39th

Winter Conference on Brain Research

January 21–28, 2006 • Steamboat Springs, Colorado

Office of Continuing Education
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN
Toll free 877-455-2687 • www.conted.uiuc.edu

Welcome to the Thirty-Ninth Annual Winter Conference on Brain Research

The Winter Conference on Brain Research (WCBR) was founded in 1968 to promote free exchange of information and ideas within neuroscience. It was the intent of the founders that both formal and informal interactions would occur between clinical and laboratory-based neuroscientists. During the past 38 years, neuroscience has grown and expanded to include many new fields and methodologies. This diversity is also reflected by WCBR participants and in our program. A primary goal of the WCBR is to enable participants to learn about the current status of areas of neuroscience other than their own. Another objective is to provide a vehicle for scientists with common interests to discuss current issues in an informal setting. On the other hand, WCBR is not designed for presentations limited to communicating the latest data to a small group of specialists; this is best done at national society meetings.

The program includes panels (reviews for an audience not necessarily familiar with the area presented), workshops (informal discussions of current issues and data), and a number of posters. The annual conference lecture will be presented at the Sunday breakfast on January 22. Our guest speaker will be Dr. Thomas R. Insel, Director, NIMH/NIH. The title of his talk will be "From the Decade of the Brain to the Decade of Translation." On Tuesday, January 24, a town meeting will be held for the Steamboat Springs community, at which Dr. Kristen Anstrom, Wake Forest University, will give a talk entitled "The Effects of Exercise on the Brain." Also, throughout the week, participants in the WCBR School Outreach Program will present sessions at local schools to pique students' interest in science. Finally, the banquet, including a special program, music, and dancing, will be held on Friday evening, January 27.

Please plan to attend the business meeting at 6:30 PM on Wednesday, January 25. We will elect a Facilities Chair Elect, Program Chair Elect and three members of the Board of Directors. Other input matters will be discussed, including the selection of future sites.

Conference Chair
Elizabeth Abercrombie

Contents

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Exhibits

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Town Meeting

Kristen Anstrom

2006 Fellowship Awardees

Veronique Andre
Cecile Beguin
Marianne Benoit-Marand
Stephanie Borglund
Katherine Burdick
Roberta Calzavara
Joseph Cheer
Horacio de la Iglesia
Sharon Eastwood
Monica Gonzalez
Yukiori Goto
Jeff Grimm
Amanda Jayne Law
Francis Lee
Michael McManus
Holly Moore
Saleem Nicola
Vinay Parikah
Peter Penzes
Jonathon Sabat

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Jakie McGinty
Patricio O'Donnell
Stafford Lightman
Joel Kleinman
Robert Schwarcz
Aldo Badiani
Paul Micevych
Barbara Lipska
Jill Becker
Kuei-Yuan Tseng
Barry Levin
Daniel Weinberger
Fulton Crews
Paul Mermelstein
Janet Finlay
Leslie Morrow
James Joseph
Peter Ruben
Daniel Geschwind

Conference Arrangements

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Exhibitors

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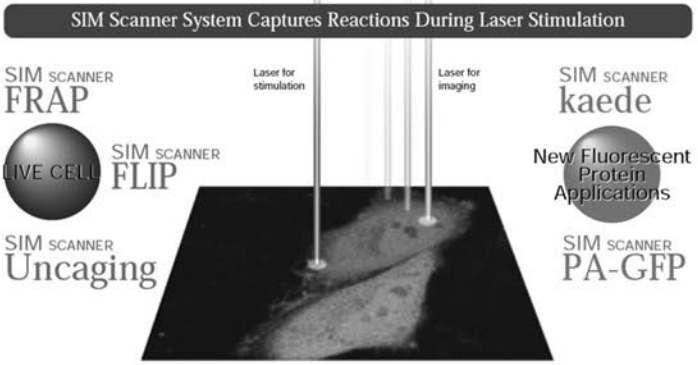
FluoView™ 1000 Confocal Microscope

The Olympus FluoView FV1000 is a next-generation imaging system designed for high-resolution, confocal observation of both fixed and living cells. The FV1000 offers advances in confocal system performance while providing the speed and sensitivity required for live cell imaging with minimal risk of damage to living specimens. In addition, the FV1000 offers a revolutionary synchronized laser scanning system.

The SIM Scanner:

The FV1000 incorporates 2 laser scanners in a single compact design for simultaneous confocal fluorescence observation and independent laser light stimulation. Synchronization of these two functions ensures that cellular reactions that occur during or immediately following stimulation are not overlooked, and makes the FV1000 the most suitable microscope for FRAP, FLIP and photo activation.



Spectral Scan System:

- Two independent spectral detection channels, each configured with a diffraction grating and variable slit enable high-resolution spectral fluorescence detection in increments as low as 1nm and wavelength resolution of 2nm.
- Accurate spectral unmixing of overlapping fluorescence emission signals can be performed using either of two modes, Normal and Blind
- High-speed spectroscopy can be performed at 1msec/100nm.
- Variable bandwidth selection is available for each spectral PMT channel through simple adjustment of each variable slit. Fluorescence detection and spectral separation can be maximized for each channel through adjustment of the variable bandwidth to match the fluorochrome's peak emission.

High Sensitivity:

- High-sensitivity PMTs, selected for high efficiency, can be used in either an Analog Accumulation mode or in a Hybrid Photon Counting Mode for low light specimens. A newly designed, high-sensitivity detection system provides efficient fluorescence detection, important for low laser conditions that minimize damage to living cells.
- Ion deposition filters are employed for increased sensitivity and wavelength coverage.
- With high signal-to-noise detection, the system excels in quantitation and photometric analysis of low-light recordings while minimizing cell damage.

High Precision and High Speed:

- Precise control of laser intensity via an advanced laser feedback system provides stable laser excitation throughout the time course of live cell studies, a necessary feature for accurate fluorescence quantitation.
- High-speed imaging at 16 frames per second.

General Information

Headquarters is the Sheraton Steamboat Resort and 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 1/21	9:00–11:00 AM	3:30–5:30 PM	6:30–10:00 PM
Sunday 1/22	7:00–8:00 AM	3:30–6:30 PM	
Monday 1/23–Friday 1/27	7:00–8:00 AM	3:30–4:30 PM	

The telephone number for messages is 970-871-6404 Ext 1103.

Registration packets containing a conference badge, registration receipt, tickets for breakfasts, mid-week lunch and 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 two different sessions during the week in Sunshine Peak: Poster Session 1, Sunday–Tuesday and Poster Session 2, Wednesday–Friday. Poster presenters will be by their posters for discussion from 3:30–4:30 PM according to the schedule listed on pages 22–26. Presenters may put up their posters after 1:00 PM on the day their session starts. Presenters should take down their posters by 10:00 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 Sunshine Peak. Coffee is available there from 9:30–10:30 AM Monday through Friday. Refreshments are provided 3:30–4:30 PM, Sunday through Friday. 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 Grand Ballroom, and on Monday through Friday, 6:30–7:30 AM, in 3 Saddles. (Social guests wishing to have breakfast between 7:30 and 10:00 AM may do so in Seven's restaurant immediately adjacent to 3 Saddles.) The tickets in your registration packet are required for admission. On Saturday morning (January 28) before departure, a continental breakfast is available in the Foyer.

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 21

Welcome Wine and Cheese Party • 7:00–10:00 PM, Grand Ballroom

Sunday, January 22

Conference Breakfast and Opening Address • 7:30 AM, Grand Ballroom (Your required ticket is in your registration packet.) The plenary keynote speaker will Dr. Thomas R. Insel, Director, NIMH/NIH

From the Decade of the Brain to the Decade of Translation • Thomas R. Insel, MD, NIMH, Bethesda, MD • Like the proverbial kid in the candy store, we are now in a period of spectacular scientific opportunity but we have only a nickel when we need a dime. While the NIH budget doubled between 1998 and 2003, both the costs of brain diseases and the costs of doing basic and clinical neuroscience are rising much faster than our current budget. How do we use our nickel to give the public the discoveries that improve human health? This lecture will describe three approaches: a focus on translation, partnerships across the neuroscience institutes, and specific support for innovation. At NIMH, much of this next decade will be devoted to translating the discovery power of neuroscience to improve the diagnosis and treatment of mental disorders. Partnerships, such as the Neuroscience Blueprint, will be essential to support new efforts, including the development of new technologies as well as an inter-disciplinary workforce. Innovation is often the first victim of tight budgets, but with careful planning and dedicated funds, support for innovative science can be preserved through a season of flat budgets. While translation, partnerships, and innovation may not turn a nickel into a dime, they should ensure that neuroscience research supported by NIH continues to help people with brain disorders.

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

Monday, January 23

First Meeting of the Board of Directors • 6:30–8:30 AM, Aspen Room

Tuesday, January 24

Town Meeting • 7:00 PM, Steamboat Springs Middle School, Steamboat Springs, CO

Wednesday, January 25

Travel Fellows and Mentors Breakfast • 6:30–7:30 AM

Smitty Stevens Memorial (NASTAR) Ski Race • 1:30–2:30 PM, Bashor NASTAR Course. NASTAR registration cards to be completed no later than Monday, January 23, 8:00 AM at WCBR Information Desk.

Mountain Lunch • 11:00 AM–1:00 PM, Bear River Bar and Grill at base of gondola. Required lunch ticket is in your registration packet.

Business Meeting • 6:30 PM, Mt. Werner
Election of Program Chair-elect, Facilites Chair-elect, and three members of the Board of Directors.

Friday, January 27

Second Meeting of the Board of Directors • 6:30–7:30 AM, Aspen Board Room

Banquet and Dance • 7:30 PM, Grand Ballroom
Required ticket is in your registration packet. Cash bar opens at 6:30 PM in the Ballroom Lobby.

Preamble to the Program

The 2006 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 22

7:30 AM

Plenary Breakfast • Grand Ballroom

From the Decade of the Brain to the Decade of Translation

Dr. Thomas R. Insel, Director, NIMH/NIH

3:30–4:30 PM

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM

Panel • Storm Peak

Steroids, Polyglutamine Toxicity, and Motor Neuron Degeneration

Diane Merry, Andrew Lieberman, Angelo Poletti, Marc Diamond

Panel • Twilight

Black Diamond (a.k.a Brain-Derived) Neurotrophic Factor: Skiing the Cortical Circuit

Beth-Anne Sieber, Kevin Jones, David Ginty, Luis Parada, Francis Lee

Panel • Rainbow

Genetics, Signalling, and Therapeutic Intervention through the GABAB Receptor

David Farb, Menelas Pangalos, Bernhard Bettler, David C.S. Roberts

Panel • Sunset

The Complexity of Monoaminergic Modulation of Neocortical Excitability

Marco Atzori, Kuei-Yuan Tseng, Alfredo Kirkwood, Zhen Yan

Panel • Skyline

As the Time Goes by: How the Brain Times Internal and External Events

Aldo Badiani, Deborah Harrington, Richard Ivry, Matthew Matell, Sean Hinton

Panel • Mt. Werner

Ischemia-induced Neuronal Death: New Channels and New Targets

R. Suzanne Zukin, Elizabeth Jonas, Roger Simon, Gabriel Haddad

8:30–10:00 PM

Panel • Twilight

Time Dependent Changes in Drug Seeking after Withdrawal: Cellular, Molecular, Systems, and Behavioral Aspects

Patricia Di Ciano, Yavin Shaham, Paul Vezina, Terry Robinson

Panel • Sunset

More Fats, Fewer Fits: The Ketogenic Diet in Epilepsy from Bedside to Bench

Maciej Gasior, Adam Hartman, Jong Rho, Kristopher Bough

Workshop • Mt. Werner

Dopamine Concentration Transients: What's the Point of Fast Dopamine Transmission?

Donita Robinson, Joseph Cheer, Saleem Nicola, Jeremy Seamans, Patricio O'Donnell

Sunday, January 22, continued

Panel • Storm Peak

Functional Properties of MicroRNAs in the Nervous System

Andrea C. Beckel-Mitchener, Kenneth S. Kosik, Wigard P. Kloosterman, Peng Jin, Michael T. McManus

Panel • Rainbow

A DISCourse on DISC

Barbara Lipska, Joseph Callicott, Akira Sawa, Nick Brandon

Panel • Skyline

Is Abnormal Phosphorylation a Common Pathway in Neurodegeneration?

David Miller, Karen Duff, Sashi Kesavapany, Mark Cookson

Monday, January 23

■ **7:30–9:30 AM**

Panel • Mt. Werner

Neuroprotective Strategies for Spinal Cord Injury: How Do We Get beyond Methylprednisolone?

Edward Hall, Lynne Weaver, Alan Faden, Scott Whittemore,

Panel • Storm Peak

Neurobiology and Clinical Pharmacology of Gammahydroxybutyrate: A Club Drug with Therapeutic Applications

Thomas Kilduff, Federica Latta, Jed Black, O. Carter Snead

Panel • Sunset

Imaging Genetics: From Genes to Brain

Daniel Weinberger, Katherine Burdick, Steven Potkin, Andreas Meyer-Lindenberg

Panel • Rainbow

Levitra for the Brain? Stronger and More Lasting Memories via PDE Inhibition

Donald Ingram, Greg Rose, James M. O'Donnell, Arjan Blokland

Panel • Twilight

Ubiquitination in Neuronal Development and Synaptic Transmission

Lian Li, Yishi Jin, Ashok Hedge, Scott Wilson

Panel • Skyline

Sensory Systems: From Receptors to Behaviors

Samer Hattar, Johannes Reisert, Jamie García-Añoveros, Ignacio Provencio, Steven Lockley

■ **3:30–4:30 PM**

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM

Panel • Mt. Werner

Potential Long-Term Effects of Psychostimulant Use in ADHD

George Ricaurte, Una McCann, Benedetto Vitiello, Susan Andersen

Panel • Storm Peak

Arriving Soon to a Clinic Near You: Personalized Psychopharmacology, Using Genes to Predict Drug Response

John Kelsoe, Anil Malhotra, Greer Murphy, Daniel Mueller

Panel • Twilight

The "Dark Side" of Aging: Cholinergic Signaling and Cognition

Donald Ingram, James Joseph, Nigel Grieg, Tetsuo Ashizawa

Panel • Rainbow

Obesity, Diabetes, and the Brain

Paul Huang, Sean Didion, David Busija, Barry Levin

Panel • Sunset

The Obsolete Cortical Module

Andrew Schwartz, Ralph Siegel, Robert Kass, Vivien Casagrande

Panel • Skyline

Role of AVP in Hypothalamo-Pituitary-Adrenal Activity

Stafford Lightman, Gabor Makara, Gilles Guillon, Greti Aguilera, Joe Herbert

8:30–10:00 PM

Panel • Mt. Werner

Extracellular Signal-Regulated Protein Kinase in Plasticity: To Pull up or To Slope Down?

Edda Thiels, Serena Dudek, Eric Klann, Arvind Govindarajan

Workshop • Storm Peak

Neurogenesis: Functions in Disease and Learning

Fritz Henn, Rene Hen, Fulton Crews, Karl Deisseroth

Workshop • Twilight

New Things Connexins Do

Michael Bennett, Vytautas Verselis, Bruce Ransom, Alberto Pereda

Panel • Rainbow

Modulation of Inflammatory Status in TgAPP Mice

Doug Feinstein, MaryJo Ladu, Steve Barger, David Morgan

Panel • Sunset

A Casualty of Neuroplasticity: The Changing Face of GABA(A) Receptors

Shelley Russek, Amy Brooks-Kayal, Warren Tourtelotte, Sheryl Smith

Panel • Skyline

New Light on the Nervous System: Applications of Ultrashort Laser Pulses

Kurt Ahrens, Michael Levene, Jeff Squier

Tuesday, January 24

7:30–9:30 AM

Panel• Mt. Werner

Novel Roles for Neuropeptides in CNS Function

James Tepper, Brian Hyland, Hagai Bergman, Jeff Wickens

Panel • Storm Peak

Cortical Dysplasia and Epilepsy in Human and Animal Models

Véronique André, Nada Zecevic, Carlos Cepeda, Steven Roper

Panel • Twilight

Glutamate and Schizophenia: It's the Endogenous Modulators, Stupid!

Carol Tamminga, Joseph Coyle, Robert Schwarcz, Laura Rowland

Panel • Rainbow

Autism Genetics: Neurobiology and Novel Approaches to Finding Genes

Daniel Geschwind, Jonathan Sebat, Christa Leese-Martin, Conrad Gilliam

Panel • Sunset

Trafficking of GABAA Receptors: Physiology and Pathology

Claude Wasterlain, Lorrena Aranciba, Richard Olsen, Bernhard Luscher

Panel • Skyline

What Do I Want and When Do I Want It: Temporal Regulation of Reward Processing in the VTA

Gary Aston-Jones, Alice Luo, Steven Henriksen, Jay Hirsh, Roy Wise, Scott Steffensen

3:30–4:30 PM

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM

Panel • Mt. Werner

Too Much or Too Little Dopamine in Neurological and Psychiatric Disorders

Michael Levine, Nigel Bamford, Nigel Maidment, Marjorie Ariano

Panel • Storm Peak

Receptor Trafficking and Synaptic Regulation

Katherine Roche, Graham Collingridge, Josef Kittler, Andres V. Maricq

Panel • Twilight

Schizophrenia: From Genes to Cortical Circuits

Daniel Weinberger, Amanda Law, Jeremy Seamans, Patricio O'Donnell

Panel • Rainbow

A Potpourri of Global Neuroscience Opportunities: or *Globus Brighticus Neuro-Unum*–One Bright Neural World

Kathie Olsen, Connie Atwell, Sharon Hrynkow, Nathaniel Pitts

Panel • Sunset

The Neuroinferno: Chronic Brain Inflammation

Susanna Rosi, Gary Wenk, Fulton Crews, Stanley Rapoport

Panel • Skyline

State Dependent Regulation of Sensory and Motor Network Operations: Role of Intrinsic Mechanisms and Extrinsic Neuromodulatory Systems

Barry Waterhouse, Manuel Castro-Alamancos, John Chapin, Craig Berridge, Gary Aston-Jones

■ **7:00 PM**

Town Meeting

■ **8:30–10:00 PM**

Panel • Rainbow

Risk Factors for Drug Abuse: Stress and the Sex of an Individual

Jill Becker, Yavin Shaham, Mary Heitzeg, Jon-Kar Zubieta

Workshop • Sunset

Glia—More than Putty

Vladimir Parpura, Wendy Macklin, Monica Carson, Douglas Fields

Workshop • Mt. Werner

What the Hell Is Parkinson's Disease?

Tim Greenamyre, Bob Burke, Heather Melrose, Dennis Dickson

Panel • Storm Peak

Central Brainstem Processing of Auditory Signals

Robert Fyffe, Ian Forsythe, Henrique von Gersdorff, Bruce Walmsley

Panel • Twilight

Modeling Schizophrenia—What's Lost in the Translation?

Janet Finlay, Nagalingam Rajakumar, Holly Moore, Craig Powell

Panel • Skyline

Mechanisms and Regulation of Metal Transport into the CNS

James Connor, Michael Aschner, Josh Dunaief, Michael Georgieff

Wednesday, January 25

■ **7:30–9:30 AM**

Panel • Mt. Werner

Does Dopamine Control Striatal Glutamate, The Other Way Around, or Both?

Patricio O'Donnell, Adrian Michael, David Sulzer, Marianne Benoit-Marand, Bryan Yamamoto

Panel • Storm Peak

Non-Homeostatic Control of Ingestion: Eating without Regard to the Body's Needs

Barry Levin, Wayne Pratt, Jeffrey Grimm, Dianne Lattemann

Panel • Twilight

Mechanisms of Structural Plasticity of Dendritic Spines

Peter Penzes, Michelle Day, Terry Robinson, Dezhi Liao

Panel • Rainbow

A Brain Divided against Itself Cannot Stand: The Importance of Teamwork Exemplified by the Neurovascular Unit

Dale Pelligrino, Sami Harik, Gregory Del Zoppo, Joseph LaManna

Wednesday, January 25, continued

Panel • Sunset

The Case against the Basal Ganglia as Primarily a Motor Structure

Suzanne Haber, Hagai Bergman, Christelle Baunez, Jacqueline McGinty

Panel • Skyline

Inner Retina Circuitry: Mechanisms Underlying Visual Processing

Maureen McCall, Laura Frishman, Jeffery Diamond, W. Rowland Taylor

■ **3:30–4:30 PM**

Exhibits and Posters • Sunshine Peak

■ **4:30-6:30 PM**

Panel • Mt. Werner

Protein Synthesis at the Synapse: It's Depressing

Oswald Steward, Kimberly Huber, Mark Bear, Bill Greenough

Panel • Storm Peak

Do Arrestins Limit or Enhance the Pleasure of Skiing?

Kim Neve, Louis Luttrell, David Sibley, Marc Caron

Panel • Twilight

Psychostimulant Exposure during Development: What and When Matter!

Heinz Steiner, Barry E. Kosofsky, Ellen M. Unterwald, Carlos A. Bolanos

Panel • Rainbow

Animal Models of Addiction Predict Human Behavior

Charles O'Brien, Conan Kornetsky, Laura Peoples, Friedbert Weiss

Panel • Sunset

Swelling, Shrinking, Living and Dying: Cell Volume Regulation in the Life and Death of Cells (or Does Size Really Matter?)

Elias Aizenman, Kevin Strange, John Cidlowski, Shan Ping Yu,

Panel • Skyline

Carving the Space–Time Continuum in the Developing Auditory System

Karl Kandler, Jeffrey Holt, Leonard Kaczmarek, Lu-Yang Wang, Gunsoo Kim

■ **6:30-7:30 PM**

Business Meeting and Elections • Mt. Werner

Don't forget to visit the exhibitors in Sunshine throughout the week.

Thursday, January 26

7:30–9:30 AM

Panel • Mt.Werner

Beyond Cheeseburgers and Sex: Treatment of Stroke and Neural Injury with Statins and Sildenafil

Michael Chopp, Matthias Endress, Zhenggang Zhang, Jieli Chen, Ruilan Zhang

Panel • Storm Peak

Neurodevelopment Disruption of Hippocampal–Prefrontal Cortical Synaptic Connectivity: Implications for Schizophrenia Pathophysiology

Kuei-Yuan Tseng, Barbara Lipska, Sharon Eastwood, Yukiori Goto

Panel • Twilight

AMPA Receptor Structure, Function, and Regulation

Stephen Traynelis, Anders Kristensen, Hiro Furukawa, Johannes Hell, Hailan Hu

Panel • Rainbow

Process guidance and pathfinding in the CNS: How do Oligodendrocyte Processes Find Their Way?

Babette Fuss, Rick Cohen, Holly Colognato, Vittorio Gallo

Panel • Sunset

Ins and Outs of Circadian Rhythms

Michael Iuvone, Robert Lucas, Susan Doyle, Gianluca Tosini, Carla Green

Panel • Skyline

What's New on the Inside?

G.F. Gebhart, Patrick Mantyh, Bradley Undem, Brian Davis

3:30–4:30 PM

Exhibits and Posters • Sunshine Peak

4:30–6:30 PM

Panel • Mt. Werner

The Light-Related Neurobiological Mechanism/s Altered in Psychiatric Disorders. How Does the Light Switch Turn Mood On and Off?

Monica Gonzalez, Horacio de la Iglesia, Laura Smale, Wallace Duncan

Panel • Storm Peak

The Alphas of Alpha-Synuclein in Neurodegeneration

Martha Bohn, Matthew Farrer, Jean-Christophe Rochet, Eric Richfield, Mohan Sapru

Panel • Twilight

Neuregulins and Related Genes in Schizophrenia

Joel Kleinman, Douglas Falls, Amanda Law, Thomas Hyde, Yoshitatsu Sei

Panel • Rainbow

Glycogen, Glucose and Lactate: A Complex Trio of Fuels for Neurons and their Synapses

Arne Schousboe, Bruce Ransom, Mary McKenna, Gulin Öz

Panel • Sunset

Lentiviral Vectors for Gene Therapy of the Diseased Brain

Luc Jasmin, Michael McManus, Stephanos Kyrkanides, Pedro Lowenstein

Panel • Skyline

Genetic Epilepsies: A New Window on a Complex Disease

William Catterall, Alan Goldin, Robert L. Macdonald, Mark Leppert, Martin Gallagher

■ 8:30–10:00 PM

Workshop • Storm Peak

Translational Neuroscience and Parkinsons Disease: Obstacles to Progress

Richard Beresford, Curt Freed, Don Gash, Evan Snyder, Karl Kieburtz

Panel • Mt. Werner

The Role of Lateral Hypothalamic Peptides in Reward

Stephanie Borgland, Gary Aston-Jones, Ralph DiLeone, Sharif Taha

Workshop • Twilight

Hallucinogens–Past, Present and Future.

John Mendelson, Gantt Galloway, William Fantegrossi, Reese Jones, Matthew Baggott

Workshop • Rainbow

Lipids as Overlooked Modulators of Neurodegeneration

Neville Marks, Luigi Puglielle, Alan Faden, Mark Mattson

Panel • Sunset

Terminator 4: Who Terminated the Nerve Fibers in Cutaneous and Gut Epithelia?

George Wilcox, William Kennedy, Frank Rice, Anne Louise Oaklander

Panel • Skyline

Executive Function and Schizophrenia

Roberta Calzavara, Mark D'Esposito, Francine Benes, Kent Kiehl

Friday, January 27

■ 7:30–9:30 AM

Panel • Mt. Werner

How Does Environment Modulate Psychostimulant-induced Behaviors?

Bruce Hope, Terry Robinson, Jennifer Bossert, Paul Vezina

Panel • Storm Peak

Interventions for Traumatic Brain Injury in Children

Kimberly Topp, Mayumi Prins, Matt Potts, Alpa Trivedi, Akiva Cohen

Panel • Twilight

Role of Astrocytic Signaling Systems in Neurophysiology and Pathology

Ken McCarthy, Phil Haydon, Brian MacVicar, Eric Newman

Panel • Rainbow

Losing Our Inhibitions: From Genes to Circuits in the Epileptic Brain

Jeff Noebels, Nick Poolos, Tom Sutula, Scott Baraban

Panel • Sunset

Pain: Trigeminal Neuralgia—The Clinical Mysteries, Therapeutic Dilemmas, and Functional MRI

Suzanne Roffler-Tarlov, Edward Tarlov, Carlos David, David Borsook

Panel • Skyline

Novel Regulators of Body Weight

Lloyd Fricker, Tamas Horvath, Mark Sleeman, Stephen Salton

■ **4:30–6:30 PM**

Panel • Mt.Werner

Psychostimulants, L-type Calcium Channels and the Yin and Yang of PKA Signaling in the Nucleus Accumbens

Chris Pierce, Paul Mermelstein, Heath Schmidt, Anjali Rajadhyaksha, Xiu-Ti Hu

Panel • Storm Peak

Molecular Mechanisms Regulating Kainate Receptor Function

John Isaac, Anis Contractor, Christophe Mulle, Geoff Swanson

Panel • Twilight

Molecular Mechanisms of Neuronal Pain Signals

Andrew Russo, Luda Diatchenko, John Quinn, Ian Dickerson, Lonny Levin

Panel • Rainbow

The Emerging Field of Cognitive Genomics: New Findings and Their Implications for Novel Treatments

Anil Malhotra, Tyrone Cannon, David Goldman, Michael Egan

Panel • Sunset

Novel Roles for Neuropeptides in CNS function

John Quinn, Liam Gray, Michael Kubek, Claude Wasterlain

Panel • Skyline

Outer Retina Circuitry and Signaling

Nick Brecha, Catherine Morgans, Steve Massey, Ron Gregg

■ **7:30 PM**

Banquet and Dance • Grand Ballroom

Poster Session 1

Sunday–Tuesday • Sunshine Peak

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

1. Modulation of Dopamine Release in Prefrontal Cortex and Striatum by GABAB Receptor Ligands

   Andrea Balla

2. Adult Human Oligondendrocytes Express Nos-3

   A.I. Boullerne

3. Expression of Schizophrenia Susceptibility Genes Across Age in the Normal Human Cerebral Cortex

   Carlo Colantuoni

4. Consensus Imaging: Emerging Methods for Coordinate-based, Voxel-wise Meta-analysis in Human Functional Brain Mapping

   Peter T. Fox

5. Spatial and Temporal Processing of Cortical Input by Ventral Striatal Spiny Neurons

   A.J. Gruber

6. Corticotropin-Releasing Factor Modulation of VTA Glutamatergic Currents After Chronic Cocaine Exposure.

   Junghyun Hahn

7. In Vivo Analysis of Dopamine Neurochemistry in Medial Prefrontal Cortex in R6/2 mouse model of Huntington's Disease

   Bahareh Hassanzadeh

9. Supramammillary Stimulation Evoked Dopaminergic Signals in the Ventral Striatum: A Fast-Scan Cyclic Voltammetry Study

   Satoshi Ikemoto

10. Effect of Aβ Structure and Human and apoE Isoform on Primary Co-Cultures of Neurons and Glia

    L. Jungbauer

11. Human Neural Stem Cell-and Embryonic Stem Cell-Derived Precursors as Replacement Therapies for Diseases of the Nervous System

    I. Nasonkin

12. Subtypes of Vagal Afferent C-fibers in Lungs and Esophagus in Guinea Pig

    M. Kollarik

13. VTA Positively Modulates Neurons in the Ventral Hippocampus.

    Witold J. Lipski

14. Ethanol Enhancement of Cocaine and Amphetamine-Regulated Peptide in the Rat Mesolimbic Dopamine System

    A. Salinas

15. Noradrenaline Protects Neurons Against Amyloid Beta and Microglial Induced Damage

    Jose LM Madrigal

16. Nucleus Accumbens Dopamine Controls Behavior Switching

    Saleem M. Nicola

17. Embryonic Exposure to Endocrine Disrupting Chemicals Impairs Male Sexual Behavior and Impacts Neuroendocrine Systems

    Mary Ann Ottinger

18. DOV 51,892, A Novel GABAA Receptor Modulator: Effects in Animal Models of Anxiety

    Piotr Popik

19. A Spatially Structured Network of Inhibitory and Excitatory Connections Directs Impulse Traffic Within the Lateral Amygdala

    Rachel D. Samson

20. Cell Proliferation in the Striatum during Postnatal Development

    R. E Stopczynski

21. The Effect of a Peptidergic Neuromodulation on the Frequency Dependent Property of Synapses and Pacemaker Neurons in an Oscillatory Network

    Vahid Tohidi

22. Over-expression of Neuronal Pentraxin 1 Reduces Neurite Outgrowth Before Cell Death in Human Neuroblastoma SH-SY5Y Cells

    A. Abad

23. Afferent Information Integration in the Nucleus Accumbens

    John Wolf

24. Adaptation of the Human VOR During Artificial Gravity

    Laurence Young

Poster Session 2

Wednesday–Friday • Sunshine Peak

Posters will be available for viewing from 3:30 PM Wednesday through 10:00 AM Friday. Presenters will be with posters on Thursday from 3:30–4:30 PM.

