Welcome to the Thirty-Seventh 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 thirty 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 25. Our guest speaker will be The Honorable John Edward Porter, former Congressman from Illinois and Chair of the House Appropriations Committee. The title of his talk will be *What's Going on in Washington: We Need to Talk!* On Tuesday, January 27, a **town meeting** will be held for the Copper Mountain community, at which Dr. Michael Zigmond, Director of the Morris K. Udall Research Center for Parkinson's Disease at the University of Pittsburgh, will give a talk entitled *Exercise and the Brain.* Also, participants in the WCBR **School Outreach Program** will present sessions at local schools throughout the week to pique students' interest in science. Finally, the banquet, including a special program, music, and dancing, will be held on Friday evening, January 30.

Generous donations from sponsors have permitted us to continue the WCBR Fellowship Award Program. These awards are given to young neuroscientists who are on the formal program of the conference. Congratulations and a warm welcome to this year's fellows: Jean-Claude Beique, James Bisley, Angela Cantrell, Jane Cavanaugh, Colm Cunningham, Pat DiCiano, Eric Dumont, Kristen Ashley Horner, Kari Hoyt, Erin Jacobs, Kimberly McAllister, Krista McFarland, Stephen Noctor, Joseph Nunez, Emmanuel Pothos, Katherine Roche, David Weinshenker, and Cyrus Zabetian. Fellow names are in italics in the session schedule.

Please plan to attend the business meeting at 6:30 PM on Wednesday, January 28. We will elect a Program Chair-elect and three members of the Board of Directors. Other important matters will be discussed, including the selection of future conference sites.

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Fellowship Program

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Exhibits

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Frank Welsh
Jeff Witkin

Town Meeting

Bill Carlezon

2004 Fellowship Awardees

Jean-Claude Beique
James Bisley
Angela Cantrell
Jane Cavanaugh
Colm Cunningham
Pat DiCiano
Eric Dumont
Kristen Ashley Horner
Kari Hoyt
Erin Jacobs
Kimberly McAllister
Krista McFarland
Stephen Noctor
Joseph Nunez
Emmanuel Pothos
Katherine Roche
David Weinshenker
Cyrus Zabetian

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Abercrombie Elizabeth
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Anthony Basile
Mike Egan
Bob Handa
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Michael Levine
Barb Lipska
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Michael Zigmond

Conference Arrangements

Scott C. Miller, Assistant Head
Conferences & Institutes
Office of Continuing Education
University of Illinois at Urbana-Champaign
302 East John Street, Suite 202
Champaign, IL 61820
Phone toll free 877-455-2687 Fax 217-333-9561
E-mail winterbrain@ad.uiuc.edu

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Phone 41-61-306-1364 Fax 41-61-306-1234
E-mail: c.maetzler@karger.ch

MED Associates, Inc.
PO Box 319
St. Albans, VT 05478
Phone 802-527-2343 Fax 802-527-5095
Contact: Karl Zurn
E-mail: karl@med-associates.com

MicroBrightField, Inc.
185 Allen Brook Lane
Williston, VT 05495
Contact: Jack Glaser
Phone 802-288-9290 Fax 802-288-9002
jglaser@microbrightfield.com

Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health
6001 Executive Boulevard, Room 7186
Bethesda, MD 20892-9641
Contact: Beth-Anne Sieber
Phone 301-443-5288 Fax 301-402-4740
E-mail: bsieber@mail.nih.gov

Nikon Inc.
PO Box 2464
Evergreen, CO 80437
Contact: Gerald Benham
Colorado Office Phone and Fax 303-674-1569
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Olympus America
Two Corporate Center Drive
Melville, NY 11797
Contact: Kathleen Karmel
Phone 800-645-8100 Box 6462 Fax 435-615-8350
Email: Kathleen.Karmel@olympus.com

General Information

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

WCBR Information Desk and Message Center are in the Copper Conference Center Upper Level. The desk hours are as follows:

	Morning	*Afternoon*	*Evening*
Saturday 1/24	9:00–11:00 AM	3:30–5:30 PM	6:30–10:00 PM
Sunday 1/25	7:00–8:00 AM	3:30–6:30 PM	
Monday 1/26– Friday 1/30	7:00–8:00 AM	3:30–4:30 PM	

The telephone number for messages is 970-968-2318, ext 47111. The Copper Conference Center fax number is 970-968-3347. The person sending or receiving faxes is responsible for all charges.

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. PLEASE NOTE that your housing reservation must be shown before these items can be issued. Conferees who do not accept WCBR-assigned accommodations are charged a facilities supplement of $100 as stated in the WCBR announcement. No exceptions can be granted. 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 Bighorn B: 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 21–24. 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 the Bighorn B. 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 the Bighorn Ballroom of the Copper Conference Center, and on Monday through Friday, 6:30–7:30 AM, in Jack's. Jack's is attached to the Copper Conference Center and adjacent to the Bighorn Ballroom. (Social guests ONLY may have breakfast until 10:00 AM in the Kokopelli Area near the Bighorn Ballroom.) The tickets in your registration packet are required for admission. On Saturday morning (February 1) before departure, a continental breakfast is available in the Bighorn Ballroom of the Copper Conference Center.

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.

Don't forget to visit the exhibit area.

Special Events

Saturday, January 24

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

Sunday, January 25

Conference Breakfast and Opening Address • 7:30 AM, Bighorn Ballroom
(Your required ticket is in your registration packet.) The plenary keynote speaker will be the Honorable John Edward Porter.

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

Monday, January 26

First Meeting of the Board of Directors • 6:30–8:30 AM, Board Room, Tucker Mountain Lodge

Tuesday, January 27

Town Meeting • 7:00 PM, Summit Middle School, Frisco, CO

Wednesday, January 28

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00–11:30 AM, Solitude Station, Mid-Mountain

NASTAR registration cards to be completed no later than Monday, January 26, 8:00 AM at WCBR Information Desk.

Mountain Lunch • Noon–2:00 PM, Solitude Station, Mid-Mountain – take American Eagle Lift
Required lunch ticket is in your registration packet. Non-skiers requiring transportation should sign up at the WCBR Information Desk.

Business Meeting • 6:30 PM, Bighorn C1
Election of Program Chair-elect and three members of the Board of Directors.

Friday, January 30

Second Meeting of the Board of Directors • 6:30–7:30 AM, Board Room, Tucker Mountain Lodge

Banquet and Dance • 8:00 PM, Bighorn Ballroom
Required ticket is in your registration packet. Cash bar opens at 7:00 PM in the Ballroom Lobby.

Preamble to the Program

The 2004 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 25

7:30 AM

BREAKFAST ADDRESS • What's Going on in Washington: We Need to Talk!

The Honorable John Edward Porter

Bighorn Ballroom

3:30 – 4:30 PM

EXHIBITS & POSTER SESSION 1 • Posters available for viewing

Bighorn B

4:30–6:30 PM

PANEL • Estrogen and Progesterone: Magic Elixir or Caustic Cocktail for Brain Aging?

M. A. Ottinger, J. Simpkins, I. Merchenthaler, R. Handa, C. Sladek

Bighorn C1

PANEL • Urocortins: Stress, Feeding, or Stress-induced Feeding?

C. Kotz, W. Vale, D. Richard, V. Bakshi

Bighorn C2

PANEL • Does Antisense Make Sense in the CNS?

B. Hoffman, D. Corey, C. Wahlestedt, C. Jones

Hasty's

PANEL • Chemokines and Neuroinflammatory Disease: New Directions

C. Pert, P. Shapshak, M. Ruff, S. Wilt

Jacque's Peak (Mountain Plaza Building)

PANEL • Neuroprotection in Traumatic Brain Injury: Will Novel Mechanistic Strategies Show It Is a Treatable Condition?

E. Hall, S. Scheff, J. Povlishock, A. Faden, M. Vitek

Ptarmigan A

PANEL • Are Antipsychotics Neuroprotective in Schizophrenia? Findings from Bedside to Benchtop

L. Nisenbaum, J. Rapoport, G. Tollefson, T. Gould

Ptarmigan B

PANEL • NMDA Receptors in Huntington's Disease

L. Raymond, M. Levine, M. Ariano, K. Murphy

Ptarmigan C

8:30–10:00 PM

PANEL • Stem Cells in CNS Development and Disease

S. Whittemore, J. Macklis, D. van der Kooy, S. Goldman

Bighorn C1

Sunday, January 25, continued

PANEL • A Head for Serotonin—Its Role in Psychostimulant Actions

K.A. Horner, K. Cunningham, B. Yamamoto, L. Parsons

Bighorn C2

PANEL • Neuropeptides Take a Holiday: Mice without Neuropeptide Processing Enzymes

I. Lindberg, L. Fricker, W. Wetsel, J. Pintar

Hasty's

WORKSHOP • New Research in Brain Stimulation: Restoring Sensory and Motor Function

D. Woodward, J. Chapin, J. Chang, J. Saint-Cyr

Ptarmigan A

WORKSHOP • Knowledge Engineering in Neuroscience

G. Burns, M. Martone, R. Cannon, A. Toga

Ptarmigan B

WORKSHOP • New Roles for Ca2+ Signaling in Circadian Clock Regulation: Membrane, Cellular and Circuit Levels of Actions

M. Gillette, C. Allen, C.S. Colwell, R. Silver

Ptarmigan C

Monday, January 26

7:30–9:30 AM

PANEL • Targeting Astrocytes to Influence Glutamatergic Neurotransmission: Lessons from Knockout Mice

R. Schwarcz, J. Coyle, P. Magistretti, C. MacLeod

Bighorn C1

PANEL • The Dynamics of Excitatory Synapses: Implications for Synaptic Plasticity

R. S. Zukin, G. Westbrook, D. Bredt, *K. McAllister*, M. Bennett

Bighorn C2

PANEL • Applying Lessons from Visual Art to Exploration of the Brain

D. H. Laidlaw, D. Kremers, A.W. Toga, F. Drury, R. E. Jacobs

Hasty's

PANEL • Obesity-Brain Interactions: Neural Mechanisms, Treatment and Complications

S. Harik, B. Levin, K. Juhasz-Pocsine, C. Billington

Ptarmigan A

PANEL • Ignored but Not Forgotten: Neuronal Apoptosis in the Normal Adult Rat Brain

D. Fujikawa, V. Koliatsos, J. Roskams, K. Gale

Ptarmigan B

PANEL The Neurovascular Unit in Cerebral Ischemia

P. Huang, M. Chopp, D. Greenberg, J. LaManna, P. Hurn

Ptarmigan C

3:30–4:30 PM

EXHIBITS & POSTER SESSION 1 • Presenters available for discussion

Bighorn B

4:30–6:30 PM

PANEL • Developmental Mechanisms for the Regulation of Synaptic Plasticity

J. Isaac, D. Bredt, V. Maricq, *K. Roche*

Bighorn C1

PANEL • The Role of AD-related Genes in Regulating Neuronal Excitability and Synaptic Transmission

A. Cantrell, D. Cook, G. Gouras, R. Malinow

Bighorn C2

PANEL • The Oligodendrocyte Precursor: Stem Cell, Adult Glial Cell or Impediment to Repair?

J. Fawcett, J. Levine, A. Nishiyama, R. Franklin

Hasty's

PANEL • Computational Properties of Cerebellar Neurons

D. Jaeger, B. Finch, W. Regehr, V. Gauck

Ptarmigan A

PANEL • Making Placodes Under Water: Using Zebrafish to Understand the Origins and Patterning of Head Placodes

R. Karlstrom, Z. Varga, M. Westerfield

Ptarmigan B

PANEL • Beyond Ataxia: Recasting the Cerebellum by Genetic Disruption

J. Welsh, E. Hess, R. Joho, C. Fletcher

Ptarmigan C

8:30–10:00 PM

PANEL • White Matter Function: A Gray Area

T. Swanson, B. Ransom, J. Koscis, S. Krahl

Bighorn C1

WORKSHOP • Nucleus Accumbens Glutamate and Addiction

M. Lynch, C. Pierce, *P. Di Ciano*, D. Self, P. Kalivas

Bighorn C2

WORKSHOP • Birdsong—Genes, Cells, Circuits, Behavior, and Evolution

H. Karten, J. Dugas-Ford, C. Mello, S. White, D. Perkel

Hasty's

WORKSHOP • Organization of the Vertebrate Circadian System

C. Green, J. Takahashi, G. Block, F. Davis

Ptarmigan A

Monday, January 26, continued

WORKSHOP • Cerebellar Function and Plasticity: A Town Hall Meeting

J. G. McElligott, V. Bracha, J.R. Bloedel, T. J. Ebner, J.L. Raymond

Ptarmigan B

WORKSHOP • The Up-Regulation of Neuronal Nicotinic Receptors: Mechanisms and Implications

K. Kellar, R. Lukas, J. Lindstrom, B. Green, M. Marks

Ptarmigan C

Tuesday, January 27

7:30–9:30 AM

PANEL • Molecular and Imaging Techniques for Monitoring the Trafficking of Synaptic Proteins in Native Neuronal Preparations

R. Morrisett, D. Mayfield, J. Chandler

Bighorn C1

PANEL • Neuroscience Meets Law: Causation, Determinism and Criminal Responsibility

R. Beresford, P. Churchland, T. Hyde, E. Ross

Bighorn C2

PANEL • Past, Present, and Future: Interactions Between Prefrontal Cortex and Hippocampus in Higher Cognitive Function

J. Cohen, P. O'Donnell, A. Wagner, K. Norman, R. O'Reilly

Hasty's

PANEL • Mechanisms of Nociception: From Mice to Medicine

S. Tate, M. Costigan, J. Mogil, M. Salter

Ptarmigan A

PANEL • To Eat or Not to Eat, or What to Eat for Brainsake

F. Gomez-Pinilla, M. Mattson, G. Cole, P. Sullivan, C. Greenwood

Ptarmigan B

PANEL • Ins and Outs of Salt and Water Homeostasis: New Insights into CNS Mechanisms

C. Sladek, F. Flynn, S. Bealer, A. K. Johnson

Ptarmigan C

3:30–4:30 PM

EXHIBITS & POSTER SESSION 1 • Posters available for viewing

Bighorn B

4:30–6:30 PM

PANEL • Gene Therapy in the CNS: Novel Vectors for Imaging and Regulating Gene Expression

M. C. Bohn, B. L. Davidson, K. Bankiewicz, X. Breakefield

Bighorn C1

PANEL • The Other Catecholamine: Norepinephrine and Working Memory

A. Lavin, G. Aston-Jones, B. Waterhouse, B. Ramos

Bighorn C2

PANEL • Sex, Aggression, and Learning in Small Brains: Lessons from Invertebrate Systems

T. Swanson, R. Huber, R. Gillette, T. Fischer, M. Van Staaden

Hasty's

PANEL • Sodium Channels: From Normal Function to Disease

T. Scheuer, D. Carr, P. Ruben, R. Wallace

Ptarmigan A

PANEL • Regulation of Neural Precursor Cell Proliferation and Differentiation During Development and Disease

M. Mayer-Proschel, S. Davies, S. Haber, M. Mehler

Ptarmigan B

PANEL • Pick Complex, FTD, and the Tauopathies

A. Kertesz, D. Dickson, M. Hutton, D. Geschwind

Ptarmigan C

7:00 PM

TOWN MEETING • Exercise and the Brain

M. Zigmond

Summit Middle School, Frisco, CO

8:30–10:00 PM

PANEL • Neuroscience Perspectives on LTD: Potential Implications for Medication-resistant Symptoms of Schizophrenia

I. Cavus and J. Krystal, T. Teyler, J. Daskalakis, R. Hoffman

Bighorn C1

PANEL • The Role of DBH and Norepinephrine in Addictive Processes

V. Olson, R. Malison, *D. Weinshenker, C. Zabetian*

Bighorn C2

WORKSHOP • Necrosis: The Forgotten Giant

C. Wasterlain, D. Fujikawa, A. Kondratyev, K. Thompson

Hasty's

WORKSHOP • Be the "Best" that You Can Be: Examining Models of Parkinson's Disease

T. Hastings, J. T. Greenamyre, S. Przedborski, T. Dawson

Ptarmigan A

WORKSHOP • Novel Forms of Communication by Astrocytes

B. MacVicar, B. Ransom, M. Nedergaard, H. Sontheimer, T. Chan-Ling

Ptarmigan B

WORKSHOP • How Cells Navigate from the Ventricular Zone to the Cortical Plate.

S. Juliano, M. Frotscher, *S. Noctor*, J. LoTurco

Ptarmigan C

Wednesday, January 28

7:30–9:30 AM

MINICOURSE • Mass Spectrometry, Proteomics, and Peptidomics in Neuroscience Research

L. Fricker, D. Desiderio, J. Sweedler

Bighorn C1

PANEL • The Enchanted Loom of Spatial Perception in the Dorsal Stream of Monkey

R. Siegel, H. Karten, *J. Bisley*, B. Krekelberg

Bighorn C2

PANEL • Do Dopamine and Glutamate Alterations in Schizophrenia Form a Vicious Circle?

