are responsible for this release are unclear, but have been hypothesized to involve the prefrontal cortex (PFC). This hypothesis was tested in urethane-anesthetized rats using microdialysis to collect acetylcholine from somatosensory, visual, or auditory cortex. Ten minute administration of the GABA-A receptor agonist muscimol (0.2 % at 2 μl/min) via reverse dialysis was used to block PFC activity. Peripheral sensory stimulation and ventral posterolateral thalamic stimulation delivered before PFC inactivation evoked a 60 and 105% increase, respectively, in acetylcholine release from somatosensory cortex. Muscimol delivery to the PFC completely abolished these evoked increases. Stimulation of the lateral geniculate and medial geniculate nuclei evoked 57% and 72% increases in acetylcholine release from visual and auditory cortices, respectively, and these increases were also blocked by PFC inactivation. These results strongly support the proposed sensory cortex-to-PFC-to-basal forebrain circuit. In addition, the spontaneous level of acetylcholine release in somatosensory, visual, and auditory cortex was reduced by 22–59% following PFC inactivation, indicating that PFC efferents provide a tonic facilitatory influence on the basal forebrain cholinergic neurons.

P60. Genetic Association and Expression of STOP (MAP6) in Schizophrenia

Andrew W. Joseph, Louis T. Joseph, E. Michael Saylor, Shruti N. Mitkus, Kristin Nicodemus, Thomas M. Hyde, Daniel R. Weinberger, Joel E. Kleinman, Barbara K. Lipska*

Stable tubule only polypeptide (STOP), also known as MAP6, is a microtubule associated protein that confers stability to microtubules and may play a role in neuronal migration, morphology, and function. The deletion of the STOP gene in mice mimics some aspects of schizophrenia, as it leads to neurochemical and behavioral abnormalities that can be alleviated by neuroleptics. In light of these findings, we investigated the genetic association of STOP with schizophrenia and the expression profile of neuronal N-STOP and embryonic E-STOP in human postmortem brain tissue. We selected 13 haplotype-tagging SNPs within the STOP gene and conducted an analysis of 198 Caucasian families (198 European American patients, 202 unaffected siblings, 10 affected siblings, and 288 parents of probands) using FBAT. We found no significant single SNP or haplotype associations with schizophrenia in our family sample. Using quantitative RT-PCR, we conducted a case-control analysis of the expression of N-STOP and E-STOP mRNA isoforms in postmortem tissue obtained from the dorsolateral-prefrontal cortex (DLPFC) and the hippocampus of 30 subjects with schizophrenia and 70 controls. We did not find any differences in mRNA expression between subjects with schizophrenia and controls. In order to investigate STOP protein expression, we utilized quantitative western blot analysis to measure N-STOP immunoreactivity in the DLPFC of 30 subjects with schizophrenia and 42 controls. We found no significant difference in immunoreactivity between subjects with schizophrenia and controls. Despite promising results from animal studies, we did not find evidence that STOP has a genetic association or altered expression in schizophrenia.

P61. Insulin-Sensitive Neuropeptide Secretory Granules May Provide their own Calcium for Exocytosis

Timothy J. Eisen, Yalan Zhang, Melissa Herman, Ghislain Nicaise, S. Arch, Leonard K. Kaczmarek, Elizabeth A. Jonas*

The processes of release of neuropeptide from neuronal cells are as yet not thoroughly understood. We have studied these processes by examining insulin-induced egg-laying hormone (ELH) secretion from the bag cell neurons of Aplysia californica. Previous data showed that a rise in cytosolic calcium occurred during insulin-induced neuropeptide secre-

tion, even in a medium lacking calcium. Our previous work suggested that the secretory granules themselves released calcium intracellularly in response to insulin application. We used electron microscopy and x-ray microanalysis to study calcium levels inside dense core granules before and after insulin treatment. After treatment with insulin in a calcium-containing medium, the calcium concentration inside the granules increased. To visualize calcium-containing granules in living cells during insulin treatment, we have now used calcium indicators. After insulin treatment, granules labeled with dye tended to disappear, presumably by exocytosis. To determine if neuropeptide is contained in the calcium-containing vesicles that are undergoing exocytosis, we transfected cultured neurons with a plasmid encoding an ELH-EGFP fusion protein. Analysis by light microscopy indicated 83% co-localization of calcium with GFP-ELH fluorescence in granules in the neurites. In addition, there was a small population of calcium-containing granules (17%) that did not co-localize with GFP-ELH fluorescence. In preliminary experiments, 20 minutes after insulin application, a decrease was observed in fluorescence of a subset of the calcium and GFP-ELH-containing granules, most likely as a result of their fusion with the plasma membrane.