25. Potassium Leak Conductance Improves Performance in an Auditory Brainstem Nucleus

    Amy Berntson

26. Chronic Stress Alters BLA Neuronal responses to Norepinephrine and Afferent Input

    Deanne M. Buffalari

27. Expression of RGS4 mRNA Is Not Altered in Schizophrenia

    Mark M. Caruso

28. Administration of the NMDA Antagonist AP-5 Into the Nucleus Accumbens Shell Reinstates Cocaine-Seeking Behavior

    Katie R. Famous

29. Differences in Quality and Yield of RNA Obtained From Multiple Brain Regions of Normal Human Brain

    Robert J. Fatula

30. Estrogen and Progesterone Regulation of 5HT1A, 2A and 2C Receptor Proteins in the Dorsal Raphe Region of Female Macaques

    Jessica A. Henderson

31. Identification of a Novel Genetic Locus at 7q36.1 in Strong LD with Schizophrenia and the Differential Expression of the Flanking Genes, NOS3 and KCNH2

    Stephen J. Huffaker

32. Isoform Specific Expression of DTNBP1 (dysbindin), MUTED and Other BLOC-1 Genes in Lymphoblasts from Schizophrenics

    Yukihiko Iizuka

33. Association of Printor with Dystonia Protein torsinA on Endoplasmic Reticulum and Nuclear Envelope

    Lisa M. Imboden

34. Altered Na (+) Currents in Auditory Neurons of Congenitally Deaf Mice

    Richardson N. Leao

35. Apoptotic Gene Expression in Alzheimer's Disease

    David L. Marcus

36. Regulation and Function of Cortical High-Affinity Choline Transporters Measured in Vivo Using Choline-Sensitive Microelectrodes

    V. Parikh

37. DAT is Sufficient to Render Non-Dopaminergic Neurons Sensitive to 6-OHDA Toxicity

    Patrick T. Redman

38. Cue- Versus Cocaine-Induced Drug Craving and Reward: Topographic and 3-Dimension (VARETA) Imaging of Quantitative EEG in Humans.

    Malcolm S. Reid

39. Ketone Bodies Reverse Glutathione Depletion Induced by Glutamate and the Thiol Oxidant Diamide

    Jong Rho

40. Egr3 Stimulation of GABRA4 Promoter Activity as a Mechanism for Seizure-Induced Upregulation of GABA(A) Receptor α4 Subunit Expression

    D.S. Roberts

41. A Mutation Underlying Inheritable Epilepsy Affects Sodium Channel Slow Inactivation

    Margaret S. Dice

42. Hyperpolarization-Activated Cation Currents in Three Auditory Brainstem Nuclei

    Katarina Svahn

43. Effects of Mesocortical Projections on Prefrontal Cortical Pyramidal Neurons and Fast Spiking Interneurons

    Kathy Toreson

44. Potential Role of T-cells on Chronic Neuropathic Pain

    David Vasquez-Dunddel

45. Novel Treatment for Multiple Sclerosis Based Upon Apolipoprotein-E

    Michael P. Vitek

46. Cerebral Preconditioning Using Cortical Application of Hyperosmotic Salts: Effect on mRNA Levels Encoding Inflammatory Mediators and Trophic Factors

    K. Kariko

47. AMPA Receptor Potentiation Driven Through Glutamate Metabotropic 2/3 (mGlu2/3) Receptor Blockade: Antidepressant-Like Activity

    Jeffery M. Witkin

48. Naltrexone and Fluoxetine for Heroin Dependence Treatment in St. Petersburg, Russia

    George E. Woody, MD

49. Uncoupling Protein 2 (UCP-2) Regulates Expression of Immune Recognition Molecules in Neural Stem Cells.

    W. Michael Zawada

50. Chronic Stress-evoked Alterations of Noradrenergic Autoreceptor Function in Locus Coeruleus Neurons

    Hank P. Jedema

51. Delta9-THC Antagonizes Endogenous Cannabinoid Signaling in Autaptic Excitatory Hippocampal Neurons

    Alex Straiker

52. Correct Trials that Follow Errors Rely on a Subcortical Feedback Circuit

    Henry H. Holcomb

53. Sustained, 6 month Antiviral Benefits in HIV Patients Receiving Peptide T: Flushing of Cellular Reservoirs and Reduction of Plasma Viral Load

    Michael Ruff

Don't forget to visit the exhibitors in Sunshine throughout the week.

Poster Abstracts

Poster Session 1 • Sunday–Tuesday • Sunshine Peak

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

1. Modulation of Dopamine Release in Prefrontal Cortex and Striatum by GABAB Receptor Ligands

Andrea Balla, Megan Nattini, Henry Sershen, and Daniel C. Javitt

Nathan Kline Institute, Orangeburg, NY and New York University, NY

Deficits in NMDA receptor-mediated neurotransmission may underlie DAergic hyperactivity in schizophrenia. Both direct and indirect NMDA glycine-site agonists reverse PCP-induced potentiation of AMPH-stimulated DA release in striatum (STR), supporting a potentially psychotherapeutic role for these agents. Administration of glycine-site agonists in isolated striatum paradoxically inhibited, rather than potentiated, NMDA receptor-mediated neurotransmission, suggesting NMDA activity at two separate sites within the isolated striatal preparation: at NMDA receptors on presynaptic DA terminals from which it would initiate GABA release leading to secondary inhibition of presynaptic NMDA release. Thus, a potential mechanism whereby glycine-site agonists may influence DA release in prefrontal cortex (PFC) and STR is by stimulation of local GABA release, leading to reduced presynaptic DA from nigrostriatal or mesocortical DA terminals. The effects of GABAB ligands on prefrontal DA release have not been conclusively investigated. Local infusion of the GABAB agonist baclofen simultaneously into PFC and STR led to significant reduction in DA levels in both regions with effects being reversed by simultaneous infusion of the GABAB antagonist CGP52432. Further, a significant inhibition of AMPH-induced DA was found in PFC by locally applied baclofen. These studies provide the first demonstration that GABAB receptors may play a critical role in mediation of downstream effects of glycine-site agonists. These studies demonstrate interaction between NMDA and GABAB systems that can have a potential role in control of DA systems relative to positive symptoms and cognitive deficits in schizophrenia and drug abuse.

2. Adult Human Oligondendrocytes Express Nos-3

Boullerne A.I.[#], Dello-Russo C.##, Polak P.[#], Galea E.[§], Frim D.M.[§§], Arnason B.G.[§§] and Feinstein D[#].

[#] University of Illinois at Chicago, Illinois, US. [##]Catholic University del S. Cuore, Rome, Italy. [§] University Barcelona, Barcelona, Spain. [§§] University of Chicago, Illinois, US.

We present evidence of NOS-3 expression in primary cultures of oligodendrocytes (OLG) originating from different species. OLG isolated from subcortical white matter of drug-intractable epileptic patients and from white matter of baboon and rat brains were maintained in culture for several weeks until full maturation was reached. We observed the presence of NOS-3 by immunostaining in OLG at all stages of maturation from bipolar stage until mature stage, characterized by large membrane extensions expressing myelin proteins. A functional role for NOS-3 in OLG physiology was suggested by studies where cells were incubated for one week with the NOS-3 inhibitor L-NMMA. It induced a flattened cell body and marked changes of arborization in human and baboon OLG with much smoother and finer processes. In agreement with a role of NOS-3 in cytoskeletal structure, the pattern of globular actin changed following treatment with L-NMMA. NOS-3 was found to co-localize with caveolin-1 and cyclic nucleotide phosphodiesterase, suggesting it is present within the specialized raft domains of the plasma membrane. Our results raise the possibility that regulation of NOS-3 could modulate OLG structure and function during development and pathology

3. Expression of Schizophrenia Susceptibility Genes across Age in the Normal Human Cerebral Cortex

Carlo Colantuoni, Thomas Hyde, Shruti Mitkuss, Leah Sartorius, Claudia Aguirre, Johanna Creswell, Elizabeth Johnson, Barbara Lipska, Daniel Weinberger, and Joel Kleinman

We have used custom Illumina cDNA microarrays in addition to quantitative PCR in order to investigate the expression of several schizophrenia susceptibility genes in the normal human brain. A list of genes potentially involved in the molecular pathology of schizophrenia was assembled from a comprehensive literature review. Expression of each of these genes was measured in the frontal cortex (BA10) of individuals without history of neuropsychiatric illness, neurological disease, or drug use. This study examines gene expression in nearly one hundred postmortem control cases spanning half a century of human aging (ages 18-67 years). The expression of several of the genes investigated appears to be part of the normal, gradual

molecular aging process: The expression of GRM3 and RGS4 was found to decrease across the entire age range interrogated, while that of ERBB2, PRODH, and DARPP32 was shown to increase over age. Particular interest was taken in gene expression during early adulthood, i.e. the years during which schizophrenia disease onset is most common (here defined as 18-30 years). The expression of NRG1 and NTRK3 (TRKC) decrease during this time window, followed by constant expression levels throughout the rest of life. This may indicate that these particular expression differences are not part of the gradual molecular aging process, but rather form part of a neurodevelopmental process bounded by early adulthood, and potentially involved in the molecular etiology of schizophrenia.

4. Consensus Imaging: Emerging Methods for Coordinate-based, Voxel-wise Meta-analysis in Human Functional Brain Mapping

Peter T. Fox, Angela R. Laird, P. Mickle Fox, and Jack L. Lancaster

Human functional brain mapping (HFBM) is an experimental discipline that establishes structure-function correspondences in the human brain through the combined application of experimental psychology, human neuroscience and non-invasive neuroimaging. The HBFM community has been remarkably successful in evolving sophisticated data-analysis methods and in adopting them as de facto community standards. The basic analytic standards of HFBM are: 1) reporting results in spatial coordinates (x, y, z), after spatial normalization and atlas registration; 2) statistical parametric imaging (SPI), in which images from different conditions are statistically contrasted in a voxel-wise manner; and 3) automated extraction of responses as local maxima, after statistical thresholding and correction for multiple comparisons. The HFBM literature compliant with these standards is roughly 4,000 articles (~16,000 experiments) with ~500 new articles (2,000 experiments) published per year. Roughly 20% of this literature is available online, in the BrainMap database. Motivated by this large volume of well-standardized data, several laboratories are developing tools for quantitative, voxel-wise meta-analysis. The most basic HFBM meta-analysis method is activation likelihood estimation (ALE), which computes voxel-wise activation probabilities for a paradigm type (e.g., the color-word Stroop task). Network analysis methods can then be applied to these ALE maps, to established inter-regional connectivity based on co-occurrence patterns. Both ALE maps and network models can be viewed as regionally explicit structure-function hypotheses which can be used to probe SPI raw data. For example, a network model can be used as a prior hypothesis for structural equation modeling (SEM) of per-subject SPI data.

5. Spatial and Temporal Processing of Cortical Input by Ventral Striatal Spiny Neurons

A.J. Gruber and P. O'Donnell

Center for Neuropharmacology & Neuroscience, Albany Medical College, Albany NY

We explored the dependence of nucleus accumbens neural responses on spatial and temporal aspects of cortical activation with intracellular recordings from medium spiny neurons (MSN). Cortical field recordings and electrical stimulation was applied through an electrode array in the ipsilateral prelimbic cortex. Cortical field potentials and spiny neuron membrane potential showed maximal covariance when spiny neurons transitioned between their hyperpolarized down state and depolarized up state. The magnitude and lag of the peak covariance are nonstationary in time for each recording location, and vary strongly across cortical locations for a given cell. We also explored the response of MSN to electrical stimulation through the cortical array. Consistent with previous work, the response to a single pulse usually consisted of multiple components: an early depolarization followed by a long lasting hyperpolarization, which was then sometimes followed by a late depolarization. Action potentials could occasionally be observed during the depolarizations. The response to a train (3-10 pulses) of high frequency (>50 Hz) stimulation normally consisted of a sustained depolarization that lasted beyond stimulus offset. The duration of depolarization is nonlinearly related to the number of electrical stimuli. MSN could fire action potentials during the first few stimuli or after train offset, but not usually during the intermediate period. Current injection revealed a reversal of the evoked response for some cells during the intermediate period, in addition to a suppression of spike firing in most cases. While these responses are typical of most stimulation locations, some locations yielded a fundamentally different response consisting exclusively of excitation. A few neurons presented both types of responses depending on stimulation location. In addition, lower frequency (20 Hz) tetanic stimulation was more efficacious for eliciting spikes in all conditions. These data indicate that spatial and temporal aspects are critical for corticostriatal processing. It is tempting to interpret these data as revealing a process of excitation masked by inhibition, for instance via feed-forward inhibition provided by striatal interneurons, in which the control of the inhibition has a spatial dependence on cortical activation.

6. Corticotropin-Releasing Factor Modulation of VTA Glutamatergic Currents after Chronic Cocaine Exposure

Junghyun Hahn, Tara Crowder, and Antonello Bonci

Ernest Gallo Clinic and Research Center, UCSF, California

Corticotropin-releasing factor (CRF) plays a key role in mediating addictive behaviors caused by stressful events. The effect of CRF in ventral tegmental area (VTA) neurons is particularly interesting since dopamine neurons in this area are implicated in drug-seeking, sensitization, and relapse. Although studies have suggested that prior exposure to drugs of abuse may sensitize the animals to physiological effects of CRF and, ultimately, stress, little is understood about the underlying mechanisms. In the present study, we hypothesized that the response of CRF in VTA dopamine neuron activity would be altered by repeated cocaine exposure producing behavioral sensitization. Our results show that the effect of CRF on NMDA currents in mice following repeated injection of cocaine was significantly increased, while repeated saline injection showed a similar CRF response on NMDA currents to naïve animals. Similar experiments performed by evoking AMPAR-mediated currents showed no effect of CRF under control conditions, but we observed a significant increase after repeated cocaine injections. Moreover, CRF increased the frequency of miniature EPSCs (mEPSCs) after chronic cocaine treatment, but not with saline treatment. These results suggest that chronic in vivo administration of cocaine induces an increased response to CRF of excitatory synaptic transmission in VTA dopamine neurons and might play a role in the expression of addictive behaviors elicited by stress.

7. In Vivo Analysis of Dopamine Neurochemistry in Medial Prefrontal Cortex in R6/2 Mouse Model of Huntington's Disease

Bahareh Hassanzadeh, Cristina Puddu, James M. Tepper, and Elizabeth D. Abercrombie

In the present study, we investigated how progression of HD affects the function and anatomy of mesocortical DA fibers in the mPFC in R6/2 transgenic mice model of Huntington's disease. R6/2 mouse is a transgenic model of HD that expresses exon 1 of the human HD gene and shows a rapid and aggressive form of disease.

In vivo microdialysis in freely moving mice at 7, 9, and 11 weeks of age was done to measure the amount of dopamine per 20µl sample in mPFC of R6/2 and wild type. As early as 7 weeks of age, the basal level of extra-

cellular DA in mPFC of the R6/2 transgenic mice trends toward lower level versus wild type. The extracellular DA decreased as a function of age in mPFC of both R6/2 transgenic (p: 0.0129; F:5.90) and wild type mice (p: 0.0049; F:7.74). We quantified tyrosine hydroxylase (TH) containing fibers in cingulated and prelimbic areas of mPFC. The total number of TH fibers showed significant reduction in mPFC across the age in R6/2 transgenic (p:0.0227; F:5.66) whereas the wild type TH fibers did not reduce (p:0.3784; F:1.07).

Age dependent decline in DA level in mPFC was more prominent than transgene effect. Although the start point of DA level in R6/2 transgenic animals was lower than the wild type littermate. Here we have shown that reduction of mesocortical DA fibers could be the underlying cause for DA level decline in mPFC of R6/2 transgenic mouse.

9. Supramammillary Stimulation Evoked Dopaminergic Signals in the Ventral Striatum: A Fast-Scan Cyclic Voltammetry Study

Satoshi Ikemoto, Joseph F. Cheer, Leslie A. Sombers, and R. Mark Wightman.

Midbrain dopamine neurons projecting to the ventral striatum have been implicated in primary reinforcement, and recent studies suggest that neurons in the supramammillary nucleus of the posterior hypothalamus also play an important role. Rats quickly learn to self-administer GABAA receptor antagonists, AMPA, or nicotine into the supramammillary nucleus; in addition, the drugs' reinforcing effects are blocked by the blockade of dopamine receptors. Therefore, electrical stimulation of supramammillary neurons may recruit the activation of reward circuitry within the mesolimbic dopamine system. We used fast-scan cyclic voltammetry to examine dopamine signals throughout the striatum as a function of electrical stimulation at the supramammillary nucleus or ventral tegmental area. The stimulation of the supramammillary nucleus evoked dopamine release in the ventral striatum and was rewarding; rats quickly learned to self-stimulate. It appears that higher currents were needed at the supramammillary nucleus (150-200 μA) than the ventral tegmental area (100 μA) to evoke comparable levels of self-stimulation and dopamine release. So far, we have not detected significant differences in temporal patterns of dopaminergic release as a function of stimulation frequency between the supramammillary nucleus and ventral tegmental area. Additional experiments designed to substantiate these preliminary observations are ongoing.

10. Effect of Aβ Structure and Human and Apoe Isoform on Primary Co-Cultures of Neurons and Glia

L. Jungbauer, A.M. Manelli, P. Sullivan, and M.J. LaDu

The etiological role of amyloid-beta (Aβ) in Alzheimer's disease (AD) is established, as is the increased risk of AD with inheritance of the apolipoprotein E (apoE) β4 allele. Of current interest is the effect of A? conformation and apoE isoform on defined aspects of AD pathogenesis. To determine the effect of apoE genotype on Aβ1-42 oligomeric- and fibrillar-induced neurotoxicity, we co-cultured wildtype (WT) neurons with glia isolated from WT, apoE-knockout (apoE-KO), and human apoE2-, E3-, and E4-targeted replacement (TR) mice. As glia are the primary apoE synthesizing cell type in the brain, the apoE-containing particles secreted by the WT and apoE-TR glia in this model is in a nascent, endogenous form. Additionally, apoE expression is under control of endogenous mouse regulatory sequences, allowing apoE to vary in response to Aβ, as well as to Aβ-induced release of pro- and anti-inflammatory factors by glial cells. Our results demonstrate that neurotoxicity induced by oligomeric Aβ 1-42 is significantly greater than fibrils in co-cultures with WT, KO, apoE2-, E3-, and E4-TR glia. This effect is dose and time dependent. Significant fibril-induced toxicity was observed only in co-cultures with apoE4 glia. Oligomer-induced toxicity was significantly greater in apoE4-TR than KO, apoE2- or apoE3-TR, with WT exhibiting even less of a neurotoxic response. Additionally, apoE isoform did not affect neurotoxicity induced by staurosporine or glutamate. These results provide a direct link between apoE isoform and oligomeric Aβ1-42, as well as a physiologically relevant in vitro model for further study of cellular and molecular mechanisms underlying the observed effects.

11. Human Neural Stem Cell-and Embryonic Stem Cell-Derived Precursors as Replacement Therapies for Diseases of the Nervous System

I. Nasonkin, J. Yan, L. Xu, L. Zhou, V. Machairaki, G. Hatfield, K.K. Johe, and V.E. Koliatsos

Irrespective of disease-specific mechanisms, neuronal cell death is a pervasive problem for traumatic and, especially, degenerative diseases of the nervous system. Therefore, the replacement of dead or dying neurons with transplantation of identical or homologous exogenous cells has been one of the central experimental therapeutic strategies for these disorders. Traditionally occupied primarily with grafting of target-specific cells of fetal

origin, the field has been recently invigorated with the advent of technologies and concepts for the optimal manipulation of neural stem and embryonic stem cells (NSCs and ESCs). The employment, at the preclinical stage, of cells of human origin has an additional therapeutic advantage. Human NSCs are derived ex vivo from fetal brain/spinal cord or from rare precursors remaining in the adult nervous system. ESC-derived precursors are differentiated and propagated in vitro from a limited set of pluripotent human ESC lines. To be of therapeutic use, human NSC- and ESC-derived neuronal precursor grafts must (1) survive in the host environment, including that of the injured and degenerating nervous system, without forming tumors (2) differentiate in large numbers into neurons or glia (3) integrate within the host circuitry at the structural and functional level and (4) by fulfilling the above requirements, ameliorate clinically relevant functional impairments in experimental animals. In our laboratory, we have achieved most of the previous steps working with human NSC- and, to an extent, human ESC-derived neuronal precursors that were grafted in the spinal cord (ventral horn) and facial nucleus of immunoprotected rodents with nerve injuries or with degenerative motor neuron disease (FALS SOD1 Tg rats and mice). Integration of stem cell-derived neurons into host circuitry appears to be based on traditional trophic mechanisms that we have previously uncovered in our laboratory, but some novel host-graft interactions have also been observed. Our experience shows that, with appropriate modifications of in vitro strategies and adjustments of grafting techniques, immunoprotected rodents are excellent models to test the preclinical applications of human NSC- and ESC-derived neuronal precursors. Although technical problems remain, these cells have great potential as tools for the repair of damaged neural circuitry.

12. Subtypes of Vagal Afferent C-fibers in Lungs and Esophagus in Guinea Pig

M. Kollarik, B. Chuaychoo, M.G. Lee, S. Yu, B.J. Undem

In most mammals, including humans, vagal sensory neurons reside in two anatomically distinct ganglia referred to as nodose and jugular (supranodose) ganglia. Neurons in these ganglia are derived from distinct embryonic sources (embryonic placodes and neural crest, respectively). We hypothesized that the C-fibers originating from nodose and jugular ganglion neurons differ in their phenotypes. Retrograde tracing studies showed that the C-fibers in lungs and esophagus arise form cell bodies situated in both nodose and jugular ganglia. Immunohistochemistry revealed that a high proportion of jugular, but not nodose, esophagus- and lung-

specific C-fiber neurons express the neuropeptide substance P. The activation profile of vagal C-fibers (conduction velocity <1m/s) was evaluated in ex vivo isolated vagally innervated lungs and esophagus preparations using standard extracellular recording techniques. Consistent with a nociceptive function, both nodose and jugular C-fibers discriminated noxious mechanical stimuli and were uniformly sensitive to the TRPV1 receptor agonist capsaicin. Both nodose and jugular C-fibers were also effectively activated by bradykinin and acidic solutions. In contrast, nodose, but not jugular, C-fibers, were responsive to selective 5-HT3 receptor agonists, purinergic P2X receptor agonists, and adenosine A1 and A2A receptor agonists. These agonists activated nodose C-fibers by direct action on their respective receptors in the neuronal membrane as demonstrated by the whole cell patch clamp recordings from the tissue-specific nodose C-fiber neurons. We conclude that the guinea pig vagal C-fibers comprise at least two distinct subtypes dictated by the ganglionic location of their neurons. Our data also indicate that vagal C-fibers retain nodose and jugular phenotype-specific properties in different tissues.

13. VTA Positively Modulates Neurons in the Ventral Hippocampus

Witold J. Lipski and Anthony A. Grace

The ventral hippocampus (vHPC) receives dopaminergic projections from the ventral tegmental area (VTA). Dopamine has been shown to facilitate LTP formation at synaptic inputs to the vHPC, suggesting that the VTA provides a salience signal that facilitates the consolidation of new memories in the hippocampus. However, how the VTA input to the vHPC affects information processing in this region has not as yet been examined electrophysiologically in vivo. To address this question, extracellular single unit recordings were obtained from neurons in the CA1 and ventral subiculum of urethane-anesthetized rats, using standard electrophysiological procedures. The VTA input to the ventral hippocampus was activated using single pulse and burst stimulation via concentric bipolar stimulation electrodes placed in the VTA. We found that VTA burst stimulation resulted in an increase in the firing of approximately 75 % of the vHPC neurons at 100 -1000 ms following stimulation (N = 15). This effect was not blocked by the D2 antagonist haloperidol but was partially blocked by the D1/D2 dopamine antagonist cisZ-flupenthixol. Our finding shows that the VTA positively modulates the excitability of neurons in the vHPC, which may signal increased levels of salience of behaviorally relevant objects in the formation of new memories.

14. Ethanol Enhancement of Cocaine and Amphetamine-Regulated Peptide in the Rat Mesolimbic Dopamine System

A. Salinas, R.A. Morrisett, and R.E. Maldve

Cocaine- and amphetamine-regulated transcript (CART) is a putative peptide neurotransmitter that has been implicated in drug reward and reinforcement. CART mRNA and peptide expression are highly concentrated in several compartments of the mesolimbic reward pathway. Several lines of evidence suggest that CART peptides may contribute to rewarding behaviors and the addiction liability of psychostimulants; however, any interactions between CART and ethanol have yet to be described. To address this issue, rats were administered a single dose of ethanol (1 g/kg or 3.5 g/kg, 1h, ip), and CART expression was measured by RT-PCR in the nucleus accumbens (NAcc). Ethanol (3.5 g/kg) increased CART transcription markedly. Confocal immunofluorescence microscopy revealed that CART peptide immunoreactivity was also enhanced in the both the core and the shell of the NAcc by ethanol administration. Total baseline CART fluorescence intensity in the shell was measured at 5.7±1.5 arbitrary O.D. units (results were quantified from 10-12 serial sections of the NAcc from 3 animals). In section-matched slices, CART immunofluorescence was markedly and significantly increased in the NAcc shell following in vivo administration of 1 or 3.5 g/kg ethanol as compared to control animals (13.9±1.2 OD and 19.5±2.1 OD, respectively). Under greater magnification, CART IR fibers with labeled varicosities were also visible and co-localized with GABA in accumbal medium spiny neurons. These data suggest that CART peptides may have a significant role in the modulation of mesolimbic dopamine activation by ethanol, thereby potentially contributing to its reinforcing and addictive liability.

NIAAA, NIH (AA13CR-INIA Project) to REM.

15. Noradrenaline Protects Neurons against Amyloid Beta and Microglial Induced Damage

Jose L.M. Madrigal, Cinzia Dello Russo, Douglas L. Feinstein

Our previous studies have shown that conditioned media from microglial cells activated with LPS or with oligomeric amyloid beta (Ab) 1-42 induces damage in primary cultures of cortical neurons. The neurotransmitter noradrenaline (NA) is able to prevent neuronal death in this model as well as the induction of NOS2 in neurons, suggesting a role for NOS2 in causing neuronal damage. We therefore analyzed the role of NOS2 in causing neuronal damage after Ab injection into cortex of wildtype versus and

NOS2 null mice. We observed a marked reduction of neuronal damage in samples from the NOS2 null mice, which points to an essential role for NOS2 in causing neuronal damage in vivo. However, in studies using neurons prepared from these mice, we found that Ab induced similar levels of LDH release, suggesting that NO production is not the only means by which Ab can induce neuronal death. We also found that NA protected neurons against damage due to direct treatment with Ab. In order to elucidate possible mechanisms of action of NA, we analyzed its effects on neurons as well as on microglial cells. In neurons, we observed that NA increased IkB-alpha and PPAR-delta expression both, which could reduce inflammatory activation. In microglial cultures, NA reduced production of nitrites as well as the expression of several inflammatory cytokines such as IL-12 and MIP-1alpha, and increased expression of the anti-inflammatory chemokine MCP-1, which can down-regulate IL-12 and MIP-1 expression. Together these data indicate that NA can provide neuroprotection against Ab by increasing anti-inflammatory expression in neurons as well as by reducing production of inflammatory mediators from activated microglial cells. This work was supported in part by a VA Merit Grant and the American Alzheimer's association.

16. Nucleus Accumbens Dopamine Controls Behavior Switching

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Dopamine (DA) receptor activation in the nucleus accumbens (NAc) is necessary for animals to respond behaviorally to salient stimuli that predict reward contingent on an operant response, but not to perform uncued operant tasks such as fixed ratio 1 (FR1). Since performance of FR1 is guided by salient stimuli such as the operandum and the reward receptacle, why is NAc DA required for responding to explicitly-presented stimuli, but not to the implicit stimuli in an FR1 task?

To answer this question, we trained rats on cued FR1 tasks. An auditory cue signaled liquid sucrose reward availability contingent on a lever press. The time-out length [interval from termination of sucrose consumption (exit from the reward receptacle) to presentation of the next cue] was fixed for each rat, but varied across 4 groups of rats: it was either 0, 3, 10 or 20 sec. Well-trained rats were injected with dopamine D1 or D2 receptor antagonists into the NAc prior to sessions. The antagonists severely impaired performance on the 10- and 20-sec time-out tasks by reducing the number of rewards obtained, but the same doses of antagonist did not affect performance of the 0-sec time-out task. The DA antagonists caused

the impairment by greatly prolonging the cue-lever press latencies in the 10- and 20-sec time out tasks, but not in the 0-sec time-out task.

An explanation for this result is that rats on the 0-sec time-out task were constantly "on-task" (either pressing the lever or consuming reward), whereas the longer time-outs gave rats the opportunity to engage in other behaviors. Hence, the cues guiding behavior in the 0-sec time-out task were fully predicted by previous events and behaviors, whereas the cue indicating reward availability in the longer time-out tasks was relatively unpredictable and was often presented while the animal was engaged in other behaviors. Accordingly, NAc DA is not required for animals to respond to cues that are themselves fully predicted by previous events, but is required to switch from an ongoing behavior to an alternative behavior elicited by a relatively unexpected reward-predictive cue.

17. Embryonic Exposure to Endocrine Disrupting Chemicals Impairs Male Sexual Behavior and Impacts Neuroendocrine Systems

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Endocrine disrupting chemicals (EDCs) include pesticides, herbicides, industrial products, and plant phytoestrogens. The Japanese quail provides a precocial avian model ideal for testing ontogenetic effects of EDCs on neural targets and determining subsequent impact on reproductive function in adults. Effects of estrogen- or androgen-active compounds were investigated on hypothalamic neural systems in hatchlings and adults. Fertile quail eggs (n=85-95/group) were injected with 20 µl sesame oil (control), 17β estradiol, trenbolone, or DDE into the yolk at either embryonic day 4 or 11 to coincide with gonadal differentiation or sexual differentiation of hypothalamic systems. Hypothalamic aromatase (AROM), catecholamines, and GnRH-I were measured. Reproductive maturation and copulatory behavior were measured in birds that were raised. Results showed EDC exposure impaired reproductive behavior and altered rates of sexual maturation. Estradiol treatment increased AROM in hatchlings injected at E11; androgenic EDCs did not affect AROM. Catecholamines were altered by some treatments, especially the higher doses of EDCs. GnRH-I was sexually dimorphic, with small effects from trenbolone. Our data suggest that chemical exposure of the embryo is expressed to some degree immediately (observable in the hatchling), but is more clinically apparent during activation of the reproductive neuroendocrine system. Hypothalamic neurotransmitters that modulate reproductive function

may provide valuable indices of endocrine disruption associated with later consequences of embryonic exposure to EDCs.

18. DOV 51,892, A Novel GABAA Receptor Modulator: Effects in Animal Models of Anxiety

Piotr Popik, Martyna Krawczyk, Anthony Basile, Arnold Lippa, and Phil Skolnick

DOV 51,892 is a pyrazolopyrimidine that is structurally related to ocinaplon, a molecule that has been reported (Lippa, et al., PNAS 102:7380-7385, 2005) to be anxioselective in humans. The objective of this study was to determine if DOV 51,892, like ocinaplon, exhibits an anxioselective profile in rodents. In the "thirsty rat conflict" model, DOV 51,892 increased punished responding at 3-24 mg/kg PO. These doses of DOV 51,892 did not affect non-punished responding. In the elevated plus maze, DOV 51,892 (3-24 mg/kg PO) increased the % of time spent in the open arms, without affecting closed arm entries. The minimum effective dose of DOV 51,892 in these tests was half that of ocinaplon. The effects of DOV 51892 in both the thirsty rat conflict test and elevated plus maze are characteristic of an anxioselective agent. In a separate set of experiments, the "side-effect" profile of DOV 51,892 was investigated. At doses 1-24 mg/kg, DOV 51892 affected neither rotarod performance (a surrogate measure of ataxia) nor grip strength (a measure of muscle relaxation). In an open field test at doses of 6-24 mg/kg, DOV 51,892 reduced, and at a dose of 1 mg/kg, increased the number of ambulations and rearings. In the absence of ataxia or muscle relaxation, these latter effects may also indicate an anxiolytic action. Additional studies are in progress to explore the behavioral and neurochemical actions of DOV 51,892.