A. Abi-Dargham, H. Tsukada, J. Seamans, J. Krystal

Hasty's

PANEL • Huntington's Disease: From Models to the Clinic

P. H. Reinhart, R. Wetzel, M-F. Chesselet, K. Marder

Ptarmigan A

PANEL • The Role of Retinal Neuronal Circuits in the Encoding and Propagation of Visual Signals

S. Bloomfield, S. Massey, P. Lukasiewicz, M. Iuvone

Ptarmigan B

PANEL • Mechanisms of Developmental Synaptic Plasticity

A. El-Husseini, T. Benke, G. Collingridge, T. Taira

Ptarmigan C

3:30 – 4:30 PM

EXHIBITS & POSTER SESSION 2 • Posters available for viewing

Bighorn B

4:30–6:30 PM

PANEL • Before and After: Regulation of Neurotransmission on the Presynaptic and Postsynaptic Sides of the Synapse

W. Catterall, J. Rettig, R. Huganir, R. Nicoll

Bighorn C1

PANEL • Promiscuity in Neuroendocrinology

J. Becker, K. Olsen, D. Dorsa, S. Mani, R. Handa

Bighorn C2

PANEL • Susceptibility Genes for Schizophrenia: Neurobiology and Pathophysiology

J. Kleinman, D. Weinberger, S. Leonard, D. Lewis

Hasty's

PANEL • From Cage to Clinic: The Painful Truth about Diabetic Neuropathy

D. Wright, N. Calcutt, T. Morrow, J. Christianson

Ptarmigan A

PANEL • Understanding and Preventing Suicide: A National Imperative

W. E. Bunney, A. Roy, D.A. Brent, J. J. Mann, S. G. Potkin

Ptarmigan B

PANEL • ERKed by Neurodegeneration: MAP Kinase Signaling in Neurodegenerative Diseases

J. Cavanaugh, Z. Xia, J. Joseph, R. Perez

Ptarmigan C

Thursday, January 29

7:30–9:30 AM

PANEL • Dynamic Control of Transmitter Uptake: New Views of Transporter Function

G. Richerson, M. Quick, H. Lester, M. Kavanaugh

Bighorn C1

PANEL • Regional Patterning and Cell Specification in the Developing Vertebrate Nervous System

E. Carpenter, A. LaMantia, *E. Jacobs*, M. Goulding

Bighorn C2

PANEL • Translational Genomics: How DISC1, GRM3, and Neuregulin Increase Risk for Schizophrenia

M. Egan, J. H. Callicott, J. Morris, D. Falls

Hasty's

PANEL • Living Without in Hibernation

K. Drew, M. Harris, W. Milsom

Ptarmigan A

PANEL • When Good Guys Go Bad: Amyloid Precursor Protein and Non-Amyloidogenic Routes to Neurodegeneration

S. Barger, T. Ikezu, L. DeGiorgio, S. Griffin

Ptarmigan B

PANEL • Nontraditional Synthesis and Actions of Progesterone on Neural Development, Sexual Differentiation, Remyelination and Reproduction

K. Sinchak, P. Micevych, S. Mellon, C. Wagner, C. Ibanez

Ptarmigan C

3:30–4:30 PM

EXHIBITS & POSTER SESSION 2 • Presenters available for discussion

Bighorn B

4:30–6:30 PM

MINICOURSE • Catch Me if You Can: Second-by-Second Measures of Glutamatergic and Cholinergic Neurotransmission

G. A. Gerhardt, N. T. Maidment, J. P. Bruno, A. C. Michael

Bighorn C1

Thursday, January 29, continued

PANEL • Immunoneuroendocrine Interactions in Brain Inflammation

G. Aguilera, *C. Cunningham*, S. Lightman, F. Tilders

Bighorn C2

PANEL • Drug Discovery for Huntington's Disease and Other Neurologic Diseases

G. Bates, R. Hughes, C. Johnson, J. Olson

Hasty's

PANEL • Role of BDNF in Addiction and Fear: An Update

G. Meredith, J. McGinty, Y. Shaham, D. Ron, K. Thomas

Ptarmigan A

PANEL • Role of Activity in the Formation of the Visual Connections: Reassessment from Recent Evidence

R. Meyer, J. Crowley, L. Chalupa, C. Riegle

Ptarmigan B

PANEL • Excitatory Amino Acids in Neonatal Brain Injury

S. Levison, *J. Nunez*, T. Wood, P. Follett

Ptarmigan C

8:30–10:00 PM

PANEL • Rounding Up Molecular Suspects in Schizophrenia; Strategies for Postmortem Studies

B. Lipska, M. Webster, W. Honer, S. Bahn

Bighorn C1

PANEL • Drug-induced Neurochemical and Neurophysiological Plasticity: Contributions to Drug Addiction and Implications for Current Theories of Addiction.

C. O'Brien, G. Koob, P. Kalivas, L. Peoples

Bighorn C2

PANEL • Allosteric Modulation of AMPA Receptors: A Novel Therapeutic Approach to Neurological and Psychiatric Disorder

E. Nisenbaum, P. Skolnick, G. Lynch, J. Witkin

Hasty's

WORKSHOP • The Tao of Tyrosine and Catecholamines for Non-believers

G. Jaskiw, T. Maher, F-A. Wiesel, B. Yamamoto

Ptarmigan A

PANEL • Stress, Drug Abuse, and Synaptic Plasticity

Y. Shaham, K. Anstrom, P. V. Piazza, *K. McFarland*, A. Bonci

Ptarmigan B

PANEL • Inflammatory Modulators are Key Factors in Amyloidosis and Neurodegeneration

J. S. Richardson, D. Mousseau, S. Frautschy, T. Golde, T. Wyss-Coray

Ptarmigan C

Friday, January 30

7:30–9:30 AM

PANEL • Hallucinogens: What a Trip from Single Neurons to Behaving Brains

R. Andrade, M. Geyer, F. Vollenweider, G. Williams, *J-C. Beique*

Bighorn C1

PANEL • Improved Experimentation through Modeling.

S.H. Koslow. G. Ascoli, G. Jacobs, G. Shepherd, D. Mountain

Bighorn C2

PANEL • Cholecystokinin (CCK) the Quintessential Neuromodulator

M. Beinfeld, *E. Pothos*, P. Micevych, N. Geary, S. Simasko

Hasty's

PANEL • Pathogenic Mechanisms and Therapeutic Implications in Models of Alzheimer's and Huntington's Disease

L. Ellerby, S. Sinha, J. Buxbaum, C. Ross

Ptarmigan A

PANEL • Man-made Marijuana: Endogenous Cannabinoid Roles in Plasticity and Reward

D. Lovinger, C. Lupica, O. Manzoni, A. Hoffman

Ptarmigan B

PANEL • The Exciting Complexities of Excitotoxicity

I. Reynolds, J. Kemp, S. Hewett, *K. Hoyt*

Ptarmigan C

4:30–6:30 PM

PANEL • Stressing in the Bed Nucleus

J. Williams, D. Rainnie, *E. Dumont*, G. Aston-Jones, G. Koob

Bighorn C1

PANEL • Reversing Consciousness

A. Jenkins, G. E. Homanics, R. A. Pearce, L. E. Nelson, M. B. MacIver

Bighorn C2

PANEL • Regulation of Gene Expression in Psychiatry

J.P. Quinn, G. Breen, R. Maier, H. Marston

Hasty's

PANEL • What Makes Parkinsonian's Parkinsonian?

T. Boraud, H. Bergman, M. Gluck, S. Haber

Ptarmigan A

PANEL • Symposium on Neuregulin and Schizophrenia: From Humans to Animals

D. Brunner, G. Corfas, J. D. Buxbaum, M. O'Donovan, D. Talmage, H. Stefansson

Ptarmigan B

PANEL • Dopamine Neurotransmission: A Functional Mystery Tour

P. Phillips, W. Schultz, M. Beckstead, W. Hopf

Ptarmigan C

8:00 PM

BANQUET AND DANCE

Bighorn Ballroom

Poster Session 1 Sunday · Tuesday Bighorn B

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.

Studies on Drug Pharmacokinetics in Human Injured Brain

*O. Alves**

Noradrenergic Alpha2 Receptor Antagonist Modulates Methylphenidate-Mediated Increase in Cortical Excitability

G.D. Andrews, A. Lavin*

Is the GFAP Promoter Astrocyte Specific?

*M. Su , Y. Lee, A. Messing, M. Brenner**

Behavioral Assessment of NRG erbB Mutant Mice

*G. Corfas, D. Brunner**

Analysis of Tyrosine Hydroxylase, GAD 67 and 5-HT2C Receptor Immunoreactivity in the Ventral Tegmental Area

*M.J. Bubar, K. A. Cunningham**

The Effect of ADHD Drugs on Regional Cerebral Glucose Utilization in the Rat Using microPET

M. D. Davis, M. J. Callahan, K. R. Zasadny*

Instructive Role PSD-95 in Neuroligin-Mediated Synapse Formation

*O.Prange, K. Gerrow, A.E. El-Husseini**

Role of a Pre-Assembled Postsynaptic Protein Complex Containing PSD-95 and GKAP in Synapse Formation

K.A. Gerrow, S. Mohammadnabi, A.E. El-Husseini.*

Behavioral Alterations in Mice with Reduced NRG1 Function

*M.D.Bradley-Moore, S.Rao, H.Moore, M.Gurney, H.Stefansson, D.Brunner, J.A.Gingrich**

Distinct Rat Neurohypophysial Nerve Terminal Populations Identified by Size, Electrophysiological Properties and Neuropeptide Content

*H. Hemmings**

Hedgehog and PI-3 Kinase Signaling Converge to Promote Cell Cycle Progression in Neuronal Precursors

*A. Kenney**

Visualization and Quantitation of Human Cerebral Nicotinic Acetylcholine Receptors with Positron Emission Tomography

*A. Kimes**

Oral Progesterone, but not Oral Estrogen or Combined Estrogen/Progesterone Increases Infarct Size after Middle Cerebral Occlusion in Rat.

M. T. Littleton-Kearney, J. Klaus, P. D. Hurn*

Identification of Neuroprotective Drug Candidates and Targets in a Novel Brain Slice-Based Model of Huntington's Disease

D. C. Lo, D. Dunn, F. Hahn, M. Hannon, M. Henson, J. Kidd, L. A. Paige, L. W. Shaughnessy, P. H. Reinhart*

Detection of Ethanol and Fluoxetine-Dependent DARPP-32 Phospho-Isoforms in the Rat Amygdala

*R. Maldve**

Induction of the Proapoptotic Gene Bax-Alpha, and Suppression of its Antagonist Bcl-2 by Beta Amyloid (1-42) Employing the Acute Splice Explant Technique

*D. Marcus *, R. Hite, M. Freedman*

Neuregulin 1 Heterozygous Mutant Mice Exhibit Changes in Ca1 Hippocampal Synaptic Plasticity and Responses to Recombinant Neuregulin 1

D.L. Misner, H. Stefansson, M.E. Gurney, T.J. Novak*

Local GABAergic Disinhibition Reveals Reorganized Hindlimb Inputs to the Sl Forelimb-Stump Representation in Neonatally Amputated Rats

*C. Pluto**

Cell Proliferation in the Striatum during Development and Following a Partial Dopamine Lesion

S. Poloskey, M. Chincholker, and S.N. Haber*

Regulation of Short-Term Plasticity Independent of Basal Release Probability

*T. Sippy, A. Cruz-Martin, A. Jeromin, and F. E. Schweizer**

Blockade of Glutathione S-Transferase pi Increases Susceptibility to MPTP-Induced Neuronal Cell Death

M. Smeyne, R. Smeyne*

Poster Session 2 Wednesday · Friday Bighorn B

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.

Susceptibility to Prolonged Seizures is Related to Amount of Wheel Running

B. Anderson and D. McCloskey*

Pronociceptive Actions of Serotonin 5-HT-2A/2C Receptors in Rat Spinal Cord: Pre- and Post-Synaptic Sites of Action

*A. K. Bertelsen**

Profound Impairment in Social Recognition and Reduction in Anxiety-like Behavior in Vasopressin V1a Receptor Knockout Mice

I. Bielsky and L. J. Young*

Synapsins Decrease Frequency Facilitation at the Mouse Neuromuscular Junction

M. Bykhovskaia, D. Samigullin, C. A. Bill*

Context Dependent Effects of Lorazepam on Regional Cerebral Glucose Metabolism Revealed by Cognitive Testing in FDG-PET

*S. Castner**

Adult Neural Progenitor Cell Proliferation and Neurogenesis is Increased During Ethanol Withdrawal

*F. Crews**

Naltrexone Effects on mu- and delta-Opioid Receptor Availability in Alcohol Dependence

J.J. Frost, G.S. Wand, Y.K. Kim, B. Bencherif, R.F. Dannals, M.E. McCaul*

Synaptogenesis on Mature Hippocampal Neurons During Recovery of Ionic and Osmotic Homeostasis Recapitulates Development.

S.A. Kirov, L.J.Petrak, K.M.Harris*

Multiple Signaling Modes in the Mesocortical Pathway

C. Lapish, L. Nogueira, A. Lavin, J.K. Seamans*

Dopamine D2 Receptor-Stimulated Activation of ERK MAP Kinases Mediated by Cell Type-Dependent Transactivation of EGF and PDGF Receptors

K. A. Neve, D. Buck, R. Yang, C. Wang*

Role of Norepinephrine (NE) in the Modulation of Cortical Excitability

L. Nogueira, A. Lavin*

Inhibiting AP-1 Transcriptional Activity in the Striatum Potentates Cocaine Sensitization and Alters Gene Expression

*R. Paletzki**

Vesicular Glutamate Transporter-Dependent Glutamate Release from Astrocytes

V. Parpura, V. Montana, Y. Ni, V. Sunjara, X. Hua*

Ocinaplon, a Novel GABAA Receptor Modulator, is Active in Animal Models of Anxiety

M. Krawczyk, P. Popik, B. Beer, A. Lippa, P. Skolnick*

Characterisation of Neural Precursors Isolated from Human Vanishing White Matter Diseased Brain.

*C. Proschel**

Exercise Activates the Phosphatidylinositol-3-Kinase Pathway in Hippocampus

*A. Russo-Neustadt**

The D1 Dopamine Receptor is Constitutively Phosphorylated By GRK4: Implications for a Novel Mechanism of Regulation

*D. Sibley**

Imaging and Genotyping the Serotonergic System in Impulsive Aggressive Personality Disorders

*L. Siever**

Alterations in N-Methyl-D-Aspartate Receptor Magnesium Sensitivity in Medium-Sized Striatal and Cortical Pyramidal Neurons in the R6/2 Mouse Model of Huntington's Disease

A. J. Starling, V. M. André, C. Cepeda, M. S. Levine.*

Dopamine Bidirectionally Modulates Inhibition in PFC via Different Receptor Subtypes and Intracellular Pathways

*H. Trantham-Davidson**

Inhibition of Phospholipid Synthesis by Reduction of Choline-Ethanolamine Phosphotransferase Activity Precedes Excitotoxic Neuronal Death

*R. Trullas**

Poster Sessions Schedule and Abstracts

Poster Session 1 Sunday · Tuesday Bighorn B

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.

Studies on Drug Pharmacokinetics in Human Injured Brain

*O. Alves**

Over 200 Phase III drug trials have failed to show any clinical benefit in severe TBI. We have recently tested the role of microdialysis as a pharmacokinetic tool to improve clinical trials design. Material and Methods: 20 severe head injured patients (GCS<9) received topiramate, a drug that inhibits glutamate release. In order to study CNS drug delivery and to relate the extracellular (ECF) concentration to its "neuroprotective" effect, topiramate and glutamate were simultaneously recovered from cerebral ECF, using a microdialysis probe. Results: Patients receiving 11.4mg/Kg of topiramate showed significantly higher levels of unbound drug in the brain compared to patients receiving 5.7mg/Kg ($p<0.05$), however, this did not double the steady state concentration (Css), suggesting an active transport mechanism across the BBB that may be partially exhausted. Doubling the dose of topiramate resulted also in a tenfold decrease in Emax for dialysate glutamate ($p<0.05$) and in a mean r-value for top/glut correlation of ^0.5 ($p<0.0001$). Conclusions: Microdialysis gives valuable information on temporal pattern of drug penetration across the BBB in the injured brain. A "neuroprotective effect" may be inferred from the dose-dependent glutamate lowering effect of the drug. This type of pharmacokinetic-pharmacodynamic analysis may be a powerful tool in clinical trial design

Noradrenergic Alpha2 Receptor Antagonist Modulates Methylphenidate-Mediated Increase in Cortical Excitability

G.D. Andrews, A. Lavin*

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neuropsychiatric disorder thought to result from alterations in dopamine and noradrenaline levels in the prefrontal cortex. Methylphenidate (MPH) is the classic drug of

treatment for ADHD, yet alpha2 noradrenergic receptor (NAR) agonists have been used with success. MPH blocks monoamine transporters thereby increasing synaptic concentrations of the monoamines. Here we provide evidence that MPH increases cortical excitability. Moreover, preliminary evidence indicates that whereas alpha 2 NAR antagonist, Yohimbine (10uM), decreases the MPH-mediated excitability, the specific alpha 1 antagonist, Prazosin (1uM), does not affect cortical excitability.

Is the GFAP Promoter Astrocyte Specific?

*M. Su , Y. Lee, A. Messing, M. Brenner**

Both human and mouse GFAP promoter fragments have been extensively used with the intent to drive astrocyte-specific transgene expression in mice. We report here that our commonly used human gfa2 promoter, which spans bp -2163 to +47, may also direct expression in neurons. Two of four independent lines of Gfa2-lacZ transgenic mice analyzed displayed extensive neuronal lacZ activity. The other two lines showed some neuronal expression, but it was extremely weak and sparse. Since apparent colocalization could be an artifact of closely apposed astrocytes and neurons, neuronal activity was confirmed by electron microscopy. Expression was also examined of a mouse GFAP-lacZ transgene kindly provided by Dr. Lennart Mucke, in which the lacZ gene is embedded within the first exon of a mouse genomic fragment spanning the entire GFAP coding region and about 2000 bp of 5'-flanking DNA. In the single line analyzed, extensive neuronal expression was also observed. To test whether the neuronal activity is due to specific sequences present in the lacZ reporter rather than being an intrinsic property of the gfa2 promoter, we studied a gfa2-GFP line, and indeed found no neuronal expression throughout the CNS. On the other hand, Dr. Alessandra d'Azzo has observed substantial neuronal expression of protective protein/cathepsin A driven by the gfa2 promoter (personal communication). It thus appears that gfa2-transgenes may or may not express in neurons depending on both the particular insertion site and the driven coding region.