P62. Morphological and Molecular Features of Early and Late Onset CMT1B

Michael E. Shy, Jun Li*

Mutations in the myelin protein zero (MPZ) gene cause Charcot Marie Tooth disease type 1B (CMT1B). CMT1B presents with a severe demyelinating/dysmyelinating neuropathy that presents in infancy, or an adult onset neuropathy that appears axonal despite being caused by a mutation in a myelin specific gene. Detailed molecular changes occurring in early or late onset CMT1B have not been described. We have had the opportunity to perform an autopsy on a late onset H10P mutation and evaluate two sural nerve biopsies on a patient with an early onset R69C mutation. The autopsy demonstrated axonal loss and re-organization of the molecular architecture of the axolemma. Segmental demyelination was negligible. In addition we identified focal nerve enlargements containing MPZ and ubiquitin in the inner myelin intra-laminar and periaxonal space that appeared to separate axons from myelinating Schwann cells. Unlike H10P, the R69C biopsies showed prominent demyelination and onion bulb formation. Both R69C biopsies showed very similar features of demyelination and axonal loss, consistent with the lack of cli-

nical progression over the 20year interval between the biopsies despite the severe nature of the neuropathy. Teased fiber immunohistochemistry of R69C revealed voltage-gated sodium channel subtype 1.8 (Nav1.8) expression at the nodes of Ranvier around the areas of segmental demyelination. Internodal length in all R69C nerve fibers was invariably very short (more than 98% of all internodes are shorter than 150μm). The switch to Nav1.8 channels at nodes and uniformly shortened internodes may provide clues into the pathogenesis of the early onset neuropathy and the short internodes may contribute to the extremely slowed conduction velocities in R69C (below 10m/s). These two studies provide insights into pathogenic mechanisms involved in early and late onset CMT1B.

P63. Modulation of Neural Stem Cell Proliferation and Differentiation by Arginase I

S. Becker-Catania, T. Gregory, J. de Vellis, S. Cederbaum, R. Iyer*

Loss of the liver isoform of arginase I (AI) results in a metabolic disorder characterized by growth retardation, increased mental impairment, and potentially fatal hyperammonemia. This syndrome plus a growing body of evidence supports a role for arginase and arginine metabolites in normal neuronal development and function. Using neural stem cells (NSCs) isolated from AI knockout (KO) mice, we analyzed proliferation and differentiation compared to heterozygous (HET) and wildtype (WT) controls. We found a 1.5 to 2-fold increase in the number of KO NSCs compared to WT using both short and long-term proliferation assays. FACS analysis showed more KO NSCs in the synthesis phase of the cell cycle versus WT cells. Following differentiation, AI-deficient cells expressed β-Tubulin, SMI81, GFAP, and CNPase, markers consistent with neurons, astrocytes and oligodendrocytes. Interestingly, many KO cells exhibited more mature morphology and expressed mature neuronal markers that were decreased or not present in HET cells. Comparative RTPCR analysis identified differences in the levels of several mRNAs encoding structural, signaling, and arginine metabolism proteins between KO and WT cells. The consequence of these changes may contribute to the differential phenotypes of KO and WT cells and suggests that AI may play an important and unanticipated role in growth and development of NSCs.

P64. IGF-I Mediated Signaling Pathways and Downstream Targets in Oligodendrocyte Progenitors

Teresa L. Wood, Robert J. Romanelli, Jennifer K. Ness, Terra J. Frederick, Stefanie C. Altieri, Jungsoo Min*

Insulin-like growth factor (IGF)-I has multiple roles in oligodendrocyte development including enhancing proliferation and survival of oligodendrocyte progenitors (OPs) and promoting maturation of differentiated oligodendrocytes. In our previous studies we demonstrated that IGF-I sustains phosphorylation of Akt in OPs and provides a long-term survival signal to protect OPs from trophic factor deprivation or glutamate excitotoxicity. Recently, we also determined that IGF-I utilizes the PI3-kinase (PI3K)/Akt pathway in OPs to regulate expression of G1 targets and S phase entry in coordination with FGF-2. The ability of IGF-I to sustain phosphorylation of Akt is critical for its specific actions in OPs. Sustained Akt phosphorylation in the presence of IGF-I was associated with prolonged stability of the IGF type I receptor (IGF-IR). This is in contrast to neurotrophin-3 that transiently phosphorylates Akt and promotes down-regulation of its receptor. The goal of our recent studies was to detemine how IGF-IR trafficking regulates Akt phosphorylation. In addition to biochemical and cell biological assays to study IGF-IR trafficking, we also utilized computational analyses to develop a model of receptor trafficking that is consistent with the time-course of IGF-IR surface availability and sustained Akt phosphorylation. The results of these studies support the hypothesis that specific cell surface localization and trafficking of the IGF-IR are essential for sustained Akt phosphorylation in OPs in response to IGF-I.