19. A Spatially Structured Network of Inhibitory and Excitatory Connections Directs Impulse Traffic within the Lateral Amygdala

Rachel D. Samson and Denis Pare

The lateral nucleus of the amygdala (LA) is the entry point of most sensory inputs into the amygdala. However, the way information is processed and distributed within the LA still eludes us. To gain some insight into this issue, we have examined the spatial organization of excitatory and inhibitory connections in the LA. We performed whole-cell patch clamp recordings of principal LA neurons and studied their responses to local pressure applications of glutamate in coronal and horizontal slices of the guinea pig amygdala. In coronal sections, glutamate puffs usually evoked inhibitory responses, except when the recorded neuron was located adjacent to

the external capsule, in which case excitatory responses could be evoked from ejection sites along the external capsule. In contrast, glutamate puffs evoked a mixture of excitatory and inhibitory responses in horizontal slices. Excitatory responses were generally evoked from stimulation sites located lateral to the recorded cell, whereas inhibitory responses were more frequently elicited from medial stimulation sites, irrespective of their rostrocaudal position. These findings confirm and extend previous tract-tracing studies where it was found that intrinsic connections within the LA prevalently run in the dorsoventral and lateromedial directions. However, our results also reveal a hitherto unsuspected level of spatial heterogeneity in the intrinsic circuit of the LA. The prevalence of excitatory responses in horizontal slices coupled to the ubiquity of inhibitory responses in coronal slices suggest that the LA network is designed to allow for associative interactions within the rostrocaudal plane while preventing runaway excitation locally.

20. Cell Proliferation in the Striatum during Postnatal Development

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The cortico-basal ganglia circuitry is involved in reward-based learning, cognition, and motor control, leading to goal-directed behaviors. Adolescence and young adulthood is a critical time for developing appropriate goal-directed behaviors and is also a time when a variety of mental health disorders predominantly emerge. The elaboration and refinement of neural connections during this developmental time may be influenced by cell proliferation within cortico-basal ganglia circuitry. This study used bromodeoxyuridine (BrdU) labeling to examine the distribution of cell proliferation in the striatum across early development in old world monkeys (macaca fasicularis). We analyzed the distribution of new cells with respect to striatal regions based on the topography of specific functional cortico-striatal inputs. The striatum was divided into regions receiving projections from limbic (anterior cingulate and orbital prefrontal), associative (dorsolateral prefrontal), and motor (premotor and motor) cortex. Tissue was processed for BrdU using immunocytochemistry (ICC), and striatal BrdU + cell counts were determined using unbiased stereology (Stereoinvestigator, Micro-Brightfield). Sections were double stained for BrdU and cell makers for glia and neurons. The results of this experiment show: 1) There is postnatal cell proliferation in the striatum. 2) There is a significantly larger

number of striatal BrdU + cells in younger age groups than in older age groups. 3) There is a differentiated number of striatal BrdU + cells which is related to the functional divisions of the striatum. For example, the striatal region receiving input from orbital prefrontal cortex has a significantly larger number of BrdU + cells in the younger age groups than the other striatal regions. 4) Most BrdU + cells did not express a glia or neuronal marker. Cell proliferation in the striatum during this developmental period may significantly influence the formation of neural connections in areas important for motivation leading to goal-directed behaviors. Animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by NIH.

21. The Effect of a Peptidergic Neuromodulation on the Frequency Dependent Property of Synapses and Pacemaker Neurons in an Oscillatory Network

Vahid Tohidi and Farzan Nadim

Many neurons show the maximum impedance (resonance) as the function of input frequency. Moreover, synaptic connections also depend on input frequency due to short-term plasticity. We are interested in understanding the role of the frequency-dependent properties of neurons and synapses in generation of network oscillations with a proper phasing between oscillatory neurons. The pyloric network of the crab C. borealis involves neurons that produce coordinated rhythmic activity across a large range of frequencies (0.5-2Hz). The pyloric oscillation is shaped by the effects of several exogenous neuromodulators. We propose that the oscillation frequency of the pyloric network is set primarily by the intrinsic resonance frequencies of the pacemaker neurons (AB/PD) and that this frequency is modified by neuromodulatory inputs. The follower neurons, in turn, affect the pacemakers through a single feedback synapse from the LP neuron to the PD neuron. We found that the intrinsic subthreshold resonances of LP and PD were at the frequencies 1.25 and 0.6 Hz, respectively. The LP to PD synapse had a resonance frequency of 0.9 Hz. Bath application of the neuromodulator proctolin did not change the LP or PD membrane resonances, but their impedance at these frequencies increased (LP from 12 to 15 MOhm and PD from 11 to 13.5 MOhm). Proctolin also resulted in a new LP to PD synaptic resonance peak at 0.2 Hz in addition to the control peak at 0.9 Hz. These results underline the importance of frequency dependent action of neuromodulatory input to modify resonant properties of the pyloric network elements and subsequently the pyloric rhythm.

22. Over-expression of Neuronal Pentraxin 1 Reduces Neurite Outgrowth before Cell Death in Human Neuroblastoma SH-SY5Y Cells

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Expression of Neuronal Pentraxin 1 (NP1) is part of the apoptotic cell death program activated in mature cerebellar granule cells by reduction of neuronal activity. NP1 is a glycoprotein homologous to the pentraxins of the acute phase immune response and it is involved in both synaptogenesis and synaptic remodeling. We hypothesized that neuronal pentraxins constitute a genetic sensor that regulates neuronal death or survival, depending on synaptic activity. We have now examined the effect of NP1 on neurite outgrowth and cell proliferation in human neuroblastoma SH-SY5Y cells. We found that lentiviral mediated transgene overexpression of NP1 produces a marked reduction in neurite outgrowth. This effect is followed by a significant increase in the number of cells with apoptotic nuclei and with active caspase 3. Silencing NP1 overexpression with lentivirus vector-mediated short hairpin RNA interference (shRNAi) prevents the reduction of neurite outgrowth and rescues cortical neurons from apoptosis evoked by NP1. In addition, different clones of SH-SY5Y cells that permanently overexpress NP1 exhibit a cell proliferation index that is markedly lower than that the observed in control neuroblastoma cells. These findings show that NP1 reduces neurite outgrowth, increases both morphological and biochemical signs of apoptosis and reduces cell proliferation, and support the hypothesis that neuronal pentraxins mediate activity-dependent regulation of cell differentiation and survival.

23. Afferent Information Integration in the Nucleus Accumbens

John Wolf

The nucleus accumbens (NAcb) integrates inputs from the prefrontal cortex (PFC), hippocampus (HC), as well as the amygdala and thalamus. Results from computational and animal studies suggesting how these afferent inputs are integrated in the MSP cell will be presented. The computational model neuron, constructed in NEURON, includes all of the known ionic currents in these cells, and receives synaptic input from simulated spike trains via NMDA, AMPA, and GABAA receptors. After tuning the model by adjusting maximal current conductances in each compartment, the model cell closely matched whole cell recordings from an adult

rat NAcb slice preparation. Altering the NMDA: AMPA ratio had a profound effect on the processing of afferent input, including the ability to entrain to oscillations in afferent input in the theta range (4-12 Hz). To investigate afferent integration in the awake animal, we chronically implanted rats with tetrodes in the NAcb and examined the response to afferent stimulation from the HC and PFC. PFC and HC were stimulated in various patterns in order to assess response summation in the NAcb. These experiments were repeated under isoflurane anesthesia in order to examine the effect of cortical activation on this type of integration. The results from these experiments suggest that the NAcb integrates inputs mainly sublinearly instead of behaving as a gate, and that anesthesia has a critical impact on input integration in the NAcb. We speculate that instead of gating the PFC, HC theta may be modulating PFC responses in the NAcb.

24. Adaptation of the Human VOR during Artificial Gravity

Laurence Young

The adaptive properties of the vedstibuo-ocular reflex are well known to any of us who wear eye glasses or snorkel. A particularly challenging task, however, arises during the Coriolis cross-coupling associated with out-of-plane head movements while rotating. The practicality of artificial gravity for astronaut conditioning rests upon the ability to generalize VOR adaptation, across axes and directions of head movements. Progress in modeling the process and developing efficient adaptation protocols is presented.

Posters will be available for viewing from 3:30 PM Wednesday through 10:00 AM Friday. Presenters will be with posters on Thursday from 3:30–4:30 PM.

25. Potassium Leak Conductance Improves Performance in an Auditory Brainstem Nucleus

Amy Berntson

Given their simple morphology, principal neurons of the auditory medial nucleus of the trapezoid body (MNTB) have a surprisingly low input resistance, suggesting the somatic membrane may contain a large number of leak channels. These leak channels are likely to influence the precise temporal processing exhibited by these neurons. The present study provides evidence that MNTB principal neurons express an openly rectifying potassium-selective leak conductance of ~3nS, probably mediated by a two-pore potassium channel. Dynamic clamp experiments demonstrated that modulating the leak conductance strongly influenced the excitability of the principal neurons independent of changes in resting voltage, as well as modulating the action potential amplitudes, summation, and latency. Removing (or increasing) the leakage conductance resulted in a hyperpolarizing (or depolarizing) shift in membrane potential by -5mV/nS, and an increase (or decrease) in neuron's input resistance. This had a strong effect on the excitability of the neurons. Blocking the leak conductance caused the neurons to fire on average 5 times more action potentials than under control conditions. In response to synaptic input, removing the leak conductance increased the summation of action potentials. We propose that a large leak conductance in MNTB neurons improves the fidelity, and precision, of firing and contributes to the fast time membrane time constant required by these neurons.

26. Chronic Stress Alters BLA Neuronal Responses to Norepinephrine and Afferent Input

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Many studies have demonstrated the importance of the basolateral amygdala (BLA) in learning and memory tasks, especially those involving an affective component. More recently, manipulations of the levels of norepinephrine (NE) within the BLA have been shown to affect task

performance as well. The amygdala plays an important role in the stress circuit and response. While there is much behavioral data on the NE system of the BLA and learning, memory, and stress, little has been done to examine how NE modulates neuronal activity within the BLA, particularly in an in vivo, in tact preparation. We examined responses of BLA neurons to iontophoretic application of NE (200uM) using single-unit, extracellular recordings in control rats and rats exposed to 14 days of chronic cold stress. NE had primarily inhibitory effects on spontaneous activity of BLA neurons (75% of cells), with few showing excitatory effects (23%). Furthermore, NE decreased the evoked responses of BLA neurons to stimulation of excitatory afferents from entorhinal cortex. Neurons from rats exposed to chronic stress displayed less inhibition (53%) and more excitation (40%) to NE application. In addition, responses to entorhinal cortex were facilitated by NE in rats exposed to chronic cold stress. These data demonstrate that chronic stress exposure alters the way in which the BLA responds to NE and afferent input, and the way in which NE modulates input to the BLA. Increased BLA responsiveness may account for exaggerated behavioral responses to stressors, or fearful responses to non-threatening stimuli seen in chronically stressed behaving rats.

27. Expression of RGS4 mRNA Is Not Altered in Schizophrenia

Mark M. Caruso, Thomas M. Hyde, Shruti N. Mitkus, Daniel R. Weinberger, Joel E. Kleinman, and Barbara K. Lipska

A cDNA microarray study found reduced mRNA expression levels of Regulator of G protein signaling 4 (RGS4) in the postmortem cerebral cortex of schizophrenics, and this was confirmed by in situ hybridization. RGS4, a gene mapped to 1q21-22 locus, has been subsequently implicated as a susceptibility gene for schizophrenia, and possibly bipolar disorder, by several independent linkage and association studies, although one negative study has also been reported. G-protein coupled receptors, such as dopamine and metabotropic glutamate receptors, can be modulated by RGS4, the predominant RGS form in brain. We investigated RGS4 mRNA expression by qPCR in the hippocampus and dorsolateral prefrontal cortex (DLPFC) in our large collection of postmortem brains (31 schizophrenic patients and 72 normal controls), and in the DLPFC of 105 postmortem brains from the Stanley Array Collection (35 schizophrenic patients, 35 bipolar disorder patients, and 35 psychiatrically normal controls). We found that postmortem brain pH, RNA quality, and age significantly affected RGS4 mRNA expression levels in both brain regions, but there was no significant effect of diagnosis on RGS4 mRNA expression in any of the cohorts. Our results show that RGS4 mRNA expression is not reduced in two brain

regions isolated from our schizophrenia cohort and the Stanley Array Collection. Although RGS4 mRNA expression is unaltered in schizophrenia, genotypic effects on mRNA expression may further elucidate the role of RGS4 as a schizophrenia susceptibility gene.

28. Administration of the NMDA Antagonist AP-5 into the Nucleus Accumbens Shell Reinstates Cocaine-Seeking Behavior

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A growing body of evidence indicates that increased glutamatergic transmission in the nucleus accumbens is critical to cocaine reinstatement, a model for human relapse. There are two major types of ionotropic glutamate receptors: AMPA/kainate and NMDA receptors. It has been shown that administration of an AMPA agonist into the accumbens will promote reinstatement, while an AMPA antagonist will block cocaine-primed reinstatement. The role of accumbal NMDA receptors in cocaine reinstatement, however, is less clear. In different studies, it has been shown that intra-accumbal microinjections of both NMDA agonists and antagonists will promote cocaine-seeking behavior. The goal of the present experiments is to determine how NMDA antagonism in the nucleus accumbens shell affects cocaine reinstatement. First, rats were anesthetized and surgically implanted with guide cannulae into the nucleus accumbens shell, and catheters were inserted into the right internal jugular vein. After recovery, rats were trained to lever-press for cocaine (0.254 mg/60µl, i.v.) on an FR5 schedule. The rats self-administered cocaine for three weeks. Subsequently, saline was substituted for cocaine and lever-pressing behavior was extinguished. Following extinction, an NMDA antagonist, AP-5 (3.0 and 30.0 µg/0.5 µl), was microinjected into the nucleus accumbens to determine its effect on cocaine seeking. The administration of AP-5 into the nucleus accumbens shell reinstated cocaine-seeking behavior. As NMDA antagonists have been shown to increase glutamate release in the accumbens, we speculate that AP-5-induced reinstatement may result from the indirect activation of AMPA/kainate receptors in the nucleus accumbens shell.

29. Differences in Quality and Yield of RNA Obtained From Multiple Brain Regions of Normal Human Brain

Robert J. Fatula, Thomas M. Hyde, Joel E. Kleinman, and Barbara K. Lipska

Studies of postmortem human brain are important for investigating pathogenic cellular and molecular mechanisms of neuropsychiatric disorders, but they are often confounded by pre- and postmortem factors, including brain tissue pH, post mortem interval (PMI), age at death, and RNA quality. It is also unclear whether confounding factors have similar impact across the brain. The goal of this study was to compare quality and yield of RNA obtained from 19 brain regions of 9 normal control subjects. Total RNA was extracted using a phenol chloroform protocol and purified on columns (Qiagen Maxi Kit). Assessment of total RNA quality was performed using an Agilent Bioanalyzer 2100 and expressed as RIN (RNA integrity number). RNA concentration was determined using UV spectrophotometry (Beckman). The yield of RNA (expressed as mg of total RNA per mg of frozen tissue) markedly varied by brain region ($p<0.0001$). Cerebellum and cortical regions (e.g., occipital, dorsolateral prefrontal, orbital frontal cortices) yielded significantly more total RNA than other regions (e.g., prefrontal white matter medulla, cervical spinal cord). RNA quality showed moderate variability between brain regions, with amygdala and substantia nigra having lowest average RIN, while superior temporal gyrus and putamen had the highest. There were also marked differences between the regions in the impact of age, pH, and PMI on RNA quality. In conclusion, pH is a better predictor of RNA quality than PMI. Regions of the brain with large amounts of white matter, e.g., cervical spinal cord, have lower yields of RNA than those that are primarily gray matter.

30. Estrogen and Progesterone Regulation of 5HT1A, 2A, and 2C Receptor Proteins in the Dorsal Raphe Region of Female Macaques

J.A. Henderson and C.L. Bethea

This laboratory aims to understand how ovarian hormones may alter various measures of serotonergic neurotransmission and how these changes may underlie mood disorders frequently associated with reproductive life events. We investigated the effects of estrogen (E) and progesterone (P) on serotonin (5HT) 1A, 2A, and 2C receptor protein expression in the dorsal raphe region, using Western Blot analysis. Adult rhesus macaques (Macaca mulatta) were spayed for 3-6 months, then treated with Silastic implants of either placebo, E for 1month (E1) or 5 months (E5), or

E+P for 1 month (EP1) or 5 months (EP5) (n=4/group). Densitometry was conducted with NIH Image followed by ANOVA and Student-Newman-Keuls statistical tests. 5HT1A receptor protein expression was lower in E1, EP1, and EP5 treatment groups (p's<0.05) compared to the placebo group. There was no difference in 5HT1A receptor protein expression between the E5 and placebo treatment groups. 5HT2A receptor protein expression was increased only in the E5 treatment group (p<0.05). 5HT2C receptor protein expression was higher than the placebo group with E5 treatment and was significantly below placebo group levels with EP5 treatment (p's<0.05). These results indicate that long-term unopposed E leads to anomalous increases in the 5HT 1A, 2A, and 2C receptor proteins in the dorsal raphe nucleus. Interestingly, these effects are ameliorated with the addition of P to the long-term treatment.

31. Identification of a Novel Genetic Locus at 7q36.1 in Strong LD with Schizophrenia and the Differential Expression of the Flanking Genes, NOS3 and KCNH2

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Increases in the level of nitric oxide synthase (NOS) activity and products of NO synthesis in the brains and periphery of individuals with schizophrenia have previously been reported. While NOS1 has been investigated at the protein and mRNA level, finding slight increases in patients with schizophrenia, increases in NOS3 were only recently observed using microarray technology. Here, using real-time quantitative PCR, we confirmed significantly increased levels of NOS3 mRNA in post-mortem brains of schizophrenia patients. Furthermore, genetic screening of SNPs in the area surrounding this gene found highly significant association within the families of schizophrenic individuals. Interestingly, this signal is located 16.7 Kb upstream of NOS3 in a neighboring gene, KCNH2. Nonetheless, an effect of genotype on NOS3 mRNA expression was observed, suggesting that the region of association may, in part, elicit effects on the regulation of NOS3 expression. Changes in KCNH, or the ERG family, potassium channels have not previously been investigated with relation to neuropsychiatric illnesses. Here we describe significantly decreased levels of KCNH2 mRNA within the post-mortem schizophrenia brain. These findings provide both genetic and expression level evidence of two new genes previously unreported as being involved with schizophrenia. Though it is unclear what precise

mechanisms might cause or be affected by these changes, the possibility of their functional involvement in glutamatergic signaling and neuronal regulating activities offers interesting avenues of further investigation for their contribution to the development and prognosis of schizophrenia.

32. Isoform Specific Expression of DTNBP1 (dysbindin), MUTED and Other BLOC-1 Genes in Lymphoblasts from Schizophrenics

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The association between genetic variation in DTNBP1 and schizophrenia has now been confirmed in multiple studies. DTNBP1 encodes dysbindin, which is a component of the biogenesis of lysosome-related organelles complex 1 (BLOC-1), and we have found that its binding partner MUTED is also a susceptibility gene. DTNBP1 expression is reduced in prefrontal cortex, midbrain, and hippocampus of schizophrenics, but little is known about the relative expression of the various isoforms. By RT-PCR, RACE, and sequencing, we found that as many as 11 different transcripts may be expressed in the prefrontal cortex alone.

Using quantitative RT-PCR, we measured a number of DTNBP1 isoforms and expression of other BLOC-1 genes (eg. MUTED, PLDN, SNAPAP, BLOC1S1) in lymphoblasts from controls (N=36) and schizophrenics (N=24). Each target transcript was normalized to three housekeeping genes, as well as to their geometric mean. We also analyzed whether expression was affected by risk genotypes and haplotypes.

Some DTNBP1 isoforms were reduced in schizophrenics, including a transcript that contained an exon inserted between Exon 1 and Exon 2 of transcript AF394226. Expression of other BLOC-1 genes (e.g., PLDN) were also decreased. Our results suggest that lymphoblasts can to some extent reflect expression patterns found in brain, and thus might be a useful adjunct to postmortem brain expression studies. In addition, they may be a convenient model system to explore the cell biology of susceptibility genes and their interaction. An inherent advantage is that the donors will have been genotyped, and their detailed cognitive and clinical phenotypes can be compared to their lymphoblast expression patterns and to other cellular phenotypes.

33. Association of Printor with Dystonia Protein torsinA on Endoplasmic Reticulum and Nuclear Envelope

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Early-onset generalized dystonia (DYT1) is a movement disorder characterized by involuntary movements and prolonged muscle contraction, resulting in twisting body motions, tremor, and abnormal posture. DYT1 has been linked to two mutations (DE302 and DF323-Y328) in the AAA+ protein torsinA. To identify additional players in the torsinA pathogenic pathway, we performed yeast two-hybrid screens to search for torsinA-interacting proteins in the brain. Here we report the identification of a novel protein named printor (protein interactor of torsinA). Printor is a 70-kDa protein with no apparent signal sequence or transmembrane domain. Western blot analysis reveals that printor is expressed in brain as well as other tissues, suggesting that printor has a functional role important to many cell types, including neurons. Subcellular fractionation studies indicate that printor exists in both cytosolic and membrane-associated pools, and cofractionates with both torsinA and ER lumenal protein calnexin. Immunofluorescence confocal microscopic analysis demonstrates that, like torsinA, printor is localized to endoplasmic reticulum and nuclear envelope, but not early endosome, lysosome, or mitochondria. We have confirmed the interaction of printor with torsinA by coimmunoprecipitation and shown that printor colocalizes with torsinA in cells by double immunofluorescence labeling. These results provide compelling evidence that printor and torsinA associate in vivo and suggest a potential role for printor in the molecular pathogenesis of DYT1.

34. Altered Na (+) Currents in Auditory Neurons of Congenitally Deaf Mice

R.N. Leao, M.M. Naves, K. Svahn, and B. Walmsley

Voltage-gated sodium channels are expressed in virtually all excitable cells. Voltage-gated Na(+) channels are essential to action potential generation and propagation. Na(+) channel subunits are differentially expressed in cellular subdomains (i.e., axon/soma) and during development. We have investigated Na(+) current properties in brainstem auditory neurons of normal and congenitally deaf (dn/dn) mice. Whole-cell recordings from visualised neurons in slices of the medial nucleus of the trapezoid body (MNTB) of P14 normal and deaf mice showed Na(+) currents with similar

amplitude and activation kinetics. However, Na(+) currents in deaf mice inactivated significantly more slowly than in normal mice MNTB neurons. Deaf mice Na(+) currents also developed inactivation more slowly than normal mice currents, but recovery from inactivation was similar. Resurgent Na(+) currents also inactivated more slowly in deaf mice MNTB neurons. Immunohistochemical techniques revealed that at P14, MNTB cells of normal and deaf mice express Nav1.1 proteins, but only deaf mice MNTB cells showed Nav1.6 labeling. At an earlier developmental stage (P7), both groups expressed Nav1.6 proteins in MNTB neurons. However, only in deaf mice, these proteins are preserved at later stages (P28). Despite the correlation between atypical Nav1.6 expression and cell death due to intracellular Ca(2+) influx through Na(+)/Ca(2+) exchangers (NCX), we did not find NCX expression in any of the groups. Using dynamic clamp techniques, we also demonstrated that atypical Na(+) currents cause APs to resist inactivation after high-frequency stimulation and also contribute to multiple action potentials in long depolarising current steps. The persistence of Nav1.6 channels in P14 deaf mice demonstrates the importance of activity for the appropriate development of voltage-gated channels.

35. Apoptotic Gene Expression in Alzheimer's Disease

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Alzheimer's disease (AD) is the major cause of dementia in the elderly, accounting for 50-70% of late-onset patients, with 17-20 million individuals affected. It is characterized by neurofibrillary tangles, neuronal loss, and amyloid plaques in tissues of the cortex, hippocampus, and amygdale. Apoptosis or programmed cell death appears to be involved in the progression of AD. In this study, we investigated the gene expression of 14 apoptotic genes (E2F1, p21/WAF, ICE-LAP3, Fas Antigen, CPP-32, GADD153, ICE-beta, c-Fos, c-Jun, Bax-alpha, Bcl-2, Bcl-(x)L, BAK, and p53) in five normal and six AD human hippocampal tissue samples, using RT-PCR. Our results show an up-regulation of gene expression in AD patients for c-Fos and BAK. ICE-β, c-Jun, Bax-alpha, Bcl-x(L), p53, and GADD153 were found to be up-regulated in some AD samples, but not detected or down-regulated in other AD or normal samples. No gene expression was found for E2F1, p21/WAF, ICE-LAP3, Fas Antigen, CPP32, and Bcl-2. This investigation indicates significant increases in c-Fos, c-Jun, and Bak. We therefore suggest that these genes may play a critical role in the apoptotic cascade leading to the neuropathology of AD.

36. Regulation and Function of Cortical High-Affinity Choline Transporters Measured in Vivo Using Choline-Sensitive Microelectrodes

V. Parikh and M. Sarter

The capacity of the high-affinity choline transporter (CHT) to import choline into presynaptic terminals is essential for acetylcholine (ACh) synthesis. Using an in vivo approach to measure changes in extracellular choline concentrations with choline-sensitive microelectrodes at a sub-second resolution, these experiments were designed to determine the contribution of cortical CHTs to the rapid clearance of exogenous choline or endogenous choline derived from hydrolysis of ACh. Ceramic-based microelectrodes, with recording sites coated with choline oxidase for the detection of changes in extracellular choline concentrations, were attached to multi-barrel glass micropipettes and implanted into the frontoparietal cortex of rats. Pressure ejections of hemicholinium-3 (HC-3), a selective CHT blocker, dose-dependently reduced the rate of uptake of exogenous choline as well as of choline resulting from terminal depolarization. Removal of CHTs from the recording region, produced by infusions of the immunotoxin 192 IgG-saporin, as well as synaptsomal choline uptake assays reflecting in vivo choline concentrations, confirmed that CHTs account for ~40% of choline clearance. Choline signal recordings from deafferented cortex also substantiated the hypotheses that the demonstration of potassium-induced choline signals, and of HC-3-induced decreases in choline clearance, require the presence of cholinergic terminals. Residual cortical choline clearance and CHT-immunoreactivity (CHT-IR) correlated significantly in lesioned animals. A highly significant correlation between choline clearance and CHT-IR was also observed in intact animals, indicating a robust inter-individual variability of cholinergic terminal properties. These results validate the usefulness of choline-sensitive microelectrodes for research on the regulation and function of the CHT in vivo.

37. DAT is Sufficient to Render Non-Dopaminergic Neurons Sensitive to 6-OHDA Toxicity

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We tested the hypothesis that ectopic expression of the dopamine transporter (DAT) would render non-dopaminergic neurons sensitive to the neurotoxic actions of 6-hydroxydopamine. Non-dopaminergic rat cortical neurons in culture were transfected with a GFP-DAT fusion protein and its functional expression was confirmed by [3H]-dopamine uptake. A

15 minute exposure to 100 mM 6-OHDA, innocuous to cortical neurons expressing an empty vector, killed approximately 50% of the GFP-DAT expressing cortical neurons. This toxicity was prevented by the DAT blocker GBR12909 and was reminiscent of the conditions necessary to induce 50% apoptotic cell death in dopaminergic neurons in vitro. As we have previously found that an enhancement of voltage-dependent K+ currents downstream of p38 MAPK activation is an essential step in oxidant-induced apoptosis, we tested whether 6-OHDA-induced toxicity occurred through a similar mechanism in GFP-DAT expressing cells. We observed a pronounced K+ current surge in these cells that was prevented by the p38 antagonist SB239063. Importantly, the p38 antagonist and the K+ channel blocker TEA were neuroprotective against 6-OHDA in GFP-DAT expressing cortical neurons. As such, we tested whether K+ channel antagonists could prevent 6-OHDA toxicity in dopaminergic neurons in vitro. 6-OHDA (100 mM, 15 min.) induced approximately 50% lethality of tyrosine hydroxylase-positive cells in rat mesencephalic cultures, and this toxicity could be abrogated with TEA. We conclude that DAT expression is a critical component for the manifestation of 6-OHDA toxicity, and that this toxin triggers a cell death pathway similar to those activated by other oxidants.

38. Cue- Versus Cocaine-Induced Drug Craving and Reward: Topographic and 3-Dimension (VARETA) Imaging of Quantitative EEG in Humans.

Malcolm S. Reid, Frank Flammino, Leslie Prichep, Bryant Howard

Clinical lab studies show evidence for both cocaine craving and cocaine high in subjects that are exposed to cocaine-cues or that self-administer cocaine. These conditioned and unconditioned response paradigms were investigated in a study with 13 cocaine dependent subjects. Patients underwent a cocaine cue session, rested 20 min, and then underwent a single-blind cocaine base (50 mg) or placebo smoking session in a cross-over study design. Cues involved handling crack cocaine paraphernalia, a video depicting crack cocaine use, and guided imagery. Cocaine high, craving, and nervousness increased following cocaine cue presentation and again after cocaine dosing, with the increase in cocaine high greater after dosing. Heart rate, skin conductance, plasma cortisol, and plasma ACTH levels increased following cocaine cue presentation and again after cocaine dosing, with the increase in heart rate, cortisol, and ACTH more prolonged after dosing. Quantitative EEG (qEEG) topography maps demonstrated activation over prefrontal cortex. Cocaine cues produced an increase in absolute delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), and beta (12.5-25 Hz) power over the frontal poles (FP1, FP2). Cocaine dosing produced a similar increase in absolute delta, theta, and beta power. Fast Fourier

analyses of the full spectrum showed the strongest effects in theta bandwidth (7.3+2.1 Hz). Comparisons of cue versus dosing conditions indicated greater delta and theta EEG coherence following dosing. Moreover, VARETA analyses of theta bandwidth generators demonstrated caudate, ventral striatum, and thalamic origins following dosing. These findings indicate that cocaine cues and dosing induce similar subjective, neuroendocrine, and neurophysiological responding on the surface which, however, differs at the subcortical level. Further VARETA analyses of cue-versus cocaine-induced qEEG, and correlations with plasma cocaine and subjective responding, will be presented.

39. Ketone Bodies Reverse Glutathione Depletion Induced by Glutamate and the Thiol Oxidant Diamide

Jong Rho, Marwan Maalouf, Do Young Kim, Jong M. Rho

Recent data suggest that ketone bodies are neuroprotective in various experimental models of neurological disease, and that their neuroprotective properties are mediated by a reduction of oxidative stress. However, the underlying mechanisms remain unclear. In the present study, we used a combination of fluorescence imaging and amphotericin B perforated patch-clamp recordings to test the hypothesis that ketone bodies prevent oxidative stress by modulating the levels of glutathione, the principal antioxidant in the brain. All experiments were performed on acutely dissociated neurons from somatosensory cortex of P10-14 rats. Initially, cells were incubated with monochlorobimane (MCB), a fluorescent glutathione marker, and then subjected to glutamate-induced excitotoxcity (10 μM glutamate with 10 μM glycine for 10 min). In the absence of ketone bodies (N=7), glutamate induced a 52.2 +/- 3.9% decrease in MCB signal, whereas, in the presence of acetoacetate and D-β-hydroxybutyrate (1 mM each), a 24.2 +/- 3.2% increase was observed (N = 8). The difference was statistically significant (unpaired t test, p = 0.01). To confirm the effect of ketone bodies on glutathione, perforated patch-clamp recordings were obtained from acutely dissociated neurons exposed to diamide, a specific thiol (glutathione) oxidant. Exposure to diamide (300 μM) for 10 min did not have any effect on the current recorded in voltage-clamp mode at -60 mV (N = 8). During washout, however, a large inward current (> 1 nA), indicative of cellular injury, occurred in all cases. A combination of acetoacetate and D-β-hydroxybutyrate (1 mM each) completely blocked that inward current (N = 8). Our results suggest that ketone bodies can delay and possibly reduce neuronal injury by preventing the decrease in glutathione induced by glutamate or the thiol oxidant diamide.