Behavioral Assessment of NRG erbB Mutant Mice

*G. Corfas, D. Brunner**

The identification of neuregulin 1 dysfunction as a risk factor in schizophrenia makes it possible to use pathophysiology-based approaches to model schizophrenia. A major problem facing those interested in NRG function is disentangling the various functions of these genes during development and in adulthood. All homozygous knockout mice of NRG1 or its receptors die during midgestation or perinatally, due to failure in heart formation or defects in peripheral nerves and neuromuscular junctions, although the heterozygous mice, in which the genes are expressed at a considerably reduced level compared to WT mice, are viable. The NRG1 +/- KOs, obtained by ei-

ther excising the transmembrane or the EGF domain (TM and EGF, respectively) show hyperactivity in the open field and in free-exploration mazes. The erbB4 +/- KOs also show some increased activity, and the erbB2 and 3 +/- KOs do not show a strong behavioral phenotype, at least in the behavioral tests used to date. We will present data from a battery of behavioral tests used to assess newly generated transgenic mice in which all NRG1 receptors (erbB2, 3 and 4) have been disabled in either astrocytes or oligodendrocytes by expression of a dominant-negative erbB4 receptor (DN-erbB4). In this way, NRG-erbB signaling outside the nervous system (such as cardiovascular function) or in the neuromuscular junction, are spared in these mice. It is important to note that not only NRG1 but also NRG2 and NRG3 function are impaired in the cells expressing DN-erbB4. Mice lacking erbB receptors in the oligodendrocytes were more active than wild type mice, as there all those mice, either males or females, were never observed inactive in a home cage observation test. Both genders showed a considerable degree of social interaction, although the females seem to be particularly aggressive. Mice lacking the erbB receptor function in the astrocytes, on the other hand, showed normal levels of activity, although seem to be more aggressive than the wild type mice, particularly the males. All mice appeared healthy and showed no gross abnormalities of behavior or morphology. We will show these results and compare against those obtained with other NRG mutants.

Analysis of Tyrosine Hydroxylase, GAD 67 and 5-HT2C Receptor Immunoreactivity in the Ventral Tegmental Area

*M.J. Bubar, K. A. Cunningham**

The behavioral and rewarding properties of psychostimulants such as cocaine and 3,4-methylenedioxymethamphetamine (MDMA; "ecstasy") appear to be mediated in part by serotonergic modulation of (DA) mesoaccumbens pathway activation. Serotonin 2C receptors (5-HT2CR) exert inhibitory influences over DA neurons in the ventral tegmental area (VTA) and DA release in the nucleus accumbens (NAc). The actions of 5-HT2CR on DA activation have been suggested to occur indirectly through stimulation of inhibitory GABA neuron, however, recent evidence from our laboratory suggests that 5-HT2CR are also localized on a subset of DA neurons in the VTA, some of which project to the NAc. The goal of the present study was to re-examine the distribution of DA and GABA neurons in the VTA and confirm localization of 5-HT2CR on both types of neurons in this region. Double-label immunofluorescence was performed on brain sections (20 mm) from naive male Sprague-Dawley rats using antibodies that recognize 5-HT2CR, the synthetic enzymes for DA (tyrosine hydroxylase; TH) and GABA (glutamic acid decaboxylase; GAD). Our results confirm that 5-HT2CR immunoreactivity was co-localized in subpopulations of both TH- and GAD-immunoreactive cells in the VTA, suggesting that 5-HT2CR are located on

both DA and GABA neurons in this brain region. Additionally, TH and GAD immunoreactivity also appeared to co-localize in some cells revealing a subset of VTA neurons that contain both DA and GABA. These results suggest that 5-HT2CR may exert both direct and indirect influence over DA mesoaccumbens pathway activation and that the interaction between DA and GABA in the VTA may be more complex than previously thought. Supported by NIDA DA 00260, DA 06511, DA 13595, DA 15259.

The Effect of ADHD Drugs on Regional Cerebral Glucose Utilization in the Rat Using microPET

M. D. Davis, M. J. Callahan, K. R. Zasadny*

Childhood and adult attention deficit hyperactivity disorder (ADHD) have traditionally been treated with the non-amphetamine stimulant, methylphenidate (Ritalin), with good results. There is some concern, however, that Ritalin may produce decreased appetitive behavior and have increased abuse liability. The recently marketed norepinephrine reuptake inhibitor (NRI), atomoxetine (Strattera), has been shown to be effective in ADHD treatment and may offer reduced potential for side effects because of its selective action on the noradrenergic system. In this report we assessed what differentiating influence methylphenidate and atomoxetine might have on regional glucose utilization in the rodent brain. Adult male Sprague Dawley rats were administered either 1.0 ml/kg saline vehicle, 15 mg/kg methylphenidate HCl or 15 mg/kg atomoxetine IP, followed 30 min later by an IV bolus of approximately 37MBq 18F-DG. 30 min later, the animals were put under ketamine/xylazine anesthesia and scanned in a Concorde Model R4 microPET camera for 20 minutes. On the subsequent day, the animals underwent a second scan with either vehicle or drug so that each rat served as its, own control. Reconstructed PET scan data were co-registered to a stereotaxic atlas and normalized to the average total brain concentrations of injected tracer. Methylphenidate administration in 11 animals produced significant increases in metabolism in the cerebellum, dorso-lateral thalamus, striatum, and frontal cortex, but not the hippocampus. In contrast, atomoxetine in 8 animals produced significantly-increased metabolism in the frontal cortex, but not the cerebellum, striatum, thalamus or hippocampus. Thus, based on these and clinical reports, atomoxetine is shown to have a more selective activation of brain regions than methylphenidate, yet is an effective treatment for ADHD. These studies also demonstrate that glucose utililzation measurements using microPET can be useful in profiling drug activity patterns in small rodents.

Instructive Role PSD-95 in Neuroligin-Mediated Synapse Formation

*O.Prange, K. Gerrow, A.E. El-Husseini**

Synapse formation is tightly regulated process that requires the rapid recruitment of specialized proteins to sites of contact. To elucidate the events that regulate the formation of excitatory synapses, we focused on the postsynaptic density (PSD) protein PSD-95 and cell adhesion molecule neuroligin (NLG), two postsynaptic molecules implicated in the assembly of elements important for synapse development. Our results show that exogenous PSD-95 recruits NLG to excitatory synapses. Our analysis shows a positive correlation between the size of PSD-95 and NLG-clusters and the excitatory terminals contacting them. Surprisingly, over-expression of NLG alone enhances both the size and the number of dendritic filopodia but does not augment the clustering of postsynaptic components. Moreover, the extracellular domain of NLG is required to increase the number and size or presynaptic contacts but is not sufficient to alter the number of dendritic filopodia/spines. Co-expression of NLG with PSD-95 further enhances the size of NLG clusters and the apposed presynaptic terminals. Furthermore, PSD-95 dramatically reduces the total number of synapses induced by NLG and excludes it from inhibitory synapses. These effects do not require the guanylate kinase (GK) domain of pSD-95. These findings indicate that PSD-95 recruits NLG to the PSD thereby playing an instructive role in regulating the formation, size and specificity of the newly formed synapses.

Role of a Pre-Assembled Postsynaptic Protein Complex Containing PSD-95 and GKAP in Synapse Formation

K.A. Gerrow, S. Mohammadnabi, A.E. El-Husseini.*

The sequence of events that occur during the establishment of synaptic contacts and the molecular interaction that trigger these events in the central nervous system remain unclear. Current studies indicate that synaptogenesis is a rapid process, taking minutes to an hour to form a synapse. The postsynaptic density protein (PSD-95) has a vital role in orchestrating the assembly of several molecules critical for synapse formation and maturation. This study addresses the role of PSD-95 in the formation of a pre-assembled protein complex, containing core molecules important for the nucleation of the postsynaptic density. Our results show that exogenous PSD-95 and GKAP faithfully cluster and co-localize in young (DIV4-6) hippocampal neurons. The clustering of GKAP was dependent on the presence of PSD-95, specifically, on the guanylate kinase (GK) domain and the palmitoylation state of PSD-95. Interestingly, in developing hippocampal neurons several PSD-95 and GKAP co-clusters were not apposed by synaptophysin positive presynaptic terminals. In addition, time-lapse mi-

croscopy revealed that PSD-95 and GKAP clusters were tightly trafficked together. Further analysis with FM4-64 for presynaptic vesicle recycling will evaluate the recruitment of pre-assembled PSD-95 and GKAP co-clusters to synaptic sites. These data suggest that synapse formation may rely on the rapid recruitment of a pre-assembled postsynaptic protein complex containing PSD-95 to the initial site of contact.

Behavioral Alterations in Mice with Reduced NRG1 Function Behavioral Alterations in Mice with Reduced NRG1 Function

*M.D.Bradley-Moore, S.Rao, H.Moore, M.Gurney, H.Stefansson, D.Brunner, J.A.Gingrich**

Two lines of mice have been created in which the transmembrane (TM) or the epidermal growth factor (EGF)-like domains of the NRG-1 gene have been partially disrupted. Both lines showed significantly increased locomotor activity relative to wild-type littermates in open field, elevated plus maze and cross maze tasks. We present an in depth phenotyping effort using the TM mutant mice. In this line we demonstrated decreased prepulse inhibition on a mixed 129S6/SvEv:C57/BL6 background, but this difference was not observed in either line when backcrossed onto a C57/BL6 background. TM mutant mice were normal in the Rotarod task. These results suggest that reduced function of different NRG-1 isoforms may share similar effects on locomotor and exploratory activity that would be consistent with increased mesolimbic dopamine activity. In addition, the apparent interaction of the NRG-1 mutations with the genetic differences between mouse strains suggests that even in the presence of vulnerability-conferring NRG-1 haplotypes, the risk for developing a specific phenotype may vary considerably across individuals.

Distinct Rat Neurohypophysial Nerve Terminal Populations Identified by Size, Electrophysiological Properties and Neuropeptide Content

*H. Hemmings**

Voltage-gated ion channels are critical to excitation-secretion coupling in nerve terminals. Using patch-clamp recording and immunochemistry, we identified two distinct populations of isolated rat neurohypophysial terminals distinguished by size, neuropeptide content and electrophysiological properties. In large terminals (10-16 μm diameter), resting membrane potential was more negative than in small terminals (5-10 μm) (-62 ± 4 mV vs. -55 ± 3 mV; $p<0.01$). Action potential amplitude was higher in large than in small terminals (69 ± 3 mV vs. 53 ± 3 mV; $p<0.01$). Current density was also greater in large than in small terminals (~470 pA/pF vs. ~300 pA/pF; $p<0.01$). A positive linear correlation of INa amplitude with terminal size showed an

inflection at a diameter of 9.2 μm. V1/2 for INa activation was more negative in large than in small terminals (-44 mV vs. -24 mV; $p<0.01$); V1/2 for steady-state inactivation was similar in both populations. Time constants for recovery of INa from inactivation were greater at a holding potential of -70 mV than at -90 mV, and were greater in small than in large terminals at a holding potential of -70 mV, but not at -90 mV. Neuropeptide content was segregated into a population of small terminals (<10 μm diameter) containing predominantly vasopressin and a population of large terminals (>10 μm diameter) containing predominantly oxytocin; a small fraction of terminals in each group contained both peptides. The electrophysiological differences between small vasopressin-containing and large oxytocin-containing neurohypophysial terminals may contribute to their differential firing and release patterns.

Hedgehog and PI-3 Kinase Signaling Converge to Promote Cell Cycle Progression in Neuronal Precursors

*A. Kenney**

Neuronal precursor cells in the developing cerebellum require activity of the Sonic hedgehog (Shh) and phosphoinositide-3 kinase (PI-3K) pathways for growth and survival. Synergy between the Shh and PI-3K signaling pathways is further implicated in the cerebellar tumor, medulloblastoma. Here we describe a mechanism through which these disparate signaling pathways cooperate to promote proliferation of cerebellar granule neuron precursors (CGNPs). Shh signaling drives expression of mRNA encoding the N-myc oncoprotein, which is essential for expansion of cerebellar granule neuron precursors (CGNP). The PI-3K pathway stabilizes N-myc protein via inhibition of GSK3-dependent N-myc phosphorylation and degradation. The effects of PI-3K activity on N-myc stabilization are mimicked by insulin-like growth factor (IGF), a PI-3K agonist with roles in CNS precursor growth and tumorigenesis. These findings indicate that Shh and PI-3K signaling pathways converge on N-Myc to regulate neuronal precursor cell cycle progression. Further, they provide a rationale for therapeutic targeting of PI-3K signaling in medulloblastoma.

Visualization and Quantitation of Human Cerebral Nicotinic Acetylcholine Receptors with Positron Emission Tomography

*A. Kimes**

The administration of nicotine, the primary addictive ingredient in tobacco smoke, increases the brain densities of the alpha4beta2 subtype of nicotinic receptors (nAChRs). The ability to image and quantify these receptors in vivo would greatly facilitate research on the role of nAChRs in nicotine

dependence and could lead to treatment strategies for smoking cessation. 2-[18F]Fluoro-A-85380 (2FA) is the first radioligand allowing visualization of nicotinic acetylcholine receptors (nAChRs) in the human brain with positron emission tomography (PET). PET data were acquired from the brains of six non-smoking adult human volunteers (3 male, 3 female) after a bolus injection of 2FA (0.043 mCi/kg). PET data (12-17 scans/subject) were acquired over 7 h. The total radioactivity accumulated in human brain was ca. 2.5% of injected dose. Anatomical sampling was performed on PET images that were coregistered to MRI scans acquired from each volunteer. Several modeling methods were used to determine total volume of distribution (VDt) and binding potential (BP), which reflect receptor density. All modeling methods yielded similar values. The corpus callosum was used as a reference region as results from PET studies with 2FA in non-human primates showed little specific binding and the CC exhibited the lowest value for VDt in all six human subjects. Using the CC as the reference region, BP values were greatest in the thalamus, moderate in the midbrain and pons and lower in all other brain regions. These results suggest that 2FA will be useful for studying the increased nAChR densities expected in smokers.

Oral Progesterone, but not Oral Estrogen or Combined Estrogen/Progesterone Increases Infarct Size after Middle Cerebral Occlusion in Rat.

M. T. Littleton-Kearney, J. Klaus, P. D. Hurn*

Recent data from the Women's Health Initiative suggest that long-term oral combination estrogen/progesterone therapy increases risk for ischemic stroke. However, our lab and others have demonstrated that female rats have smaller cerebral infarcts relative to males or ovariectomized (OVX) females and that treatment with parentral estrogen reduces infarct volume after stroke. The effects of chronic oral hormone replacement in animal stroke models have not been extensively investigated. Therefore, we sought to determine if chronic oral estrogen, progesterone or combined estrogen/progesterone treatment alters the size of infarct volume after experimental stroke. OVX rats were fed premarin (EST), medroxyprogesterone (PRO), a combination of E and PRO (EP), or strawberry jelly vehicle (VEH). After 2 months rats were anesthetized with halothane and subjected to 1 hour middle artery occlusion (MCAO) using the intraluminal filament technique. Animals were allowed to reperfuse for 22 hr and brains were harvested for measurement of infarction volume. Laser Doppler flow was continuously monitored insure a consistent reduction in cortical blood flow below 45 % of baseline during ischemia. No differences were observed in cortical infarction volume between VEH, EST and EP. In contrast rats fed PRO alone had greater cortical infarcts relative to EP (19.2 Å} 6.0 vs 5.1 Å} 2.9 %). These data are consistent with our previous work in rats treated with IP progesterone indicating that chronic progesterone can exacerbate infarction in sub

cortical brain regions. We conclude that combined oral estrogen/progesterone has little protective effect early after stroke at doses equivalent to doses administered to postmenopausal women.

Identification of Neuroprotective Drug Candidates and Targets in a Novel Brain Slice-Based Model of Huntington's Disease

D. C. Lo, D. Dunn, F. Hahn, M. Hannon, M. Henson, J. Kidd, L. A. Paige, L. W. Shaughnessy, P. H. Reinhart*

A major goal in translational research on Huntington's disease (HD) is the development of new therapeutics that delay the onset and/or slow the progression of the disease. The identification of such new drugs and their molecular targets requires model systems that can faithfully recapitulate the major cellular and molecular events during HD pathogenesis, are amenable to experimental manipulations including transfection and RNAi knockdown, and can be readily scaled to provide throughput levels necessary for screening and validating new small molecule drug candidates. To this end, we have developed a brain slice-based model of HD neuronal dysfunction and degeneration that supports the acute transfection of human huntingtin (Htt) fragments into living rat and mouse brain slices. Medium spiny neurons (MSNs) in the striatum are readily identified by expression of fluorescent reporters, and, upon transfection with Htt DNAs containing expanded polyglutamine repeats, are shown to recapitulate key morphological and functional features of the cellular pathogenesis of HD. These include changes in electrical properties, gradual degeneration of the dendritic arbor, and formation of inclusion bodies containing Htt protein fragments. Moreover, the rate and extent of MSN neurodegeneration varies in proportion to the length of the polyglutamine tract in the Htt protein, paralleling that observed in the human patient population. We have used this living brain slice-based model as a the basis of a novel drug and drug target screening and validation platform for the development of new neuroprotective drug lead candidates for the treatment of HD.