P65. Differential μ-Opioid Receptor Regulation Following Chronic Treatment with Morphine or Methadone

Michael S. Virk, John T. Williams*

The analgesic and euphoric effects of opioids are mediated through activation of the μ-opioid receptor (MOR) and chronic use of these drugs results in tolerance. Though the mechanisms underlying opioid tolerance remain unknown, studies suggest that tolerance may develop in an agonist-specific manner. To examine agonist-specific MOR regulation, rats were chronically treated with morphine or methadone. Acute MOR desensitization and recovery, as well as cellular tolerance, were studied in brain slices containing locus coeruleus (LC) neurons.

G protein-coupled inward rectifying potassium (GIRK) currents were measured with whole-cell voltage-clamp experiments to monitor MOR signaling. Chronic morphine treatment facilitated acute MOR desensitization and inhibited recovery from desensitization, whereas chronic methadone treatment had no effect on MOR recovery. Three different, clinically relevant doses of morphine and methadone were administered to rats via osmotic minipump and the results on MOR regulation were unique, but consistent, for each drug regardless of dose. However, both morphine and methadone treatment resulted in the same 2-fold right-shift in EC50 values, as measured by concentration-response curves, to two MOR agonists. Thus, in addition to agonist-specific MOR regulation, the data suggest that the mechanisms responsible for acute MOR regulation—desensitization and recovery—are fundamentally different from those governing cellular tolerance.

P66. Pharmacological Studies of mGlu2/3 Drugs on Glutamate Release Utilizing Ceramic-Based Microelectrode Arrays

Peter Huettl*, George E. Quintero, Erin Rutherford, Francois Pomerleau, Kirk Johnson, Darryle D. Schoepp, Greg. A. Gerhardt

L-glutamate (Glu) is the predominate excitatory neurotransmitter in the CNS and is involved in maintaining normal brain function and it is implicated in various disease states. Glu neurotransmission is tightly regulated in part by metabotropic Glu (mGlu) receptors. We evaluated the effects of the mGlu2/3 agonist, LY379268 and antagonist, LY341495, in the neocortex of coronal rat brain slices and in awake rats by utilizing an enzyme-based microelectrode array. Repeated stimulation with a 50 sec., 70 mM KCl superfusion revealed a 36 % decrease in the ratio (S2/S1) of Glu peak amplitudes when slices were superfused with 10 μM LY379268 (S2/S1 = 0.6 ± 0.1), compared to vehicle alone (S2/S1 = 0.9 ± 0.1). Superfusion with 10 μM LY379268 also decreased Glu release by 45% following a rapid, local application of isotonic 70 mM KCl. Additionally, the orthosteric-site mGlu2/3 agonist, LY354740 (0.5 μM), attenuated KCl-evoked Glu release by 55% (S2/S1 = 0.40 ± 0.11). In prefrontal cortex of awake rats, the agonist LY379268 decreased resting Glu levels by ~2 μM while the antagonist, LY34195, increased resting baseline Glu levels by ~12 μM. Our results support that activation of mGlu2/3 receptors likely decreases stimulus-dependent Glu release through presynaptic receptors. The differential effects of the mGlu2/3 drugs in slices vs awake animals illustrate the importance of intact neural networks.

P67. BLOC-1 Complex Components Dysbindin (DTNBP1) and MUTED Modulate Dopamine D2 Receptor Endocytosis in Human Neuroblastoma Cells and Lymphoblasts

Yukihiko Iizuka, Yoshitatsu Sei, Daniel R. Weinberger, Richard E. Straub*

DTNBP1 has been shown in multiple studies to influence both cognition and risk for schizophrenia. DTNBP1 encodes dysbindin, which is a component of the biogenesis of lysosome-related organelles complex 1 (BLOC-1) which includes at least 7 other proteins (e.g. MUTED, BLOC1S2, SNAPAP). Dysbindin expression is reduced in brains from schizophrenic patients, but little is known about the BLOC-1 complex function in neurons. Dysregulation of dopaminergic neurotransmission is associated with multiple neurological and psychiatric conditions such as schizophrenia. An increased density of dopamine D2 receptors (DRD2) has been observed in some brain regions in schizophrenics and the therapeutic effect of antipsychotics may require antagonism of DRD2.