40. Egr3 Stimulation of GABRA4 Promoter Activity as a Mechanism for Seizure-Induced Upregulation of GABA(A) Receptor α4 Subunit Expression

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GABA is the major inhibitory transmitter at CNS synapses. Changes in subunit composition of the pentameric GABAA receptor, including increased levels of α4 subunit in dentate granule cells (DGCs) and associated functional alterations such as increased zinc blockade of GABA currents, are hypothesized to be critical components of epileptogenesis. We now report that the minimal promoter of the human α4 subunit gene (GABRA4p), when used to drive reporter gene expression from adeno-associated viral vectors, controls condition-specific upregulation in response to status epilepticus (SE), defining a transcriptional mechanism for seizure-induced changes in levels of α4 subunit containing GABAA receptors. Transfection studies in primary hippocampal neurons show that inducible early growth response factor 3 (Egr3) upregulates GABRA4p activity as well as the levels of endogenous α4 subunits. Further analysis in culture suggests that activation of PKC/MAPK-dependent pathways increase GABRA4 mRNAs, Egr3 mRNAs, and binding of Egr3 to the minimal GABRA4 promoter region. Given that Egr3 knock-out mice display around 50 % less GABRA4 mRNAs in the hippocampus and that increases in α4 and Egr3 mRNAs in response to pilocarpine-induced SE is accompanied by increased binding of Egr3 to GABRA4 in DGCs, our findings support a role for Egr3 as a major regulator of GABRA4 in developing neurons and in epilepsy.

41. A Mutation Underlying Inheritable Epilepsy Affects Sodium Channel Slow Inactivation

Margaret S. Dice, Jennifer Abbruzzese, and Peter C. Ruben

We studied the biophysical properties of neuronal sodium channels by co-expressing the pore-forming α-subunit of NaV1.2 with either WT β1-subunit or with the C121W mutation of the β1-subunit, and by expressing the NaV1.2 α-subunit alone. The C121W mutation is associated with generalized epilepsy with febrile seizures (GEFS+). Channels were expressed in Xenopus oocytes, and currents were assessed using cell attached macropatch. As in NaV1.3 channels, the voltage dependence of activation was depolarized when channels were expressed with C121W or without the β1-subunit. Since the shift in voltage dependence would not, by itself, increase membrane excitability, we also studied effects on slow inactivation. The voltage dependence of slow inactivation (60 second

prepulses) is depolarized in channels co-expressing C121W. The maximum probability of slow inactivation is decreased by both C121W and when channels are expressed without the β1-subunit, as previously reported for NaV1.4. The onset of slow inactivation was slower and less complete with co-expression of C121W than with the WT β1-subunit. Unlike results with NaV1.3, we found that the time constants of fast inactivation were greater when NaV1.2 was expressed alone or with C121W than when expressed with WT β1-subunit. Our results are consistent with defects in fast and slow inactivation that would be expected to increase NaV1.2 excitability when co-expressed with C121W. Our results are also consistent with a reasonable prediction of hyperexcitability in GEFS+. Supported by NS29204 to PCR.

42. Hyperpolarization-Activated Cation Currents in Three Auditory Brainstem Nuclei

Katarina Svahn, R.N. Leao, H. Su, A. Paolini, A. Berntson, R. Fyffe, and B. Walmsley,

Auditory brainstem neurons are tuned to process signals with high fidelity. The hyperpolarization-activated cation current (Ih) may influence this precise neural processing. Ih helps set the resting membrane potential and modulate excitability. Here, using whole-cell patch clamp recordings and immunohistochemistry, we investigate the properties of Ih in three nuclei of the superior olivary complex (SOC) in mice; the anteroventral cochlear nucleus (AVCN), the medial nucleus of the trapezoid body (MNTB), and the lateral superior olive (LSO). These nuclei work together to detect interaural level differences in high frequency sound arriving at the two ears. Current-clamp recordings show that 50% of the AVCN bushy cells exhibit a substantial sag in membrane voltage during a hyperpolarizing current step, and 38% display rebound action potentials (APs) upon repolarization, indicative of Ih activation. This is in contrast to MNTB neurons, where the majority of cells show only a weak sag and no rebound depolarization. Most LSO cells display a smaller sag, but 33%: exhibit rebound APs. In the SOC, Ih has the following order of magnitude; LSO>AVCN>MNTB. Kinetically, Ih is faster in LSO neurons; and more active at rest, compared to AVCN and MNTB cells. Immunohistochemistry shows that the AVCN expresses HCN1 and HCN4 channels, while the MNTB has low expression of HCN1 and only moderate expression of HCN2 and 4. The LSO exhibits mostly HCN1 labeling. In vivo data suggests that rebound spiking is not present in the MNTB but is occasionally observed in AVCN and LSO. We conclude that Ih is important in auditory processing but has a variable role in rebound spiking of SOC neurons.

43. Effects of Mesocortical Projections on Prefrontal Cortical Pyramidal Neurons and Fast Spiking Interneurons

Kathy Toreson and Patricio O'Donnell

Dopaminergic fibers from the ventral tegmental area (VTA) synapse onto pyramidal projection neurons (PN) and fast spiking interneurons (FSI) in the prefrontal cortex (PFC). Both the PN and FSI express dopamine (DA) receptors. Mesocortical DA is important for PFC information processing, and its critical role in cognitive functions is likely to depend on a crucial balance between PN and FSI activity. Here we used in vivo juxtacellular recordings of PN and FSI in the medial PFC of chloral hydrate-anesthetized animals to investigate their modulation by DA. Electrophysiological characteristics combined with neurobiotin staining and parvalbumin immunohistochemistry confirmed the identification of recorded cells. FSI were parvalbumin immunoreactive whereas PN were not. FSI had shorter duration action potentials and faster mean firing rates compared to PN. Activation of the VTA by electrical stimulation (20 Hz five pulse train) produced an increase in cell firing in FSI and a decrease in PN cell firing in most cases recorded. The effects of systemic administration of DA receptor antagonists were also assessed. The results suggest that activation of PFC interneurons may be a critical component in the response of PN to mesocortical system activation.

44. Potential Role of T-cells on Chronic Neuropathic Pain

David Vasquez-Dunddel and David C. Johns

A consequence of peripheral nerve injury is the development of chronic neuropathic pain. The immune system is activated after a nerve injury, and it has been demonstrated that besides activation of microglia and schwann cells, T-cells are recruited to the nerve injury site. However, the physiological significance and the contribution of T-cells to this condition remains unclear. In this study, we compare the development of neuropathic pain after a nerve injury model at the Lumbar spinal nerve L5 (Chung model) in nude (athymic) rats and their heterozygous counterparts, as well as the analysis on the pattern of Wallerian degeneration presented on each group. The four experimental groups were: 1) Nude animals with sham surgery, 2) Nude animals with nerve injury, 3) Heterozygous animals with sham surgery, 4) Heterozygous animals with nerve injury. Behavioral tests were performed twice before nerve injury to determine baseline values. Baseline values of mechanical thresholds were not different between the

nude and the heterozygous rats. However, the nude rats developed a significantly reduced mechanical hiperalgesia, compared to their heterozygous counterparts. The behavioral difference was evident as soon as the third day after the surgical procedure (pL≥0.05) to the end of the experiment (pL≥0.01).This difference was evident on the pattern of Wallerian degeneration too, showing a higher degeneration proximal to the nerve injury on the heterozygous than on the homozygous or the sham groups, suggesting that T-cell may play an important role on the development of the neuropathic pain that follows an injury nerve.

45. Novel Treatment for Multiple Sclerosis Based upon Apolipoprotein-E

Michael P. Vitek, Feng Qiao Li, Daniel T. Laskowitz, and Carol A. Colton

Inflammatory cells invading the brain and spinal cord are associated with the progressive demyelination, oligodendrocyte and neuronal degeneration that characterizes Multiple Sclerosis (MS). Recent reports have shown that MS patients carrying the Epsilon-4 allele of the Apolipoprotein-E gene (APOE4 gene) more rapidly attain clinical severity scores and have worse disability than those lacking APOE4. We recently reported that humans or animals carrying APOE4 genes were more inflamed than their APOE3 counterparts with respect to release of nitric oxide (NO), Interleukin-1 (IL1) and Tumor Necrosis Factor alpha (TNFa), suggesting that apoE3 protein may suppress inflammation better than apoE4 protein. Based on these data, we created a small peptide derived from residues 133 to 149 of the holo-apoE protein that functions to reduce NO, IL1, TNFa and phosphorylated-p38 MAP kinase in stimulated microglia or macrophages. Starting with an EAE model of MS, we used paradigm where MOG treatment was followed by treatment on day 6 with apoE 133-149 (aka COG133) and found significant, dose-dependent declines in clinical scores compared to vehicle treated controls. As most existing therapies are given during a clinical episode, we used a paradigm in which animals reached a clinical score of 2, and were then treated with peptide. Using this post-treatment paradigm, COG133 significantly reduced maximal clinical scores, accelerated the rates of recovery and increased the amount of recovery, compared to controls. Additional efforts to characterize inflammatory cells in spinal cord, by number and cytokine release, as a function of peptide treatment and clinical scores will be presented.

46. Cerebral Preconditioning Using Cortical Application of Hyperosmotic Salts: Effect on mRNA Levels Encoding Inflammatory Mediators and Trophic Factors

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Preconditioning the brain with a sublethal stress induces profound tolerance to a subsequent episode of ischemia. One of the preconditioning stimuli is application of high concentrations of KCl or NaCl to the cerebral cortex. Application of KCl causes a small lesion in the frontal cortex and evokes multiple episodes of cortical spreading depression (CSD), while NaCl causes a small lesion in absence of CSD. The objective of the present study was to compare the effects of KCl versus NaCl on the levels of mRNAs encoding neuroprotective proteins, such as trophic factors and inhibitors of inflammation. Male Sprague-Dawley rats were anesthetized with halothane/nitrous oxide, and the brain was preconditioned by applying KCl (2 M) or NaCl (5 M) to the intact dura over the frontal cortex of the left hemisphere for 2 hours. Samples from the frontal, parietal, and occipital cortices of both hemispheres were homogenized and extracted for RNA, and the extracts were analyzed using Northern blots. Application of KCl increased levels of mRNAs encoding feedback inhibitors of inflammation, tristetraprolin (TTP) and suppressor of cytokine signaling-3 (SOCS3), and brain-derived neurotrophic factor (BDNF) in both the frontal and parietal cortex. Application of NaCl also increased the levels of TTP and SOCS3 mRNA, but only in the frontal cortex. In this region, NaCl also increased levels of mRNA-encoding ciliary neurotrophic factor (CNTF), but not BDNF. These results demonstrate that upregulation of TTP, SOCS3, and BDNF following application of KCl is due to CSD, rather than the cortical lesion. By contrast, the induction of tolerance to ischemia following application of NaCl may be related to upregulation of CNTF.

47. AMPA Receptor Potentiation Driven through Glutamate Metabotropic 2/3 (mGlu2/3) Receptor Blockade: Antidepressant-Like Activity

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The glutamate metabotropic 2/3 receptor (mGlu2/3) antagonist 9H-Xanthene-9-propanoic acid, α-amino- α -[(1S,2S)-2-carboxycyclopropyl]-, (αS)-(9CI) or LY341495 could have antidepressant activity. Using pharma-

cological tools and transgenic mice, we evaluated the role of mGlu2 and mGlu3 receptors in these in vivo effects. LY341495 decreased immobility in the mouse forced swim test as did imipramine and decreased marble burying as did fluoxetine without impairing rotorod performance. The effects of 341495 in both assays were prevented in mice devoid of mGlu3 receptors. Deletion of the mGlu2 receptor attenuated the effects of LY341495 in the forced swim test but not in marble burying. The role of AMPA receptors was defined in the forced swim test by the demonstration that the antagonist NBQX prevented the effects of LY341495 but not the effects of imipramine. The confluence of data indicates that LY341495 produces its effects in vivo in mice through its interaction with mGlu2 and mGlu3 receptors, an effect which functionally amplifies AMPA receptor function. AMPA receptor potentiators also decrease immobility in the forced swim test. A model of antidepressant efficacy is proposed in which AMPA receptor potentiation plays a pivotal role, an effect that can be modulated both by traditional antidepressants and by blockade of mGlu2/3 receptors.

48. Naltrexone and Fluoxetine for Heroin Dependence Treatment in St. Petersburg, Russia

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Methods: 280 heroin addicts who provided informed consent were randomized to a 6 month course of biweekly drug counseling and one of four groups of 70 subjects/group: Naltrexone 50 mg/day (N) + Fluoxetine 20 mg/day (F); N + Fluoxetine placebo (FP); Naltrexone placebo (NP) + F; or NP + FP. Medications were administered under double-dummy/double-blind conditions.

Results: 414 patients were asked if they would be interested; 343 gave informed consent and 280 met study entrance criteria and were randomized. At the end of 6 months, 43% of subjects in the N+F group remained in the study and had not relapsed as compared to 36% in the N+FP group, 21% in the NP+F group, and 10% in the NP+FP group. Based on retention and non-relapse at 6 months, N+F was more effective than NP+FP ($p<0.001$), or NP+F ($p<0.01$); N+FP was more effective than NP+FP ($p<0.001$) or NP+F ($p<0.05$); NP+F was not more effective than NP+FP ($p=0.1$), and N+F did not differ significantly from N+FP ($p=0.2$). However women receiving N+F showed a trend toward statistical significance as

compared to women receiving N+FP (p=0.09), probably due to a higher level of depression, anxiety, and anhedonia in women at study initiation.

49. Uncoupling Protein 2 (UCP-2) Regulates Expression of Immune Recognition Molecules in Neural Stem Cells

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Although oxidative stress is an important mediator of neural cell death in neurodegenerative disorders, its effects on neural stem cells (NSCs) are virtually unknown. We hypothesize that reactive oxygen species (ROS), purported mediators of neurodegeneration, induce the expression of immune recognition molecules on the surface of NSCs, making them vulnerable targets for destruction by the immune system. By examining the mouse C17.2 NSC line using flow cytometry, we found that NSCs express the Fas (CD95) death receptor and B7.1 co-stimulatory molecule. Furthermore, hydrogen peroxide and rotenone (ROS-forming pesticide) upregulated B7.1 expression. To investigate whether NSC's response to ROS can be attenuated, we examined the role of UCP-2, a protein which increases anti-oxidative capacity and reduces expression of immune recognition molecules on tumor cells. For this purpose, we developed a C17.2 cell line stably expressing mouse UCP-2. Stable transfectants expressing high levels of UCP-2 had a decreased upregulation of B7.1 in response to rotenone when compared to controls. Although these transfectants also contained greater amounts of ROS, their survival under rotenone stress was equal to that of control transfected cells. We conclude that NSCs upregulate surface expression of immune recognition molecules in response to oxidative stress and that overexpression of UCP-2 moderates this response in spite of increasing cellular stress.

50. Chronic Stress-evoked Alterations of Noradrenergic Autoreceptor Function in Locus Coeruleus Neurons

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Previous studies show that chronic stress exposure intensifies the response of noradrenergic neurons of the locus coeruleus (LC) to excitatory inputs. We have demonstrated that chronic exposure of rats to cold stress enhances both the increase in extracellular norepinephrine (NE) levels and

LC firing rate in response to electrical activation of sensory input or ICV administration of CRH. The sensitized response of LC neurons is at least in part due to changes within the LC neurons themselves because the sensitized response is sustained in the in vitro brain slice. Based on the observation that the sensitization of LC neurons is most evident under evoked conditions, we hypothesized that chronic stress exposure altered inhibitory feedback control of LC neurons. In the present experiments, we assessed the inhibitory response to increasing doses of the α_2-autoreceptor agonist, clonidine, using single unit recordings of LC neurons following chronic cold exposure.

By plotting dose-response curves for individual neurons, we observed that the ED50 of clonidine-evoked inhibition was significantly increased following chronic stress exposure (2 weeks, 5°C) both during in vivo recordings in halothane-anesthetized rats as well as in vitro recordings. The increased ED50 observed in vitro was correlated with an increase of basal firing rate of LC neurons, perhaps as a result of decreased autoreceptor-mediated inhibition.. These results demonstrate that α_2-autoreceptor signaling is decreased following chronic cold exposure. Regulators of G-protein Signaling (RGS) proteins, by suppressing G protein signaling, are good candidate mediators of the reduced autoreceptor signaling following chronic cold stress. To assess whether RGS protein activity mediates aspects of diminished autoreceptor function in LC neurons, we have begun to examine the effect of chronic cold exposure on RGS proteins expression using quantitative Western blotting.

Alterations in autoreceptor function may contribute to adaptations in the noradrenergic system in response to physiological challenges and help to maintain optimized vigilance, but may eventually contribute to the pathologically enhanced activation of the noradrenergic system observed in patients suffering from mood disorders.

51. Delta9-THC Antagonizes Endogenous Cannabinoid Signaling in Autaptic Excitatory Hippocampal Neurons

Alex Straiker and Ken Mackie

Depolarization-induced suppression of excitation and inhibition (DSE/DSI) appear to be important forms of short-term retrograde neuronal plasticity mediated by endocannabinoids and activating presynaptic cannabinoid CB1 receptors. CB1-dependent DSE can be elicited from autaptic cultures of excitatory mouse hippocampal neurons. We sought to explore the relationship between the chief psychoactive ingredient of marijuana and hashish--delta9-tetrahydrocannabinol (delta9-THC)—-and DSE. Interest-

ingly, delta9-THC fails to inhibit autaptic EPSCs, yet readily occludes both DSE and EPSC inhibition by a synthetic CB1 agonist, WIN 55212-2. Furthermore, with long-term exposure (~18 hrs), delta9-THC desensitizes CB1 receptors.

In addition to DSE there exists a parallel Gq-coupled receptor-dependent retrograde inhibition--also via endocannabinoids and CB1 receptors--that we will refer to as metabotropic suppression of excitation (MSE). MSE is also antagonized by delta9-THC.

Thus it appears that in autaptic hippocampal neurons delta9-THC acts primarily by antagonizing cannabinoid signaling. These observations stand in considerable contrast to what has been assumed over the last 40 years, i.e. rather than mimicking or 'hijacking' endogenous signaling, delta9-THC may instead act by antagonizing the endogenous cannabinoid signaling system.

52. Correct Trials that Follow Errors Rely on a Subcortical Feedback Circuit

Henry H. Holcomb, Laura M. Rowland, Julie McEntee, Elena Spieker, Carlos Cortes, Matthew Tinnirella, and Malle Tagamets

Background. When learning how to make accurate judgments about subtle or ambiguous phenomena people rely heavily on feedback. In this functional magnetic resonance imaging (fMRI) study we studied how healthy subjects learn in conjunction with trial-by-trial feedback. Provided with a visual match-to-sample spatial task our subjects were expected to learn by maintaining neural activity patterns associated with correct choices, and by changing neural activity patterns following incorrect choices. This event-related fMRI study expected to find significantly different patterns in those correct choices that followed correct choices(C/C), compared to those correct choices that followed incorrect trials (I/C). Methods. Seventeen healthy subjects (mean age = 36.8 years, SD = 10.1) participated (6 females). Scans were acquired on a Philips 3 Tesla magnet at the F.M. Kirby Functional Imaging Center. The first twenty minutes of scanning used a visual-match-to-sample task without feedback. The second twenty minutes of scanning provided feedback regarding the accuracy of every trial. Results. C/C trials exhibited a significantly different BOLD activity pattern from I/C trials. IC trials were characterized by a significant BOLD response in a subcortical feedback ensemble including: midbrain, putamen, thalamus, and habenula. CC trials were characterized by robust BOLD responses in dorsal and ventral frontal cortical regions. IC and CC trials exhibited similar high signals in anterior cingulate and parietal cortex. Comment. These findings suggest that the neural substrate for task correction depends substantially on dopa-

mine related brain regions. In contrast the neural substrate for task maintenance may depend heavily on dorsal and ventral frontal cortex.

53. Sustained, 6 Month Antiviral Benefits in HIV Patients Receiving Peptide T: Flushing of Cellular Reservoirs and Reduction of Plasma Viral Load.

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Persistently HIV infected monocyte/macrophages and derivative brain microglia, comprise difficult to treat reservoirs that contribute greatly to NeuroAIDS and are the main impediment to a durable treatment or cure. Current HAART therapies do not control monocyte infection and infected T cells remain, sources of continual reinfection in the body. Therapies, especially non-toxic ones, which address these current therapeutic limitations are needed and hold promise to achieve new benchmarks in patient antiviral treatment. We have therefore studied the CCR5 entry inhibitor DAPTA (Dala1-peptide T-amide) for antiviral effect by analyzing stored plasma samples from the randomized double-blind placebo-controlled trial of peptide T for HIV-associated cognitive impairment conducted in the mid-1990's (Heseltine et al., Arch Neurol. 1998 55(1): 41-51.) PCR (Roche Amplicor) analysis of plasma (16 placebo, 17 DAPTA) found a significant reduction (0.54 log 10, p=. 037) change in viral load between baseline and month 6. Analyses of CSF (44 placebo, 48 DAPTA) found that the placebo group showed slight increase (.06 log 10), while the DAPTA showed a slight decrease (-.024 log10), ns. A 6 month open-label study of eleven long-term infected (mean=17 years) patients with stable persistent plasma HIV RNA examined cellular and plasma viral burden. Low plasma viral load did not change in this stable non-progressor cohort, and infectious virus could not be isolated from their plasma suggesting it was noninfectious. Cell derived, infectious virus was however detected and progressively less virus could be isolated from white blood cells (PBMC's) with DAPTA. All patients which were positive for virus isolation by co-culture at baseline (6/11) became co-culture negative by 24 weeks. DAPTA also flushed the persistently infected blood monocyte reservoir to undetectable viral levels in most patients as shown by PCR analysis. Integrated HIV in total PBMCs became undetectable after 44 weeks in one patient we have followed. Five of eleven had a mean CD4 increase of 33%. Immune benefits also included a four-fold increase in gamma-interferon-secreting T-cells (antiviral cytotoxic T cells)

which peaked at 8-12 weeks and preceded viral declines suggesting viral clearance may be immune mediated. Peptide T therefore can be shown to have antiviral effects on both cellular and plasma viremia, with no toxicities, and these effects were apparent at 6 months indicating that viral resistance to therapy was not apparent.

Don't forget to visit the exhibitors in Sunshine throughout the week.

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Panel • Sunday 4:30–6:30 PM • Storm Peak

Steroids, Polyglutamine Toxicity, and Motor Neuron Degeneration

Diane Merry, Andrew Lieberman, Angelo Poletti, and Marc Diamond

Neurodegenerative disorders caused by expanded CAG/glutamine tracts share many common mechanisms, but only spinal and bulbar muscular atrophy (SBMA) is characterized by hormone-dependent disease onset and progression. The finding that androgens are required for motor neuron toxicity in SBMA has suggested new therapeutic avenues and has promoted studies into the biochemical and cellular sequelae of ligand binding to the mutant androgen receptor. New animal and cell-based models have been developed that reproduce important features of SBMA and provide a clearer understanding of disease mechanisms. These models have highlighted the importance of intracellular localization of the mutant protein, and have led to a closer examination of proteasomal dysfunction, receptor misfolding and oligomerization, and altered androgen receptor function in disease pathogenesis. Many of these same factors may affect disease progression in other degenerative disorders caused by expansions of CAG repeats.

This panel will discuss the molecular and cellular consequences of ligand binding to the mutant androgen receptor in several models of SBMA. Diane Merry will lead off and describe the importance of nuclear degradation of the expanded glutamine androgen receptor by the ubiquitin-proteasome pathway. Andy Lieberman will describe features of a new knock-in mouse model of SBMA that has refined our understanding of the relative roles of loss-of-function and toxic gain-of-function in the disease phenotype. Angelo Poletti will review the effect of ligand binding to the mutant receptor on nuclear and cytoplasmic proteasomal degradation of protein substrates, and Marc Diamond will discuss the effect of hormones on androgen receptor oligomerization.

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

Black Diamond (a.k.a Brain-Derived) Neurotrophic Factor: Skiing the Cortical Circuit

Beth-Anne Sieber, Kevin Jones, David Ginty, Luis Parada, and Francis Lee

Brain-Derived Neurotrophic Factor (BDNF) modulates a wide range of CNS processes including neuronal survival, growth, neurogenesis, synaptic plasticity, and neurotransmission. In addition, a single nucleotide polymorphism (Val66Met) in the human BDNF gene resulting in a prodomain substitution at position 66 from a valine (Val) to methionine (Met) has recently been linked to hippocampal-dependent memory impairments and susceptibility to neuropsychiatric disorders. This panel will present novel transgenic models for the basic neurobiological mechanisms through which BDNF signaling affects the development and function of related cortical circuitry. Kevin Jones will discuss use of tissue-specific BDNF knockouts to explore the functions of this factor in the development and plasticity of neocortical dendrites. David Ginty has developed a chemical-genetic strategy enabling conditional and reversible inhibition of neurotrophin/Trk receptor signaling in vivo. Using Trk receptor knock-in mouse models, he will address the role of TrkB signaling in the maintenance of neuronal connections and function in the adult nervous system. Luis Parada will discuss conditional knockout strategies designed to assess TrkB function in neurogenesis and synaptic plasticity in adult hippocampus. Francis Lee will present new observations in transgenic knock-in mice containing the variant BDNF (Val66Met), which exhibit hippocampal alterations and may provide an in vivo model system to assess clinical abnormalities associated with this human genetic variant. This panel will highlight new findings on the mechanisms by which neurotrophic factors contribute to the development and plasticity of cortical circuitry, as well as to consider how these discoveries impact our understanding of CNS function relevant to both health and disease.

Panel • Sunday 4:30–6:30 PM • Rainbow

Genetics, Signalling, and Therapeutic Intervention through the GABAB Receptor

David Farb, Menelas Pangalos, Bernhard Bettler, and David C.S. Roberts

GABA acts through G-protein coupled GABAB receptors to hyperpolarize the postsynaptic membrane and modulating synaptic transmission. GABAB receptors have been implicated in a variety of neurological and psychiatric disorders. For example, pre-clinical and clinical evidence suggest

that GABAB agonists may be useful in the treatment of drug addiction. But linking the behavioral, cellular, genetic, and pharmacological actions of GABAB agonists through a comprehensive model for GABAB receptor physiology remains a challenging goal.

Functional GABAB receptors are usually observed only upon co-expression of subunit subtypes GABAB1a or GABAB1b with GABAB2 subunits in heterologous cells, providing strong evidence for heteromerization between GABAB1 and GABAB2 subunits. GABAB1 subunits are also essential for all GABAB signaling in vivo: Mice lacking GABAB1 subunits lack detectable electrophysiological, biochemical, or behavioral responses to GABAB agonists.

There remains a long-standing controversy regarding the molecular make-up of pre- and postsynaptic GABAB receptors and whether receptors localize to excitatory or inhibitory terminals, or both. Menelas Pangalos will discuss the GABAB signalosome as a case study for understanding effective partnering of GPCRs. David Farb will discuss how GABAB1a and GABAB1b, arise from the GABAB1 gene by differential promoter usage and transcriptional regulation of GABABR subunit gene expression. Bernhard Bettler will discuss the genetic dissection of GABAB receptor physiology using the knock-in mice and pre-embedding electron microscopy to directly visualize the GABAB1a and GABAB1b protein at the subcellular level. David Roberts will discuss how the development of a new generation of GABAB agonists holds promise for the treatment of addictive disorders.

Panel • Sunday 4:30–6:30 PM • Sunset

The Complexity of Monoaminergic Modulation of Neocortical Excitability

Marco Atzori, Kuei-Yuan Tseng, Alfredo Kirkwood, Zhen Yan

Monoaminergic modulations of neocortical neuronal activity have important physiological implications and are involved in many neurological conditions from drug addiction to psychiatric disease. Understanding the cellular and molecular mechanisms of these neuromodulations will contribute to the establishment of the critical neural basis relevant for monoamine-dependent cognitive function and synaptic plasticity in the neocortex.

In this panel, we will provide an integrative point of view on how monoamines can exert a powerful influence on cortical short- and long-term synaptic plasticity and their fine-tuning underlying their postnatal devel-

opment. Alfredo Kirkwood will show how norepinephrine determines the polarity of synaptic plasticity in the visual cortex. Kuei Tseng and Zhen Yen will present an example of major functional rearrangements occurring during postnatal development of the prefrontal cortex by demonstrating the modulatory action of different dopamine and serotonin receptors on the excitability of pyramidal neurons. Marco Atzori will present data suggesting that dopamine interferes with muscarinic-mediated inhibition of fast neurotransmission in the temporal cortex, presumably through cross-talk between second-messenger cascades.

We will discuss and integrate the complex modulation of synaptic plasticity with the behavioral and cell physiology perspective by proposing a possible common mechanism coupling the impact of dopamine, norepinephrine, and serotonin on cortical functioning during different periods of postnatal maturation.

Panel • Sunday 4:30–6:30 PM Skyline

As the Time Goes By: How the Brain Times Internal and External Events

Aldo Badiani, Deborah Harrington, Richard Ivry, Matthew Matell, Sean Hinton

The manner in which the brain is able to represent temporal information has been the subject of considerable study. Until recently the weight of evidence in favor of, or against, the existence of internal clocks has come more from theoretical considerations than from hard core neuroscience. This state of affairs has changed dramatically in the last decade owing to the emergence of a considerable set of empirical studies investigating the neural systems involved in a wide range of tasks involving temporal processing. Furthermore, specific alterations of subjective and objective time processing have been demonstrated in individuals affected by psychiatric and neurological conditions.

The speakers in this panel were instrumental not only in bringing about the recognition that interval timing plays a crucial role in cognitive, behavioral, and motor tasks but also in mapping the relevant brain circuits using various methodologies of cognitive neuroscience. Deborah Harrington will review the evidence, from converging approaches, in favor of the existence of specific neural substrates of temporal processing. Matt Matell will discuss the involvement of the basal ganglia in temporal control, as indicated by pharmacological and lesion studies, and by electrophysiological

recordings. Sean Hinton will discuss the role of frontal-striatal circuitry and the cerebellum in the production of rhythmic timing in healthy controls and patients with Parkinson's disease and Huntington's disease. Finally, Richard Ivry will discuss the involvement of the cerebellum, conceptualized as a network of interval-based timing elements, in the temporal processing of cognitive and motor functions.

Sunday • 4:30–6:30 PM • Mt. Werner

Ischemia-induced Neuronal Death: New Channels and New Targets

R. Suzanne Zukin, Elizabeth Jonas, Roger Simon, and Gabriel Haddad.

Transient forebrain or global ischemia induces delayed cell death with many features of apoptosis. A hallmark event in the early postischemic period is enhanced permeability and disruption of functional integrity of the outer mitochondrial membrane. The precise mechanisms by which mitochondrial function is disrupted are unclear. Recent studies have revealed new channels implicated in ischemic cell death. Zukin will review evidence for a role for Ca2+-permeable AMPA receptors in the neuronal death associated with global ischemia. She will present findings that these channels mediate the late rise in zinc and death of hippocampal CA1 neurons. Jonas will present recent evidence that ischemia triggers activation of large, multi-conductance channels in the mitochondrial outer membrane. The channels are inhibited by NADH, indicative of a role for VDAC and by the membrane-permeant Zn2+ chelator TPEN, indicative of a role for Zn2+ in channel activation. These findings suggest novel mechanisms by which ischemia disrupts functional integrity of the outer mitochondrial membrane and initiates the caspase cascade. Simon will discuss evidence that acidosis activates Ca2+-permeable acid-sensing ion channels (ASICs), inducing glutamate receptor-independent, Ca2+-dependent, neuronal injury inhibited by ASIC blockers. Whereas cells lacking endogenous ASICs are resistant to acid injury, transfection of Ca2+-permeable ASIC1a promotes sensitivity. These findings reveal a previously unappreciated role for ASICs in neuronal death. Haddad will review evidence that Ca2+-activatable K+ channels are critical to hypoxia-induced cell death. Together, these studies reveal advances in our understanding of molecular and cellular mechanisms underlying neuronal death and disclose new potential therapeutic targets for stroke.