Detection of Ethanol and Fluoxetine-Dependent DARPP-32 Phospho-Isoforms in the Rat Amygdala

*R. Maldve**

It is well accepted that agents that enhance serotonin neurotransmission are effective in reducing ethanol consumption in animal models. Fluoxetine, a serotonin reuptake inhibitor, has recently been shown to regulate the phosphorylation state of DARPP-32, a dopamine and cAMP-regulated phosphoprotein (32 kD) (Svenningsson et al, 2002). When phosphorylated at Thr34 by PKA, DARPP-32 is converted into a potent inhibitor of protein phosphatase-

1. In addition to Thr34, DARPP-32 is phosphorylated at three alternate sites by different protein kinases which can then potentiate or antagonize the PKA/Thr34-DARPP-32/PP-1 cascade. We have previously demonstrated a role for DARPP-32 in the ethanol sensitivity of the NMDA receptor in the NAc (Maldve et al., 2002). However, current theories suggest that the amygdala may play a role in the addictive liability of drugs and alcohol, particularly the anxiety and angst associated with drug withdrawal. Therefore, in this study, we examine the acute effects of ethanol on DARPP-32 phosphorylation in the amygdala and the effectiveness of fluoxetine in abrogating the effects of ethanol on pDARPP-32 isoforms. Acute coronal slices containing the amygdala were exposed to 25 mM ethanol for 0-20 min and evaluated for Thr34-, Thr75- and Ser137-pDARPP-32 expression by Western analysis. Ethanol treatment inhibited Thr34-pDARPP-32 expression across all time points as compared to baseline. However, Thr75 expression increased linearly from 6% over baseline at 1 min to nearly 2-fold control levels by 20 min (n=4). Ser137 phosphorylation was initially blocked by ethanol treatment at 1 min (-16% ±12% SEM; n=4) but increased to14%±23% SEM over control at 5 min, 23%±21% SEM at 10 min and 29%±44% SEM at 20 min. Overall, the effects of ethanol on DARPP-32 phosphorylation in the amygdala suggest a complexity in the regulation of the PKA/DARPP-32/PP-1 cascade. Additional studies examined the role of fluoxetine on ethanol-induced DARPP-32 phosporylation. In amygdala slices treated with 10 mM fluoxetine for 2 min, Thr34-pDARPP-32 increased ~3-fold over control levels (n=3); whereas Ser137-pDARPP-32 was unaltered by fluoxetine treatment. When slices were pretreated with 10 mM fluoxetine and then exposed to ethanol, Thr34-pDARPP-32 expression was inhibited to a greater extent than observed with ethanol treatment alone. There was no difference in Ser137-pDARPP-32 expression in fluoxetine pre-treated slices. We therefore conclude that ethanol regulates DARPP-32 phosphorylation at multiple sites in the amygdala possibly via serotonergic neurotransmission. Supported by NIAAA grant AA13CR as part of the INIA to REM.

Induction of the Proapoptotic Gene Bax-Alpha, and Suppression of its Antagonist Bcl-2 by Beta Amyloid (1-42) Employing the Acute Splice Explant Technique

*D. Marcus *, R. Hite, M. Freedman*

Alzheimer's Disease (AD) appears to be mediated by apoptosis or programmed cell death, which involves the activation of the immediate early genes c-Fos and c-Jun. The appearance of the p-53 protein suggests entry of the neuronal cells into the apoptotic pathway. The cascade thus activated leads to the production of neurofibrillary tangles and neuritic plaques, the neuropathological hallmarks of this disease. We determined that Beta Amyloid incubation in the ASE produced a 475% increase in c-Jun, a 375% increase in c-Fos, and 215% increase in p-53. We now report that Bax-alpha

transcription is induced using Reverse Transcriptase PCR. In addition we have identified that the antagonist to Bax-alpha, Bcl-2, is significantly repressed in the treated tissue by the same RT-PCR technique. The induction of proapoptotic Bax-alpha and suppression of anti-apoptotic Bcl-2 further support the induction of cellular apoptosis, as Bax-alpha is an inducible protein that may be activated by the presence of p-53. Analysis of transcription levels have produced a more detailed description of the cascade, including fas and Caspase-3, whose activation leads to apoptosis in neuronal cells. These results suggest: (1) that the apoptotic cascade is activated very rapidly in the presence of beta Amyloid as evidenced by the production of the protein products of the immediate early genes, c-Fos, c-Jun, and p-53; and (2) that the cell is actively regulating its transcription levels of apoptotic genes by inducing Bax-alpha, while at the same time repressing Bcl-2. Activation of Caspase-3, DFF, JUN, lead to nuclear disintegration. Using expression profiling, it will be possible to discover which step of the apoptotic cascade can be disrupted by application of therapeutic compounds.

Neuregulin 1 Heterozygous Mutant Mice Exhibit Changes in Ca1 Hippocampal Synaptic Plasticity and Responses to Recombinant Neuregulin 1

D.L. Misner, H. Stefansson, M.E. Gurney, T.J. Novak*

Neuregulin 1 (NRG1) has been shown to suppress tetanus-induced long-term potentiation (LTP), suggesting a role for NRG signaling in hippocampal synaptic plasticity (Neuron 26:443, 2000). More recently NRG1 has been identified as a candidate gene for schizophrenia, a disease marked by significant impairment in cognitive function. Therefore, we investigated the effects of neuregulin gene mutation on LTP in area CA1 of hippocampal slices. Previously generated neuregulin heterozygous mutant mice (Development 124:4999, 1997) were extensively backcrossed to wild-type C57BL/6 mice. Hippocampal slices were prepared from adult female wild-type and heterozygous mutant mice (genotypes blinded), and the slopes of field excitatory postsynaptic potentials (fEPSPs) evoked by stimulation of Schaffer collaterals were measured and expressed as mean potentiation above baseline 30-40 minutes after LTP induction. LTP was induced by tetanic stimulation (5 trains of 100 Hz stimulation lasting 200 ms, 10 s intertrain interval) in both wild-type (130.1 + 4.7%, n = 24 slices) and mutant slices (123.8 + 3.4%; n = 17 slices), but no differences between the two groups were observed ($p > 0.05$, unpaired t-test). Interestingly, when 0.1 nM recombinant human NRG- 1 was applied to slices, tetanus-induced LTP was slightly impaired in wild-type slices (118.4 + 3.4%, n = 18 slices; $p = 0.07$, unpaired t-test), in agreement with previous findings, but was significantly enhanced in mutant slices (148.2 + 9.5%, n = 8 slices; $p = 0.006$, unpaired t-test). Additionally, LTP induced by theta burst stimulation (TBS, 10 bursts of 4 stimuli at 100 Hz, 200 ms interburst interval) was significantly impaired in mutant

slices (116.1 + 3.1%, n = 13 slices) compared to control slices (130.2 + 4.2%, n = 13 slices; p = 0.009, unpaired t-test). These results further strengthen the importance of NRG signaling in hippocampal synaptic plasticity.

Local GABAergic Disinhibition Reveals Reorganized Hindlimb Inputs to the SI Forelimb-Stump Representation in Neonatally Amputated Rats

*C. Pluto**

Adult rats that have sustained neonatal forelimb amputation exhibit numerous multi-unit recording sites in the forelimb-stump representation of primary somatosensory cortex (SI) that also respond to cutaneous stimulation of the ipsilateral hindlimb. These hindlimb inputs, which are detected during blockade of cortical GABA (A+B) receptors (disinhibition), originate in the SI hindlimb representation and follow a multi-synaptic pathway through the dysgranular cortex before projecting onto SI forelimb-stump neurons. The GABAergic suppression of this circuit may play a role in maintaining an orderly topographic representation of the body surface. Previously, we have revealed this input by topically applying GABA receptor antagonists to the surface of SI. This global disinhibition has not allowed us to determine the location along this circuit where GABA synapses supress excitatory hindlimb inputs to the forelimb-stump region. We address this issue here by using focal injections of GABA receptor antagonists to three distinct regions involved in the cortical hindlimb to forelimb-stump pathway. Blocking GABA receptors at the forelimb-stump recording site reveals over 80% of the normally suppressed hindlimb inputs in SI forelimb-stump neurons. In contrast, blocking GABA receptors in the dysgranular cortex or in the SI hindlimb representation is minimally effective in revealing hindlimb inputs (~10% in both cases). Thus, GABAergic interneurons within the forelimb-stump representation suppress reorganized excitatory inputs to the region. A circuit model incorporating these observations is presented and discussed.

Cell Proliferation in the Striatum during Development and Following a Partial Dopamine Lesion

S. Poloskey, M. Chincholker, and S.N. Haber*

The cortico-basal ganglia circuit is associated with several mental disorders, including schizophrenia, obsessive-compulsive disorder (OCD) and drug addiction, all of which emerge primarily during adolescence or young adulthood. This circuit, which is important for learning and the development of habits shows a high degree of plasticity and is particularly vulnerable to disruption during development. There are unique features of the cortico-basal ganglia circuit, which may underlie both functional and vul-

nerability differences during adolescence and aging. One feature is its close proximity to the subventricular zone, the region that gives rise to the largest group of progenitor cells. These cells, which follow a migratory route to the olfactory bulb, form the medial border of the striatum and separate it from the ventral cingulate cortex and medial orbital cortex. While much attention has been paid to new cells with the possibility of neurogenesis in the cortex, little is known about migration of cells into the striatum. Furthermore, studies of cell proliferation, migration and neurogenesis focus on pre- or post-natal development, or on adulthood, but not adolescence. Thus, little data exist on whether new cells migrate into the striatum or the orbital and medial prefrontal cortex during the important developmental time of adolescence. However, clustering of stem cells adjacent to the striatum suggests that this rostral pool of progenitor cells may contribute to neurogenesis in the striatum at specific times later in life. We undertook this study to examine the distribution cell proliferation during post-natal non-human primate development: ages 5 mo., 1 year, 2 years, and 3 years. We compared cell proliferation during these times with normal, control adult animals and with two animals that had a partial dopamine lesion. The results show that, compared to normal adult animals, cell proliferation in the caudate and putamen increase significantly during development. Furthermore, following partial dopamine depletion, cell proliferation is also greater compared to controls, but to a lesser degree than during development. Animal procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the NIH. Support: MH 45573.

Regulation of Short-Term Plasticity Independent of Basal Release Probability

*T. Sippy, A. Cruz-Martin, A. Jeromin, and F. E. Schweizer**

Short-term synaptic plasticity in the range of tens to hundreds of milliseconds is a defining feature of neuronal activity, but surprisingly little is known about the underlying molecular mechanisms. While depression might be due to limited vesicle availability, facilitation is thought to result from elevated calcium levels although the protein(s) linking calcium to facilitation remain elusive. Furthermore, it is unclear if the sign of plasticity is simply a consequence of synaptic strength, or whether it can be regulated by a separate mechanism. Using paired recordings from hippocampal neurons, we show that selective increases in the calcium binding protein NCS-1 can switch paired-pulse depression to paired-pulse facilitation without altering calcium entry, basal synaptic transmission or initial release probability. Facilitation persists during high frequency trains, indicating that NCS-1 can recruit “dormant” vesicles or prevent vesicles from becoming “dormant.” Expression of a mutated form of NCS-1 with impaired calcium binding ability resulted in a significantly reduced effect on short term facilitation while expression of GFP alone had no effect. Our results indicate that NCS 1 acts

as a calcium sensor for short-term plasticity by facilitating neurotransmitter output independent of initial release. We conclude that separate mechanisms are responsible for determining basal synaptic strength and short-term plasticity.

Blockade of Glutathione S-Transferase pi Increases Susceptibility to MPTP-Induced Neuronal Cell Death

M. Smeyne, R. Smeyne*

Oxidative stress is hypothesized to contribute to the onset of neurodegenerative disorders, including Parkinson's disease. One system that acts to counter the free radicals produced during oxidative stress is glutathione. The functionality of glutathione is dependent on enzymes called glutathione S-transferases (GSTs). Three isoforms of GST exist in the brain, pi, mu and alpha. These molecules form multimers in different combinations and work by adding glutathione to electrophiles within any number of proteins. Thus, depletion of glutathione or inhibition of its function can lead to increased vulnerability and possibly death of susceptible neurons. MPTP is a toxin that has structural similarities to a number of environmental agents that have been shown to increase free-radical production, as well as induce parkinsonism in a number of mammals including man. In mice, susceptibility to cell death is strain dependent. We have developed an in vitro system that can recapitulate these strains differences. Swiss-Webster (SW) mice are normally resistant to SN cell death after exposure to MPTP. However, after exposing SW SN neurons to MPTP in the presence of ethacrynic acid, a specific inhibitor of GSTpi, we can increase cell death to a level equal to that of MPTP-sensitive mice. This suggests that regulation of GSTpi may underlie strain sensitivity to MPTP in mice and provide an entrée for examining the function of this protein in human Parkinson's disease.

Poster Session 2 Wednesday · Friday Bighorn B

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.

Susceptibility to Prolonged Seizures is Related to Amount of Wheel Running

B. Anderson and D. McCloskey*

Forced exercise prior to amygdala kindling has been shown to increase seizure threshold (Arida, 1998). The present study was designed to test whether voluntary wheel running in male rats is related to the likelihood of developing status epilepticus (SE), a prolonged seizure that damages the hippocampus, and causes spatial memory impairments. Male rats were given one month access to running wheels followed by an injection of kainic acid (KA, 10 mg/kg i.p.). The highest seizure stage reached was analyzed using a likelihood ratio chi square analysis. When the exercise animals were divided into high and low runners based on the median, high runners responded to KA differently than non-runners and low-runners, but low-runners did not differ from non-runners. High running rats stayed in lower stage seizures longer. The proportion of animals that developed SE following KA was also analyzed with a likelihood ratio chi square analysis. High-runners were less likely to develop SE (18%) following KA injection than non-runners (63%) and low-runners (90%). There was no significant difference in likelihood between low-runners and non-runners. Although animals that ran more than the median number of wheel rotations were less likely to develop SE than those that ran less, the failure to progress to SE left high runners in lower stage seizures longer. In conclusion, the amount of exercise in male rats is associated with susceptibility to SE.

Supported by NIMH 62075

Pronociceptive Actions of Serotonin 5-HT-2A/2C Receptors in Rat Spinal Cord: Pre- and Post-Synaptic Sites of Action

*A. K. Bertelsen**

Serotonin (5-hydroxytryptamine; 5-HT) is one of the main neurotransmitters in descending nociceptive modulation. Previous studies have indicated that activation of spinal 5-HT2A/2C receptors enhances transmission of nociceptive impulses, possibly due to an increased release of substance P from presynaptic terminals. The present studies apply the 5-HT2A/2C receptor agonist DOI (5 nmol, 50 nmol and 500 nmol) and antagonist ketanserin (50 nmol) intrathecally via indwelling catheters threaded ros-

trally from the L5-L6 space (behavioural studies) or topically on exposed spinal cord (dialysis study) in rats, accompanied by behavioural testing or in vivo micodialysis. SP-like immunoreactivity (SP-LI) was measured in diasysate obtained from indwelling dialysis fibers implanted transversely through dorsal horn using radioimmunoassay (RIA). DOI caused a dose-dependent increase in spontaneous pain-like behaviour, an effect blocked by ketanserin. DOI increased the nociceptive response induced by intrathecal injection of NMDA or the neurokinin 1 receptor agonist substance P. In vivo microdialysis showed that 5-HT2A/2C receptor activation increased release of SP-LI (50 but not 500 nmol dose) as well as potentiating capsaicin-induced SP-LI release in the presence and absence of carrageenan-induced peripheral inflammation. These data indicate that 5-HT2A/2C receptors in the dorsal horn exert a facilitating effect on nociceptive signaling in acute pain and pain due to peripheral inflammation. An increased release of substance P in the dorsal horn may contribute to this effect. The lack of a high dose effect on SP-LI release may explain the opposite antinociceptive effects previously reported, supporting the idea of a dual 5-HT2A/2C effect.

Profound Impairment in Social Recognition and Reduction in Anxiety-like Behavior in Vasopressin V1a Receptor Knockout Mice

I. Bielsky and L. J. Young*

Considerable evidence suggests that arginine vasopressin (AVP) is critically involved in the regulation of many social and non-social behaviors, including emotionality. The existence of two AVP receptors in the brain, namely the V1a and V1b subtypes, and the lack of clear pharmacological data using selective agonists or antagonists, make it difficult to determine which receptor is responsible for the AVP mediated effects on behavior. Here we report the behavioral effects of a null mutation in the V1a Receptor (V1aR) in male mice. Male mice lacking functional V1aR (V1aRKO) exhibit markedly reduced anxiety-like behavior and a profound impairment in social recognition. V1aRKO performed normally on spatial and non-social olfactory learning and memory tasks. Acute central administration of AVP robustly stimulated stereotypical scratching and autogrooming in wildtype, but not V1aRKO males. Adeno-associated viral vector gene transfer was used to re-express the V1aR in the lateral septum of V1aRKO mice. We are currently assessing anxiety-related behavior and social recognition in these animals. AVP and oxytocin (OT) mRNA and OT receptor binding levels were similar in WT and V1aRKO mice. Given the current findings, the V1aR may provide a novel potential pharmacological target for social and affective disorders including autism, and anxiety disorders.

Synapsins Decrease Frequency Facilitation at the Mouse Neuromuscular Junction

M. Bykhovskaia, D. Samigullin, C. A. Bill*

Synapsins control the size of the readily realizable pool of vesicles in the presynaptic terminal. To understand the relationship between the releasable pool of vesicles and facilitation, we combined electrophysiology and ultrastructure study of the hemidiphragm synapse of Synapsin I and Synapsin II knockout mice. Quantal content of EPSPs was measured at different stimulation frequencies and at different Ca2+ concentrations. We found that at reduced extracellular Ca2+, quantal release and facilitation were significantly higher in Synapsin (-) animals than in the wild type. Electron microscopy analysis revealed that the density of synapstic vesicles in the vicinity of presynaptic membrane was significantly reduced in Synapsin II knockout animals. Both quantal release and ultrastructure were affected stronger in Synapsin II (-) than in Synapsin I (-) animals, suggesting that Synapsin II has the primary role at the neuromuscular synapse. These findings are consistent with the idea that synapsin inhibits the recruitment of vesicles into the releasable pool. Thus, lack of synapsin results into massive vesicles recruitment, pronounced transmitter release and facilitation, and, consequentially, in the depletion of the total vesicles store. Our results confirm the hypothesis that facilitation is associated with the enhanced vesicles recruitment. Supported by NIH grant R01 MH61059.