To examine whether BLOC-1 is involved in the maintenance of basal cell surface expression of DRD2, using flow cytometric analysis we studied the effects of DTNBP1 and MUTED siRNAs on surface DRD2 levels and also on dopamine-induced internalization of DRD2 in human SH-SY5Y neuroblastoma cells and lymphoblasts from schizophrenic patients and controls. DTNBP1 or MUTED siRNA transfection reduced dysbindin protein, increased surface expression of DRD2 and blocked dopamine-induced internalization of DRD2 in SH-SY5Y cells. We found that DRD2 is also upregulated in lymphoblasts by siRNA transfection. These results suggest that BLOC-1 may be involved in ligand-induced internalization of DRD2 as well as in the maintenance of basal levels. DTNBP1 risk haplotypes contribute to the reduction in dysbindin observed in schizophrenia, and reduced dysbindin compromises BLOC-1 function, increasing levels of DRD2. Receptor upregulation may be an important mechanism by which genetic variation in DTNBP1 increases the risk for schizophrenia.

P68. EAE-induced CNS Inflammation Accelerates ALS-like Disease in the hmSOD Transgenic Rat Model

B. T. Harris, K. K. Bercury, D. J. Graber, T. S. Davidson, R. M. van Hoff, W. F. Hickey*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with no effective therapy in which the degeneration of motor neurons results in atrophy of most muscles, leading to death within several years.

Transgenic rats that over-express the human mutant form of superoxide dismutase (hmSODG93A), found in some familial cases of ALS, are a relatively new animal model of this disease. These animals show progressive weight loss as well as hind and forelimb paralysis from about at several months of age. In order to determine if inflammation in the spinal cord would alter SOD-related paralysis, we induced experimental autoimmune encephalomyelitis (EAE) in this animal model. This is an inflammatory and sometimes demyelinating condition of the spinal cord, often used as an animal model of multiple sclerosis (MS). SOD transgenic animals that had mild and self-limiting EAE developed more rapid weight loss and earlier onset of paralysis compared to SOD animals without EAE induction. In addition, SOD transgenic animals were more susceptible to EAE induction and had increased severity of EAE symptoms. Immunohistochemistry and RT-PCR was performed on spinal cord tissues from control and experimental animals to compare the expression of several inflammatory cytokines and glial markers of activation. The data show that early, pre-symptomatic induction of inflammation in the central nervous system of SOD transgenic animals accelerates the course of ALS-like symptoms.

P69. Short-Term Limb Immobilization Produces Behavioral and Cortical Plastic Changes in Normal Subjects.

M. Felice Ghilardi*, Clara Moisello, Reto Huber, Fortunato Battaglia, Giulio Tononi

Immobilization studies focused on long-term (more than two weeks) effects. Effects of short-term (less than 24 hours) immobilization have not been studied. Here we study the changes induced by short-term limb immobilization. Motor performance was assessed in twenty-five healthy subjects before and after a period of either 6 or 12 hours of immobilization of the Left elbow joint. The motor task consisted in moving a cursor on a digitizing tablet to reach with out-and-back motions for targets appearing on a computer screen. In a subset of subjects we also recorded somatosensory evoked potentials (SEP), motor evoked potential (MEP) before and after 12 hours of immobilization and sleep after 12 hours of immobilization. Only after 12 hour of immobilization, the hand starting position drifted significantly in the course of the motor task. We also found significant increases in the movement normalized area and in the timing of inter-joint coordination. After 12 hours of immobilization, we also found changes in the amplitude of cortical SEP and MEP. The SEP changes were significantly correlated with the increases in movement areas. Slow wave activity during sleep locally increased over the sensori-

motor cortex contralateral to the immobilized limb. These results suggest that limb disuse, even for a short period of time, produces plastic changes in cortical plasticity, which results in modifications of limb kinematics and dynamics.

P70. Spinal Cord Injury Is Followed by Gene Expression Changes in the Rat Hippocampus

Nicole C. Berchtold, Monica M. Siegenthaler, Hans S. Keirstead, Carl W. Cotman*

Spinal cord injury (SCI) is characterized by an initial mechanical trauma, followed by secondary events that exacerbate damage to the spinal cord. While the molecular, biochemical, and gene changes that occur in the injury epicenter have been well-characterized, little is known about changes occurring in the brain following SCI. To address this, Affymetrix high density oligonucleotide arrays were used to profile gene responses in the rat hippocampus at 1 and 6 weeks following a moderate contusion injury to T-9. Data were filtered to remove unannotated probe sets and those called 'absent' in >50% of the chips, reducing the 31,000 probe sets to 7,338 probe sets. Expression values were calculated using 3 different algorithms (dChip, RMA, and GC-RMA), and t-test comparison ($p<0.01$) of uninjured vs injured animals identified genes that showed consistently altered expression after SCI. The 3 methods of analysis produced gene lists with varying degrees of overlap, with 98 genes identified by all of the analysis methods as significantly altered. Data mining based on GO annotation revealed functional categories of genes that were significantly overrepresented among these 98 genes. Notably, plasticity-related function (synaptic transmission, glutamate signaling), intracellular signaling cascades, and genes regulating neurogenesis and neurite morphogenesis showed altered expression, with the majority showing decreased expression. The classes of genes that responded suggest that SCI may have long-lasting effects on hippocampal plasticity, physiology and function.