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

Time Dependent Changes in Drug Seeking after Withdrawal: Cellular, Molecular, Systems, and Behavioral Aspects

Patricia Di Ciano, Yavin Shaham, Paul Vezina, and Terry Robinson

In the present panel we will present new data on the neuronal mechanisms underlying the time-dependent changes in cocaine-taking behavior after withdrawal from the drug, as measured in rat models. Yavin Shaham (IRP/NIDA) will present recent results from studies in which his research group examined the role of ERK signalling in the amygdala and GDNF in the VTA in the progressive increase in cue-induced cocaine seeking after withdrawal from drug self-administration, a phenomenon termed incubation of cocaine craving. Terry Robinson will discuss the enduring consequence of limited versus extended access to self-administered cocaine on brain, behavior and cognitive function following varying periods of withdrawal. Patricia Di Ciano will present behavioral and neuroanatomical data derived from studies in which she used a novel learning model where rats demonstrate persistent drug seeking in the presence of the cocaine-associated conditioned reinforcers over extended withdrawal periods. Di Ciano will present data suggesting that blockade of protein synthesis in the BLA disrupts a reconsolidation process that mediates the persistent cocaine-seeking in her model. Paul Vezina will review evidence indicating that long-lasting neuroadaptations in dopamine and glutamate neurotransmission in the nucleus accumbens underlie the enhanced drug-taking and reinstatement observed in psychostimulant-sensitized rats. In this context, recent evidence for changes in AMPA receptor trafficking, its potential link to enhanced dopamine overflow and the modulation of both by CaMKII will be reviewed.

Panel • Sunday 8:30–10:00 PM • Sunset

More Fats, Fewer Fits: the Ketogenic Diet in Epilepsy from Bedside to Bench

Maciej Gasior, Adam Hartman, Jong Rho, and Kristopher Bough

The Ketogenic Diet (KD) had been considered an effective treatment option for patients with epilepsy before it was completely overshadowed by the introduction of antiepileptic drugs in the late 1930s. Unfortunately, even the newest antiepileptic drugs fail to control seizures in nearly 30% of all epileptic patients. The renaissance of the KD in the mid-1990s has underscored the true medical need for alternative treatments of epilepsy.

Despite extensive clinical experience, how the KD works remains the most pertinent and unresolved question. Understanding the mechanisms of KD action is crucial for optimizing conditions of the diet to achieve the best therapeutic outcome, better understanding of the pathophysiology of refractory epilepsy, and subsequent development of new treatment modalities.

This panel will focus on reviewing current clinical and experimental findings relevant to the mechanisms of action of the KD. Adam Hartman will review current clinical literature on different modifications of the KD and their efficacy in patients with specific types of epilepsy. Maciej Gasior will compare anticonvulsant efficacy of the KD and antiepileptic drugs with known mechanisms of action in experimental models of seizures. Two later presentations will introduce new concepts on how the KD may work. Jong Rho will talk about the antioxidant actions of the ketogenic diet; he will focus on the effects of fatty acids and ketone bodies. Kristopher Bough will discuss possible theories of anticonvulsant and antiepileptogenic actions of the KD based on recent findings with cDNA microarray experiments.

Workshop • Sunday 8:30–10:00 PM • Mt. Werner

Dopamine Concentration Transients: What's the Point of Fast Dopamine Transmission?

Donita Robinson, Joseph Cheer, Saleem Nicola, Jeremy Seamans, and Patricio O'Donnell

Technical advances in real-time measurements of dopamine concentrations demonstrate that dopamine fluctuates on a subsecond timescale in awake, behaving animals. These dopamine transients occur at a baseline frequency and increase with behavioral activation, environmental stimuli and drug administration. To date, the post-synaptic effects of these rapid release events remains elusive. One conceptual obstacle is the temporal mismatch between the signal and the putative effect: if dopamine post-synaptic actions last minutes, what's the point of transients occurring at faster frequencies, time locked to discrete behavioral events? Do dopamine transients have a different function than the slower changes in extracellular dopamine measured with microdialysis? Joseph Cheer will discuss results from emerging technology that allows simultaneous measurements of dopamine transients and unit activity in behaving animals: do transients build the neuronal code, or just shape it? Saleem Nicola will discuss the effects of reducing dopaminergic neurotransmission on the firing of neurons in the ventral striatum of behaving animals. Jeremy Seamans will discuss evidence of glutamate release from dopamine neurons that might provide the "fast" in fast transmission while DA mediates slow transmis-

sion in the same cells. Patricio O'Donnell will discuss dopamine effects on membrane potential and excitability in anesthetized rats—does it translate into awake animals? The discussants will limit their formal comments to < 5 min. and one slide to ensure ample time for discussion. Dopamine enthusiasts and skeptics are invited to participate.

Panel • Sunday 8:30–10:00 PM • Storm Peak

Functional Properties of MicroRNAs in the Nervous System

Andrea C. Beckel-Mitchener, Kenneth S. Kosik, Wigard P. Kloosterman, Peng Jin, and Michael T. McManus

The role of miRNAs in living systems is an emerging area of investigation. Through various methods and in a number of model systems, numerous miRNAs have been identified, many of which are present in the nervous system, and elucidation of their functional properties will likely yield important insights into unexplored post-transcriptional regulatory pathways. MicroRNAs are ~21 nucleotides long and are derived from a precursor RNA that is processed by the enzyme Dicer. MicroRNAs are able to anneal to cellular transcripts forming double-stranded RNA species that may be subsequently targeted for degradation or may be maintained in an "untranslatable" state. Studies indicate that there is a high level of spatial and temporal specificity for a number of the miRNAs identified, suggesting some degree of restricted or targeted functionality. Panel presentations will focus on various aspects of miRNA expression. Kenneth Kosik will provide an overview of miRNA processing and will speak on the role of miRNAs in cell identity. Wigard Kloosterman will discuss neural expression patterns of miRNAs from multiple organisms. Peng Jin will speak on the possible involvement of the miRNA pathway in Fragile X syndrome, a developmental disorder and the most commonly inherited form of mental retardation. Finally, Michael McManus will discuss recent data from conditional Dicer-knockout mice, that should provide important insights into the biology of small RNAs in development and disease.

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

A DISCourse on DISC

Barbara Lipska, Joseph Callicott, Akira Sawa, and Nick Brandon

Susceptibility genes for psychiatric disorders represent basic mechanisms of disease and identify pathogenic molecular pathways. DISC1 (Disrupted-in-Schizophrenia-1) is a promising candidate susceptibility gene

for schizophrenia and affective disorders with molecular effects related to development and neuroplasticity. This panel will present new evidence that DISC1 is a complex multifunctional protein that interacts via distinct domains with numerous components of intracellular machinery. In cell and animal models, mutant C-terminus-truncated DISC1 disrupts intracellular transport, neural architecture, and migration, perhaps because it fails to interact with its binding partners. Putative aberrant DISC1 protein in individuals carrying high-risk mutations engages in abnormal interactions with specific binding partners and causes abnormalities in a DISC molecular pathway involved in mitochondrial transport and synaptic development and plasticity. Joe Callicott will present genetic evidence for the involvement of DISC1 in schizophrenia illness from linkage mapping and association studies and evidence that allelic variation in DISC1 affects hippocampal structure and function. Akira Sawa will present data indicating that DISC1 is a multifunctional protein with several isoforms localized to centrosome, synapse and the nucleus, and involved in neurodevelopment. Sawa will also show data from genetically-engineered DISC1 mice, transgenics, and knockouts. Nick Brandon will describe the expression and localization of DISC1 and its protein interaction network, including functional characterization studies with DISC1 interactors such as Nudel. Barbara Lipska will show that the expression of three DISC1-interacting molecules, FEZ1, LIS1 and NUDEL, is altered in brain tissue of patients with schizophrenia and that high-risk DISC1 genotypes predict levels of their expression.

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

Is Abnormal Phosphorylation a Common Pathway in Neurodegeneration?

Karen Duff, Sashi Kesavapany, David Miller, and Mark Cookson

Several recent lines of evidence from Alzheimer's disease (AD) and Parkinson's disease (PD) research suggest that aberrant phosphorylation is an important pathogenic mechanism in neurodegeneration. This panel will examine the roles of phosphoproteins (tau, alpha-synuclein) and kinases (cdk5, GSK3, PINK1, dardarin) in neurotoxicity. Karen Duff will discuss the effects of kinase-mediated abnormal phosphorylation on tauopathy and amyloidosis with particular reference to the role of GSK3 and cdk5. Her group has shown that enhancement of p25/cdk5 can enhance both tau phosphorylation and tangle formation, as well as increase beta-amyloid production. Inhibition of GSK3 by lithium can reduce early tauopathy, and reduce beta-amyloid production. Sashi Kesavapany will focus on the ability of cdk5 inhibitory peptide (CIP), which is derived from its activator p35, to

selectively inhibit p25/cdk5 activity as well as decrease both the presence of both hyperphosphorylated tau and apoptosis caused by neurotoxic insult with beta-amyloid. David Miller has found that phosphorylated alpha-synuclein is abundant in brain extracts from PD patients that carry a triplication of the SNCA gene. Hyperphosphorylation of alpha-synuclein at serine 129 may be a critical event in alpha-synuclein pathogenesis. Mark Cookson will describe the impact of PINK1 and dardarin on cell loss in PD. Recent work suggests kinases can have neuroprotective properties that are lost with recessive mutations (PINK1) or may be damaging when gain of function mutations leads to neurotoxic effects (dardarin). The alluring theory that alpha-synuclein is a direct or indirect substrate of these kinases will be addressed. These talks will provide an assessment of how this burgeoning research topic may provide new advances in the understanding and treatment of neurodegenerative diseases.

Panel • Monday 7:30–9:30AM • Mt. Werner

Neuroprotective Strategies for Spinal Cord Injury: How Do We Get beyond Methylprednisolone?

Edward Hall, Lynne Weaver, Alan Faden, Scott Whittemore

Spinal cord injury (SCI) is one of the most devastating consequences that a human being can suffer. However, most SCIs do not involve transaction of the spinal cord, but rather involve contusion, compression, or stretch-induced injuries. Much of the damage that occurs to the spinal cord tissue is due to a secondary injury process which is potentially modifiable by pharmacological treatments. The only agent that has been demonstrated to improve neurological recovery in clinical SCI trials is the glucocorticoid steroid methylprednisolone (MP), which acts to inhibit post-traumatic free radical-induced lipid peroxidation when administered in high doses. However, the effects are modest on average, and the treatment is controversial due to the potential for serious glucocorticoid side effects. Thus, there is a need for improved neuroprotective strategies to build upon, or replace, MP. The panel will explore some of the more promising and novel neuroprotective approaches that are on the horizon. Edward Hall will briefly overview post-SCI secondary injury and the neuroprotective efficacy and limitations of MP therapy followed by a discussion of newer concepts for inhibition of oxidative damage in the injured spinal cord. Lynn Weaver will discuss the role of inflammatory mechanisms and the efficacy of anti-inflammatory agents in rat models of SCI. Alan Faden will present his studies on the role of cell cycle activation in secondary neurodegeneration and the neuroprotective effects of cell cycle inhibitors, which limit neuronal/oligodendroglial apoptosis, reduce glial scar formation, and

inhibit activation of microglia and associated inflammation. Lastly, Scott Whittemore will present recent data on modulating acute and sub-acute vascular responses after SCI as a means to preserve damaged tissue.

Panel • Monday 7:30–9:30AM • Storm Peak

Neurobiology and Clinical Pharmacology of Gammahydroxybutyrate: A Club Drug with Therapeutic Applications

O. Carter Snead, Federica Latta, Jed Black, and Thomas Kilduff

Gammahydroxybutyrate (GHB), a product of intermediary metabolism, has profound effects on the activity of the central nervous system, particularly on consciousness. Because of its extreme soporific effects, GHB has become both a drug of abuse and, paradoxically, a clinically useful therapeutic for treatment of the sleep disorder narcolepsy. Carter Snead will review the history of GHB, its emergence as a drug of abuse, current thoughts as to the mechanism of action of GHB, the absence of seizures observed in GHB-treated animals, and insights on GHB gained from studies of an inborn error of metabolism (succinic semialdehyde dehydrogenase deficiency). Federica Latta will discuss GHB facilitation of cortical slow wave activity and slow wave sleep in humans and compare the concomitant endocrine changes in GHB-induced and normal sleep. Jed Black will discuss the clinical trials that led to FDA approval of Xyrem®, the sodium salt of GHB, for treatment of the cataplexy symptom of narcolepsy, and more recent studies which demonstrate that GHB consolidates nocturnal sleep in narcoleptic patients, resulting in increased alertness on the subsequent day. Tom Kilduff will discuss behavior pharmacological studies of GHB in hypocretin/ataxin-3 mice, a murine model of narcolepsy, and the effects of GHB on hypocretin neurons and other brain regions involved in the regulation of sleep and wakefulness. The panel will thus integrate both clinical and pre-clinical studies on this fascinating molecule.

Panel • Monday 7:30–9:30AM • Sunset

Imaging Genetics: From Genes to Brain

Daniel Weinberger, Katherine Burdick, Steven Potkin, Andreas Meyer-Lindenberg

Most common neuropsychiatric disorders involve multiple genes, each with small biologic effects. One of the main difficulties in characterizing the genetic etiologies of common brain disorders has been identifying

the neurologic mechanisms by which the genes confer increased susceptibility. Neuroimaging has unique potential as a biologic readout in living brain to characterize these complex mechanisms. This panel will introduce the emerging field of imaging genetics and review recent breakthroughs in this rapidly evolving area. Katherine Burdick will discuss the relationship between functional variation in several dopamine subsystem genes, including DAT, DRD1, DRD2, DRD4, COMT & MAO-A, and the reactivity of corticostriatal reward circuits and their prediction of related behaviors such as novelty seeking and delayed gratification. Steven Potkin will review applications of fMRI to study genes related to psychosis (e.g.,COMT and BDNF). Specifically, Potkin will explain how these genes affect the patterns of functional connectivity of the prefrontal cortex during working memory. Andreas Meyer-Lindenberg will illustrate the unique capability of functional neuroimaging to validate the effects of ambiguous haplotypes within a gene, using fMRI as a functional readout of the biologic state of gene function in brain. Imaging may represent the only readily available strategy to functionate balanced polymorphisms within a gene that complicates genetic association analyses. Finally, Daniel Weinberger will illustrate how functional imaging can be used to study interactions between genes that affect brain development and plasticity, using 5'HTTLPR and BDNF as examples.

Panel • Monday 7:30–9:30AM • Rainbow

Levitra for the Brain? Stronger and More Lasting Memories via PDE Inhibition

Donald Ingram, Greg Rose, James M. O'Donnell, Arjan Blokland

Providing various enzymatic functions in different tissues, phosphodiesterases (PDEs) act primarily to catalyze the hydrolysis of cyclic nucleotides. Encoded by at least 21 genes, 11 different PDE families, many with isoforms, have been identified. Increased attention has focused on brain PDEs as targets for cognitive enhancing drugs. Several known functions at the NMDA glutamate synapse, such as hydrolysis of cGMP by PDE-5 and hydrolysis of cAMP by PDE-4, have driven this interest. Thus, inhibiting specific PDE activity could enhance both presynaptic and postsynaptic NMDA receptor activity. Such drugs are already in use for other conditions, such as erectile dysfunction in the case of PDE5 inhibition. This panel will present recent research addressing the potential of PDE inhibition for cognitive enhancement. Donald Ingram will review the pharmacology involved and present data describing maze performance of young and aged rats following inhibition of PDE4 and PDE5. Greg Rose will focus on effects of

novel PDE4 inhibitors on learning and memory in rodents shown to extend memory in young animals, as well as to attenuate memory deficits in aged animals and in transgenic models of Alzheimers disease. James O'Donnell will also discuss data demonstrating the activity of various PDE4 inhibitors in models of short- and long-term memory, including a PDE4 subtype-deficient mouse, and relate findings to PDE4 involvement in NMDA receptor-mediated signaling. O'Donnell will also present new data on a PDE2 inhibitor. Arjan Blokland will review results from rodent studies comparing various PDE inhibitors on cognitive performance and dissecting their time-dependent effects.

Panel • Monday 7:30–9:30AM • Twilight

Ubiquitination in Neuronal Development and Synaptic Transmission

Lian Li, Yishi Jin, Ashok Hedge, Scott Wilson

Ubiquitination is a post-translational modification of proteins by covalent attachment of ubiquitin, a 76 amino acid polypeptide. Ubiquitination not only targets proteins for degradation by the proteasome, but also modulates protein activity and location in a manner analogous to phosphorylation. Recently, ubiquitination has gained attention of neuroscientists because of the growing importance of ubiquitination in controlling the nervous system function and in the pathogenesis of neurological diseases, such as Parkinson's disease, Alzheimer's disease, and spinocerebellar ataxia.

The focus of this panel is on the neuronal mechanisms of protein ubiquitination, and the science discussed will be highly interdisciplinary, encompassing genetic, molecular, cellular, and electrophysiological approaches to understand the role of ubiquitination in neuronal development and function. The speakers are among the most active in the ubiquitin neurobiology field and are also skilled and committed to provide an informative overview of neuronal protein ubiquitination/deubiquitination processes. Yishi Jin will discuss the role of E3 ubiquitin-protein ligase RPM-1/Highwire in regulating MAP kinase signaling pathway and synapse formation. Ashok Hedge will discuss the role of the ubiquitin-proteasome pathway in synaptic plasticity. Scott Wilson will discuss how a mutation in deubiquitinating enzyme Usp14 causes defective synaptic transmission and ataxia. Lian Li will discuss the identification of novel E3 ubiquitin-protein ligases and their role in regulating the neurotransmitter release machinery. We expect that this panel will foster extensive discussion of protein ubiquitination in both normal and pathological states.

Panel • Monday 7:30–9:30 AM • Skyline

Sensory Systems: From Receptors to Behaviors

Samer Hattar, Johannes Reisert, Jamie García-Añoveros, Ignacio Provencio, Steven Lockley

Organisms live in environments that are constantly presenting rewarding or punishing challenges and stimuli. Sensory systems allow organisms to detect and decipher stimuli, and respond accordingly either, consciously or subconsciously. Without such innate systems, organisms could not survive and adapt to the changing environmental inputs. Yet different sensory systems seem to achieve these functions using vastly different mechanisms. In recent years, atypical mechanisms have been discovered on how sensory systems detect stimuli and transduce their effects to the behavior of organisms. In this panel, we have chosen to present a sample of the advances made in some of the sensory fields from receptors sensing the environmental stimuli to behaviors being modified accordingly.

Olfaction, hearing and light detection for non-image forming functions are fundamental processes in nature across many organisms. Reisert will present research on the signal transduction pathway in the olfactory system. In his presentation, the differences between the phototransduction pathway and the olfactory signaling pathway will be highlighted, stressing the importance and roles of different molecular components of the pathway using electrophysiological analysis. García-Añoveros will report the identification of a Trp (transient receptor potential) channel that converts the sound signal into an electrical signal in ear hair cells. This channel is also responsible for transducing pain signals, a very different sensory modality from hearing. Provencio will show yet another surprising phenomena, which is that of photoreceptors in the retinal ganglion cells of the mammalian and primate retinas. In his presentation, the atypical roles and mechanisms of action of the new photopigment melanopsin will be highlighted. Finally, Lockley will present how different colors of light (activate different sets of photoreceptors) can differentially affect the circadian clock in humans and, consequently, the quality of sleep.

Panel • Monday 4:30–6:30 PM • Mt. Werner

Potential Long-Term Effects of Psychostimulant Use in ADHD

George Ricaurte, Una McCann, Benedetto Vitiello, Susan Andersen

Psychostimulants such as methylphenidate and amphetamine are mainstays of pharmacotherapy for the treatment of Attention Deficit

Hyperactivity Disorder (ADHD). Although the mechanisms by which psychostimulants improve symptoms of ADHD are not known, they are believed, at least in part, to be mediated via brain dopamine systems. Despite their proven efficacy, there has been concern that treatment with psychostimulants might be associated with lasting untoward effects on behavior, including an increased propensity for drug abuse. In addition, amphetamine is known to have the potential to damage brain dopamine axons and axon terminals in animals, and little is known about the neurotoxic potential of amphetamine in humans at doses used clinically. This panel will focus on preclinical and clinical research on the pharmacology and toxicology of psychostimulants, as used for the treatment in ADHD. Una McCann will set the stage for the panel, by reviewing neuroimaging studies of brain dopamine systems in humans with ADHD. Benedetto Vitiello will present data from studies demonstrating the efficacy and potential untoward effects of psychostimulants for the treatment of ADHD. Susan Andersen will present preclinical data in rodents addressing the possibility that treatment with methylphenidate might lead to lasting behavioral changes. George Ricaurte will conclude by presenting recent data in nonhuman primates suggesting that clinically relevant amphetamine regimens have the potential to produce persistent changes in brain dopamine systems. Each of the panelists will highlight areas in which there are gaps in current knowledge, and will suggest future research directions.

Panel • Monday 4:30–6:30 PM • Storm Peak

Arriving Soon to a Clinic Near You: Personalized Psychpharmacology, Using Genes to Predict Drug Response

John Kelsoe, Anil Malhotra, Greer Murphy, Daniel Mueller

The highly individual variation in drug response frequently makes clinical treatment a trial and error process requiring several months. It is likely that a substantial portion of this variability is genetic in nature. Pharmacogenetics offers the promise that drug response may be predicted and the sequence of treatments optimzed based on DNA tests. Positive results are now emerging from this field, suggesting that the era of such personalized psychopharmacology may not be far away. John Kelsoe will review the literature regarding genetic prediction of response to mood stabilizers in bipolar disorder. He will also present data suggesting that the gene for the BDNF receptor, NTRK2, is associated with lithium response. Anil Malhotra will review the first generation of pharmacogenetic studies of clozapine response and discuss new data from an ongoing prospective: randomized clinical trial in first episode schizophrenia suggesting that two DRD2

promoter region polymorphisms influence sustained clinical response to olanzapine and risperidone. Greer Murphy will present data from studies of polymorphisms in genes affecting antidepressant pharmacodynamics (receptors, transporters, signal transduction molecules) and pharmacokinetics (cytochromes, p-glycoprotein) in elderly patients with major depression treated with mirtazapine or paroxetine. Results showed strong effects for markers related to pharmacodynamics, but surprisingly little effect for variants affecting pharmacokinetics. Daniel Mueller will discuss the role of genetic factors on drug-induced side effects, including the relationship between functional polymorphisms in the serotonergic system and weight gain associated with second-generation antipsychotic drug administration, and data suggesting a role for dopaminergic receptor variation and typical antipsychotic-induced movement disorders.

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

The "Dark Side" of Aging: Cholinergic Signaling and Cognition

James Joseph, Donald Ingram, Nigel Grieg, Tetsuo Ashizawa

It is well known that neurodegenerative diseases such as Alzheimers disease (AD) increase as a function of age. However, it is also clear that the aged brain is "fertile ground" for the development of this disease since the vulnerability to various inflammatory or oxidative stress insults is enhanced as a function of age. The cholinergic system appears to be one of the most vulnerable to the ravages of time showing declines in both muscarinic receptor signaling and sensitivity that lead to declines in cognitive function. Given these considerations, it is important to ask what factors might pre dispose the aged brain to express these deficits and, ultimately, to sensitize it to the development of neurodegenerative disease. To attempt to answer these questions J. Regino Perez-Polo will discuss the effects of chronic aging on transcriptional regulation of the choline acetyl transferase (ChAT) promoter activity by the transcription factor NF-B. Jim Joseph will focus his discussion on second messenger systems in neuronal signaling and receptor properties that can enhance vulnerability to oxidative stress and inflammation in brain. Don Ingram will discuss effects of dietary restriction on cholinergic systems, and Nigel Greig will describe pharmacological interventions that might be useful to restore cholinergic function and cognition in aging and AD.

Panel • Monday 4:30–6:30 PM • Rainbow

Obesity, Diabetes, and the Brain

Paul Huang, Sean Didion, David Busija, Barry Levin

Obesity and diabetes are important clinical problems. The metabolic syndrome is a clinical constellation of features including abdominal obesity, insulin resistance, hyperlipidemia, and hypertension. Obesity, diabetes, and metabolic syndrome increase the risk for cardiovascular disease, including stroke and other forms of cerebrovascular disease. This panel explores the two-way interactions between the brain and the metabolic abnormalities seen in obesity, diabetes, and metabolic syndrome. Paul Huang will give an overview of the metabolic, vascular, and neurohumoral features seen in obesity and diabetes. Sean Didion will discuss molecular mechanisms of vascular dysfunction in diabetes and hypertension. David Busija will extend this theme to the CNS, describing specific effects of insulin resistance unique to the cerebrovasculature. Finally, the discussion will come full circle as Barry Levin discusses the influence of the brain and neurohumoral on metabolism and behavior, leading to the development of obesity and metabolic syndrome.

Panel • Monday 4:30–6:30 PM • Sunset

The Obsolete Cortical Module

Andrew Schwartz, Ralph Siegel, Robert Kass, Vivien Casagrande

A fundamental principle of systems neuroscience is that the brain is composed of discrete modules, each of which has a unique function. This concept began with neuroanatomical identification of distinct structures and was substantiated by mapping and lesion studies. As scientists and engineers, we are comfortable with modular construction, as all machines are built this way, with each piece having a distinct function. Electronic circuits are built with components, each having an identifiable input and output, and equations are used to describe their function. Recently however, the notion of neural modularity has become controversial. The borders of neural structures are rarely delineated clearly and the structures themselves were often defined with somewhat arbitrary criteria. Neurons composing these structures do not have uniform properties and always fire in relation to multiple parameters. Cells with similar functional properties can be found in multiple structures.

Finally, the maps often used to delineate a module are non-stationary.

Andrew Schwartz will describe findings from premotor and primary motor cortical studies in which neurons have the same high-level relation to movement in some contexts but differ in others. Ralph Siegel will show how maps, identified with optical imaging, vary over time. Rob Kass, will describe new methods that will make it possible to classify groups of cells with common combinations of functional properties. Vivien Casagrande will display new anatomical evidence for delineating cortical structures and the way they change.

We hope that someone can come forward to defend the concept of a cortical model from the WCBR attendees.

Panel • Monday 4:30–6:30 PM • Skyline

Role of AVP in Hypothalamo-Pituitary-Adrenal Activity

Stafford Lightman, Gabor Makara, Gilles Guillon, Greti Aguilera, Joe Herbert

CRH and vasopressin are both secretagogues for ACTH that act on pituitary corticotrophs in a synergistic manner to activate ACTH secretion. In this session, we will be discussing the importance of vasopressin in the regulation of HPA function and reactivity. Stafford Lightman will introduce the background with particular reference to the potential importance of AVP both in acute and chronic stress. Gabor Makara will then present a critical analysis of data both in support of and against a critical role of AVP on HPA axis responsiveness. Gilles Guillon will discuss the design of selective V1b agonists for rat VP receptors and how modification of VP on positions 1, 4, and 8 lead to a series of agonists with in vivo and in vitro selectivity demonstrated using pharmacological as well as functional tests. He will also talk about the structural-functional characteristics of the V1b receptor, with focus on the identification of residues responsible for receptor affinity and selectivity. Greti Aguilera will present evidence that VP has multiple roles in pituitary function, including upregulation of the V1b receptor, potentiation of CRH-stimulated ACTH secretion and trophic actions. Acutely, VP facilitates ACTH secretion by potentiating the stimulatory effect of CRH, while inhibiting basal and CRH-stimulated POMC transcription. Chronically, VP contributes to mitogenic activity in the pituitary without increasing the number of ACTH containing corticotrophs. These effects of VP may involve physical interaction between receptors, as suggested by the ability of V1b receptors to form homodimers as well as heterodimers with type 1 CRH receptors.

Panel • Monday 8:30–10:00 PM • Mt. Werner

Extracellular Signal-Regulated Protein Kinase in Plasticity: To Pull Up or To Slope Down?

Edda Thiels, Serena Dudek, Eric Klann, Arvind Govindarajan

Extracellular signal regulated kinase (ERK) has been the focus of important findings on activity dependent potentiation of synaptic strength (LTP) and memory formation. The attention on ERK stems from the enzymes' ability to couple activation of cell surface proteins to gene transcription. However, it recently has become clear that ERK also plays a crucial role in activity-dependent depression (LTD) and in RNA translation during synaptic and behavioral plasticity. In this panel, the regulation of ERK and its role in LTP and LTD as well as in transcription and translation will be discussed.

Serena Dudek will describe findings on the relation between NMDA receptor activation and action potentials, and the role of these two events in the activation of ERK at the synapse versus in the nucleus. Edda Thiels will discuss work on ERK coupling to the transcription factors CREB and Elk-1 during LTP versus LTD, and the role of these transduction pathways in general versus specific plasticity operations. Eric Klann will present evidence that the activation of both PI3K and ERK signaling cascades are required for metabotropic glutamate receptor-dependent LTD and that the two cascades converge to regulate translation initiation. Arvind Govindarajan will describe data that implicate ERK in translational regulation of diverse mRNAs in both LTP and LTD and that suggest a model in which ERK-mediated translational regulation, together with synaptic tagging and capture, facilitate the formation of long-term engrams at synapse clusters.

Workshop • Monday 8:30–10:00 PM • Storm Peak

Neurogenesis: Functions in Disease and Learning

Fritz Henn, Rene Hen, Fulton Crews, Karl Deisseroth

Neurogenesis clearly takes place throughout life in two sites in the CNS, one being the dentate gyrus of the hippocampus. Its role here is unclear. It has been proposed to be essential for learning, for the action of antidepressants, and decreases in neurogenesis have been suggested as a possible etiological factor in depression and possibly in addiction. All of these positions have been both supported and viewed critically in the literature. This workshop will present an outline of the evidence, the areas of conflict, and one model from computational neuroscience that suggests a function for the cycle of apoptosis coupled to the continual production of new cells. Behavioral models of depression and anxiety as well as drinking behavior

will be examined, and proponents of differing views should spark a lively discussion about the function of neurogenesis in the hippocampus.

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

New Things Connexins Do

Michael Bennett, Vytautas Verselis, Bruce Ransom, Alberto Pereda

Connexins used to form gap junctions containing channels between cells that you could see under the microscope. Now they do many more things (and some less—i.e., a visualized channel may not open). This workshop will address a few of these new phenomena.

Connexins have four membrane spanning domains, which contribute to channel lining. Orginally, M3 was thought to be the primary element. The substituted cysteine accessibility method (SCAM) indicates that M2 and part of the cytoplasmic loop are the major contributors (Vytautas Verselis).

Gap junction hemichannels were thought to be too leaky for the cell to allow opening before docking with a hemichannel in an apposed membrane. This reasonable argument turns out to be wrong, and many connexins make hemichannels that can open before docking with another hemichannel (Michael Bennett). The ATP lost can be signal to neighboring cells, and the Ca entering can initiate a propagated wave of rise in Ca.

In astrocytes, hemichannels provide a route for release of glutamate in addition to vesicular release and reverse operation of the transporter (Bruce Ransom). Thus, regulation of hemichannel opening is integral to astrocyte neuron reciprocal signaling. Hemichannel opening and glutamate receptor activation both regulate subsequent hemichannel activity and release of glutamate.

LTP of chemical and electrical transmission occurs at club endings on the Mauthner cell. Potentiation is NMDA mediated and limited to the single synapse; neighboring synapses are unaffected. This mode of facilitation may occur at vertebrate dendrodendritic synapses close to NMDA inputs from other cells.

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

Modulation of Inflammatory Status in TgAPP Mice

Doug Feinstein, MaryJo Ladu, Steve Barger, David Morgan

The inflammatory status of glial cells can contribute to both the exacerbation of AD pathology, as well as to disease resolution via Ab removal.

Knowledge of factors that regulate glial inflammation are therefore critical to understanding AD pathogenesis and therapy. In this session, Dave Morgan will discuss how microglial cells can adopt distinct activation states having different impacts on amyloid deposits in TgAPP brains. Steve Barger will describe the role of excitatory amino acids in microglial activation states that are neurodegenerative. Mary Jo Ladu will describe the ability of ApoE to regulate Ab-dependent inflammation and neurotoxicity. Finally, Douglas Feinstein will describe studies implicating endogenous noradrenaline as a key regulator of brain inflammation and Ab processing. Together, these talks will emphasize the fact that glial inflammation can have both beneficial as well as toxic consequences during the course of AD disease.