Context Dependent Effects of Lorazepam on Regional Cerebral Glucose Metabolism Revealed by Cognitive Testing in FDG-PET

*S. Castner**

Lorazepam is a full GABAA- benzodiazepine receptor agonist used in the treatment of a variety of neuropsychiatric disorders including anxiety, panic disorder, and insomnia, and is known to have sedative-hypnotic effects. It has been previously shown that lorazepam reduces brain glucose metabolism in a number of key regions including thalamus, caudate nucleus and cerebellum. However, a recent study has indicated that there may be a differential recruitment of neuronal circuitry by bezodiazepine receptor agonists dependent upon the conditions under which the subjects are scanned. We studied the effects of acute lorazepam (1 mg; p.o.) on regional cerebral glucose metabolism (rCMglu) using [18F]-flouro-2-deoxyglucose (FDG-PET). In a randomized cross-over design the subjects performed either a visual discrimination or cognitive tasks (PASAT, Maze learning, CPT) in either placebo or drug conditions during FDG uptake. The actions of lorazepam could be dissociated between the cognitive and associative testing conditions. The magnitude and extent of reduced rCMglu in cuneus,

precuneus, retrosplenial cortex and occipital gyri was far greater in the cognitive condition but the actual areas of effect remained very similar. By contrast, cognitive testing not only dramatically increased the elevations in rCMglu seen in the visual discrimination task but also generated increases in rCMglu in key regions, including hippocampus, dorsolateral prefrontal and posterior parietal cortices of the right hemisphere, and anterior cingulate bilaterally. Multivariate analysis revealed that the effects of lorazepam on rCMglu were far more predictable and reproducible when tested during performance of the cognitive tasks. [Supported by: Pfizer, Inc.]

Adult Neural Progenitor Cell Proliferation and Neurogenesis is Increased During Ethanol Withdrawal

*F. Crews**

Neural progenitor cells (NPCs) produce new neurons in at least two regions of the adult brain, including the subgranular zone (SGZ) of the dentate gyrus (DG). We previously reported that during intoxication, binge alcohol (EtOH) exposure inhibits the proliferation and survival of NPCs that contribute to adult neurogenesis. To investigate the effect of EtOH withdrawal and especially withdrawal-induced seizures on NPC proliferation and neurogenesis, rats were administered EtOH or control diet in a binge paradigm (i.e. 3 times a day for 4 days with ~9g/kg/day). Seizures were observed between 10 and 25 h after the last dose of EtOH then rats were sacrificed at various times. Cell proliferation was labeled by Bromo-deoxyuridine (BrdU; 300mg/kg 4 h before sacrifice) immunohistochemistry in rats sacrificed at 48 h, 72 h, 168 h or 28 days after EtOH. In the DG and SGZ, the number of BrdU+ cells was increased at 48 h ($p<0.02$) and 168 h ($p<0.01$) but returned to control levels by 28 days. This increase in cell proliferation differs both qualitatively and quantitatively between the 48 h and 168 h time points. At 48 h, BrdU+ cells were visualized across the hippocampus and significantly increased in the CA1 and molecular layer ($p<0.05$). At 168 h, BrdU+ cells were increased five-fold, though the new cells were restricted to the SGZ. Immunohistochemistry for Ki-67, an endogenous marker of cell proliferation, showed a similar increase at 168 h ($p=0.002$). Rats with high seizure scores (>1.0, scale 0 to 4) had significantly more BrdU+ cells at 168 h (106±22 cells/section) than either low seizure-activity rats (<1.0 seizure score, 35±6 cells/section) or controls (18±2 cells/section; $p<0.001$). To examine whether the increase in NPC proliferation affected neurogenesis, we analyzed DG cell differentiation in rats injected with BrdU at 168 h and sacrificed after 4 wks. Neurogenesis was determined by confocal microscopy of triple fluorescent labeling for BrdU, neuronal, and glial markers. EtOH withdrawal seizures were associated with an aberrant increase in the number of neurons 28 days after the proliferative burst at 168 h. Theses changes in cell proliferation and neurogenesis following EtOH withdrawal may contribute to CNS dysfunction associated with alcoholic binge drinking.

Naltrexone Effects on mu- and delta-Opioid Receptor Availability in Alcohol Dependence

J.J. Frost, G.S. Wand, Y.K. Kim, B. Bencherif, R.F. Dannals, M.E. McCaul*

Alcohol craving and reward are partially mediated by the endogenous opioid system. Naltrexone, a non-selective opioid receptor antagonist, is used to treat alcohol dependence; however, there is variability in effectiveness across patients. This study quantified mu- and delta- opioid receptors in alcohol dependent patients and assessed changes in receptor availability after naltrexone administration. Eleven, hospitalized alcohol-dependent patients (mean age: 44 ± 3 y.o, male:female = 7:4) underwent 11C-carfentanil and 11C-naltrindole PET studies for mu- and delta- opioid receptor imaging. On day 5 of supervised abstinence, a baseline study was completed; a second study was completed on day 17 of abstinence following 50 mg naltrexone p.o. for three days. Regional receptor availability was assessed as VT, BP (V3/V2) for mu and Ki (K1 x k3/(k2+k3)) for delta opioid receptor by Logan/Patlak graphical analysis using metabolite corrected arterial input and tissue activity derived from standard anatomical ROIs. The mean percent decrease of receptor availability (BP or Ki) was calculated by (naltrexone-basal)/basal x 100 %. Mu-opioid receptor binding was almost completely blocked in all regions. Mean percent decrease of BP was > 97% in frontal, temporal, parietal regions and caudate, 88% in putamen, 87% in thalamus, 95% in amygdala, and 75% in hippocampus. In contrast, delta opioid receptor binding was only partially blocked in receptor rich regions during naltrexone administration. Mean percent decrease of Ki was 35% in cingulate gyrus and caudate nucleus, 30% in putamen, 35% in frontal, 35% in temporal, and 21% in parietal cortex. Inhibition of delta opioid receptors by naltrexone showed large individual variability(range of %COV: 51-95%). The almost complete inhibition of mu receptor binding in all subjects suggests that variability in the clinical response to naltrexone is not explained by variability in mu receptor inhibition. The lower percent inhibition and greater intersubject variability for delta receptors may contribute to naltrexone clinical response variability. Further study of naltrexone effects on alcohol craving and relapse and correlation with receptor availability will be performed.

Synaptogenesis on Mature Hippocampal Neurons During Recovery of Ionic and Osmotic Homeostasis Recapitulates Development.

S.A. Kirov, L.J.Petrak, K.M.Harris*

Changes in dendritic spine number alter synaptic activity in neuronal networks. There are three stages to hippocampal developmental synaptogenesis consisting of filopodial extension, formation of shaft synapses, and spine outgrowth. Mature hippocampal neurons in slices have more dendritic spine synapses than in perfusion fixed brain. Blocking synaptic transmission dur-

ing slice preparation and incubation further increases spine number. Here, we used 2-photon microscopy to test whether synaptogenesis in mature hippocampal slices results from a temperature or energy related disruption in ionic and osmotic homeostasis. To resemble ice-cold slicing conditions, slices recovered for several hours in vitro were exposed to the cold (5º-6ºC) artificial cerebrospinal fluid (ACSF). During 20±13 min of exposure dendrites became varicose and spines were lost. Upon re-exposure to ACSF at 32ºC dendritic varicosities disappeared, dendritic spines lengthened, and spine density increased 18±3% above the original density. Replacement of NaCl with a cell plasma membrane impermeant sucrose prevented dendritic swelling and spine loss during exposure to cold ACSF. Hence, another set of slices was prepared with sucrose based ACSF. However, serial EM analysis revealed that blocking synaptic transmission during slice preparation even under these less disruptive conditions resulted in more nonsynaptic protrusions with pointy tips, atypical spines with multiple synapses and stubby spines. These findings suggest that spine formation in mature slices may be triggered by disruption of ionic and osmotic homeostasis and recapitulates development. Preservation or elimination of the excess spines depends on synaptic activity. Supported by NIH KO1MH02000 and NS21184, NS33574 and the Packard Foundation.

Multiple Signaling Modes in the Mesocortical Pathway

C. Lapish, L. Nogueira, A. Lavin, J.K. Seamans*

Dopamine (DA) release occurs on timescales of hundreds of milliseconds to hundreds of minutes, yet the time course of postsynaptic effects of DA are rarely discussed. We propose a three time-scale scheme for classifying DA's effects in prefrontal cortex (PFC) based on the following data. Electrical or chemical stimulation of the ventral tegmental area (VTA) evokes a fast EPSP-IPSP sequence recorded in PFC neurons intracellularly in vivo. This response is unaffected by complete DA receptor blockade in PFC, but is eliminated by a glutamate antagonist, 6OHDA lesions of the VTA, or TTX injection in the medial forebrain bundle. These data suggest a fast mode of mesocortical signaling that is mediated by co-release of glutamate from DA containing neurons. Transient burst stimulation of the VTA (20Hz for 2s) produced an increase in the evoked excitability of PFC neurons that lasted for >45min in vivo. Peripheral administration of a D1 antagonist not only decreased the basal excitability of PFC neurons, but also blocked this long-lasting increase in evoked excitability. This type of D1 mediated change in excitability in vivo had a similar time course to many of the D1 mediated effects we have reported in vitro. In between the very fast acting EPSP-IPSP response and the long-lasting D1 mediated effect, is a D2 mediated modulation. In vitro, application of a D2 agonist reduced layer V IPSCs for a period of ~10min after application. Therefore, there are at least three temporally discrete and receptor specific modes of modulation in the mesocortical pathway.

Dopamine D2 Receptor-Stimulated Activation of ERK MAP Kinases Mediated by Cell Type-Dependent Transactivation of EGF and PDGF Receptors

K. A. Neve, D. Buck, R. Yang, C. Wang*

One of the mechanisms by which G protein-coupled receptors (GPCRs) activate the extracellular signal regulated kinases (ERKs) is via transactivation of receptor tyrosine kinases (RTKs), including epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR). The dopamine D2 receptor belongs to the GPCR superfamily and signals primarily through the pertussis toxin-sensitive Gi/o proteins to regulate many signaling pathways, including ERKs. In CHO cells expressing recombinant D2 receptor, activation of ERKs has been shown to be mediated by transactivation of PDGFR. We now report that dopamine D2 receptor activation of ERKs in non-neuronal human embryonic kidney 293 cells was also dependent on transactivation of PDGFR, as demonstrated by the effect of PDGFR inhibitors on quinpirole-induced phosphorylation of ERKs and by quinpirole-induced tyrosine phosphorylation (activation) of the PDGFR. In contrast, in NS20Y neuroblastoma cells where PDGF causes only weak activation of ERKs, stimulating recombinant D2 receptors with quinpirole caused activation of ERKs that was mediated by the EGFR; quinpirole stimulation also caused tyrosine phosphorylation of the EGFR and co-precipitation of the D2 receptor and EGFR. Similarly, in primary cultures of rat neostriatal neurons, quinpirole stimulation of endogenous D2-like receptors activated ERKs, a response that was decreased by the EGFR inhibitor tyrphostin AG1478, but not by the PDGFR inhibitor tyrphostin AG340. These results demonstrate that D2-like receptors activate ERKs via transactivation of EGFR in some neuronal cells and demonstrate the importance of cell selection in signaling studies.

Role of Norepinephrine (NE) in the Modulation of Cortical Excitability

L. Nogueira, A. Lavin*

Numerous studies indicate that catecholamines are playing a fundamental role in mediating cognitive functions in the prefrontal cortex (PFC). However, the majority of studies have been focus on the role of dopamine (DA) in the PFC. DA is not the only catecholamine modulating PFC activity, the noradrenergic (NE) projection from the Locus Coeruleous (LC) plays an important role in PFC (Berridge, et al., 1993; Coull, 1994). We examined the role of the NE modulation of cortical activity using intracellular recordings in vivo in anesthetized rats. A train of high frequency stimulation (20 Hz/ 2sec), was applied to LC and cortical excitability was measured by counting the number of spikes evoked by a constant pulse of current injection every 30 seconds. It was found that following LC stimulation there is a decrease in

the evoked and spontaneous cortical firing. Moreover, a decrease in cortical bistability was observed in several cases. The administration of the specific μ2 agonist (clonidine 25 mg/kg i.v.), reverts the decrease in the evoked and spontaneous firing. These results suggest that NE is modulating the excitability of neurons in PFC.

Inhibiting AP-1 Transcriptional Activity in the Striatum Potentates Cocaine Sensitization and Alters Gene Expression

*R. Paletzki**

Cocaine administration produces changes in transcriptional activity in the striatum, which have been proposed to underlie the behavioral alterations observed following chronic use. Cocaine has been shown to increase the activity of many transcriptional promoter sites including AP-1. To investigate the effect of activity at the AP-1 site we have expressed A-FOS, an inhibitor of AP-1 DNA binding, selectively in striatal neurons of adult mice. When A-Fos expressing mice are chronically treated with cocaine they demonstrate an enhanced locomotion relative to controls whereas, the basal locomotion and locomotion induced following an acute cocaine treatment were not different. A condition place preference assay indicates that A-FOS expressing mice have a greater preference for the cocaine-associated environment. Microarray analysis of striatal mRNAs identified genes misregulated in A-FOS mice following cocaine treatment although no differences were identified in untreated A-FOS mice relative to controls. These data indicate that altering activity at the AP-1 site modifies the genetic and behavioral responses of mice to chronic cocaine.

Vesicular Glutamate Transporter-Dependent Glutamate Release from Astrocytes

V. Parpura, V. Montana, Y. Ni, V. Sunjara, X. Hua*

Astrocytes exhibit excitability based on variations of their intracellular Ca2+ concentrations, which leads to glutamate release, that in turn can signal to adjacent neurons. This glutamate-mediated astrocyte-neuron signaling occurs at physiological Ca2+ levels in astrocytes and includes modulation of synaptic transmission. The mechanism underlying Ca2+-dependent glutamate release from astrocytes is most likely exocytosis, since astrocytes express the protein components of the soluble N-ethyl maleimide-sensitive fusion protein attachment protein receptors (SNAREs) complex, including synaptobrevin 2, syntaxin and synaptosome-associated protein of 23 kDa (SNAP-23). Although these proteins mediate Ca2+-dependent glutamate release from astrocytes, it is not well understood whether astrocytes express functional vesicular glutamate transporters (VGLUTs) that are critical for vesicle refilling. In this work, we find in cultured and freshly-iso-

lated astrocytes the presence of brain-specific Na+-dependent phosphate inorganic co-transporter (BNPI) and differentiation-associated Na+-dependent inorganic phosphate co-transporter (DNPI), that have recently been identified as VGLUTs 1 and 2. Indirect immunocytochemistry showed a punctate pattern of VGLUT immunoreactivity throughout the entire cell body and processes, while pharmacological inhibition of VGLUTs abolished mechanically- and agonist-evoked Ca2+-dependent glutamate release from astrocytes. Taken together these data indicate that VGLUTs play a functional role in exocytotic glutamate release from astrocytes.

Ocinaplon, a Novel GABAA Receptor Modulator, is Active in Animal Models of Anxiety

M. Krawczyk, P. Popik, B. Beer, A. Lippa, P. Skolnick*

In patients with generalized anxiety disorder, ocinaplon produces a robust reduction in anxiety in the absence of side-effects typically associated with benzodiazepines (Beer, et al., 2002). The objective of this study was to examine the effects of ocinaplon in two widely used animal models (the "thirsty rat" conflict test [TRC] and elevated plus maze [EPM]) that are predictive of anxiolytic activity. In the TRC, ocinaplon (minimum effective dose [MED], 6 mg/kg, p.o.) produced dose dependent increases in punished responding at doses of up to 24 mg/kg, the highest dose planned in this study. The MED of diazepam was 10 mg/kg (p.o.) in the TRC; higher doses disrupted performance. In the EPM, ocinaplon (MED 6 mg/kg, p.o.) increased the % time in open and % open entries, the two measures in this procedure that are most closely linked to an anxiolytic action. The MED of diazepam was 5 mg/kg (p.o.) in the EPM. Like benzodiazepines, the effects of ocinaplon in the TRC and EPM were sensitive to Ro 15-1788, consistent with a GABAA receptor-mediated action. The "side-effect" profile of ocinaplon and diazepam were also investigated. Ocinaplon (100 mg/kg p.o.) did not affect grip strength but did impair rotarod performance. This latter effect was flumazenil sensitive. Diazepam (20 mg/kg, p.o.) significantly impaired rotarod performance and reduced grip strength. The present data are consistent with the hypothesis that ocinaplon is an "anxioselective", useful in the treatment of generalized anxiety disorder. Reference: B. Beer, et al. Soc.Neurosci.Abstr. 396.15, 2002.

Characterisation of Neural Precursors Isolated from Human Vanishing White Matter Diseased Brain.

*C. Proschel**

Diseases of myelinated white matter tracts in the central nervous system (CNS) represent one of the most frequent neurological disorders. Those known to be inheritable are referred to as leukodystrophies. The identification of specific genetic lesions has helped explain the pathology observed

in some patients. This has not been the case for the recently identified mutations in the subunits of translation initiation factor 2B (eIF2B) in patients diagnosed with autosomal recessive Childhood Ataxia with Diffuse CNS Hypomyelination (CACH)/Vanishing White Matter Disease. The lack of a suitable experimental system allowing to test the effect of eIF2B mutations on the biology of neural cell populations is a major obstacle in understanding the etiology of CACH/VWM disease. By applying our experience in isolating and culturing neural stem cells and progenitors from both the rodent and human CNS, we established cultures of cells with the characteristics of neural precursors from the brain of a CACH/VWM disease patient with known mutations in the epsilon subunit of eIF2B (EIF2B5). This is the first example of an in vitro system using cells directly isolated from a CACH patient. We present the analysis of these cultures using lineage specific markers. In light of the clinical pathology, we focused on the oligodendrocyte compartment. Initial results indicate oligodendrocytes derived from the patient's brain appeared normal by morphological criteria and progressive maturation of oligodendroglial lineage cells could be observed. We are currently extending this analysis in VWM patient derived cells to include other neural lineages and their interactions with oligodendrocytes.