P71. PTEN-induced Protein Kinase, PINK1: Cellular and Subcellular Localization, its Interacting Molecules and Possible Function

M. Shimoji, C. Xie, H. Shim, M. P. vanderBrug, A. G. Beilina, H. Cai*

Parkinson's Disease (PD) is the second most common progressive neurodegenerative disorder affecting approximately 1 % of the population over age 50. A hallmark feature of PD pathology is the relatively selective loss of nigrostriatal dopminergic neurons often accompanied with inclusion

bodies. The molecular mechanisms underlying the pathogenesis of PD are not understood. While majority of PD is idiopathic, genetic studies identified six familial forms of PD. Recessive gene mutations of PTEN induced protein kinase 1 (PINK1) have been linked to an autosomal recessive early onset PD. The mechanisms how these mutations cause PD are not understood. PINK1 cDNA encodes 581 amino acid protein with a predicted molecular mass of 62.8 kDa. PINK1 has mitochondrial localization signal peptide at its N-terminus, and has a putative catalytic domain with high degree of homology to serine/threonine protein kinase. Most of PINK1 gene mutations identified occur within this putative protein kinase catalytic domain. Biochemical function of PINK1 or its substrate molecules have not been characterized. Although PINK1 cellular localization has been reported to be at mitochondria in vitro, the endogenous PINK1 localization has not been documented. To clarify PINK1 function and understand its role in PD etiology, we have documented endogenous PINK1 localization at cellular and subcellular levels in cell line and mouse tissues. We have found that endogenous PINK1 expression is not limited to mitochondria only, but also other subcellular fractions and post-synaptic density area. This finding may shed a light on understanding function of PINK1 and its role in the PD pathogenesis.

P72. GABA Spillover to Extrasynaptic GABAA Receptors: A Major Component of Inhibition during Conditions of Synchronous Transmitter Release

*David E. Naylor**

While postsynaptic GABAA receptors mediate phasic inhibitory currents in hippocampal granule cells, extrasynaptic GABAA receptors containing delta subunits are responsible for tonic inhibitory currents. It is uncertain how much GABA transmitter spillover from the site of synaptic release to adjacent areas contributes to GABAergic inhibition and how important such spillover is in mediating cross-talk between neighboring sites. To explore the role of transmitter spillover to extrasynaptic GABAA receptors, we used measurements of miniature inhibitory postsynaptic currents and tonic currents to develop kinetic models of synaptic and extrasynaptic GABAA receptors, respectively. The differences in receptor kinetics and location of the two GABAA receptor subtypes was then used to estimate the spatiotemporal profile of GABA transmitter concentrations at synaptic and extrasynaptic locations. Under conditions of vigorous transmitter release, we found that approximately 4 delta subunit-containing extrasynaptic receptors per synapse and 36 postsynaptic receptors per synapse contribute to inhibitory responses. Despite

their smaller number, the perisynaptic delta subunit-containing GABAA receptors have a higher GABA binding affinity without desensitization that allows them to be activated by low concentrations of GABA that diffuse from synapses. Consequently, they can account for up to 60% of the charge transfer of an evoked inhibitory response. In addition, our results suggest that, compared to extrasynaptic receptors, diffusion to other GABAergic synapses is unlikely to make a significant contribution to inhibition. The augmentation of inhibition that occurs with spillover to extrasynaptic receptors may be important during conditions of high-level synchronous transmitter release, including pathological states of seizures and status epilepticus.

P73. There Is No Spoon—The Misrepresentations of Association Cortex

*Ralph M. Siegel**

One key principle in understandings the function of cerebral cortex is the cortical map. A map is an orderly progression of features across the physical extent of the cortical surface. This principle arises from the orderly impact of the external world on our sensorium. The visual system has a mapping of the retina. Other examples are the natural mapping of skin to physical location on our body and tonotopy in the auditory cochlea.

The manner by which light, touch and sound reach strike our sensorium is certainly constant. Physiologists and neurologists concluded that the internal cortical map corresponding to the external world is also constant, except perhaps under injury. This conclusion is supported by extensive modern imaging and electrophysiological studies in primary visual cortex. By default this principle of a static primary sensory map is believed to extend to association cortices.