Panel • Monday 8:30–10:00 PM • Sunset

A Casualty of Neuroplasticity: The Changing Face of GABA(A) Receptors.

Shelley Russek, Amy Brooks-Kayal, Warren Tourtellotte, Sheryl Smith

Many of the processes that are crucial to the development of the nervous system and, subsequently, to its higher cognitive functions such as learning and memory, are also associated with the brain's dysfunction. Why is it that the immediate early genes (IEGs), such as the early growth response factors (Egrs), as well as their downstream targets such as CREB, are poised to respond to changes in excitability during normal brain function, and yet, the same responses may be maladaptive during conditions of imbalance? Although little is known regarding the molecular genetics of neuronal physiology, it is clear that the history of synaptic activity leaves its mark on the number and kind of GABA(A) receptors that are found in individual neurons.

Alteration in GABA(A) receptor subunit gene expression may play an important role in the etiology of temporal lobe epilepsy (TLE) as evidenced from the study of dentate granule cells (DGCs) in adult TLE patients and rodent models. DGCs in chronically epileptic rats express GABA(A) receptors with a unique pharmacology that reflects an increase in alpha 4 and decrease in alpha 1 subunit expression. In this Panel, Shelley Russek and Amy Brooks-Kayal will discuss regulation of alpha 4 gene (GABRA4) expression by Egr3, and regulation of GABRA1 by CREB and its co-repressor, ICER. Warren Tourtellotte will give a perspective on the role of Egrs in modulation of synaptic activity through induced effector genes, such as Arc. Sheryl Smith will show that withdrawal of neurosteroids that specifically activate alpha 4 containing GABA(A) receptors autologously upregulates GABRA4,

establishing another example that links receptor modulation to subunit gene expression.

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

New Light on the Nervous System: Applications of Ultrashort Laser Pulses

Kurt Ahrens, Michael Levene, Jeff Squier

The monumental difficulty of fully describing the structure and function of the mammalian brain continues to drive the development of novel measurement techniques. Optical methods that make use of the unique properties of high-intensity laser light are becoming increasingly popular and are better suited to take advantage of our rapidly growing body of genetic knowledge than other commonly used technologies (e.g., electrophysiology and functional magnetic resonance imaging).

Ultrashort pulses of laser light are now being used to illuminate the mammalian brain in a variety of ways. This panel will explore some of the new approaches that rely on nonlinear interactions between high-intensity coherent light and neural tissue. The examples presented by this Panel will provide insight into the current state of the art and future prospects for neural imaging with multiphoton laser microscopy. Kurt Ahrens will introduce the subject and present his research employing in vivo expression of genetically encoded fluorescent biosensors imaged with two-photon microscopy in awake, behaving Macaque monkeys. Michael Levene will discuss his work using nonlinear optical techniques and micro-optics enabling in vivo microscopy of deep brain structures. Finally, Jeff Squier will describe his method for all-optical histology, in which the laser is used to serially image and ablate tissue, allowing large volumes to be digitized with minimal disruption.

Panel • Tuesday 7:30–9:30 AM • Mt. Werner

Novel Roles for Neuropeptides in CNS Function

James Tepper, Brian Hyland, Hagai Bergman, Jeff Wickens

Dopaminergic Neurons–What are they really saying?

Midbrain dopaminergic neurons and their efferent targets have been studied intensively for over 30 years due to the central roles they play in mediating normal voluntary movement, response to drugs of abuse, and as sites of action for antipsychotic drugs. But over the past decade and a half, perhaps the most interesting aspect of central dopaminergic

pathway function has been the behavioral neurophysiology of dopaminergic neurons. The neurons are now known to be active during reward learning and to respond to multimodal stimuli that convey some aspect of the predictability, novelty, and/or salience of the conditioned stimulus. Most of the early studies of the stimulus response properties of dopaminergic neurons and the theories as to what is being coded for by these responses have come from studies in primates. However, recent studies have shown that dopaminergic neurons in the rat show very similar sorts of conditioned responses. This creates a valuable new experimental model for understanding the nature of the natural stimuli that drive dopaminergic neurons and their behavioral significance.

Jim Tepper will introduce the panel with an overview of the physiology and anatomy of the substantia nigra dopaminergic neurons and their afferent connections in rat. Brian Hyland will describe recent findings on conditioned responses of dopaminergic neurons in freely moving rats. Hagai Bergman will extend this by describing the role of dopaminergic neurons in decision making in the primate. Finally, Jeff Wickens will pull all of this together, describing recent computational models of dopaminergic neuron and basal ganglia function.

Panel • Tuesday 7:30–9:30 AM• Storm Peak

Cortical Dysplasia and Epilepsy in Human and Animal Models

Véronique André, Nada Zecevic, Carlos Cepeda, Steven Roper

Cortical dysplasia, one of the leading causes of intractable epilepsy in children, is a disorder of neuronal migration and differentiation characterized by cortical dyslamination, ectopic neurons in the white matter, and the presence of cytomegalic neurons and balloon cells. Such cortical malformations and abnormal cells may be responsible for seizures in cortical dysplasia. The panel's emphasis will be on integration of anatomical and electrophysiological data from both patients and animal models and to show that excitatory and inhibitory systems are altered in this disorder although it is still unknown which substrate causes increased excitability and seizures. Nada Zecevic will present data on normal human brain development using embryonic cortical cell markers. Carlos Cepeda will present electrophysiological data on abnormal cells and changes in excitatory and inhibitory synaptic events recorded in slices from pediatric epilepsy patients. Véronique André will talk about electrophysiological responses to application of neurotransmitters in acutely dissociated neurons and immunohistochemical staining for GABAergic markers in brain tissue from epileptic patients. Finally, Steven Roper will present anatomical and elec-

trophysiological findings in the irradiated rat model of cortical dysgenesis showing a reduction in the number of GABAergic cells and in inhibitory postsynaptic currents, with no changes in excitatory postsynaptic currents. Comparison of the human pathology with animal models reproducing some of the features of the human disease will provide a better understanding of epileptic mechanisms in cortical dysplasia.

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

Glutamate and Schizophrenia: It's the Endogenous Modulators, Stupid!

Carol Tamminga, Joseph Coyle, Robert Schwarcz, Laura Rowland

Glutamate has been implicated in the manifestations of schizophrenia based on human behavioral, postmortem, and brain imaging findings. Because schizophrenia remains an illness with high medical need, considerable focus has been placed on finding mechanistic explanations for symptoms that will lead to molecular targets for treatment development. Current findings suggest that dysfunction of a single neurotransmitter system cannot fully explain schizophrenia. Instead, the involvement of glutamate with other molecular systems, especially in those brain regions where glutamatergic influence is pervasive such as the limbic- and neocortex, may be more likely in schizophrenia. Increasingly, data suggest that glutamate-mediated neurotransmission, especially at the NMDA receptor, can interact with other regulatory molecules e.g., neurotransmitter or neurotrophic systems to influence neural activity and plasticity in schizophrenia. Genetic analyses of risk factors have implicated several molecular systems interrelated to glutamate in schizophrenia. Alterations within these systems may better explain several aspects of the disease.

Joseph Coyle will begin the Panel with a presentation on molecular approaches to understanding the NMDA receptor modulation with behavioral and electrophysiologic data from GlyT1 and serine racemase knockout mice. Robert Schwarcz will provide new data demonstrating the ability of endogenous kynurenic acid to affect glutamatergic and cholinergic function in dopamine-rich brain areas. Carol Tamminga will present data on the interaction of BDNF with NMDA neurotransmission in schizophrenia brain, suggesting an activity-based linkage between the two systems. Laura Rowland will describe 1H-MRS and behavioral data supporting the interaction between GABAergic and glutamatergic systems within the context of the NMDA receptor hypofunction model of schizophrenia. These presentations will highlight several examples of neural systems that are capable of modulating glutamatergic transmission in the brain and provide evidence to suggest their association with schizophrenia.

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

Autism Genetics: Neurobiology and Novel Approaches to Finding Genes

Daniel Geschwind, Jonathan Sebat, Christa Leese-Martin, Conrad Gilliam

Autism is a devastating neurodevelopmental disorder, whose underlying neurobiological basis is not well defined and whose etiology involves a significant underlying genetic risk. It has been challenging to identify susceptibility genes because of autism's heterogeneity. Daniel Geschwind will put autism in the context of other complex neurogenetic conditions, emphasizing approaches using more precise quantifiable cognitive or behavioral phenotype definitions, rather than relying only on the broad diagnosis of autism. This approach has provided considerable power for identifying autism genes. Jonathan Sebat will discuss the extension of the novel method ROMA, recently published in *Science*, to study of large-scale copy number variation (CNP) in autism. Examination of the gene content of CNPs from autism patients suggests that submicroscopic variations in gene copy number may play a role in common inherited psychiatric disorders such as autism. Christa Leese-Martin has used molecular methods to study chromosome abnormalities, identifying potentially novel genes or regions involved in autism. Leese-Martin has also been able to verify CNPs, using standard cytogenetic techniques. Her work also involves the use of several distinct microarray platforms to assess copy number variation, which will be compared. Conrad Gilliam will discuss the use of Bio-informatics and neurobiological pathway approaches, using a strategy to predict and rank-order network relationships among suspect candidate genes, integrating genomic databases with current neuroscience knowledge. The combination of these approaches has great promise and already has led to preliminary success identifying autism genes, which can than be studied in animal models to understand their affect on neural systems.

Panel • Tuesday 7:30–9:30 AM • Sunset

Trafficking of GABAA Receptors: Physiology and Pathology

Claude Wasterlain, Lorrena Arancibia, Richard Olsen, Bernhard Luscher

Recently, we have realized that the very short-term regulation of ion channel function is, in part, ruled by trafficking of those proteins (or their subunits) to and from the membrane. GABAA receptors are the dominant receptors mediating rapid inhibition in the mammalian CNS. A complex set of protein-protein interactions and posttranslational modifications

control their movement in and out of the plasma membrane and thereby modulate the receptor concentration in the postsynaptic membrane and synaptic inhibitory function.

Stephen Moss will give an overview of that machinery, and will focus on synaptic targeting of GABA-A receptors, and on the role of phosphorylation in some of those changes. Bernhard Luscher will discuss the role of the gamma2 subunit, gamma2 subunit-directed receptor palmitoylation and novel gamma2 subunit interacting proteins in modulating inhibitory postsynaptic function, and how subtle deficits in postsynaptic GABA-A receptors contribute to the development of emotional disorders. Richard Olsen will review the function of GABARAP and other receptor-associated proteins in trafficking of GABAA receptors. Claude Wasterlain and Stephen Moss will discuss pathological changes in GABAA receptor trafficking in epileptic seizures (where drug- or seizure-induced internalization of GABAA receptors may be responsible for certain types of drug resistance, and for the transition from single seizures to status epilepticus), and in Huntingtons disease (where Huntington-associated protein 1 regulates recycling of GABAA receptors).

The discussion will illustrate the mechanisms of GABAA receptor trafficking and its many physiological and pathological roles.

Panel • Tuesday 7:30–9:30 AM• Skyline

What Do I Want and When Do I Want It: Temporal Regulation of Reward Processing in the VTA

Gary Aston-Jones, Alice Luo, Steven Henriksen, Jay Hirsh, Roy Wise, Scott Steffensen

The mesocorticolimbic circuit is critical to the regulation of natural and pathological reward processes, including drug addiction. Recently, the timing of input signals to this system has gained attention as an important factor for understanding reward circuitry. On a short time scale, these signals may contribute to the expression of immediate reward-seeking behavior. On a longer time scale, circadian inputs may regulate the animal's overall responsiveness for present and future behaviors. This panel will highlight recent advances in our understanding of how the timing of input signals to reward circuits influences their activity and the behaviors they regulate. Roy Wise will discuss his work on the regulation of ventral tegmental area (VTA) dopamine levels during cocaine self-administration. He will describe GABAergic, glutamatergic and cholinergic inputs during cocaine self-administration and their regulation of dopamine levels. Alice

Luo will present evidence for diurnal fluctuations in the impulse activity of VTA neurons. She will discuss her work on delineating a synaptic circuit from the core circadian clock, the suprachiasmatic nucleus, to the VTA. Steve Henriksen will discuss arousal processes as a downstream target of circadian regulation. Henriksen will present evidence for a VTA arousal circuit that may in turn influence reward behavior. Jay Hirsh will discuss his use of molecular genetics in both Drosophila and mice to study the interactions of circadian and cocaine response pathways. Hirsh will present his work in Drosophila on circadian signaling requirements for the modulation of cocaine responses, and in mice, a novel method for intra-nasal cocaine self-administration.

Panel • Tuesday 4:30–6:30 PM • Mt. Werner

Too Much or Too Little Dopamine in Neurological and Psychiatric Disorders

Michael Levine, Nigel Bamford, Nigel Maidment, Marjorie Ariano

This panel will discuss dopamine (DA) function in models of neurological and psychiatric disorders. Nigel Bamford will show how DA alteration changes striatal function. He combined optical recordings of presynaptic glutamate release with postsynaptic recordings in DA-deficient mice and showed that DA depletion caused hypersensitive D2 receptors and altered corticostriatal subsets responding to DA. Chronic methamphetamine treatments and withdrawal caused long-term depression of corticostriatal release as well. Genetic mutations are known to cause familial PD by mechanisms that may also operate in sporadic PD. These genetic mouse models do not exhibit DA cell loss but behavioral analyses in the parkin knockout and alpha synuclein overexpressing mice revealed motor deficits indicative of nigrostriatal dysfunction. These mice may model early stages of PD prior to overt cell loss. Maidment will present evidence of a counter-intuitive increase in striatal extracellular DA in these mice. Michael Levine will show physiological abnormalities in DA modulation of striatal glutamate receptors in parkin knock out, alpha synuclein overexpressing mice and in a DA transporter knock-down, which is a model of ADHD. The abnormalities in neurotransmission are all different, indicating the that mechanisms are unique. Marjorie Ariano has produced a partial DA depletion in rats to neurochemically mimic the early stage of human PD. Significant changes in cell stress proteins occurred that were preferentially expressed in striatopallidal neurons. Physiological experiments showed heightened responsiveness to cortical stimulation. Overall, this panel will provide new information about DA function in neurological and psychiatric disorders and novel insights that could lead to development of rational therapies.

Panel • Tuesday 4:30–6:30 PM • Storm Peak

Receptor Trafficking and Synaptic Regulation

Katherine Roche, Graham Collingridge, Josef Kittler, Andres V. Maricq

At both excitatory and inhibitory synapses, the precise trafficking and targeting of neurotransmitter receptors are critical for efficient neurotransmission. It is clear that a variety of intracellular proteins bind to neurotransmitter receptors and these interactions regulate the expression of receptors at synaptic sites. Presentations in this panel will describe recent findings on this topic, discussing the molecular mechanisms regulating receptor function in neurotransmission and in synaptic plasticity. Katherine Roche will discuss the trafficking and functional regulation of metabotropic glutamate receptors (mGluRs). She will describe the role of phosphorylation on mGluR5 signaling and receptor binding to cytosolic proteins, as well as the role of phosphorylation in regulating the endocytosis of mGluR7. Graham Collingridge will present recent work on the role of proteins that interact directly with AMPA receptor subunits at synapses in the regulation of synaptic strength during long-term synaptic plasticity in the hippocampus. Josef Kittler will discuss the role of GABAA receptor associated proteins (including HAP1 and GABARAP) and kinesin family member microtubule motor protein complexes in regulating the cell surface transport, synaptic targeting, and endocytosis of GABAA receptors. Villu Maricq will discuss the identification of a novel stargazin-like auxiliary glutamate receptor subunit, STG-1, from C elegans. STG-1, together with the CUB-domain protein SOL-1 and the C. elegans glutamate receptor GLR-1, is sufficient to reconstitute glutamate-gated currents in Xenopus oocytes or C. elegans muscle. This panel will provide information on the latest findings on receptor trafficking mechanisms and allow comparison of these mechanisms between different ionotropic receptors and in different organisms.

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

Schizophrenia: From Genes to Cortical Circuits

Daniel Weinberger, Amanda Law, Jeremy Seamans, Patricio O'Donnell

The anticipated existence of predisposing genes for schizophrenia has now been established, and pathological alterations in post-mortem and neuroimaging studies suggestive of neural circuitry and functional changes are found in diverse brain regions. This panel will present recent findings about how predisposing genes alter cortical development and abnormal local circuit organization in critical cortical regions, including the prefrontal

cortex (PFC) and the temporal lobe. Dr. Weinberger will focus on evidence that susceptibility genes (e.g., GRM3, COMT, GAD1,and DISC1) for schizophrenia impact aspects of cortical excitability in microcircuits, suggesting a common neural system phenotype. Amanda Law will present postmortem and genetic evidence showing that the pathogenic mechanism of NRG1 association with schizophrenia involves aberrant transcriptional regulation, potentially limiting the efficiency of NRG1 effects on cortical neural development and plasticity. JeremySeamans will present recent evidence that mesocortical dopamine neurons co-release glutamate and dopamine, yet each transmitter system has distinctly different functions. Alterations in glutamate and dopamine signaling from mesocortical neurons may explain certain aspects of the disorder and the effects of dopamine and glutamate related susceptibility genes. Patricio O'Donnell will present electrophysiological data from a developmental animal model showing that an early interference with hippocampal projections to the prefrontal cortex (perhaps imitating the consequences of predisposing genes) results in postpubertal emergence of abnormal interneuron activity, causing abnormal function in prefrontal circuits.

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

A Potpourri of Global Neuroscience Opportunities: or Globus Brighticus Neuro-unum—One Bright Neural World

Kathie Olsen, Connie Atwell, Sharon Hrynkow, Nathaniel Pitts

The world of research has become smaller over time due to many technological innovations, improved communications, and the increased cooperation of countries, industries, and institutions. From formal programs sponsored by the world's premier non-governmental organizations to informal collaborations through academic institutions, brain scientists with a broad and international vision have increasing opportunities to exhibit leadership in their science through international collaborations. They forge unusual relationships, interact on the world stage of science, and become science diplomats in the process. International research collaborations are sponsored through a variety of mechanisms and on every scale, but one has to know where to look and how to become involved. Four "neuroscientists" from various federal agencies will discuss and critique this range of opportunities and how to take advantage of them. Kathie Olsen, White House Office of Science and Technology Policy, will cover major international fellowship opportunities such as the Human Frontier Science Program (HFSP) and research opportunities sponsored by large international organizations such as the Organization for Economic Coop-

eration and Development (OECD); the United Nations Educational, Scientific and Cultural Organization (UNESCO); and the Asia-Pacific Economic Cooperation (APEC). Connie Atwell, formerly of the National Institute of Neurological Disorders and Stroke, will discuss opportunities through the International Brain Research Organization (IBRO). Sharon Hrynkow, Acting Director of the Fogarty International Center, will focus on neuroscience opportunities in the developing world. Nat Pitts, National Science Foundation, will present the international component of the NSF research portfolio.

Panel • Tuesday 4:30–6:30 PM • Sunset

The Neuroinferno: Chronic Brain Inflammation

Gary Wenk, Susanna Rosi, Fulton Crews, Stanley Rapoport

Gary Wenk will present a general theory on unique aspects of inflammation in brain as well as how chronic brain inflammation can influence the development and regional distribution of the pathology associated with Alzheimers disease.

Susanna Rosi will outline a novel animal model of chronic neuroinflammation that investigates the consequences of brain inflammation upon hippocampal immediate early gene expression involved in synaptic plasticity and memory formation. Rosi will also describe possible therapies to restore the altered hippocampal function during neuroinflammation.

Fulton Crews will discuss the interaction of systemic cytokines with microglia and induction of enzymes including NADPH oxidase and COX2. In vivo studies of adult progenitor formation of new microglia will be related to neuronal progenitors and neurodegeneration. Crews will present studies supporting the hypothesis that microglial cytokines potentiate glutamate neurotoxicity using inhibitors of NfkB, NMDA and other pharmacological approaches.

Stanley Rapoport will discuss a new method to quantitatively image neuroinflammation in unanesthetized animal models and in patients with Alzheimer's disease; using intravenously injected radiolabeled arachidonic acid with quantitative autoradiography or PET. Taken together these studies support the critical role for chronic neuroinflammation in neurodegenerative diseases.

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

State Dependent Regulation of Sensory and Motor Network Operations: Role of Intrinsic Mechanisms and Extrinsic Neuromodulatory Systems

Barry Waterhouse, Manuel Castro-Alamancos, John Chapin, Craig Berridge, Gary Aston-Jones

Anatomical connections within and between sensory and motor networks of the mammalian brain have been well characterized. Likewise, the electrophysiological properties of cells in these circuits have been thoroughly investigated. Thus, for many sensory and motor regions of the brain we have fundamental expectations about how afferent signals are coded and transmitted through these hardwired networks. However, under physiologic conditions, these circuits operate in dynamic modes that often reveal unexpected, state and behavior-dependent neuronal response properties. Such properties emerge as a result of the dynamics occurring between functionally related sets of neurons and/or influences exerted by extrinsic neuromodulatory systems. The panel will discuss mechanisms that underlie state dependent shifts in local circuit and neural network operation. Manuel Castro-Alamancos will provide evidence of spatial and temporal transformations of thalamocortical receptive fields during arousal, and compare the effects of different neuromodulators on two main inputs to the thalamus: primary sensory and corticothalamic afferents. John Chapin will describe ensemble neuronal coding of information in the sensorimotor cortex and the fact that slight changes in the weights of individual cells in the responding array allow different movement parameters to be specified. For example, the output of the neuronal population can be configured to very accurately predict movement position or force, with relatively slight changes in the neuronal weightings. Craig Berridge will offer an explanation of how the locus coeruleus-norepinephrine (LC-NE) system and drugs that interact with it are capable of regulating behavioral and forebrain neuronal activity states appropriate for the collection and modulation of salient sensory information. Gary Aston-Jones will review data from neurophysiological and modeling studies that suggest a role for the LC-NE system in optimizing task performance following the decision to engage in specific goal-directed behaviors.

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

Risk Factors for Drug Abuse: Stress and the Sex of an Individual

Jill Becker, Yavin Shaham, Mary Heitzeg, Jon-Kar Zubieta

Drug-taking behavior is a complex disorder that results from the interplay of genetic predisposition and environmental factors. This panel will discuss evidence that the sex of an individual, exposure to stressful events during development or in adulthood, and genetic factors can affect whether an individual is susceptible to the addictive properties of drugs of abuse. Jill Becker will discuss research that demonstrates that female rats are more sensitive to the psychomotor activating effects of psychostimulants than are males. Yavin Shaham will discuss the role of the noradrenergic system in stress-induced reinstatement of drug taking behavior. In experiments with rodents, stress has been found to be an important factor in determining whether an individual reinitiates drug-taking behavior after abstinence. Mary Heitzeg will discuss studies using fMRI, to investigate the effects of early stress on the neural systems involved in impulsivity and negative affect in a group of adolescent boys and girls. Her results suggest that early-life stress may increase risk for substance abuse through its effects on the neural systems involved in impulse and emotion regulation. Recent studies from Jon-Kar Zubieta's laboratory, in humans with PET, have examined the response of the opioid and dopaminergic systems to stressors and individual variations as a function of common genetic polymorphisms. A more substantial activation of the μ-opioid system is observed in response to the experimental stressor for allelic variants associated with increased drug abuse risk. Sex of the individual and circulating gonadal hormones are additional risk factors.

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

Glia—More than Putty

Vladimir Parpura, Wendy Macklin, Monica Carson, Douglas Fields

The mammalian nervous system is composed of more than 100 billion neurons surrounded by glial cells. There are 10-50 times as many glial cells as neurons. They clearly exceed the neurons not only by their numerical preponderance, but also in the variety of their different types. The major classes of glial cells in the vertebrate central nervous system (CNS) are astrocytes, oligodendrocytes, and microglia, whereas Schwann cells are the predominant glial type in the peripheral nervous system (PNS). Glial cells were first described in 1856 by the German pathologist Rudolf Virchow,

who termed them *nervenkitt* (nerve putty) or neuroglia. It was proposed that glia serve as ''a real putty, which binds the nervous elements together." This original concept has radically changed, although the name survived.

In the proposed workshop, all speakers will explore more active roles of glia in mammalian nervous system. Our exploration will start with astrocytes, where Vladimir Parpura will discuss the exocytotic release of glutamate from these cells. Next, Wendy Macklin will discuss molecular cues involved in the role of oligodendrocytes in myelin formation. Monica Carson will discuss the role of microglia during development and CNS inflammation raising the issue of their neuroprotective versus neurodestructive function. Douglas Fields will discuss the activity-dependent communication between axons and glia in the CNS and PNS.

Together, these speakers will provide a fertile ground for the discussion in regard to the active role of glia within mammalian brain.

Workshop • Tuesday 8:30–10:00 PM • Mt. Werner

What the Hell IS Parkinson's Disease?

Tim Greenamyre, Bob Burke, Heather Melrose, Dennis Dickson

Traditionally, neurologists have diagnosed Parkinson's disease (PD) based on an individual's history, motor signs and symptoms, and response to levodopa, with the ultimate diagnosis resting on neuropathological confirmation of specific nigrostriatal degeneration with Lewy bodies. Geneticists, of course, couldn't leave well enough alone, and they have screwed this up for all of us, claiming that PD should be defined by specific mutations or molecular mechanisms. While intellectually appealing, a fundamental problem with this approach is that a given gene mutation may cause multiple phenotypes, some of which bear little resemblance to what most clinicians would call PD. If neither the neurologist nor the geneticist has the perfect definition of PD, surely the answer must lie with the neuropathologist. After all, this is the gold standard for diagnosis. . .or, rather, it was. Unfortunately, it's now clear that clinically typical PD can have multiple pathologies, and may or may not be associated with Lewy bodies. So, just what the Hell IS PD? This is the focus of this interactive workshop.

Tim Greenamyre will introduce the topic and generally keep things stirred up. Bob Burke will provide the perspective of a clinical neurologist, Heather Melrose will discuss PD as a group of distinct molecular entities, and Dennis Dickson, a neuropathologist, will explain how the pathology of PD is a moving target. This workshop may not settle the issue of what PD is, but it will raise consciousness and perhaps a few tempers.

Panel • Tuesday 8:30–10:00 PM • Storm Peak

Central Brainstem Processing of Auditory Signals

Robert Fyffe, Ian Forsythe, Henrique von Gersdorff, Bruce Walmsley

The transmission and processing of sound information requires incredible timing precision by the central nervous system. This is epitomized by the brainstem pathways involved in sound localization, which, in some mammalian species, rely on resolving timing at the level of tens of microseconds. This panel is focused on recent structure-function studies that reveal the fundamental mechanisms underlying brainstem auditory processing. A powerful combination of techniques has been applied to these studies. Ian Forsythe, who pioneered direct patch-electrode recordings from central synaptic terminals in the mammalian CNS, will summarize what we have learned about neurotransmitter release and modulation at giant auditory synapses in the brainstem. Henrique von Gersdorff will present results on simultaneous pre- and post-synaptic recordings, in combination with electron-microscopic studies. These studies have revealed the basic events underlying developmental maturation of auditory synapses. Robert Fyffe will demonstrate that quantitative immunolabelling can provide much insight into the formation of ion channel gradients and tonotopic maps in auditory brainstem nuclei. Bruce Walmsley will present combined electrophysiological and structural results that reveal the consequences of congenital deafness on synaptic and neuronal membrane properties in brainstem nuclei. The results of all of these studies provide an unprecedented picture of the basic mechanisms underlying brainstem auditory processing and the role of activity and development in regulating the properties of auditory synapses and neurons.

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

Modeling Schizophrenia—What's Lost in the Translation?

Janet Finlay, Nagalingam Rajakumar, Holly Moore, Craig Powell

Several structural changes have been described in postmortem studies of schizophrenic brain tissue. Many of these changes appear to be a consequence of disrupted brain development. Frequently, the impact of these structural abnormalities on functional capacity cannot be directly assessed in the living human. This panel will provide an overview of several animal models developed to examine the functional consequences of specific neurodevelopmental abnormalities associated with schizophrenia. These models include: 1) neonatal 6-hydroxydopamine lesions of mesoprefrontal

dopamine neurons designed to reduce prefrontal cortical dopamine nerve terminals to an extent similar to that seen in schizophrenia (Janet Finlay), 2) ablation of subplate neurons of the developing prefrontal cortex induced by a saporin-conjugated antibody to the p75 neurotrophic receptor resulting in abnormalities in thalamocortical glutamate and mesocortical dopamine innervations (Raj Rajakumar), 3) genetic manipulation of the presynaptic, active zone protein RIM1a resulting in altered glutamatergic synapse function in cortex (Craig Powell), and 4) MAM-induced disruptions in DNA methylation early in development which decreases the size in several cortical and limbic structures implicated in schizophrenia (Holly Moore). Discussion will focus on the extent to which this directed translation approach produces meaningful results and gives rise to information that can be translated back into clinical research programs.

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

Mechanisms and Regulation of Metal Transport into the CNS

James Connor, Michael Aschner, Josh Dunaief, Michael Georgieff

Interest in the role of biometals in neuroscience has never been at a higher level. There are a number of common neurological disorders such, as Alzheimer's and Parkinson's, in which excess accumulation of metals in brain is under investigation as contributory if not causative agents. Clinical trials are underway using metal chelators as a means of therapeutic intervention. At the other end of the spectrum, insufficient accumulation of metals, particularly during sensitive developmental periods results in neurological and cognitive impairment, which can last a lifetime. Because metals must be transported into the brain, elucidation of the mechanisms by which these metals gain entry into the brain is critical to understand the role of metals in neurobiology. In this panel, we will discuss newly discovered multiple mechanisms for iron transport into the brain, using a novel in vitro model of the BBB. The presentation will also demonstrate how the protein profile for iron management proteins is regulated at the regional level in brain microvasculature, using novel animal models. A reciprocal relationship between iron status and Manganese uptake has been established based on the knowledge that Fe and Mn compete for the same carrier transport systems into the CNS. This reciprocal relationship between Fe and Mn has potential clinical implications for individual and population-based risks of Mn toxicity. The panel will also address how altered metal transport in the retina is associated with age-related macular degeneration, the most common cause of irreversible vision loss in this country. The discussion will introduce a novel animal model that increases under-

standing of retinal iron and copper homeostasis and the pathogenesis of retinal degeneration. Finally, we will compare and contrast the expression, localization, and potential mechanisms of action of metal transporters in three systems of vectoral iron transport: the intestine, the placenta, and the brain.

Panel • Wednesday 7:30–9:30 AM • Mt. Werner

Does Dopamine Control Striatal Glutamate, the Other Way Around, or Both?

Patricio O'Donnell, Adrian Michael, David Sulzer, Marianne Benoit-Marand, Bryan Yamamoto

There is evidence that striatal glutamate can modulate dopamine (DA) release and vice versa. The panel will discuss emerging data characterizing striatal DA–glutamate interactions, their mechanisms, and potential functional relevance. Michael will describe the use of DA- and glutamate-selective microelectrodes for the study of these interactions in the striatum of anesthetized rats. Intrastriatal infusion of a glutamate antagonist decreases DA-related voltammetric signals, while intrastriatal infusion of the D2 antagonist, eticlopride, decreases the glutamate-related amperometric signal. These findings suggest that a reciprocal, tonic DA:glutamate interaction occurs in the striatum. Sulzer will talk about the reciprocal effects of DA on cortical inputs and of cortical glutamate on DA inputs. These effects may not be classically inhibitory or excitatory, but rather provide a high pass filter, and the kinetics of the responses may control the timing required for motor and habit learning. Marianne Benoit-Marand will present data on D2 modulation of glutamatergic responses in sagittal corticoaccumbens slices. This modulation matures during adolescence, shifting from a strictly inhibitory effect to a complex excitatory response that involves a D2 inhibition of interneurons. Bryan Yamamoto will describe the role of glutamate in mediating the neurotoxic effects of methamphetamine to DA terminals. Conversely, he will also provide evidence that DA in the basal ganglia may mediate the excitotoxic effects of methamphetamine. The presentations will provide several novel pieces of information regarding this interaction, of high relevance to information processing in a brain region critical for drug addiction and neuropsychiatric disorders.