Exercise Activates the Phosphatidylinositol-3-Kinase Pathway in Hippocampus

*A. Russo-Neustadt**

Physical exercise is known to enhance psychological well-being and coping capacity. Voluntary physical exercise in rats also robustly and rapidly upregulates hippocampal brain-derived neurotrophic factor (BDNF) mRNA levels, which are potentiated following a regimen of chronic antidepressant treatment. Increased BDNF levels are associated with enhanced activity of cyclic AMP response element binding protein (CREB). So far, relatively little is known about the intracellular signaling mechanisms mediating this effect of exercise. We wished to explore the possibility that exercise activates the hippocampal phosphatidylinositol-3 (PI-3) kinase pathway, whose signaling molecules mediate cellular survival. We examined the effects of 2 weeks of daily voluntary wheel-running activity on the levels of the active forms of protein-dependent kinase-1 (PDK-1), phospho-PI-3 kinase, phospho-thr308-Akt, phospho-ser473-Akt, and phospho-glycogen synthase kinase-3-beta (GSK3-beta; inactive form), as well as BDNF, activated CREB, and the phospho-trkB receptor, in the rat hippocampus, and compared these with sedentary controls. At the end of the experiment, rats were sacrificed by rapid decapitation, their brains excised, and their hippocampi dissected. Immunoblotting analyses revealed that there was a significant phosphorylation (activation) of PDK-1, PI-3 kinase and Akt, and a significant phosphorylation (inactivation) of GSK-3-beta. In addition, significant increases in phospho-CREB, BDNF and phospho-trkB were observed in the hippocampi of exercising animals. These results suggest that the exercise-induced

expression of BDNF is associated with the activation of intracellular pathways enhancing neuronal survival, and may be mediated, in part, by the PI-3 kinase/Akt pathway. Supported by NIH grant MH59776.

The D1 Dopamine Receptor is Constitutively Phosphorylated By GRK4: Implications for a Novel Mechanism of Regulation

*D. Sibley**

Homologous desensitization of G protein-coupled receptors (GPCRs) is mediated by G protein-coupled receptor kinases (GRKs). Upon agonist binding and activation, the GPCR becomes a substrate for GRK phosphorylation at serine and/or threonine residues. In the present study, we present evidence that the GRK4 isoform exhibits constitutive or agonist-independent phosphorylation of the D1 dopamine receptor. Co-expression of GRK4 and the rat D1 receptor in HEK293T cells results in increased basal phosphorylation of the receptor that is similar to the level of phosphorylation induced by dopamine stimulation in the absence of GRK4 co-expression. The addition of dopamine to GRK4 co-transfected cells produces only a modest increase in phosphorylation over basal levels. Radioligand binding assays and confocal fluorescence microscopy, using a D1 receptor-GFP chimera, reveals that GRK4 co-expression promotes sequestration/internalization of the D1 receptors into intracellular compartments even in the absence of agonist stimulation. GRK4 co-expression also results in a ~50% decline in the accumulation of cAMP in response to a maximally effective concentration of dopamine. Mutation or truncation of serine and threonine residues at the extreme end of the carboxyl terminus of the D1 receptor completely eliminates the GRK4-mediated constitutive phosphorylation. These data suggest that the D1 dopamine receptor can be constitutively phosphorylated by GRK4 in an agonist-independent manner and that this phosphorylation results in constitutive desensitization and internalization of the receptor. GRK4 might thus play a critical role in regulating the D1 receptor within cells or tissues that co-express these two proteins. Supported by NIH.

Imaging and Genotyping the Serotonergic System in Impulsive Aggressive Personality Disorders

*L. Siever**

Reduced serotonergic activity has been associated with impulsive aggressive behaviors in a variety of disorders, especially in impulsive aggressive personality disorder such as borderline and antisocial personality disorders. Neuroendocrine responses to serotonergic probes such as dl-fenfluramine and mCPP suggest reduced capacity of the serotonergic system correlated

with the degree of impulsive aggressive behavior in personality disordered patients. Reduced metabolic responses to fenfluramine have been reported in orbital frontal and related prefrontal regions in impulsive aggressive personality disordered patients compared to controls. Recent studies utilizing mCPP as a probe suggest reduced basal activity in anterior cingulate cortex associated with physical aggression, reduced responsiveness in anterior cingulate and orbital frontal cortex in response to mCPP compared to placebo in administration in impulsive personality disorder patients compared to controls ($p<0.05$). Studies using radiotracing ligands to label presynaptic transporter sites and postsynaptic 5-HT2a receptors suggest increased 5-HT2a receptor binding and decreased transporter numbers in the neocortex and limbic cortex, particularly cingulate cortex for the transporter, in patients with impulsive aggressive personality disorders ($p<0.05$). Impulsive aggressive behaviors and/or suicide attempts are significantly associated with variations of polymorphisms for the sertonin transporter, 5-HT2a receptor, and 5-HT1b receptor. New studies identifying intermediate phenotypes such as the Point Subtraction Aggression Paradigm (PSAP) may help in generating more homogenous phenotypes for genotyping studies as well as paradigms to measure brain activation during PET imaging and preliminary data will be presented regarding these studies.

Alterations in N-Methyl-D-Aspartate Receptor Magnesium Sensitivity in Medium-Sized Striatal and Cortical Pyramidal Neurons in the R6/2 Mouse Model of Huntington's Disease

A. J. Starling, V. M. André, C. Cepeda, M. S. Levine.*

Huntington's Disease (HD) is a genetic disorder involving the corticostriatal pathway via presynaptic and/or postsynaptic mechanisms. Although striatal neurodegeneration has been the hallmark pathology in HD, cortical atrophy is markedly present. Glutamate via the NMDA receptor has been implicated in HD neurotoxicity. We examined possible changes in NMDA receptor function in the striatum and in its major input structure, the sensorimotor cortex, in the R6/2 transgenic mouse model which expresses exon 1 of the human HD gene with about 150 CAG repeats. Whole-cell voltage-clamp recordings from acutely dissociated medium-sized striatal and cortical pyramidal neurons were obtained from different age groups (15, 21, and 40 days for striatal and 40 and 80 days for cortical pyramidal neurons. We characterized NMDA responses and Mg2+ sensitivity at different holding potentials in all neurons. At hyperpolarized potentials, a subpopulation of striatal neurons demonstrated a significant decrease in NMDA receptor Mg2+ sensitivity in all age groups. Cortical pyramidal neurons displayed a significant increase in NMDA receptor Mg2+ sensitivity at all potentials at 40 days and at the most hyperpolarized potential at 80 days. The abnormal

Mg2+ sensitivity indicates that corticostriatal neurotransmission is significantly altered from presymptomatic stages. Supported by the Hereditary Disease Foundation, The Cure HD Initiative and USPHS NS41574.

Dopamine Bidirectionally Modulates Inhibition in PFC via Different Receptor Subtypes and Intracellular Pathways

*H. Trantham-Davidson**

In vivo DA levels in PFC vary from the low nM to uM range during different behaviors or stress. DA may act through D1 vs. D2 receptors at different concentrations to differentially modulate PFC function. Since GABAergic transmission has already shown to be differentially affected by D1 and D2 receptor activation (Seamans et al. 2001), we used IPSC amplitude as a functional assay. Low doses of DA (10nM-500nM, n=26) increased (58.03 ±21.1%) whereas higher doses of DA (1-20uM, n=20) decreased (-29.4 ± 6.9%) IPSC amplitude. Application of a D1 antagonist (SCH 23390 5 uM) or PKA inhibitor (H-89 10 uM) blocked the increase in IPSC amplitude seen with lower DA concentrations, indicating that low DA levels interact preferentially with D1 receptors and PKA to increase IPSC amplitude. In contrast, the D2 antagonist (Sulpiride 10 uM) and PDGFR (platelet-derived nerve growth factor receptor) antagonist (AG1433 5 uM) blocked the decrease in IPSC amplitude observed with higher DA concentrations. We predicted that PDGFR transactivation would lead to an increase in [Ca2+]i that would result in either activation of CaMKII and subsequent phosphorylation of the b3 subunit of the GABAA receptor or activation of PP1/2A and dephosphorylation of this subunit, both of which could decrease the amplitude of IPSC's. Calyculin A (PP1/2A inhibitor;100 nM) blocked the IPSC reduction by high DA whereas KN-62 (CaMKII inhibitor; 1 uM) did not. These results suggest that DA exerts concentration-dependent effects on PFC cells via different DA receptor subtypes and intracellular signaling pathways.

Inhibition of Phospholipid Synthesis by Reduction of Choline-Ethanolamine Phosphotransferase Activity Precedes Excitotoxic Neuronal Death

*R. Trullas**

Excitotoxic neuronal death evoked by glutamate receptor overactivation is characterized by marked alterations in cellular membranes. Excessive Ca2+ entry through glutamate receptors activates a large array of potential neurotoxic processes. However, the mechanism by which all of these different neurotoxic processes contribute to the membrane damage associated with excitotoxicity is unknown. We studied synthesis and degradation of major membrane phospholipids in the early stages of the excitotoxic process. Ex-

posure of cortical neurons to neurotoxic concentrations of NMDA increases extracellular choline and activates hydrolysis of phosphatidylcholine and phosphatidylinositol by phospholipase A2, but does not induce significant degradation of phosphatidylcholine, phosphatidylinositol, phosphatidylethanolamine, or phosphatidylserine. In contrast, NMDA strongly reduces the incorporation of [3H]choline and [3H]ethanolamine into their respective phospholipids. This effect occurs well before any significant membrane damage and cell death. Metabolic labeling experiments in whole cells showed that NMDA receptor overactivation does not modify the activity of phosphocholine or phosphoethanolamine cytidylyltransferases, but strongly inhibits choline/ethanolamine phosphotransferase activity. These results show that membrane damage by NMDA is preceded by inhibition of phospholipid synthesis and not by phospholipid degradation, and that NMDA receptor overactivation decreases phosphatidylcholine and phosphatidylethanolamine synthesis by inhibiting choline/ethanolaminophosphotransferase activity, the last step of the Kennedy pathway of phospholipid synthesis. Supported by grants BFI2001-1035, Ministerio de Ciencia y Tecnologia and PI020555, Fondo de Investigaciones Sanitarias of Spain.

Session Abstracts

Panel · Sunday, January 25 · 4:30–6:30 PM · Bighorn C1

Estrogen and Progesterone: Magic Elixir or Caustic Cocktail for Brain Aging?

M. A. Ottinger, J. Simpkins, I. Merchenthaler, R. Handa, C. Sladek, D. Ingram

The debate about the actions, efficacy, and potential benefits of HRT continues, due in part to the complexity of the issue. Further confusion arises from the use of native versus conjugated steroids for therapy. This session is focused primarily on the action of estrogens, progestins, and ligands that interact with these receptors on estradiol receptors,with attention to cross-talk and inter-modulatory effects with selected neuropeptide systems, and potential benefits in neurodegenerative pathology. Jim Simpkins and Istvan Merchenthaler will both present data on structure-function efficacy of steroids and ligands that interact with specific receptors in neuroprotection. Bob Handa will discuss his recent data on ERbeta and the role of steroid hormones in responses via this receptor subtype. Celia Sladek will discuss the role of the steroid hormone receptors on the oxytocin neuronal system and the implications of cross-talk between neuropeptide and neuroendocrine systems. Mary Ann Ottinger and Don Ingram will serve as discussants and may contribute to the discussion with data collected on estrogen effects in transgenic models of neurodegeneration, if time permits.

Panel · Sunday, January 25 · 4:30–6:30 PM · Bighorn C2

Urocortins: Stress, Feeding or Stress-Induced Feeding?

C. Kotz, W. Vale, D. Richard, V. Bakshi

Urocortins (I, II, III) are neuropeptides that bind with high affinity to CRH receptors and are thought to be additional ligands, especially for type II CRH receptors. Urocortins influence feeding and are involved in stress responses. Distinction between CRH and urocortin function is unclear and controversy exists over specific roles of urocortins, CRH and CRH receptors. Dr. Wylie Vale will give an overview describing present status of urocortin/CRH research in energy balance, and will discuss his group's work on the anatomic distribution of urocortin III and its central and peripheral effects on metabolism. He will focus on the potential role of this peptide as a local regulator of pancreatic islet functions. Dr. Catherine Kotz will describe anorectic effects of urocortins I and III in the lateral septum, and interactions between urocortin and other energy regulatory substrates (orexin A, neuropeptide Y,

opioids) in the hypothalamus that mediate energy expenditure. Dr. Denis Richard will describe changes in brain gene expression of urocortin III in an obese animal model and in response to energy deficits. His data demonstrate decreased expression in parallel with stimulation of appetite and the hypothalamic-pituitary axis, suggesting a role for UCN III in metabolic and neuroendocrine controls in obesity. Finally, Dr. Vaishali Bakshi will wrap up by discussing the extent to which anorectic effects of UCN overlap with stress-like responses, and neuroanatomical substrates (lateral septum, amygdala) underlying CRH agonist- or stress-induced reductions in feeding. The relative contributions of the CRH receptor subtypes to mediating these behaviors will be reviewed.

Panel · Sunday, January 25 · 4:30–6:30 PM · Hasty's

Does Antisense Make Sense in the CNS?

B. Hoffman, D. Corey, C. Wahlestedt, C. Jones

This panel will review recent advances in the application of RNA inhibition technologies, including newer ASO chemistries and RNA interference (RNAi) technologies, for in vivo target validation in the CNS. Approaches for the transient knockdown of gene expression through RNA inhibition in the CNS, such as antisense (ASO) technologies, afford many potential advantages for the validation of novel gene function in the CNS. However, despite the availability of ASO technologies for over a decade, there has not been a widespread acceptance and application of ASO technologies for in vivo target validation in the CNS. Such broader applications have been hindered by several factors including the use of older antisense chemistries with limited in vivo half-lives and CNS toxicity as well as experimental. This panel will focus on (1) criteria for success and (2) recent successes in the application of novel ASO and RNAi technologies in the CNS. Beth Hoffman will provide a brief historical overview and introduction to the topic. David Corey will review the past successes and failures of in vivo applications of ASO technologies and present data using several novel oligonucleotide chemistries including the peptide nucleic acids and siRNA. Carl Wahlestedt will present efficacy data comparing the novel locked nucleic acid (LNA), siRNA, and LNA-substituted siRNA oligonucleotide chemistries, discuss how to optimize the selection of mRNA targets for each approach and how to enhance efficacy in the brain. Carrie Jones will present a comparison of the in vivo delivery, distribution and efficacy of phosphorothioate, ISIS 2,-MOE and siRNA oligonucleotide chemistries for two CNS targets, one neuronal and one glial.

Panel · Sunday, January 25 · 4:30–6:30 PM · Jacques's Peak (Mountain Plaza Building)

Chemokines and Neuroinflammatory Disease: New Directions

C. Pert, P. Shapshak, M. Ruff, S. Wilt

Chemokines, comprising over 50 related peptide agonists and their G-protein coupled receptors, were first appreciated as agents of leukocyte migration and activation in the immune system, and more recently as playing critical roles in neurodevelopment and neuronal survival. Monocytes/macrophages and derivative cells such as brain microglia constitute the first line of local host defense to invading microorganisms. These cells respond to a large number of chemoattractants with directed movement, activation of integrins, and generation of free radicals and other mediators. A number of laboratories have converged on the notion that activated microglial cells are the final common pathway in Alzheimer's Disease, Multiple Sclerosis, NeuroAIDS and a number of other important diseases with hypothesized neuroinflammatory etiologies (Dr. Shapshak). In an elegant rat model of neuroinflammatory disease in which every cellular step in the etiology of the disease can be visualized (including axonal and neuronal destruction by activated microglial cells), neonatal rats infected with mouse leukemia virus show symptoms of neurological disease including tremor, ataxia, spasticity and hind limb weakness, whose onset are postponed by a chemokine receptor antagonist (Dr.Wilt). Since over 30 distinct virally encoded chemokine and chemokine receptor mimetics have been identified from the herpes, poxvirus, and retrovirus families which can act as chemokine antagonists, entry factors, growth factors, angiogenic factors, and chemoattractants, the exploitation of chemokine ligands and receptors seems to be a common theme in viral pathogenesis and also holds promise for clinical applications in immunologically mediated brain diseases (Dr. Ruff).

Panel · Sunday, January 25 · 4:30–6:30 PM · Ptarmigan A

Neurorprotection in Traumatic Brain Injury: Will Novel Mechanistic Strategies Show It is a Treatable Condition?

E. Hall, S. Scheff, J. Povlishock, A. Faden, M. Vitek

The major foci of neuroprotection research aimed at traumatic brain injury (TBI) have been glutamate-mediated (NMDA receptor) excitotoxicity, intracellular calcium overload and reactive oxygen-induced lipid peroxidation. Multiple NMDA receptor antagonists, the L-type calcium blocker nimodipine and the antioxidants superoxide dismutase and tirilazad have been the subject of phase II and III TBI clinical trials. With the exception of nimodipine and tirilazad, which appear to have efficacy in the subset of patients with traumatic subarachnoid hemorrhage, no drug has produced

a significant overall improvement in neurological recovery. Several reasons for these trial failures are apparent including inadequate preclinical evaluation, poor clinical trial design, imprecise endpoints and impractically short therapeutic windows associated with the targeted mechanisms. In regards to the latter problem, this panel will discuss newer mechanistic targets and compounds that appear to possess longer, more practical post-injury therapeutic windows. S. Scheff will detail the neuroprotective effects and lengthy (24 hr) efficacy window of the immunosuppressive agent cyclosporin (CsA) in rodent TBI models. He will also present early results from phase I and II CsA TBI trials. J. Povlishock will discuss the ability of CsA and another immunophilin FK-506 to attenuate delayed post-traumatic axonal damage. A. Faden will review the timing of apoptotic mechanisms in TBI secondary injury and the neuroprotective efficacy of novel di- and tri-peptides that are entering clinical trials. Finally, M. Vitek will present exciting new data from a closed TBI model concerning the behavioral recovery-promoting effects and anti-inflammatory/neuroprotective mechanism of action of a novel peptide analog of apolipoprotein E.