Optical recording data from the inferior parietal lobule do not support that conclusion. Single unit recordings, maps of eye position, optic flow, and attention can change over time. A summary of evidence from these areas will be presented. What really matters is not what is outside, but what is inside the animal's head. What really matters is not the static map, but the functions that are constructed by the complex neuronal machinery. Anatomy does not dictate function.

These results dictate a radical new approach for understanding and modeling cortical function. The outlines of a new paradigm to model cortex will be presented.

P74. Ventral Hippocampal Inputs to the Amygdala and the Prefrontal Cortex Have Dissociable Roles in Emotional Learning

Witold J. Lipski, Anthony A. Grace*

The ventral hippocampal formation (vHPC) is reciprocally connected with the basolateral nucleus of the amygdala (BLA), as well as with the prefrontal cortex (PFC), areas which encode emotional memories. It is generally believed that the hippocampus processes episodic events, which are then stored elsewhere, according to context. However, it is not known how the interaction between the vHPC, the BLA and the PFC may be involved in emotional learning. To investigate the changes in plasticity that occur in vHPC output pathways, we induced LTP in the BLA and PFC of anesthetized in rats following Pavlovian fear conditioning to a contextual cue. LTP was induced by applying tetanic stimulation to the vHPC. We found that Pavlovian fear conditioning has dissociable effects on LTP induction in the BLA and the PFC. Conditioning resulted in reduced BLA LTP compared with naïve animals. This result suggests that the vHPC-BLA pathway is potentiated as a result of fear conditioning, which occludes vHPC-BLA LTP induced via HFS. Conversely, contextual fear conditioning resulted in enhanced PFC LTP compared with control animals. This finding suggests that the vHPC-PFC pathway is depressed during fear conditioning, which enhances subsequent potentiation induced via HFS. Taken together, these findings support the conclusion that contextual information processed in the vHPC is incorporated into the BLA and PFC via modification of synaptic connections with these regions. The hippocampal formation thus plays an important role in the assignment of emotional relevance to specific stimuli based on context.

P75. Nucleus Accumbens Injection of MT-II in Mice Decreases Food Intake

A. L. Sharpe, M. J. Low*

The proopiomelanocortin (POMC) containing neurons in the arcuate nucleus of the hypothalamus are involved in regulation of feeding and energy homeostasis. POMC neurons project to many areas of the brain including the nucleus accumbens (NAc), which is critical to reward related processes. Melanocortin 4 receptors (MC4) are expressed in the NAc, but it is unknown whether melanocortin peptides mediate any aspect of energy balance at this site. We injected melanotan-II (MT-II), an MC3/MC4 agonist, into the NAc of male C57BL6/J mice and assessed the effect on food consumption using both homecage and operant pro-

cedures. In the homecage study the mice were injected with 0, 0.1, 0.3 and 1 nmol MT-II/side following 16-h food restriction, while mice in the operant study were maintained on a fixed ratio 30 for each 20 mg food pellet and were injected with 0 and 0.3 nmol MT-II/side 1 hour before the beginning of lights out. In both studies, the amount of food consumed was measured 1, 2, 4, 6 and 24 hours after microinjection. MT-II significantly reduced the amount of food consumed in both the homecage and the operant studies when compared to vehicle, with a return to baseline food intake at 24-h. Results from the operant procedure indicated that MT-II decreased both the size and the frequency of meals in the first 3-4 hours. These data suggest that activity at MC4 receptors in the nucleus accumbens is sufficient to regulate feeding.

P76. Ketone Bodies Decrease Hyperexcitability in Acute Hippocampal Slices from Kcna1-null Mice

Timothy Simeone, Kristina Fenoglio, Heather Milligan, Jong Rho*

The Kcna1 gene encodes the delayed-rectifier voltage-gated potassium channel alpha subunit protein, Kv1.1. Kcna1-null mice exhibit frequent recurrent spontaneous seizures by P21-28. A previous study found increased CA3 hippocampal excitability only in response to provocation; however, no clear electrophysiological alterations were identified to explain the frequent epileptic seizures and interictal epileptiform activity observed in vivo. To determine whether acute hippocampal slices exhibit evidence of hyperexcitability, we employed a novel planar multielectrode array recording system (Panasonic MED64) to record network activity and responses to ketone bodies (substrates produced in blood of humans or animals fed a high-fat ketogenic diet—an effective nonpharmacological treatment for medically refractory epilepsy). Spontaneous interictal epileptiform-like activity was evident in each slice from null mice. The interictal events propagated from the dentate gyrus through CA3 to CA1 on millisecond time scales, and occurred at a frequency of ~1-2 Hz. Paired-pulse facilitation in CA1 in response to Schaffer collateral stimulation appeared normal. Application of ketone bodies to Kcna1-null slices reduced the interictal activity by ~20%. Conversely, ketones had no effect on I-O curves or paired pulse facilitation. Co-application of CNQX and D-AP5 eliminated all epileptiform activity. Using a unique microelectrode array, we demonstrate for the first time that Kcna1-null hippocampal slices are intrinsically hyperexcitable. Furthermore, our data support the hypothesis that ketone bodies may be in part responsible for the clinical efficacy of the ketogenic diet.