Panel • Wednesday 7:30–9:30 AM • Storm Peak

Non-Homeostatic Control of Ingestion: Eating without Regard to the Body's Needs

Barry Levin, Wayne Pratt, Jeffrey Grimm, Dianne Lattemann

The brain regulates energy homeostasis, i.e., energy intake, expenditure, and storage. Obesity and eating disorders occur when normal homeostatic controls of eating are overridden by non-homeostatic signals involved in craving, motivation, and reward. Barry Levin will introduce the concepts of homeostatic and non-homeostatic controls of intake and energy homeostasis and the neural, metabolic, and hormonal factors that regulate them. He will set the stage for the panel members who will provide examples of how neural and hormonal factors interact to control food intake through non-homeostatic pathways. Wayne Pratt will describe the interplay between striatal cholinergic and enkephalinergic pathways in the control of intake. These pathways may have evolved to coordinate feeding and arousal, and to prolong the feeding central motivational state beyond the fulfillment of acute energy needs, thereby promoting "overeating" and the consequent development of an energy reserve for potential future food shortages. Jeffrey Grimm will discuss the concept of "incubation of sucrose craving" as a model for cue-induced reward seeking elements of eating disorders. Grimm will provide examples of how it compares to psychostimulant sensitization and the behavioral, anatomical, and neurochemical indices of incubation of craving for drugs of abuse. Finally, Dianne Lattemann will demonstrate how leptin and insulin, two peripheral hormones normally associated with homeostatic controls of intake, can also affect the rewarding properties of food by acting on ventral tegmental dopamine neurons.

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

Mechanisms of Structural Plasticity of Dendritic Spines

Peter Penzes, D. Michelle Day, Terry Robinson, Dezhi Liao

Dendritic spines are the sites of majority of excitatory synapses in the brain, and spine morphogenesis plays a central role in synaptic development, plasticity, mental illness, and addiction. However, the molecular mechanisms that regulate spine formation and plasticity are just beginning to be uncovered. The speakers will present recent findings from their labs that cover key aspects of spine structural plasticity. Activity-dependent mechanisms are of particular importance because they may mediate experience-

dependent remodeling of neuronal circuits and information storage. Peter Penzes will discuss recent findings regarding the "Regulation of activity-dependent structural plasticity of dendritic spines by small GTPases." Spine plasticity occurring in striatal dopaminergic neurons may contribute to the pathology of Parkinson's disease. Hence Dr. Day will present data addressing the "Role of Cav1.3 calcium channels in regulating synapse and spine number in medium spiny neurons in the striatum." Spine structure and function appear coordinated, therefore Terry Robinson will speak about correlating structural and functional plasticity in cultured hippocampal neurons. Spine morphogenesis depends on actin dynamics, which are regulated by actin-binding proteins, such as drebrin. Hence Dezhi Liao will discuss the "Role of drebrin in morphological change of spines."

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

A Brain Divided against Itself Cannot Stand: The Importance of Teamwork Exemplified by the Neurovascular Unit

Dale Pelligrino, Sami Harik, Gregory Del Zoppo, Joseph LaManna

The concept of the neurovascular unit (NVU) has arisen out of a need to explain the complex interplay between neurons and astrocytes and the vasculature that supports them. Recent findings regarding the intricacies of this structural and functional entity have enhanced our understanding of how the various components of the NVU interact in supporting normal brain function and how specific changes may contribute to neuropathologies. The members of this panel will provide up-to-date information, integrated with a historical perspective, regarding how brain cells and vascular cells affect one another, with respect to: blood-brain barrier (BBB) integrity, functional activation and brain perfusion, and angiogenesis; and discuss how breakdowns in various components may promote brain damage. Sami Harik will provide an overview of brain cell regulation of BBB function. Greg Del Zoppo will discuss the mechanisms of BBB disruption (e.g., loss of extracellular matrix) following stroke or brain trauma, and the implications of such an occurrence (e.g., hemorrhagic transformation). Joe LaManna will cover how brain cells (neurons, glia) contribute to angiogenic factors in response to hypoxic/ischemic challenges. Dale Pelligrino will discuss how astrocytes might regulate the interplay between neurons, vascular endothelium, and vascular smooth muscle in attempting to provide sufficient perfusion (substrate delivery) to support the demands of neurons.

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

The Case against the Basal Ganglia as Primarily a Motor Structure

Suzanne Haber, Hagai Bergman, Christelle Baunez, Jacqueline McGinty

Accumulating anatomical, physiological, and molecular data have recently revealed the non-motor aspects of BG function. These findings indicate that a large dorsal BG region, conventionally thought to be involved in the control of movement, contains cells that respond to reward and/or are involved in associative learning. Using different techniques, this panel will show in rats and monkeys how the dorsal BG areas are connected and respond to reward incentives. Suzanne Haber will begin by addressing the complex organization of the cortico-striatal loops, demonstrating a complex interaction between reward, associative, and premotor circuits. Hagai Bergman will show evidence that most pallidal neurons respond to multiple phases of a task that involved reward, and associative and motor elements. Christelle Baunez will show in both rat and primate subthalamic nucleus, that neurons respond to expectation of reward or to reward itself in addition to movement-related events, even in sub-regions considered "motor" or "associative." Jacqueline McGinty will discuss enduring changes in mRNA and protein expression in the dorsal striatum 3 weeks after cessation of cocaine self administration that may have enduring consequences for incentive processing.

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

Inner Retina Circuitry: Mechanisms Underlying Visual Processing

Maureen McCall, Laura Frishman, Jeffery Diamond, W. Rowland Taylor

Inner retinal circuitry modifies the visual information that is transmitted via the bipolar cells. Mechanisms that underlie these refinements include: amacrine cell-mediated feedforward and feedback inhibition, expression of diverse synaptic receptors, and intrinsic properties of cells. These inner retinal synaptic interactions enhance sensitivity, refine receptive field center/surround organization, and establish direction selectivity.

The presenters will discuss how various aspects of the functional organization of inner retinal circuits impact visual responses. Laura Frishman will discuss how the rod bipolar pathway sets the exquisite sensitivity that underlies scotopic vision. She will focus on the synaptic mechanisms that reduce transmission of continuous noise without greatly affecting trans-

mission of single photon signals to rod bipolar cells, and subsequently to AII amacrine and to ganglion cells. Jeffery Diamond will discuss the inhibitory feedback circuit from A17 amacrine to rod bipolar cell terminals. He will focus on A17 amacrine post-synaptic elements that detect the bipolar signal and generate an intracellular calcium signal required to elicit GABA release that mediates feedback inhibition. McCall also will discuss an inhibitory feedback circuit. She will focus on post-synaptic elements of the ON and OFF bipolar cell terminals that detect GABA release and create asymmetries in visual processing through ON and OFF pathways. Taylor will discuss the circuitry that underlies retinal direction selectivity. He will focus on the generation of dendritic spikes in retinal ganglion cells, and how interactions with local inhibitory inputs translate into directional tuning of somatic spikes and direction selectivity.

Panel • Wednesday 4:30–6:30 PM • Mt. Werner

Protein Synthesis at the Synapse: It's Depressing

Oswald Steward, Kimberly Huber, Mark Bear, Bill Greenough

It is now well accepted that the maintenance phase of LTP and LTD require protein synthesis during a critical time window, and in some cases, the critical protein synthetic events occur in dendrites. In addition, a form of LTD that is triggered by mGluR activation requires protein synthesis for induction. In this panel, we will discuss new findings regarding the regulation of mRNA translation in dendrites by mGluR receptor signaling, and consider the hypothesis that induction of LTD activates the translation of a unique complement of dendritic mRNAs. Kim Huber will present the key evidence that the form of hippocampal LTD that depends on mGluR activation requires protein synthesis in dendrites. Mark Bear will summarize evidence that a dys-regulation of the protein synthetic processes that are regulated by mGluR signaling underlies the signaling defects in Fragile X Mental Retardation Syndrome. Bill Greenough will describe activation of translation in dendrites via mGluR-dependent activation of the Map Kinase pathway, and will show that a deficiency in this pathway. He likely due to reduced availability of PAK (whose mRNA is an FMRP cargo), leads to a slower rate of ERK phosphorylation coupled with a reduced protein synthetic response in FMR1-KO mice. Os Steward will describe mGluR regulation of local translation of the mRNA for elongation factor 1 alpha in dendrites, and discuss the hypothesis that local synthesis of EF1alpha alters the translational capacity of dendritic protein synthetic machinery. A topic for discussion will be whether the protein synthesis-dependence of LTP actually reflects a requirement for compensatory LTD at inactive synapses.

Panel • Wednesday 4:30–6:30 PM • Storm Peak

Do Arrestins Limit or Enhance the Pleasure of Skiing?

Louis Luttrell, David Sibley, Kim Neve, Marc Caron

Arrestins are G protein-coupled receptor-interacting proteins first identified because of their requisite role in desensitization of rhodopsin (visual arrestin) and the beta2-adrenergic receptor (beta-arrestin-1 and -2). These arrestins are also known by their systematic names arrestin-1, -2, and -3, respectively. According to the classical model, phosphorylation of the agonist-occupied receptor by a G protein-coupled receptor-specific kinase creates a high-affinity binding site on the receptor for arrestin. The ability of the arrestin-bound receptor to activate G proteins is decreased; that is, the receptor is desensitized. This classical model has been extended, first to reflect that arrestin-2 and -3 bind to clathrin adaptor protein to mediate receptor internalization and resensitization, and more recently to reflect that arrestins bind many other signal transduction proteins and are required for G protein-coupled receptor signaling via certain pathways. Thus, depending on the signaling pathway, arrestins may limit or enhance signaling.

Lou Luttrell will open the session by describing the role of arrestins as scaffolding proteins for mitogen-activated protein kinase cascades. Dave Sibley will show that receptor phosphorylation is not required for dopamine D2 receptor-induced translocation of arrestin to the membrane and arrestin-mediated receptor internalization, in contrast to the canonical model. Kim Neve will describe determinants of arrestin binding to dopamine receptors and the functional consequences of preventing arrestin binding. Marc Caron will present evidence from arrestin null mutant mice that arrestins contribute to dopamine receptor signaling.

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

Psychostimulant Exposure during Development: What and When Matter!

Heinz Steiner, Barry E. Kosofsky, Ellen M. Unterwald, Carlos A. Bolanos

The developing nervous system is especially vulnerable to recurrent psychostimulant exposure. However, the developing brain may sustain such psychostimulant insults, for example, in utero because of drug-abusing mothers, or during school age with prescription stimulants such as methylphenidate (Ritalin) prescribed for the treatment of attention-deficit

hyperactivity disorder. How such early exposure affects development and the liability imparted for adult drug addiction and other behavioral changes remains controversial. This panel will discuss new findings in animal models that shed light on the neurobiological and behavioral consequences of early stimulant exposure. Carlos Bolanos will describe long-term behavioral effects of chronic methylphenidate during pre- and periadolescence in rats including alterations in behavioral reactivity to stimuli such as natural rewards, sex, stress, and anxiety-evoking situations. Ellen Unterwald will talk about neuroadaptations resulting from psychostimulant exposure in post-weanling and adolescent mice in contrast to adults, and their consequences in several behavioral assays (e.g., place preference conditioning). Barry Kosofsky will discuss the effects of prenatal cocaine exposure on locomotor behavior and gene regulation in the basal ganglia in preadolescent, adolescent, and adult mice. Additionally, he will compare the effects of preadolescent methylphenidate versus cocaine treatment on cocaine-induced behavior in adults. Heinz Steiner will provide an update on methylphenidate-induced regulation of gene expression in adolescent and adult rodents. He will contrast these methylphenidate effects with those of cocaine and amphetamine. Together, these studies indicate that the molecular neuroadaptations and long-term behavioral consequences of psychostimulant exposure depend on the type of stimulant and the age of exposure.

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

Animal Models of Addiction Predict Human Behavior

Charles O'Brien, Conan Kornetsky, Laura Peoples, Friedbert Weiss

Pre-clinical models of addictive states have been found to be very useful in the development of new treatments in the clinic. Conan Kornetsky will describe the changes in electrical stimulation thresholds that provided the first objective evidence of a cocaine withdrawal syndrome and led to the development of a clinical scale useful in rating stimulant withdrawal in humans. Laura Peoples will describe the unit activity of neurons in the nucleus accumbens before, during, and after cocaine self-administration and will show new data on drug-induced changes in accumbal neurophysiology that may contribute to ambivalence, an important characteristic of human addict relapse. Friedbert Weiss will describe the differential effects of stress and drug related cues in provoking relapse to alcohol drinking. Suppression of relapse in these models is effective according to the medication used, opiate antagonist or CRF antagonist. Human studies that translate these findings are in progress. Charles O'Brien will present

data on the surprisingly consistent effects of naltrexone in alcoholism that began in the animal laboratory and has progressed to clinical trials, human lab studies, population genetic studies, and pharmacogenetic research.

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

Swelling, Shrinking, Living and Dying: Cell Volume Regulation in the Life and Death of Cells (or Does Size Really Matter?)

Elias Aizenman, Kevin Strange, John Cidlowski, Shan Ping Yu

Regulatory mechanisms controlling cell volume are critically important in many physiological and pathophysiological processes. For example, dividing cells must precisely double their size during each cell cycle in order to maintain constant volume. In contrast, apoptotic cells must shrink in order to allow for engulfment and clearance while preserving membrane integrity. Additionally, there are signal transduction pathways that become activated in response to osmotic shock, which are in place to maintain cellular volume homeostasis. How cells regulate volume and what are the main signaling pathways, ion channels, and pumps involved in these processes are the subjects of this panel. Kevin Strange will kick things off by describing his work exploiting the molecular and genetic tractability of C. elegans to define the molecular pathways by which cells sense volume changes and osmotic stress. John Cidlowski will then present evidence that cell shrinkage, often thought as a passive event in apoptosis, is, in fact, an actively regulated process that can be experimentally dissociated from critical cytoplasmic ion concentration changes necessary for cell death. Shan Pin Yu will follow with a presentation on the role of the Na/K ATPase pump in cell volume regulation and neuronal injury as well as the signal transduction pathways linking alteration in potassium channel function to cell adhesion and cell death. Finally, Elias Aizenman will describe the molecular components of a phosphorylation-dependent pathway that leads to trafficking of potassium channels in a model of neuronal apoptosis.

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

Carving the Space-Time Continuum in the Developing Auditory System

Karl Kandler, Jeffrey Holt, Leonard Kaczmarek, Lu-Yang Wang, Gunsoo Kim

Processing of auditory information involves transformations of time into space and space into time. A number of developmental learning disabili-

ties such as specific language impairment or dyslexia are characterized by impaired auditory processing of temporal and spatial information. The highly organized neuronal circuits necessary for proper hearing appear early in the developing brain but the events and mechanisms that underlie the maturation and fine-tuning of these circuits are hardly known. This panel will highlight recent progress in our understanding of some key processes that occur during the emergence of specialized auditory synapses and circuits.

Jeffrey Holt will discuss the abrupt onset of mechanotransduction in hair cells of the developing inner ear and present a model for the rapid assembly of the transduction apparatus, which includes myosin 1c and TRPA1. In contrast, acquisition of hair cell sodium and potassium channels is gradual, following a distinct sequential order. Leonard Kaczmarek will focus on mechanisms that fine-tune the excitability of central auditory neurons. His results will demonstrate how changes in Kv3 family channels, the sodium-activated Slick and Slack channels, and the two pore TWIK channel alter the ability to follow specific patterns of stimulation. Lu-Yang Wang will present results that show that the emergence of high-fidelity neurotransmission at the calyx of Held is mediated by an increased coupling of presynaptic voltage-gated calcium channels to synaptic vesicle release. Finally, Gunsoo Kim will provide new evidence that the cholinergic efferent innervation of inner hair cells before hearing onset is necessary for carving a topographically accurate and physiologically fine-tuned inhibitory sound localization circuit.

Panel • Thursday 7:30–9:30 AM • Mt. Werner

Beyond Cheeseburgers and Sex: Treatment of Stroke and Neural Injury with Statins and Sildenafil

Michael Chopp, Matthias Endress, Zhenggang Zhang, Jieli Chen, Rui Lan Zhang

There are two general approaches to the treatment of stroke and neural injury; an acute, early intervention designed to reduce vascular dysfunction and ischemic cell death, and a delayed treatment designed to remodel brain and to restore neurological function. In this workshop, the speakers will describe their research on the use of two very commonly employed agents, which have remarkable neuroprotective and neurorestorative effects: statins and sildenafil. Statins are widely used for the reduction of cholesterol and LDL, while sildenafil, commercially marketed as,Viagra, is employed to treat erectile dysfunction. Matthias Endress will describe his pioneering work on the microvascular effects of statins, the expression of

G-proteins, and the potential use of statins as prophylactic and neuroprotective agents in acute stroke. Zhenggang Zhang will describe his studies on the acute treatment of embolic stroke with statins, including the combination of statin treatment with thrombolytic therapy, and the effects of statins on gene expression in endothelial cells. Jieli Chen will demonstrate that statins have neurorestorative effects, and that therapy initiated one or more days after stroke or traumatic brain injury induces brain plasticity and results in a significant reduction of neurological deficits. Rui Lan Zhang will present data on the use of agents increase cGMP, such as sildenafil, to restore neurological function in experimental embolic stroke in young and old rodents. Since statins and sildenafil are in clinical use, these agents may warrant rapid translation for the treatment of stroke from the animal to the patient.

Panel • Thursday 7:30–9:30 AM • Storm Peak

Neurodevelopmental Disruption of Hippocampal-Prefrontal Cortical Synaptic Connectivity: Implications for Schizophrenia Pathophysiology

Barbara Lipska, Sharon Eastwood, Yukiori Goto, Kuei-Yuan Tseng

Schizophrenia has been recognized as a neurodevelopmental disorder caused by an interaction between genetic and environmental factors. These may lead to abnormal synaptic connectivity in several brain regions, including the hippocampal formation (HIP) and the prefrontal cortex (PFC). From post mortem studies to animal models, we will present an integrative standpoint of how these factors are tightly linked and are relevant to this disorder. First, Barbara Lipska will discuss the impact of genotypes on the expression of susceptibility genes in the PFC and HIP in postmortem schizophrenic brain. Secondly, Sharon Eastwood will summarize evidence from postmortem studies indicating that HIP glutamatergic (Glu) synapses may be preferentially (although not exclusively) involved in this disorder and its relationship to the expression of another potential susceptibility gene, calcineurin. Yukiori Goto will provide a series of data showing how the dopamine (DA) dependent HIP-PFC synaptic plasticity is affected during stress and in animals with a prenatal disruption of neurogenesis. Finally, Kuei Tseng will present several plausible cellular/synaptic mechanisms of how a neonatal disruption of HIP synaptic transmission affects adult PFC glutamatergic and GABAergic systems. The complexity of these interactions constitutes an important factor for developing mature PFC cognitive abilities from the early postnatal period through adolescence and adulthood. A functional disturbance of this normal neurodevelopmen-

tal process may be relevant to understanding several cortical pathophysiological changes observed in schizophrenia.

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

AMPA Receptor Structure, Function, and Regulation

Stephen Traynelis, Hiro Furukawa, Anders Kristensen, Johannes Hell, Hailan Hu

AMPA-selective glutamate receptors mediate the majority of fast excitatory synaptic transmission in the central nervous system. Changes in excitatory synaptic strength may underlie memory formation, and involve both post-translational modifications of AMPA receptors as well as changes in the number of receptors in the postsynaptic membrane. Recent progress on the structure of tetrameric AMPA receptors continues to distinguish this class as perhaps the best understood among ligand-gated channels. In addition, a number of studies now support a working hypothesis in which each subunit can bind agonist and undergo a subsequent conformational change that partially opens the channel pore. Lastly, this receptor is dynamically regulated through insertion and removal from the postsynaptic membrane. This panel brings together all of these themes by presenting a view on structure of the receptor, an evaluation of regulation by serine threonine phosphokinases PKA and CamKII, and information on trafficking of AMPA receptors as a means of regulating synaptic strength. The session will start with a discussion of recent advances in glutamate receptor structure (Hiro Furukawa), followed by Anders Kristensen's presentation of a mechanism by which CamKII can increase GluR1 receptor efficacy and single channel conductance through phosphorylation of Ser831 (Anders Kristensen). Johannes Hell will present PKA regulation of AMPA receptors through phosphorylation of nearby Ser845. Hailan Hu will follow this with new views on the roles and mechanisms underlying AMPA receptor trafficking into and out of synapses. The goal of this panel is to present the latest ideas about AMPA receptor structure, function, and regulation.

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

Process Guidance and Pathfinding in the CNS: How Do Oligodendrocyte Processes Find Their Way?

Rich Cohen, Vittorio Gallo, Babette Fuss, Holly Colognato

This scientific session focuses on the mechanisms that regulate the outgrowth of processes coming from the myelinating cells of the CNS, oligodendrocytes. For neuronal cells, process outgrowth and pathfinding has been intensively studied due to its importance for establishing neuronal

networks during development. For oligodendrocytes, process formation and remodeling is tightly associated with the differentiation from a bipolar, migratory to a myelinating, post-migratory cell. Similar to neuronal processes, oligodendroglial processes have to navigate through the CNS to assist migration and to find their target, that is, the axonal segment to be myelinated. However, little is known abut how these events are regulated. Recent findings demonstrate that in analogy to neuronal cells, oligodendroglial processes are able to "sense" and respond to extracellular cues, and that the extracellular environment plays an important regulatory role for oligodendrocyte differentiation and thus oligodendroglial process outgrowth.

In this session, Rick Cohen from the Coriell Institute for Medical Research will present examples for extracellular cues steering both neuronal processes and oligodendrocyte progenitor cells. Vittorio Gallo from the Children's Research Institute in Washington DC will introduce some of the extracellular cues that affect both oligodendrocyte progenitor migration and differentiation. Interestingly, not only bipolar and migratory oligodendrocyte progenitor cells follow extracellular cues, but also the processes of multipolar and likely post-migratory oligodendrocytes. These findings will be presented by Babette Fuss from Virginia Commonwealth University. All the above responses are mediated by interactions of the cell with components of the extracellular matrix. Holly Colognato from the State University of New York at Stony Brook will present findings related to the role of laminins and their signaling effector molecules for the regulation of oligodendrocyte survival, process outgrowth and myelin membrane formation.

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

Ins and Outs of Circadian Rhythms

Michael Iuvone, Robert Lucas, Susan Doyle, Gianluca Tosini, Carla Green

Circadian clocks are self-sustaining, genetically-based molecular machines that impose ~24 hour rhythmicity on physiology and behavior, and synchronize these functions with the solar day-night cycle. Complete circadian systems require an input or entrainment pathway, the molecular clockwork, and mechanisms to couple the clock's timing to physiological outputs. The discovery of inner retinal photoreceptors in mammals requires the generation of an integrated model of their contribution to visual and circadian functions that includes the rods and cones. Rob Lucas will address this challenge by employing a series of systems levels assessments of visual function in mice with various genetic modifications of each photoreceptor class. Susan Doyle will present data revealing interactions between rods, cones and melanopsin-containing retinal ganglion cells.

She will provide evidence for an inhibition of the melanopsin system by classical photoreceptors, and discuss recent work on retinal determinants of diurnal versus nocturnal behavior. Gianluca Tosini will present new evidence for a hierarchical organization of multiple circadian clocks within the retina that optimize retinal function by driving rhythms from gene expression to visual sensitivity. Circadian clocks depend on post-transcriptional regulatory mechanisms to generate proper rhythmicity. Nocturnin is a circadian expressed deadenylase that regulates rhythmic mRNAs at the post-transcriptional level. Carla Green will present new information about the biochemical mechanism that allows specific mRNA recognition by nocturnin and how nocturnin's function affects the outputs of the circadian clock. Collectively, the panelists will provide cutting edge examples of the organization of the circadian input and output pathways that govern circadian physiology.

Panel • Thursday 7:30–9:30 PM • Skyline

What's New on the Inside?

G.F. (Jerry) Gebhart, Patrick Mantyh, Bradley Undem, Brian Davis

Pain, predominantly visceral pain, is the principal reason people seek medical attention. Study of the viscera has lagged behind studies of more easily accessible somatic tissue, and this panel will highlight new knowledge about visceral innervation and visceral pain.

Pat Mantyh will describe a model of pancreatic cancer, the 4th most common cause of cancer death, and discuss potential neural mechanisms that drive and modulate pancreatic cancer pain throughout progression of the disease as well as unique challenges/opportunities pancreatic pain presents in aiding earlier diagnosis, survival, and increased quality of life of pancreatic cancer patients.

It is commonly believed, mistakenly, that the vagus nerve plays no role in visceral pain. Brad Undem will describe distinct subtypes of vagal nociceptive fibers in the airways and esophagus, revealing that nerve phenotype seems to be more dependent on ganglionic location (and thus embryonic history) than the tissue it innervates (e.g., nodose C-fibers are phenotypically different than DRG and jugular C-fibers).

Use of knockout mice has also provided new knowledge. Artemin is a member of the GDNF family that supports survival and growth of sensory and autonomic neurons during development. Brian Davis examined the sensory innervation of the heart in artemin knockout mice and found it was decreased (based on the number of CGRP-positive fibers) and that the heart was significantly atrophied (thin left ventricular wall). Jerry Gebhart studied mechanosensitive afferents innervating the colon and bladder, finding that a subset of stretch-sensitive afferents are significantly less responsive in TRPV1 null and ASIC3 null mice.

Panel • Thursday 4:30–6:30pm • Mt. Werner

The Light-Related Neurobiological Mechanism/s Altered in Psychiatric Disorders. How Does the Light Switch Turn Mood On and Off?

Monica Gonzalez, Horacio de la Iglesia, Laura Smale, Wallace Duncan

Bright light therapy is recognized in the Clinical Practice Guidelines, issued by U.S. Department of Health and Human Services, as an effective anti-depressant. However, the mechanisms by which light exerts its beneficial effects are still unknown. Light resets the phase of the master circadian pacemaker located within suprachiasmatic nucleus (SCN), and thus regulates the rhythmicity of most physiological and behavioral processes. Limited light exposure induces depression that is associated with the impairment of norepinephrine and serotonin, a feeling of helplessness, and alteration of the circadian rhythms.

The goal of this panel will be to shed some light into "the dark side of depression" by integrating clinical and basic studies that have identified possible neural mechanisms by which light can affect mood.

Horacio de la Iglesia will address the importance of dual oscillators within the SCN as a possible substrate for different circadian disorders. Laura Smale will discuss daily rhythms within and beyond the SCN in day-active compared to night-active mammals. Wallace Duncan will provide clinical evidence that extended darkness is associated with extended biological night in patients with winter depression as well as in healthy subjects. Monica Gonzalez will present a new rat model of depression in which the impairment of the norepinephrinergic and serotoninergic systems after long-term light deprivation is associated with alterations in the circadian sleep-waking cycle and helplessness.

Panel • Thursday 4:30–6:30 PM • Storm Peak

The Alphas of Alpha-Synuclein in Neurodegeneration

Martha Bohn, Matthew Farrer, Jean-Christophe Rochet, Eric Richfield, Mohan Sapru

Alpha-synuclein (SNCA), long known to be a component of Lewy bodies and Lewy neurities, the pathological hallmarks of Parkinson's disease (PD) and dementia with Lewy Bodies, has been receiving considerable attention recently due to its clear involvement in neurodegenerative diseases. Several mutations in the SNCA gene, as well as SNCA gene duplication and triplication have been linked to familial forms of PD. Moreover, there is evidence that genetic variability in the SNCA promoter is associated with PD. This panel will provide an overview of this rapidly evolving field. The panel will begin by reviewing our current understanding of SNCA gene structure and biochemistry and then will discuss approaches to target SNCA for developing novel animal models and clinical therapies for PD. Martha Bohn will introduce the speakers and raise timely issues for discussion. Matthew Farrer will review recent kindred studies from which genetic links to familial PD have emerged and present data on SNCA gene promoter variability that promise to lead to biomarkers for PD. Jean-Christophe Rochet will discuss the biochemistry of different forms of SNCA, including Parkinson's-linked mutants and post-translationally modified versions of the protein, and possible mechanisms involved in the vulnerability of dopamine neurons to SNCA toxicity. Eric Richfield will discuss various issues related to SNCA transgenic and gene deletion mouse models of PD, including different outcome measures aimed at identifying the most useful models for intervention testing. Mohan Sapru will discuss SNCA as a therapeutic target for PD, including the use of gene therapy vectors to deliver small interference RNA molecules to silence SNCA expression.

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

Neuregulins and Related Genes in Schizophrenia

Joel Kleinman, Douglas Falls, Amanda Law, Thomas Hyde, Yoshitatsu Sei

Recently, neuregulin 1 (NRG1) has been identified as a susceptibility gene for schizophrenia. Neuregulin1 proteins (NRG1s) are ligands for the receptor tyrosine kinases ErbB3 or ErbB4; NRG1-ErbB signaling mediates interactions between cells in the brain, heart, breast, and other organs. This panel will review the evidence implicating NRG1s in the pathogenesis of

schizophrenia and mechanisms by which abnormalities in NRG1 signaling might increase susceptibility to schizophrenia. The data discussed will range from basic molecular biology to clinical association studies. Douglas Falls will discuss the basic biology of the NRG1s, and their role in neuronal migration and brain development. Amanda Law will present postmortem and genetic data on NRG1 and ErbB4 splice isoform abundance in the brain in schizophrenia and discuss how interactions between NRG1 and ErbB4 disease associated polymorphic variants potentially affect NRG1 signaling in schizophrenia. Thomas Hyde will discuss the interface between NRG1 and other neurotransmitters in the brain, and their relationships to the intermediate phenotypes that characterize the clinical abnormalities associated with schizophrenia. Finally, Yoshitatsu Sei will demonstrate that NRG1-induced, ErbB receptor-mediated, cell migration can be tested using B lymphoblasts and discuss how this cellular model can be used to assess genetic interference and molecular defects in neuronal migration in schizophrenia.

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

Glycogen, Glucose and Lactate: A Complex Trio of Fuels for Neurons and Their Synapses.

Arne Schousboe, Bruce Ransom, Mary McKenna, Gulin Öz

Glucose is normally believed to be the most important energy substrate in the brain. However, it is extensively debated whether lactate derived from glucose may be even more important for neurons, particularly at glutamatergic synapses. Moreover, astrocytic glycogen may serve as an important energy reserve, which can be efficiently mobilized by glycogen phosphorylase. In this case, lactate can be generated and, depending on the stimulus condition, some may be transferred from the glial to the neuronal compartment to support energy production. These issues will be reviewed in the light of novel knowledge of key energy-requiring functions. Bruce Ransom will discuss the role of glycogen in the optic nerve as a fuel to maintain axon excitability during intense axon discharge and during hypoglycemia. Mary McKenna will elaborate on the relative importance of glucose and lactate as energy substrates and for maintenance of glutamate and GABA levels in synaptosomes. Gulin Öz will summarize the findings of in vivo measurements of glycogen metabolism in the rat and human brain and focus on its potential contribution to neuroglial energy metabolism during hypoglycemia. In relation to this Arne Schousboe will discuss the role of glycogen and glycolytic versus TCA cycle produced energy in vesicular glutamate release and high affinity glutamate transport

in a tissue culture model of a glutamatergic synapse. It is expected that the panel will provide novel insight into astrocyte-neuron energy homeostasis with focus on highly controversial issues.