Panel · Sunday, January 25 · 4:30–6:30 PM · Ptarmigan B

Are Antipsychotics Neuroprotective in Schizophrenia? Findings From Bedside to Benchtop

L. Nisenbaum, J. Rapoport, G. Tollefson, T. Gould

Current theories suggest that schizophrenia is a genetically mediated neurodevelopmental disorder. However, overt clinical symptoms do not typically manifest themselves until the second or third decade of life. The prodromal phase, which is typically diagnosed in retrospect, consists of attenuated positive symptoms as well as mood and cognitive symptoms and social withdrawal. The appearance of frank psychotic symptoms marks the onset of the first episode of schizophrenia. While most patients recover from the first episode of psychosis, the majority suffer from recurring relapses eventually leading to a progressive clinical decline. In general, the greater the number of episodes and greater duration of untreated illness, the worse the prognosis. These findings suggest that recurring psychotic relapses may be neurotoxic. Thus, preventing relapse through use of efficacious antipsychotics may be neuroprotective. This session will present findings ranging from human neuroimaging studies through clinical outcome measures to basic preclinical studies examining changes that may underlie therapeutic effects in the diseased brain. J. Rapoport will describe ongoing research with very early onset schizophrenia patients showing progressive loss of cortical gray matter during adolescence. G. Tollefson will present recent data demonstrating the effects of typical and atypical antipsychotics on gray matter loss in first episode schizophrenic patients. The effects of antipsychotic drugs on neurotrophic-signaling cascades in preclinical studies will be discussed by H. Manji. Finally, L. Nisenbaum will describe the

effects of both typical and atypical antipsychotic drugs on changes in gene expression related to neuroprotection in an animal model (PCP) of schizophrenia.

Panel · Sunday, January 25 · 4:30–6:30 PM · Ptarmigan C

NMDA Receptors in Huntington's Disease

L. Raymond, M. Levine, M. Ariano, K. Murphy

Huntington's Disease (HD) is an inherited neurodegenerative disorder characterized by progressive dysfunction of movement, cognition and behaviour. Selective degeneration of striatal GABAergic, medium-sized spiny projection neurons (MSNs), and certain hippocampal and cortical pyramidal neurons, is caused by a polyglutamine expansion near the N-terminus of huntingtin. There is no enrichment of huntingtin or its interacting proteins in affected brain regions, and mechanisms underlying selective neuronal vulnerability are not completely understood. However, striatal MSNs receive glutamatergic inputs from the cortex, and previous studies have shown that striatal injection of agonists for calcium-permeable NMDA-type glutamate receptors in rodents or non-human primates produces neurochemical, neuropathological, and behavioural changes characteristic of HD. Recent development of transgenic mouse models of HD facilitates testing the hypothesis that NMDA receptors (NMDARs) play a role in pathogenesis. This panel will describe how dysregulation of NMDAR-mediated synaptic transmission contributes to neuronal dysfunction during symptomatic stages of HD, and may initiate events leading to cell death. In the R6/2 transgenic mouse model, Mike Levine will show that NMDARs in subpopulations of MSNs exhibit altered magnesium sensitivity that may correlate with altered subunit composition in presymptomatic and symptomatic stages. Marjorie Ariano will discuss biochemical evidence for changes in NMDAR subunit composition and phosphorylation state at the symptomatic stage. Kerry Murphy will describe alterations in NMDAR-mediated transmission and synaptic plasticity in hippocampal circuits, potentially contributing to dementia in HD. In the YAC transgenic mouse model, Lynn Raymond will discuss changes in NMDAR current, present from birth, that could contribute to selective neuronal degeneration.

Panel · Sunday, January 25 · 8:30–10:00 PM · Bighorn C1

Stem Cells in CNS Development and Disease

S. Whittemore, J. Macklis, D. van der Kooy, S. Goldman

As we continue to gain insight into the molecular mechanisms that control stem cell proliferation and differentiation, their potential for use in the therapuetic treatment of CNS diseases becomes nearer to a clinical reality. This is true for both intrinsic stem cells and stem or precursor cells that are grafted into the damaged sites. However, it has proven to be exceedingly

difficult to induce endogenous stem cells to facilitate repair in the CNS in terms of directing their proliferation, migration, and appropriate differentiation. Similar problems exist when grafting pluripotent stem cells into the damaged CNS as they most often do not differentiate to the cell fates that would best support functional repair. It is becomimg evident that more lineage-restricted precursor cells may be necessary for sucessful grafting approaches. This panel will detail present understanding of the molecular regulation of CNS stem cell development as well as the capacity of endogenous and grafted, exogenous stem cells to repair the damaged CNS. Derek van der Kooy will discuss neural induction and where brain stem cells come from in the rodent embryo, Jeff Mackliss will present data on the reconstruction of complex cortical circuits by endogenous stem cells in birds and rodents, Scott Whittemore will detail the difficulties of trying to repair the injured adult rodent spinal cord with exogenous stem cells, and Steve Goldman will talk about the molecular restriction of progenitor phenotype in the adult human brain.

Panel · Sunday, January 25 · 8:30–10:00 PM · Bighorn C2

A Head for Serotonin: Its Role in Psychostimulant Actions

K. A. Horner, K. Cunningham, B. Yamamoto, L. Parsons

Psychostimulants induce release of dopamine and serotonin in the basal ganglia. This increase in release of monoamines into the basal ganglia is thought to be responsible for changes in brain function and behavior. While the role of dopamine and dopamine receptors in the effects of psychostimulants has been well characterized over the past several years, the role of serotonin in the effects of psychostimulants has received less attention. However, recent studies have implicated serotonin in psychostimulant-induced changes in gene expression as well as behavior. The goal of this panel is to provide an overview of the current research on the role of serotonin and its receptors in psychostimulant-induced changes in gene expression, behavior, monoamine release and stimulant-induced neurotoxicity. The panel will begin with Ashley Horner who will provide a general overview of the effects of psychostimulants on the function of the basal ganglia. She will discuss how serotonin influences psychostimulant-induced changes in neuropeptide gene expression in the striatum. Kathryn Cunningham will then discuss the role of 5-HT2A/2C receptors in the behavioral effects of cocaine, and the role of 5-HT1B/1D and 5-HT2 receptors in MDMA-induced locomotive activity. Next, Larry Parsons will discuss the role of serotonin in psychostimulant-induced changes in monoamine and amino acid neurotransmission, and the influence of these effects on psychostimulant-maintained operant behavior. He will also present data on the effects of long-term psychostimulant exposure and abstinence on serotonergic mechanisms. Lastly, Bryan Yamamoto will discuss the involvement of 5-HT receptors and transporters in MDMA-induced dopamine release and neurotoxicity to 5HT terminals, respectively. This panel will

demonstrate the critical role of serotonin in the detrimental effects of stimulants on brain function and behavior.

Panel · Sunday, January 25 · 8:30–10:00 PM · Hasty's

Neuropeptides Take a Holiday: Mice without Neuropeptide Processing Enzymes

I. Lindberg, L. Fricker, W. Wetsel, J. Pintar

Neuropeptides are known to be synthesized from larger precursors through the action of various processing enzymes. Recently knockout mice have been created which lack each of these enzymatic activities; these mice exhibit a variety of interesting phenotypes, each of which provides novel information on peptide function. Iris Lindberg will discuss mice null for the prohormone convertase PC2 and the PC2 binding protein 7B2; these mice lack many important neuropeptides and exhibit a background-dependent ACTH hypersecretion disorder, lethal in 129/Sv but not in C57Bl/6J mice. Lloyd Fricker will discuss mice that lack carboxypeptidase processing activity and the consequences of this loss on feeding and body weight regulation. Bill Wetsel will present information on infertility of the carboxypeptidase-deficient mice. Processing of the hypothalamic neurohormone, gonadotropin- releasing hormone, is aberrant in both males and females. The processing deficiency is the primary contributor to the infertility in females, whereas reproductive deficits in males appear to be due to the absence of sexual behavior. Finally John Pintar will discuss the phenotype of mice lacking one or two copies of the peptidyl alpha amidating enzyme (PAM) gene. Homozygous null mice exhibit generalized edema; adrenomedullin may play a role in mediating the PAM knockout phenotype. Discussion will focus on similarities and differences in the phenotypes that result from disruption of enzymes in the same overall pathway, with an emphasis on what these phenotypes tell us about the function of neuropeptides in the brain.

Workshop · Sunday, January 25 · 8:30–10:00 PM · Ptarmigan A

New Research In Brain Stimulation: Restoring Sensory And Motor Function

D. Woodward, J. Chapin, J. Chang, J. Saint-Cyr

Recent years have seen a renaissance in the use of brain stimulation to address otherwise intractable problems in neuroscience and neurology. For example, deep brain stimulation has become one of the most effective techniques for alleviating tremor and other problems associated with Parkinson's disease. Another promising area is the use of microstimulation to restore function in sensory systems. New research in all of these areas has shown the importance of precise electrode placement and stimulus patterning in

determining the functional result of the stimulation. This workshop will explore the promises and pitfalls of the use of microstimulation in different regions of the brain. Both neuroscientific and clinical applications will be discussed. Donald Woodward will introduce this topic, recount its long and sometimes sordid history, and explore the technical issues surrounding this technique. John Chapin will report recent results of microstimulating through multi-electrode arrays in the somatosensory system of rats to produce a virtual brain interface capable of eliciting remarkably normal neurophysiological and psychophysical responses. Jim Chang will report recent results of motor effects of focused microstimulation in the basal ganglia of rats. Finally, Jean Saint-Cyr will report results of deep brain stimulation in human patients, along with both neuropsychological and neuroanatomical results from the same patients.

Workshop · Sunday, January 25 · 8:30–10:00 PM · Ptarmigan B

Knowledge Engineering in Neuroscience

G. Burns, M. Martone, R. Cannon, A. Toga

The creation of scientific theory requires that isolated facts (*i.e.,* data,) be brought into formal relationships with one another to form knowledge. In neuroscience, such representations of knowledge occur as research papers, review articles, books, neuroanatomical atlases, computational models, simulations, *etc*. The development of theoretical representations from these components can be assisted by the use of new tools and approaches from knowledge engineering to design, construct, populate and use useful large-scale knowledge representations. This workshop will provide a practical introduction to these knowledge engineering tools for experimental neuroscientists from any discipline (software will be distributed on CD to attendees). We will discuss the process of formalization that is required to build useful knowledge representations as well as the computational infrastructure required to share data and create knowledge. Inference techniques will be described that provide limited capabilities for reasoning in large data sets. We will also describe existing repositories and resources that may be useful for attendees.

Gully Burns will introduce the workshop and present a system that permits end-users to build knowledge representations from the online neuroscientific literature. Maryann Martone will discuss ontologies and spatial databases that integrate data from distributed multi-scale databases within the Biomedical Informatics Research Network (BIRN) project. Robert Cannon will discuss user-level information management tools and the creation of integrated scientific knowledge resources from distributed and diverse sources. Arthur Toga will discuss solutions for managing large amounts of image data from men and mice describing structure and function in health and disease.

Workshop · Sunday, January 25 · 8:30–10:00 PM · Ptarmigan C

New Roles for Ca2+ Signaling in Circadian Clock Regulation: Membrane, Cellular and Circuit Levels of Actions

M. Gillette, C. Allen, C. S. Colwell, R. Silver

From recent studies of the circadian clock in the suprachiasmatic nucleus (SCN), Ca2+ is emerging as a multi-faceted and critical regulatory element. Ca2+ fluxes and Ca2+-binding proteins are used in the light entrainment system, in regulating action-potential firing and cell-cell communication and, possibly, in regulating clock gene expression. M. Gillette will evaluate the roles of Ca2+ signaling via ryanodine receptor-mediated activation of calpain, a Ca2+-sensor that contributes to neuronal plasticity. C. Allen will provide evidence that membrane NMDA receptors can regulate nuclear [Ca2+]. Intracellular Ca2+, which oscillates in a circadian pattern, may be a clock-driven output, regulating action potential firing frequency via Ca2+-activated K+ channels. C. Colwell will discuss the intercellular signaling mechanisms by which SCN neurons inter-communicate. Possible roles of both electrical and chemical synaptic transmission in coupling SCN neurons will be considered. Finally, R. Silver will examine the role of the Ca2+-binding protein, calbindin, in the regulation of circadian rhythmicity, from gating retinal inputs to clock gene expression to controlling behavior.

Panel · Monday, January 26 · 7:30–9:30 AM · Bighorn C1

Targeting Astrocytes to Influence Glutamatergic Neurotransmission: Lessons from Knockout Mice

R. Schwarcz, J. Coyle, P. Magistretti, C. MacLeod

Astrocytes are increasingly recognized for their role as active participants in normal and abnormal excitatory neurotransmission. In particular, astrocytes regulate several neuronal features linked to glutamatergic function, such as cellular energy metabolism and vulnerability to excitotoxic injury. In the past, the characteristics of glial effects on neurons have been investigated mainly in vitro and by using a variety of pharmacological agents. Recently, genetically manipulated mice have been added as analytical tools. This panel will review the generation and properties of four mutant mice, each with a targeted disruption of a specific astrocytic protein. First, Pierre Magistretti will describe the use of a mouse deficient in glial glutamate transporters for the study of functional metabolic cross-talk between neurons and astrocytes in the developing cortex. Using electrophysiological endpoints, Joseph Coyle will then explain how the elimination of astrocytic glycine transporters affects neuronal NMDA receptor function. Carol MacLeod will present data from mice deficient in the cationic amino transporter 2,

which is normally responsible for arginine uptake into astrocytes and sustained NO formation via inducible NO synthase. These mutant mice show spinal neuroprotection in the experimental allergic encephalomyelitis model of multiple sclerosis. Finally, Robert Schwarcz will show evidence for increased dendritic spine density and enhanced vulnerability to quinolinate in mice deficient in kynurenine aminotransferase II, an enzyme responsible for the glial production of the glutamate receptor antagonist kynurenic acid. Taken together, the presentations will emphasize the value of targeting individual astrocytic proteins for the study of glutamate function in health and disease.

Panel · Monday, January 26 · 7:30–9:30 AM · Bighorn C2

The Dynamics of Excitatory Synapses: Implications for Synaptic Plasticity

R. S. Zukin, G. Westbrook, D. Bredt, A. K. McAllister, M. Bennett

Dynamic regulation of synaptic efficacy is thought to play a critical role in formation of neuronal connections and for experience-dependent modification of neural circuitry. The molecular and cellular mechanisms by which synaptic changes are triggered and expressed are the focus of intense interest. This panel will focus on recent evidence that AMPARs and NMDARs undergo dynamically regulated trafficking and targeting and that the physical transport of ionotropic glutamate receptors in and out of the synaptic membrane is critical to several forms of long-lasting synaptic plasticity. Topics include the role of scaffolding proteins in targeting of AMPARs and NMDARs to synaptic sites (David Bredt), tranlateral movement of NMDARs to and from synaptic sites (Gary Westbrook), rapid recruitment of receptor transport packets along microtubules (Kim McAllister), and protein kinase-regulated NMDA receptor trafficking and gating(Michael V.L. Bennett). Bredt will present findings that the synaptic scaffolding protein PSD-95 not only targets NMDARs to synaptic sites, but acts via stargazin to recruit AMPARs. Westbrook will present physiological evidence that NMDARs move laterally in the postsynaptic membrane, a mechanism thought to underlie experience-dependent forms of synaptic plasticity. McAllister will present evidence that both NMDARs and AMPARs are present in mobile transport packets in neurons before and during synaptogenesis; NMDAR transport packets are more mobile than AMPARs, moving along microtubules at about 4 microns/min and are recruited to sites of axodendritic contact within minutes. Bennett will present recent evidence that protein kinasse C regulates NMDAR trafficking to the synaptic membrane by a SNARE-dependent mechanism; in contrast, protein kinase A regulates calcium permeability of NMDARs. These mechanisms are thought to play a critical role in regulation of synaptic strength in the developing and mature nervous system.

Panel · Monday, January 26 · 7:30–9:30 AM · Hasty's

Applying Lessons from Visual Art to Exploration of the Brain

D. H. Laidlaw, D. Kremers, A. W. Toga, F. Drury, R. E. Jacobs

Real brains in the real world exist in 3 dimensions with complex relationships among the various anatomical and functional parts. Multi-modal nueroimaging data provides us with different views of these complex relationships: MRI shows us how T1, T2, and diffusion vary spatially; sequences of stained microsections show tissue chemical composition and microstructure; and EEG, MEG, and fMRI provide insight into functionality. But understanding these multi-valued 3D volumes of data and how they related to one another is a significant challenge. Because the eye is our highest bandwidth sense, it is the natural choice for exploring these complicated datasets. For centuries, Artists have studied how best to produce effective visual artifacts for many communication purposes; this visual design process is a clear way to make data displays more effective, and yet expert visual designers are rarely included in the process. Jacobs will present work on constructing multidimensional ontologically annotated atlases of development of the mouse and quail that incorporate data from a wide range of in vivo and ex vivo imaging modalities. Toga will discuss multimodal human atlases. Kremers, an artist and visual design expert who has collaborated with both Jacobs and Laidlaw, will discuss new concepts to make interfaces to exploratory software both richer and more sensitive, not only visually, but also by incorporating more of our senses into the exploration process. Drury, who teaches illustration at the Rhode Island School of Design and who co-taught a graduate-level scientific visualization class with Laidlaw, will discuss the challenges of training visual design students to be collaborators in this scientific visualization process.