P77. The Ketogenic Diet Is Neuroprotective and Reduces Mitochondrial Oxidative Damage in Mouse Models of Acute and Chronic Seizures

Heather Milligan, Timothy Simeone, Kristina Fenoglio, Patrick Sullivan, Jong Rho*

The ketogenic diet (KD) is an effective treatment for medically refractory epilepsy, but the anticonvulsant mechanisms remain largely unknown. Here, we focused on examining the effects of the KD on neuronal and mitochondrial damage following acute and chronic seizures. Kainic-acid (KA) was used to induce acute seizures and chronic seizures were examined in Kcna1-null mice (a potassium channel deletion which causes mice to have recurrent, spontaneous limbic-like seizures). Adult wild-type mice maintained on the ketogenic diet for 10-12 days were compared to those on the standard diet. Even though diet did not influence the cumulative behavioral seizure scores (Racine scale), KD protected mice against neuronal damage in the CA1 hippocampal region (Fluoro-Jade B) and mitochondrial oxidative damage (lipid peroxidation, protein oxidation and protein nitration) 72h after KA-induced acute seizures. In the chronic seizure model, the KD increased the life-span of Kcna1-null mice from ~P45 to ~P66 indicating possible neuroprotective effects. KD-treated null mice had fewer limbic seizures per day and lower overall behavioral seizure scores. In addition, these mice had reduced mitochondrial oxidative damage. These data support a mitochondrial site of action for the KD, either by enhancing mitochondrial capacity to withstand the high-energy demand caused by seizures or assisting in the reduction of mitochondrial oxidative damage.

P78. A Multi-Electrode Array Investigation of Intrinsically Epileptic Human Hypothalamic Hamartoma Tissue

Kristina Fenoglio, Timothy Simeone, Heather Milligan, Harold Rekate, John Kerrigan, Jong Rho*

The human hypothalamic hamartoma (HH) is a developmental malformation that is intrinsically epileptogenic. Even though HH represents one of the best characterized human models for subcortical epilepsy, the mechanisms underlying its epileptogenicity remain unknown. In this study, the network properties of surgically-resected HH tissue were examined using a planar multi-electrode array recording system. HH tissue was placed on an 8x8 electrode array and perfused with oxygenated aCSF. We found that spontaneous field potentials (5-300mV) and single unit firing of individual cells (ranging from 1-14 Hz) were detectable

throughout the HH tissue. Application of the $GABA_A$ receptor agonist muscimol (30μM) reduced the spontaneous single unit discharges and increased the frequency of the field potentials. Conversely, the $GABA_A$ receptor blocker picrotoxin (100μM) increased and decreased spontaneous single units and field potentials, respectively. Paired-pulse stimulation of specific electrodes evoked local field potentials and single units in several neighboring electrodes. A 5-20% paired-pulse depression of the field potentials evident under normal aCSF conditions was converted to a similar magnitude of paired-pulse facilitation after administration of picrotoxin, whereas all evoked responses were eliminated with muscimol. These data elucidate the novel finding that populations of neurons within HH tissue give rise to spontaneous synchronous and asynchronous slow wave discharges and that both spontaneous and evoked network activity are strongly modulated by $GABA_A$ receptor-mediated mechanisms.