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

Lentiviral Vectors for Gene Therapy of the Diseased Brain

Luc Jasmin, Michael McManus, Stephanos Kyrkanides, Pedro Lowenstein

Recombinant lentiviral vectors are capable of infecting non-dividing cells, including differentiated neurons of the brain, allowing for their use for the treatment of clinical disorders requiring long-term gene expression.

Michael McManus will describe how short hairpin RNAs that mitigate RNA interference can be expressed from lentiviruses, allowing for high efficiency transfection of a variety of cell types. This new tactic allows for the rapid interrogation of gene function, and approaches and methodologies for deriving RNAi-transgenic cells and animals will be discussed. Stephanos Kyrkanides will discuss how systemic and local administration of feline immunodeficiency virus (FIV) vectors are used for gene therapy. Systemic administration of recombinant beta-hexosaminidase FIV vectors has successfully resolved GM2 storage, brain inflammation, and clinical behavior, as well as restored skeletal development in a mouse model of Sandhoff disease. FIV vectors are being used to stably transduce bone marrow-derived monocytes used for the treatment of Sandhoff disease following ex vivo systemic transplantation. In addition, FIV vectors are being tested for the transfer of anti-nociceptive genes to sensory ganglia via retrograde transport for the treatment of chronic pain. Pedro Lowenstein will discuss the efficacy and limitations of viral vectors for gene transfer for the treatment of brain diseases.

Although effective, the ultimate potential and safety of viral vectors for gene therapy of brain diseases is limited by host immune responses. The existence of significant brain cell loss during an immune response to a viral vector in the brain highlights the need to understand the mechanisms by which the immune system modulates transgene expression in the brain. This will allow us to devise effective ways of counteracting the immune effects, and thus increase the efficacy and safety of brain gene therapy.

Panel • Thursday 4:30–6:30 PM • Mt. Werner

Genetic Epilepsies: A New Window on a Complex Disease

William Catterall, Alan Goldin, Robert L. Macdonald, Mark Leppert, Martin Gallagher

Mutations in sodium channels, potassium channels, and GABA receptors cause inherited forms of idiopathic generalized epilepsy. This panel will examine new insights into the molecular mechanisms through which these mutations cause epilepsy. Following an Introduction by the Panel Chair, A Goldin will present work on the functional effects of mutations in the Type I sodium channel (Nav1.1) that cause Generalized Epilepsy with Febrile Seizures Plus. These mutations cause a variety of functional changes in sodium channels, which all are predicted to result in increased propensity to fire repetitive action potentials under physiological conditions. W.A. Catterall will present studies of a mouse model of Severe Myoclonic Epilepsy of Infancy, which is caused by loss-of-function mutations in one allelle of the gene encoding Nav1.1 channels. These mice have a specific reduction of sodium current in hippocampal GABAergic interneurons, which may cause epilepsy by disinhibition of pyramidal cell excitability. M.J. Gallagher and R.L. Macdonald will describe mutations in GABA-A receptor alpha1(A322D), gamma2 (R43Q, K289M, Q351X), and delta (R220H, E177A) subunits that are associated with different epilepsy syndromes. Effects of these mutations on GABA-A receptor gating, expression, and trafficking to the cell surface will be discussed. M. Leppert will present work on mutations in the KCNQ family of potassium channels that cause Benign Familial Neonatal Convulsions. Recent studies have expanded the spectrum of clinical impairment observed with these mutations and determined their selective effects on heteromultimeric KCNQ2/KCNQ3 channels. The panel will end with discussion of the implications of these findings for idiopathic epilepsy syndromes.

Panel • Thursday 8:30–10:00 PM • Mt. Werner

The Role of Lateral Hypothalamic Peptides in Reward

Stephanie Borgland, Gary Aston-Jones, Ralph DiLeone, Sharif Taha

The orexins and melanin-concentrating hormone (MCH) are recently identified neuropeptides synthesized in the lateral hypothalamus (LH) and have been demonstrated to be critically involved in motivated behaviors such as arousal and feeding. In this session, we will discuss the role of LH

peptides in reward. Gary Aston-Jones will present new data showing that activation of LH orexin neurons is highly associated with the rewarding properties of natural and drug rewards, and that exogenous stimulation of these neurons produces reinstatement of an extinguished place preference for morphine. This effect is blocked by the orexin antagonist SB 334867 and mimicked by local administration of orexin into the ventral tegmental area (VTA). Stephanie Borgland will discuss the effects of orexins on excitatory synaptic plasticity of dopaminergic VTA neurons and will provide in vitro and in vivo evidence for a critical role for orexin signaling in the VTA in neural plasticity relevant to addiction. Ralph DiLeone will present information on a LH-nucleus accumbens circuit mediated by the MCH neuropeptide. In addition to modifications in animal behavior, DiLeone will present cellular and biochemical data exploring the mechanism and effects of MCH receptor signaling in nucleus accumbens (NAcc) neurons. Sharif Taha will present data from electrophysiological recordings of neurons in the NAcc, a striatal nucleus that projects to and modulates neural activity in the LH. Taha will present evidence that a subset of NAcc neurons gates reward-directed behavior through disinhibition of target brain regions, and discuss these data in the context of evidence that LH orexin neurons are an important target of NAcc projections.

Workshop • Thursday 8:30–10:00 PM • Storm Peak

Translational Neuroscience and Parkinsons Disease: Obstacles to Progress

Richard Beresford, Curt Freed, Don Gash, Evan Snyder, Karl Kieburtz

Parkinson's disease (PD) is a progressive neurodegenerative disease that features tremor, rigidity, bradykinesia, and postural instability. Available drug therapies often alleviate symptoms early in PD but do not appear to slow progression and may produce debilitating side-effects (e.g., dyskinesias, psychosis). Advances in genetics, biochemistry and physiology relevant to PD have generated innovative and incrementally helpful treatments (e.g., targeted neurosurgery, deep brain stimulation). But the need for still more effective treatments is compelling. Promising approaches include transplants of fetal brain tissue, targeted growth factor infusions, and neural stem cell implants. The goals of this workshop are to outline the therapeutic potential of these approaches and to portray perceived scientific, clinical, and regulatory obstacles to realizing their promise. Curt Freed will share his experience with using fetal brain transplants to treat PD and comment on its future prospects. Don Gash will address the current and projected status of growth factor infusions for treating PD. Evan Snyder will portray how neural stem cells may be utilized in treatment. Karl Kieburtz

will consider the problem of how to design clinical trials of novel and potentially high-risk treatments that both optimize satefy and yield reliable outcome data. The presenters will highlight what they view as the principal barriers to therapeutic application of particular approaches and weigh how these barriers might be surmounted. Beresford will introduce the workshop and comment on legal and regulatory issues that may influence the conduct of clinical trials. Formal presentations will be brief and slide-poor, and every effort will be made to engender discussion among workshop participants and attendees.

Workshop • Thursday 8:30–10:00 PM • Twilight

Hallucinogens—Past, Present and Future.

John Mendelson, Gantt Galloway, William Fantegrossi, Reese Jones, Matthew Baggott

Hallucinogenic drugs alter sensory perception and consciousness and have intrigued people in all walks of life since the dawn of civilization. Drugs that perturb conscious experience and distort sensations have also fascinated Neuroscientists. These compounds have been used to understand crucial aspects of the human experience and to probe mechanisms of diseases as diverse as schizophrenia, migraine and addiction. This panel focuses on current studies of abusable sensory distorting drugs. Reese Jones will review the history of hallucinogen research. Matthew Baggott will discuss new neurocognitive approaches to understanding hallucinogens in people. Gantt Galloway will review recent human work with MDMA. William Fantegrossi will reviw abuse liability and animal self administration. Reese Jones will discuss the pharmacology of Salvinorin A, and John Mendelson will review human studies with Salvia divinorum. Workshop participants will be able to discuss future directions of research and help set the agenda for the reemergence of research with these compounds.

Workshop • Thursday 8:30–10:00 PM • Rainbow

Lipids as Overlooked Modulators of Neurodegeneration

Neville Marks, Luigi Puglielle, Alan Faden, Mark Mattson

Abnormal increase in native ceramides in brains from AD, HIV dementias, ageing or after ischemia implicate lipids as long neglected modulators to induce or exacerbate neurodegeneration. Rather than acting as inert membrane components, emerging evidence indicates lipids play dynamic roles in transcription, growth, differentiation, and viability highly relevant

to neurodegeneration. While lipid storage diseases resulting from enzyme deficiencies dramatically alter brain growth and behavior, equally, subtle changes in lipid metabolism may result in cognitive dysfunction providing new targets for therapeutic intervention. This is illustrated for rapid ceramide turnover contributing to multidrug resistance (MDR) as a basis to develop alternative chemotherapeutic strategies. Neville Marks will provide background on biochemistry of ceramides and morphological consequences of abnormal increase in an isolated primary neuronal model that may replicate pathology. Alan Faden will focus on lipid-induced apoptosis via kinase or cell death mediated pathways and evaluation of neuroprotective agents. Mark Mattson will describe a proteomic approach to monitor the structure of perturbed lipid rafts, and their function in different neurological disorders including Alzheimer's and Huntington disease. Luigi Puglielli will provide evidence the role of ceramide as a second messenger for the general programming of aging processes as mediated by IGF1-receptor, the relevance to neurotrophin signaling, and neurodegeneration. Taken together these studies affirm the view lipids are important modulators and focus interest on environmental factors such as diet and lipid metabolism in the CNS as a new targets for drug design and treatment.

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

Terminator 4: Who Terminated the Nerve Fibers in Cutaneous and Gut Epithelia?

George Wilcox, William Kennedy, Frank Rice, Anne Louise Oaklander

Unmyelinated nerves constitute the majority of nerves in the central and peripheral nervous systems and almost all nerves in the enteric nervous system. Until recently, investigation of epidermal nerve fibers (ENF) has been difficult because the fibers could not be reliably stained, electrically stimulated, or recorded from. Meaningful clinical studies first began by application of immunocytochemical methods to accessible unmyelinated nerves. The most accessible nerves in humans are the ENFs obtained by skin biopsy. Practical clinical applications include a variety of peripheral neuropathies associated with painful symptoms, including diabetic neuropathy, HIV, postherpetic neuralgia, small fiber neuropathy (burning feet), Fabry disease, and others. The approach has recently been extended to include the gastrointestinal tract, urinary bladder, and other internal organs where lack of motility is often accompanied by epithelial denervation.

George Wilcox will describe the development of the immunohistochemical approaches used by all four panelists to objectively assess ENF loss

and to test hypothesized mechanisms underlying their loss. The findings of cutaneous denervation accompanying diabetic and other neuropathies will provide a discussion vehicle. Anne Louise Oaklander will review data from two neuralgic syndromes (postherpetic neuralgia and complex regional pain syndrome), and multiple unilateral nerve injury animal models demonstrating "mirror-image" effects after unilateral nerve injuries, including behavioral/anatomical "cross-over" effects and ascending spinal cord signaling. Frank Rice will discuss ENF loss and exposure of remaining nerves to algogens. Immuno-confocal imaging of ENFs and surrounding structures of Fabry skin biopsies suggest relationships among pain, ENF loss, and immune cell activation. Finally, Bill Kennedy will present immuno-confocal images of neurons and nerves of the gastrointestinal tract of diabetic pancreas transplantation candidates with gastroparesis, diarrhea, and constipation.

Audience involvement will be encouraged by lively exchanges among the presenters concerning the meaning implied by the immunohistochemical images presented.

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

Executive Function and Schizophrenia

Roberta Calzavara, Mark D'Esposito, Francine Benes, Kent Kiehl

The DLPFC is involved in working memory and strategic planning processes, playing an important role in executive functions. It is strategically located adjacent to, and functionally associated with, the dorsal anterior cingulate cortex (ACC) medially, and the premotor cortex caudally. These two adjacent cortical regions are important for behavior monitoring and action planning respectively. The interactions between the DLPFC and ACC are important for appropriate planning of actions. Pathophysiology in these areas is associated with schizophrenia. In this panel, we will discuss the anatomical and functional circuitry involved in the executive function, with the aim of understanding the pathological aspects in schizophrenia. Specific attention will be on the DLPFC and the related frontal regions, ACC and premotor.

Roberta Calzavara will present recent anatomical data on the relationship between DLPFC, ACC, and premotor areas in the frontal cortico-striatal and cortico-thalamic circuitry in the macaque monkey. She will discuss the integration between these different functional inputs. Mark D'Esposito will present functional imaging data showing the critical role of the DLPFC in selective attention behavior. Francine Benes will talk about the role of the amygdala in regulating the activity of GABAergic interneurons in the

hippocampus and anterior cingulate region of schizophrenic and bipolar subjects. Kent Kiehl will present imaging data from studies of schizophrenia illustrating abnormal functional connectivity between frontal (anterior cingulate and DLPFC) and temporal lobes.

Panel • Friday 7:30–9:30 AM • Mt. Werner

How Does Environment Modulate Psychostimulant-induced Behaviors?

Terry Robinson, Bruce T. Hope, Jennifer Bossert, Paul Vezina

Psychostimulant drug effects on brain and behavior are modulated by environmental stimuli present during drug administration. The global set of stimuli that makes up environmental context has particularly strong modulatory effects on drug-associated behaviors such as sensitization, self-administration, and relapse and may be related to the effects of environmental context on craving in human addicts.

The current emphasis on the neuroadaptatations hypothesis to explain the effects of repeated administration of these drugs has underestimated the impact of environmental context and what it says about the mechanisms underlying behaviors such as sensitization, self-administration, and relapse. As a form of associative learning between context and drug effects, one would expect specific sets of neurons within various brain regions to be selected by the environmental stimuli for unique types of molecular and cellular alterations. Unfortunately, nearly all techniques to date have analyzed molecular and cellular alterations without distinguishing between neurons selected by the environment and all other neurons not selected by the environment—a strategy that emphasizes non-specific changes unlikely to be related to associative learning.

Terry Robinson will introduce how an animal's environment dramatically modulates its behavioral and neural responses to psychostimulants. Bruce Hope will describe molecular and cellular alterations in nucleus accumbens neurons selectively activated during cocaine-induced behavior. Jennifer Bossert will describe the role of environment in reinstatement of cocaine and heroin seeking. Paul Vezina will describe some of the neural circuitry that allows environmental stimuli to modulate sensitized responses to psychostimulants.

Panel • Friday 7:30–9:30 AM • Storm Peak

Interventions for Traumatic Brain Injury in Children

Kimberly Topp, Mayumi Prins, Matt Potts, Alpa Trivedi, Akiva Cohen

Traumatic brain injury accounts for more than 50% of deaths and disability in the pediatric population, with a peak in children younger than 6 years of age. Children frequently show milder injuries than adults, although their outcomes are significantly worse. Children show cognitive deficits that may permanently alter their ability to concentrate, make decisions, learn, and interact socially. Children may suffer from focal brain injury caused by direct contusion, laceration, or hemorrhage, or diffuse brain injury including concussion and diffuse axonal injury. Several models of head trauma that mimic human injuries have been developed and are used in the developing brain to investigate neuropathological features and assess novel therapeutic interventions. Kimberly Topp will introduce the topic and the speakers. Mayumi Prins will show that age-dependent ketogenic neuroprotection after traumatic brain injury is related to age-related differences in the "inducibility" of the ketone transporter, suggesting that alternative substrate therapy has potential applications for younger head injured patients. Matt Potts will show that controlled cortical impact injury to the immature murine brain results in reduced hippocampal neurogenesis, prior to the development of cognitive deficits, and that neurogenesis continues at a normal rate in the hippocampi of transgenic mice that overexpress the antioxidant enzyme glutathione peroxidase. Alpa Trivedi will discuss the use of allogeneic Sertoli cells as gene delivery vehicles and the ability to track cells in vivo using MRI. Akiva Cohen will discuss activity-dependent recovery and the use of exercise to elevate the levels of neurotrophic factors in the hippocampus after traumatic brain injury.

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

Role of Astrocytic Signaling Systems in Neurophysiology and Pathology

Ken McCarthy, Phil Haydon, Brian MacVicar, Eric Newman

Astrocytes exhibit a wide variety of signaling systems that enable them to respond and modulate the activity of other neural cells in brain. Panel participants will engage two critical questions that loom in this area. First, under what conditions do astrocytes respond and/or modulate the activity of neural cells? Second, what are the physiological and/or pathological consequences of astrocytic conversation with other neural cells?

Ken McCarthy will discuss findings from transgenic mice expressing unique Gi-, Gs-, and Gq-linked GPCRs in astrocytes and from conditional knockout mice with targeted deletion of signaling molecules in astrocytes. Findings indicate that perturbations in astrocytic signaling leads to phenotypes ranging from hydrocephalus to ataxia. Phil Haydon will discuss findings from mice expressing a dominant-negative mutation that selectively blocks neurotransmitter release from astrocytes. Results indicate that astrocytes tonically release ATP via a SNARE-dependent process to modulate synaptic plasticity and coordinate heterosynaptic depression in the hippocampus. Brian MacVicar will discuss the roles for astrocytes in the control of cerebral blood vessels. Results from two photon lsm and uncaging studies indicate that astrocyte calcium waves cause constrictions of cerebral blood vessels and that neuronal activity increases cerebral blood flow, in part, by preventing astrocyte-induced vasoconstriction. Eric Newman will discuss signaling between glia, neurons, and blood vessels in the acutely isolated rat retina. When the retina is stimulated with a flickering light, Ca2+ increases are evoked in Müller cells, the principal retinal glial cells. Further, stimulation of Muller cells modulates both neuronal activity and arteriole constriction/dilation, indicating that these cells play an important role in the physiology of the retina.

Panel • Friday 7:30–9:30 AM • Rainbow

Losing Our Inhibitions: From Genes to Circuits in the Epileptic Brain

Jeff Noebels, Nick Poolos, Tom Sutula, Scott Baraban

Recent gene discoveries as well as cellular and systems studies point to the loss of inhibitory control mechanisms as a general predisposing feature in human and experimental models of epilepsy. Inhibitory mechanisms can be impaired at multiple biological levels: gene mutations, post-translational channel modulation, synaptic network alterations, and cell loss. In the hippocampus and cortex, clear examples of these changes can now be identified.

This panel discussion will explore four major sites of disinhibition in hippocampal neural networks drawing on new experimental models. Jeff Noebels will provide an overview that includes mouse models with diminished gating of cortical input by dentate granule cells. Nick Poolos will discuss modulation of Ih currents in pyramidal cells that limits dendritic excitability, and the case for h-channelopathy in epilepsy. Tom Sutula will examine synaptic network changes leading to loss of inhibition in the dentate gyrus that are associated with spontaneous seizures. Scott Baraban

will describe a mouse mutant featuring delayed interneuron loss in neocortex and hippocampus, reduced inhibition, and epilepsy.

Panel • Friday 7:30–9:30 AM • Sunset

Pain—Trigeminal Neuralgia: The Clinical Mysteries, Therapeutic Dilemmas, and Functional MRI

Suzanne Roffler-Tarlov, Edward Tarlov, Carlos David, David Borsook

Trigeminal Tic Douloureux–paroxysmal, provokable, unpredictable and severe–is a painful, chronic, disabling condition that predominantly affects the elderly. The trigeminal system, the anatomy of which Suzanne Tarlov will review, is unique in having a large autonomous distribution, whereas other sensory nerves overlap considerably in their distribution. Probably for this reason, trigeminal pain can be successfully treated surgically.

How is trigeminal pain removed? There are two views of the best approach and these are linked to opposing theories of the origin of the pain. Ed Tarlov advocates percutaneous controlled radiofrequency thermocoagulation of the trigeminal ganglion and rootlets. This approach rests on the view that ephaptic transmission due to demyelination may be part of the mechanism of pain. Trigeminal c fibers are more sensitive to heat than are touch fibers, making it possible to coagulate the pain pathway while preserving the sensation of touch. Carlos David supports the theory that external compression of the trigeminal posterior root by a vascular loop is the cause of the pain. He will describe the operation that treats trigeminal pain by intracranial microvascular decompression.

David Borsook will describe functional MRI imaging of the human trigeminal pathway to provide insights into physiological and pathological pain in healthy individuals and patients with clinical conditions affecting the trigeminal system from ganglion to cortex. Functional measures may contribute to better understanding and a more objective measure of changes occurring with treatment of pain.

Panel • Friday 7:30–9:30 AM • Skyline

Novel Regulators of Body Weight

Lloyd Fricker, Tamas Horvath, Mark Sleeman, Stephen Salton

Obesity is basically a problem of energy balance, and there are a number of well-known CNS regulators of this system (such as neuropeptide Y and alpha-MSH). The overall goal of this panel is to draw attention to neuropeptides and other proteins that have only recently been found to participate

in energy homeostasis. Tamas Horvath will introduce the basic issues of body weight control and provide an overview of the hypothalamic circuits that regulate this system. He will then describe recent work in his lab that examines the role of hypothalamic mitochondrial uncoupling in the regulation of the melanocortin system; UCP2 is present in NPY and POMC neurons where it controls mitochondria number and function depending on metabolic state. Mark Sleeman will discuss the roles of ghrelin in regulating metabolic fuel preference and the lipid phosphatase SHIP2 in conferring resistance to dietary obesity. Lastly he will discuss AgRP and the hypothalamic-pituitary-thyroid axis. Next, Lloyd Fricker will describe the role of proSAAS-derived peptides in controlling body weight, and also present a peptidomics study on the regulation of hypothalamic peptides during food deprivation and other paradigms that alter body weight of mice. Steve Salton will then discuss the function of VGF and VGF-derived peptides in the regulation of energy expenditure and peripheral fat storage, based on studies of transgenic and knockout mice. Ample time for discussion will be provided to integrate the various talks into a better understanding of the overall regulation of energy balance at multiple levels.

Panel • Friday 4:30–6:30 PM • Mt. Werner

Psychostimulants, L-type Calcium Channels and the Yin and Yang of PKA Signaling in the Nucleus Accumbens

Chris Pierce, Paul Mermelstein, Heath Schmidt, Anjali Rajadhyaksha, Xiu-Ti Hu

A growing body of evidence indicates that L-type calcium channels are important effectors for dopamine receptor signaling. Moreover, repeated exposure to psychostimulants alters the manner in which dopamine receptors activate PKA, which leads to changes in intracellular calcium and the stimulation of calcium-mediated kinases and phosphatases. This panel is dedicated to reviewing psychostimulant-induced changes in dopamine receptor signaling involving calcium, which may contribute to withdrawal or craving. The first three talks will focus on D1-like dopamine receptor stimulation of PKA and the subsequent activation of L-type calcium channels. Paul Mermelstein will outline recent results indicating that D1-like dopamine receptor-induced activation of L-type calcium channels influences the expression of GluR2 AMPA glutamate receptor subunits via the serial activation of the phosphatase calcineurin and the transcription factor NFATc4. Heath Schmidt will present data suggesting that intra-accumbal shell administration of a D1-like dopamine receptor agonist promotes

cocaine seeking by activating L-type calcium channels and stimulating CaM-KII, which may result in increased insertion of GluR2-containing AMPA receptors into the membrane. Anjali Rajadhyaksha will summarize recent results indicating that an amphetamine challenge injection decreases p-Ser 845-GluR1 in the nucleus accumbens of amphetamine-sensitized mice, a process that requires the activation of L-type calcium channels. Xiu-Ti Hu will focus on D2 dopamine receptor-induced decreases in PKA, which facilitate intracellular calcium signaling. His work indicates that repeated cocaine injections decrease intracellular calcium signaling by reducing calcineurin and increasing p-Thr.34-DARPP-32, which collectively reduce voltage-sensitive sodium currents in medium spiny neurons of the nucleus accumbens.

Panel • Friday 4:30–6:30 PM • Storm Peak

Molecular Mechanisms Regulating Kainate Receptor Function

John Isaac, Anis Contractor, Christophe Mulle, Geoff Swanson

Kainate receptors are one of the three ionotropic glutamate receptor subtypes and are tetramers composed of GluR5-7 and KA1&2 subunits. They are widely expressed in the CNS, and are critically involved in excitatory and inhibitory neurotransmission, the induction and expression of long-term potentiation (LTP), and strongly implicated in diseases such as epilepsy. Despite their wide expression and role in the mammalian brain, until recently almost nothing was known about the mechanisms regulating kainate receptor function. In this panel, we will discuss the recent advances in understanding the molecular mechanisms regulating kainate receptor function in neurons and the physiological impact of such regulation. Anis Contractor will discuss new data concerning the mechanisms of activity-dependent endocytic sorting of kainate receptors. John Isaac will present recent findings on the rapid co-ordinated regulation of AMPA and kainate receptors at thalamocortical synapses in the barrel cortex during LTP. Christophe Mulle will focus on processes that regulate the cell surface delivery of kainate receptors of particular subunit compositions in neurons. Geoff Swanson will discuss recent work on ER retention motifs and forward trafficking motifs found in particular kainate receptor subunits and the impact of this on the regulation of kainate receptor surface expression. This panel will provide the most recent information on the variety of mechanisms that can acutely regulate subunit composition and surface expression of kainate receptors in neurons and the impact this has on their physiological function.

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

Molecular Mechanisms of Neuronal Pain Signals

Andrew Russo, Luda Diatchenko, John Quinn, Ian Dickerson

Recent advances in human genetics, gene imaging, and intracellular signaling proteins have provided new opportunities for understanding the mechanisms underlying pain. This panel will present recent strategies for studying pain signal transmission at a molecular level. Genetic mapping of polymorphisms are providing new insights that can potentially be exploited by in vivo imaging of promoter activity. Luda Diatchenko will describe the convergence of human gene mapping of SNPs in the COMT gene to pain susceptibility and functional consequences on the metabolism of catecholamine transmitters. John Quinn will briefly describe regulatory VNTRs within neurotransmitter genes. Andrew Russo will briefly describe how CGRP neuropeptide promoter activity can be measured in trigeminal neurons of the live mouse. The last talk will focus on the identification of an unusual G protein coupled receptor. Ian Dickerson will describe recent experiments modulating the subunits of the CGRP receptor and activation of intracellular signaling pathways. These presentations will provide an overview of the mechanisms controlling pain signals from neurotransmitter synthesis, metabolism, receptor activation, and signal transduction.

Panel • Friday 4:30–6:30 PM • Rainbow

The Emerging Field of Cognitive Genomics: New Findings and Their Implications for Novel Treatments

Anil Malhotra, Tyrone Cannon, David Goldman, Michael Egan

Molecular genetic studies of human cognitive function offer the prospect of novel treatment strategies specifically targeted to cognitive impairment. In this panel, we will review the first data identifying specific genetic contributions to neurocognitive function, present functional data that suggest mechanism of actions for these genetic effects, and discuss the implications of these finding for the development of cognitive enhancement strategies in neuropsychiatric disorders such as schizophrenia. Anil Malhotra will present molecular genetic evidence that the schizophrenia susceptibility genes catechol-o-methyltransferase (COMT) and dystrobrevin binding

protein 1 (DTNBP1) produce significant effects on distinct aspects of neurocognitive function in healthy volunteers, in patients with bipolar disorder, and in patients with schizophrenia. Tyrone Cannon (UCLA) will present the results of genetic association analyses evaluating haplotypes of putative susceptibility genes for schizophrenia and bipolar disorder in relation to neurocognitive and neuroimaging-based phenotypes. In particular, he will highlight the role of DISC1 (Disrupted in Schizophrenia 1) on chromosome 1q42 in the determination of deficits in short- and long-term memory functioning and associated reductions in regional gray matter density in patients with these disorders. David Goldman will report on new studies that examine the role of these risk genotypes on mRNA expression, as well as in vitro data on the functional consequences of specific cognitive candidate polymorphisms. Finally, Michael Egan will discuss the impact of this work on the development of new treatment strategies for neuropsychiatric disorders in which cognitive dysfunction is prominent, including new data suggesting that gene-based treatments may be efficacious for cognitive enhancement in schizophrenia.

Panel • Friday 4:30–6:30 PM • Sunset

Novel Roles for Neuropeptides in CNS Function

John Quinn, Liam Gray, Michael Kubek, Claude Wasterlain

Neuropeptides have many roles in addition to their traditional function as modulators of synaptic activity. This session will illustrate some of those roles and the complex interactions that make neuropeptides so critical to the integrated functioning of the central nervous system. John Quinn will show that modulation of neuropeptide gene expression controls the modulation of cytokine expression, which in turn modulates the expression and function of ion channels inside and outside the nervous system. Liam Gray will show that neuropeptide Y acting through NPYR1 receptors controls neurogenesis in dentate gyrus cultures, and that NPYR1 -/- mice and NPY KO rats show reduced neurogenesis in vivo. Mike Kubek will discuss the role of TRH and new ways to deliver peptides like TRH to specific temporal lobe targets. Claude Wasterlain will suggest a possible role for tachykinins in directing trafficking of excitatory glutamate receptors, and will show that galanin, like NPY, modulates neurogenesis in the dentate gyrus. These presentations highlight some unconventional roles for neuropeptides in brain function.

Panel • Friday 4:30–6:30 PM • Skyline

Outer Retina Circuitry and Signaling

Nick Brecha, Catherine Morgans, Steve Massey, Ron Gregg

In the outer retina, visual information is initially transferred from photoreceptors at a specialized synaptic complex, known as the photoreceptor synaptic triad. This synaptic complex consists of a photoreceptor terminal, bipolar cell dendrites, and horizontal cell endings. The photoreceptor terminal is highly specialized and contains a synaptic ribbon and a unique set of ribbons, vesicular and synaptic proteins that mediate a graded release of the neurotransmitter, glutamate. Structurally, the triad is characterized by an invaginating ON-bipolar cell dendrite that is flanked by two horizontal cell endings. Outside the invagination, OFF-bipolar cell dendrites form basal contacts on photoreceptor terminals. Horizontal cells transmit visual signals across the outer retina, while bipolar cells transmit visual signals to the inner retina.

The presenters will discuss new findings regarding the functional organization of outer retinal circuitry. Catherine Morgans will discuss alpha-1F Ca2+ channels, which influence glutamate release from photoreceptors, and new findings that suggest this channel plays an essential role in forming the photoreceptor ribbon synapse. Steve Massey will discuss horizontal cell microcircuitry and gap junction coupling with rod and cone photoreceptor terminals. Nick Brecha will discuss vesicle and SNARE protein expression in horizontal cell endings, and the possibility that transmitter release from horizontal cells is mediated by a vesicular mechanism. Ron Gregg will discuss nyctalopin, a small leucine rich repeat protein that is expressed extracellularly on ON-bipolar cells, and its role in gating a non-specific cation channel that mediates signal transfer from outer to inner retina.

Don't forget to visit the exhibitors in Sunshine throughout the week.

WCBR Thanks

IES Brain Research Foundation

for the 2006 travel fellowship!

The Irene & Eric Simon (IES) Brain Research Foundation was recently organized in honor of Dr. Eric Simon's continued outstanding work, while also honoring the undying support of his wife, Irene.

The goal of this Foundation is to help advance research and education in the area of brain research, with a focus on addiction, pain, and other diseases and conditions of the brain, such as Alzheimer's, schizophrenia, and aging. The Foundation will encourage outstanding young scientists to enter this important field as well as focus public attention on the importance of basic research.

IES Brain Research Foundation Summer Fellowship Program has been established, for brilliant college seniors and beginning graduate students to work in laboratories with established scientists, to give young science-oriented students a chance to see whether brain research is a career that they wish to pursue and hopefully will help attract excellent new talent to the field.

Speakers Bureau will provide speakers to community groups and businesses to talk about the current state of the art of brain research and how basic research contributes to the cure and prevention of brain diseases, such as drug & alcohol addiction, pain, and other diseases.

Future goals for funds raised: lectures, symposia, modest grants or purchasing of needed equipment for a lab doing outstanding brain research

Irene & Eric Simon Brain Research Foundation

"Brain Research – A Bright Idea"

For info or to help: (973) 726-6218

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