P79. The Equlibruim of GAT1 Helps to Determine the Level of Tonic Inhibition

George Richerson, Yuanming Wu, Wengang Wang, Ana Diez-Sampedro*

GABA transporters take up synaptically released GABA, but they can also reverse. Theoretical considerations and indirect evidence suggest that reversal should occur at conditions near physiological. Here we tested this possibility directly using a novel functional assay of heterologously expressed GAT1. One set of CHO cells ("GAT1 cells") was transfected with cDNA for rat GAT1. A second set of CHO cells ("sniffer cells") was transfected with cDNA for GABAA receptors. Whole-cell patch clamp recordings were made from sniffer cells that were then lifted off the substrate and closely apposed to GAT1 cells to assay GABA release. Whole-cell patch clamp recordings from GAT1 cells were used to measure the minimum voltage at which GABAA receptor activation occurred in the sniffer cell (i.e. the reversal potential), while systematically changing the transmembrane gradients for Na+, Cl and GABA in the GAT1 cell. The membrane potential at which GABA release occurred closely approximated the calculated reversal potential for GAT1 assuming coupled translocation of two Na+ ions, one Cl- ion and one GABA molecule per thermodynamic reaction cycle. For example, under near physiological conditions GABA release occurred when GAT1 cells were voltage clamped at potentials above the calculated reversal potential for GAT1 of 71 mV. We conclude that GABA transporters control the level of tonic inhibition, sometimes by reversing, and at other times by establishing a relatively high floor level for ambient [GABA].

P80. Encoding of "Value" by Mesolimbic Dopamine Reflects Benefits but not Costs of Future Rewards

Jerylin O. Gan, Michael L. Lee, Sheena D. Barnes, Scott B. Evans, Mark E. Walton, Paul E. M. Phillips*

Though we continuously gather information to guide decisions and choices, the mechanisms by which the brain assesses costs and benefits are yet unknown. Mounting evidence indicates that dopamine may contribute to this mechanism. Dopamine neurons are phasically activated on presentation of reward-predicting cues and encode (average) expected reward. Systemic dopamine antagonism causes rats to be less tolerant of time delays to gain larger rewards. Also, dopamine depletion or antagonism in the nucleus accumbens decreases the effort rats are willing to put forth for larger rewards. Combined, these data suggest that one role of dopamine transmission is to use predictive information about pending reward magnitudes to generate appropriate thresholds for overcoming response costs to obtain these rewards. To test this hypothesis, we established a series of operant decision-making tasks in rats assessing cost-benefit analysis while measuring subsecond dopamine transmission in the nucleus accumbens core using fast-scan cyclic voltammetry. Trained animals exhibited robust and predictable behavior when single reward options or concurrent choices were available. Rats consistently chose the lever yielding the larger bounty when the response requirement was equal. Likewise, rats chose the option requiring fewer lever presses when the reward was equal. In these animals, the amplitude of subsecond dopamine release in the nucleus accumbens tracked reward magnitude but was not modified by the response requirement. Thus, dopamine in the nucleus accumbens core encodes the expected reward value rather than net utility after modulation by response costs, providing a useful signal for generating appropriate cost thresholds for response.

P81. Modulation of Anterior Cingulate Cortical Activity Associated with Sacral Nerve Root Stimulation for Treating Urogenital Distress

Daniel H.S. Silverman, Nasim Zabihi, Cheri L. Geist, Veronica Triaca, Christian Twiss, Shlomo Raz, Larissa V. Rodriguez*

Sacral neuromodulation has been successfully utilized in the treatment of a variety of urogenital distress syndromes, but the neurologic basis of its effects remains unknown.

Methods: At least six months after surgical implantation of neuromodulation devices designed to deliver electrical stimulation to sacral nerve

roots, six subjects underwent eight brain PET scans each, following administration of 555 MBq (15 mCi) [O-15]water. PET data were spatially transformed to MNI template space using the software package SPM2, and examined using statistical parametric mapping methods of analysis to assess for significant changes in regional activity across four conditions—neuromodulation device off (O), expectation (E) of neuromodulation (but current actually set to zero), sacral neuromodulation of sufficiently high (H) intensity to result in patient sensations, and sacral neuromodulation at a lower (L) threshold resulting in no detectable sensations to the patient—with each condition presented twice in counterbalanced fashion, to control for order effects.

Results: After statistical correction for multiple comparisons for the brain regions examined, it was found that high-intensity sacral neuromodulation was associated with significantly decreased activity in left dorsal anterior cingulate cortex, relative to both the off and expectation control conditions (at peak voxel, $t=4.14, p<0.0005$ for H-O comparison; $t=3.47, p<0.001$ for H-E comparison), while no significant modulation of activity in this area occurred during low-intensity modulation relative to either control condition. Concurrently, sacral neuromodulation was associated with significantly increased activity in right perigenual anterior cingulate cortex relative to the no-modulation control ($t=3.36, p<0.002$ for H-O; $t=2.86, p=0.005$ for L-O).

Conclusions: Sacral neuromodulation in patients suffering from urogenital distress syndromes was associated with decreased activity in the dorsal anterior cingulate cortex (a region of the brain which has been specifically linked with perception of painful somatic stimuli), and concurrently increased activity in the perigenual anterior cingulate cortex (a region of the brain which has been specifically linked with descending pain inhibitory central mechanisms in perception of viscerosensory stimuli).

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