Panel · Monday, January 26 · 7:30–9:30 AM · Ptarmigan A

Obesity-Brain Interactions: Neural Mechanisms, Treatment and Complications

S. Harik, B. Levin, K. Juhasz-Pocsine, C. Billington

The prevalence of obesity and diseases associated with it are steadily increasing in the U.S. Although multifactorial, many experts believe that obesity may be a brain disease. The brain both senses and regulates the metabolic status for the body via neural inputs and metabolic and hormonal signals from the periphery. "Metabolism sensing" neurons integrate a host of signals to regulate energy intake, storage and expenditure. Anabolic NPY and catabolic proopiomelanocortin (POMC) peptidergic neurons in the arcuate nucleus are two opposing systems largely concerned with energy homeostasis. Other neurons in the lateral hypothalamus (orexin) or

paraventricular nucleus (CRH) are probably involved in other physiological functions, but altered energy homeostasis is part of their larger biological role. Gut hormones act mostly to decrease food intake, although ghrelin, a recently described hormone made in the stomach, actually increases food intake. Gastric bypass operations are being performed with rapidly increasing frequencies to induce marked and maintained weight loss largely by producing a malabsorption syndrome. Bariatric operations may also produce weight loss by altering the balance of peripheral orexigenic and anorexigenic peptides. Although successful, a small percentage of patients develop major neurologic complications after bariatric operations. It is not entirely clear that a single nutrient deficiency underlies these complications. The management of obesity, however, remains largely by dieting. Recent evidence suggests that Atkins the diet is not simply a fad but actually may be successful inducing and maintaining weight loss. Yet, the consumption of large quantities of fat and protein is not without adverse long-term side effects. Sami Harik will introduce the subject of obesity and its health related consequences. Barry Levin will discuss the neural mechanisms that underlie food intake and satiety, the various metabolic and hormonal signals, and the putative targets for the rational treatment of obesity. Katalin Juhasz-Pocsine will discuss her experience with the disabling neurologic abnormalities that were observed months to years after gastric bypass surgery. Charles Billington will provide an update on the medical management of obesity with particular attention to the Atkins diet and ketosis.

Panel · Monday, January 26 · 7:30–9:30 AM · Ptarmigan B

Ignored but not Forgotten: Neuronal Apoptosis in the Normal Adult Rat Brain

D. Fujikawa, V. Koliatsos, J. Roskams, K. Gale

Although neurogenesis in the adult mammalian brain has been a topic of intense investigation, there is little information about natural or induced apoptotic neuronal death in the normal adult brain. This lack of information is at least partly because it has been stated that neuronal apoptosis in rats becomes "negligible" by the third postnatal week, and because it has been assumed that cellular apoptosis is a rapid process, with rapid phagocytosis and disappearance of apoptotic cells, making them difficult to study. Under what circumstances do morphologically apoptotic neurons appear in the adult brain, and what do we know of the mechanisms by which they are produced? Fujikawa will describe the appearance and distribution of naturally occurring apoptotic neurons in the adult rat brain, and caspase-3 activation in these neurons (caspase-3 is of central importance in the caspase-dependent programmed cell death pathways). Koliatsos will show that in piriform cortex, elimination of cortico-cortical inputs induces neuronal apoptosis through a novel mechanism, and will discuss the implica-

tions for neurodegenerative diseases. Roskams will describe the roles of the extrinsic and intrinsic caspase-dependent programmed pathways in apoptosis of olfactory receptor neurons, produced by olfactory bulbectomy or by direct infusion of NMDA. Finally, Gale will present data on adrenalectomy-induced hippocampal granule cell apoptosis and the protective effect of brief electroshock seizures, and will discuss mechanisms that could be the basis for the neuroprotection. The adult rat brain can produce morphologically apoptotic neurons, normally found during development, and developmental programmed mechanisms appear to be responsible.

Panel · Monday, January 26 · 7:30–9:30 AM · Ptarmigan C

The Neurovascular Unit in Cerebral Ischemia

P..Huang, M. Chopp, D. Greenberg, J. LaManna, P. Hurn

The outcome of cerebral ischemia depends not only on intrinsic neuronal susceptibility, but also on interactions between cerebral blood vessels, neurons, circulating cells, extracellular matrix, and surrounding tissues˜together the neurovascular unit. Vascular, cellular, and matrix signaling play key roles in modulating the response to cerebral ischemia and hypoxia. This panel will focus on the concept of the neurovascular unit, as it relates to cerebral ischemia. Dr. Michael Chopp will outline microvascular alterations following stroke, including the expression of matrix metalloproteinases, proinflammatory cytokines, and VEGF. Dr. David Greenberg will discuss the effects of VEGF on the neurovascular unit, including its signal transduction pathways, and molecular mechanisms of effects on neurogenesis and angiogenesis. Dr. Joe Lamanna will continue the theme, describing evidence that cerebral capillary density is matched to local energy demand by local tissue hypoxia signals such as HIF-1 and downstream effects on angiogenesis. Finally, Dr. Patricia Hurn will discuss gender differences in neurovascular signaling and the potential of therapies based on hormonal signaling in the cerebrovasculature.

Panel · Monday, January 26 · 4:30–6:30 PM · Bighorn C1

Developmental Mechanisms for the Regulation of Synaptic Plasticity

J. Isaac, D. Bredt, V. Maricq, K. Roche

There has been considerable interest in the molecular mechanisms underlying long-term synaptic plasticity at glutamatergic synapses since these mechanisms are thought to underlie learning and memory, development and certain pathological conditions of the nervous system. However, it has recently become apparent that many of these mechanisms are developmentally regulated. Indeed, it is likely that such a developmental progression of

synaptic plasticity mechanisms is critical for the normal development of excitatory circuitry. This panel brings together experts from a number of complementary fields to discuss, at the molecular, cellular and systems levels, the mechanisms and consequences of such developmental regulation. John Isaac will discuss the role of NMDA and kainate receptors in early developmental plasticity in the neonatal rodent barrel cortex. David Bredt will discuss recent work on the role of stargazin in the development of hippocampal and cerebellar synapses. Katherine Roche will describe molecular mechanisms by which NMDA receptor function is developmentally regulated and the consequences this may have for subsequent synaptic plasticity. Villu Maricq will discuss the role of glutamate receptors in the development and function of neural circuits that subserve avoidance behaviours in C.elegans. The multidisciplinary nature of the work described in this panel will allow a comparison of mechanisms of developmental plasticity across multiple levels of analysis. This is anticipated to be of interest to a wide audience and generate interesting cross discipline discussions.

Panel · Monday, January 26 · 4:30–6:30 PM · Bighorn C2

The Role of AD-related Genes in Regulating Neuronal Excitability and Synaptic Transmission

A. Cantrell, D. Cook, G. Gouras, R. Malinow

Alzheimer's disease (AD) is characterized by a hallmark pattern of neuropathology consisting of the formation of beta-amyloid (A beta) plaques, neurofibrillary tangles, depressed brain function and neuronal death. The mechanisms underlying cognitive impairment in AD are not fully understood but growing evidence indicates that such impairment may occur prior to or independent of neuronal loss and plaque formation. In fact, the most consistent marker of cognitive decline in AD patients has been synaptic pathology consisting of alterations in synaptic function, morphology and molecular composition. In light of these observations, this panel will explore the most recent evidence implicating the AD-related genes (APP, PS1 and PS2) and their cleavage products in the regulation of neuronal excitability and synaptic transmission. We will also discuss the potential implications of the FAD-related mutations in these genes for neuronal and synaptic physiology. Angela Cantrell will present recent findings demonstrating the involvement of PS1 in the regulation of intracellular calcium homeostasis via its effects on the activity of high-voltage activated calcium currents in cortical neurons. David Cook will follow with a discussion of recent findings addressing the mechanisms by which PS1 regulates glutamate uptake and glutamate transporter activity. Gunnar Gouras will present results from recent imaging studies confirming the accumulation of A beta in multivesicular bodies in pre- and post-synaptic compartments and its association with abnormal synaptic morphology. Robert Malinow

will discuss recent work from his laboratory demonstrating that A beta modulates synaptic strength in the hippocampus and may play a role in normal synaptic physiology via a novel, negative-feedback mechanism.

Panel · Monday, January 26 · 4:30–6:30 PM · Hasty's

The Oligodendrocyte Precursor: Stem Cell, Adult glial Cell or Impediment to Repair?

J. Fawcett, J. Levine, A. Nishiyama, R. Franklin

Oligodendrocyte precursors (OPCs) are a glial cell population found throughout the CNS in large numbers. Various diverse functions have been identified for these cells. They can divide, migrate and make new oligodendrocytes in regions of demyelination, they are participants in synapses, they contact nodes of Ranvier, they can turn into multipotential stem cells and produce new neurons and glia, and they produce axon growth inhibitory molecules. Joel Levine will describe the properties of the NG2 proteoglycan, an inhibitor of axon regeneration expressed on oligodendrocyte precursors and upregulated after injury. Akiko Nishiyama will describe the biology of the OPC population and their response to various types of injury. Robin Franklin will focus on the behaviour of OPCs in response to demyelination. The cells respond to demyelination by dividing, migrating into the lesion and replacing lost myelin. The various factors that control of this process will be described. James Fawcett will talk about OPCs in the context of CNS injury. OPCs proliferate rapidly after CNS damage, and make some of the inhibitory molecules that block axon regeneration. However they have the potential to de-differentiate into mulitpotential progenitors which could promote CNS repair, and ways of promoting this process will be discussed.

Panel · Monday, January 26 · 4:30–6:30 PM · Ptarmigan A

Computational Properties of Cerebellar Neurons

D. Jaeger, B. Finch, W. Regehr, V. Gauck

The cerebellum is a brain structure for which many computational algorithms have been proposed. None of these algorithms have firm experimental support, however. One problem is that functional concepts of the cerebellum are typically based on very simplified models of single neuron function. In this panel we present data indicating that complex integrative properties of cerebellar neurons at molecular and electrical levels are important to understand neural computation in the cerebellum. Beth Finch will discuss how interactions among calcium influx and calcium release pathways determine the spatial and temporal dynamics of dendritic calcium signaling. She will (also) present studies demonstrating that calcium

release from stores regulates both synaptic transmission and dendritic excitability, thereby providing a link between chemical and electrical signaling. Wade Regehr will report about studies in his lab uncoveringsynaptic plasticity controlled by endogenous cannabinoids as retrograde transmitter. This form of plasticity leads to new insights on possible cerebellar learning algorithms. Dieter Jaeger will present data showing how cerebellar cortical interneurons generate precisely timed spike patterns in response to complex conductance waveforms applied witt dynamic clamping, and how Purkinje cells may respond to the ensuing inhibition. Finally, Volker Gauck will describe properties of synaptic integration in the deep cerebellar nuclei. He will present dynamic clamp data suggesting that NMDA receptors play an important role in the synaptic integration of Purkinje cell inhibition. We will invite the audience to discuss how such complex single cell properties help or hinder our functional understanding of the cerebellum.

Panel · Monday, January 26 · 4:30–6:30 PM · Ptarmigan B

Making Placodes Under Water: Using Zebrafish to Understand the Origins and Patterning of Head Placodes.

R. Karlstrom, Z. Varga, M. Westerfield

Sensory and neuroendocrine structures in the head arise from specialized regions at the margins of the developing neural plate called ectodermal placodes. Inductive events within these marginal cells lead to the formation of the ear, nose, lens, and adenohypophysis of the pituitary gland. Recent work is identifying the cell-cell signaling molecules and transcription factor response code that is responsible for placodal induction and patterning. Major questions remain regarding how pre-placodal regions are specified, how cell-cell signaling systems are integrated to divide pre-placodal regions into distinct placode types, as well as how the complex patterning of these structures is regulated. This panel will discuss recent findings from combined genetic and embryological approaches in the zebrafish model system. Zoltan Varga will discuss the origins of lens and pituitary placodes at the anterior margin of the nervous system, and the signals that distinguish these two placodal structures. Rolf Karlstrom will discuss how Hedgehog signaling, mediated by the Gli family of transcription factors, acts to both induce pituitary development and pattern the adenohypophysis. Monte Westerfield will discuss the molecular mechanisms guiding ear placode formation and patterning. The panel will discuss similarities and differences in the formation of different placodes and how this information can be integrated to provide a more comprehensive understanding of the mechanisms that regulate vertebrate placode development.

Panel · Monday, January 26 · 4:30–6:30 PM · Ptarmigan C

Beyond Ataxia: Recasting the Cerebellum by Genetic Disruption

J. Welsh, E. Hess, R. Joho, C. Fletcher

Cerebellar disorders classically have been thought as being of the ataxic variety while other movement disorders such as myoclonus, dystonia, and resting tremor have been considered striatal in origin. Recent work in molecular neuroscience and neurophysiology is quickly blurring this distinction and is expanding the cerebellar contribution to all of the above, including migraine. Recent breakthroughs in molecular neuroscience are building upon the firm foundation of cerebellar anatomy and neurophysiology to bring new insights into the bases of dyskinetic disorders. This panel will bring together 4 investigators who have been working on models of paroxysmal dyskinesia and tremor produced by channelopathy, receptor mutation, and ischemia. The striking common findings from these labs are three: 1) channelopathies specific to the cerebellar circuit produce dyskinetic disorders not traditionally viewed as "cerebellar;" 2) neuron loss in the cerebellum associated with dyskinesia are exquisitely patterned and determined by an interaction of membrane properties and biochemistry; 3) alterations in the ensemble properties of cerebellar electrophysiology due to channelopathy, paradoxically, may produce episodic dyskinesia without changing normal motricity. Ellen Hess will discuss the involvement of kainate receptors in cerebellar Purkinje cells in a mouse model of dystonia. John Welsh will discuss the role of the electrical synapses in the olivocerebellar system for producing ischemic myoclonus and essential tremor. Rolf Joho will discuss the role of voltage-gated Kv3.1/ 3.3 channels in cerebellar excitability, spontaneous myoclonus and tremor. Colin Fletcher will discuss the effect of mutations in cerebellar P/Q calcium channels in neuronal degeneration, episodic dyskinesia, and migraine.

Panel · Monday, January 26 · 8:30–10:00 PM · Bighorn C1

White Matter Function: A Gray Area

T. Swanson, B. Ransom, J. Koscis, S. Krahl

Once higher cortical neurons process information, a function well suited to dendrites and cell bodies, there is an express advantage to sending the information out to the body quickly, on high speed connections. The axon rich white matter, organized in bundles and tracts, form these high-speed intra-, inter-,and extra-hemispheric connections. However, there are many aspects of axon development and structure that are inconsistent with this cable function, suggesting that the axons may play other, more active roles in information processing. In addition, it is odd that epilepsy, a clear gray matter disease, occurs 5 times more frequently among patients with mul-

tiple sclerosis, a clear (predominately) white matter disease, than amongst the normal population. Axon-initiated action potentials; seizures initiated from MS placques, ion channels hidden under myelin, branch point failure, and neurotransmitter receptors on axons, all support a more dynamic role for white matter. This panel will focus on novel roles of axons in development, injury, and disease. Swanson will introduce the speakers and give some brief background and an overview of the session. Ransom will introduce known pathologies of white matter and discuss mechanisms of axon injury. As the axon responses to injury can be varied, and result in separate clinical problems, he will also discuss novel insights into axon responses to injury. Koscis will discuss the electrophysiology of axon excitability by neurotransmitter receptors and give more insight into the axon response to injury focusing on mechanisms and consequences of re-myelination. Swanson will demonstrate immunocytochemical evidence for adenosine and GABA receptors on axons, and discuss the possible ramifications of axonal adenosine receptors. Krahl will show electrophysiological evidence that adenosine receptors modulate axon impulse transmission, high-lighting the difference between un-myelinated and myelinated axons. The aim of these talks is to generate controversy and discussion about non-traditional roles for axons.

Workshop · Monday, January 26 · 8:30–10:00 PM · Ptarmigan C

The Up-Regulation of Neuronal Nicotinic Receptors: Mechanisms and Implications

K. Kellar, R. Lukas, J. Lindstrom, B. Green, M. Marks

Nicotine administration to rodents for a about week or longer increases the number of neuronal nicotinic receptor binding sites in brain. A similar increase is found in autopsied brains from smokers. This up-regulation of nicotinic binding sites in brain has been an interesting and potentially important theme running through neuronal nicotinic receptor biology for 20 years. The cellular/molecular mechanisms underlying these increases and their functional consequences are still a matter of debate, but understanding these issues has important implications related to nicotine addiction and possibly to diseases in which nicotinic receptors have been targeted for therapy, including Alzheimer's disease, Parkinson's disease, other neurodegenerative diseases and Tourette's syndrome. This session will present new data overlaid on background information related to the mechanisms of the regulation of nicotinic receptor binding sites and function in brain. There is good agreement that in vivo nicotine administration can markedly increase (50-100%)nicotinic receptors in some brain structures, such as the cerebral cortex, but not in others; furthermore, not all of the subtypes of nicotinic receptors are affected. There is also agreement that the increase in receptor binding sites is not accompanied by an increase in

mRNA for the component subunits of the receptors, and that in cell models it is not blocked by protein synthesis inhibitors, suggesting that the mechanisms underlying up-regulation do not depend on synthesis of new protein. The goals of this session will be to compare the current hypotheses that could explain the up-regulation of the binding sites and the data that do or do not support these hypotheses.

Workshop · Monday, January 26 · 8:30–10:00 PM · Bighorn C2

Nucleus Accumbens Glutamate and Addiction

M. Lynch, C. Pierce, P. Di Ciano, D. Self, P. Kalivas

Repeated exposure to cocaine results in alterations to glutamate transmission in the nucleus accumbens (NAcc). While the precise role of accumbal glutamate transmission in the process of drug addiction remains to be elucidated, preclinical models of "reinstatement" have proven useful for studying the putative mechanisms underlying relapse to addiction. While some studies argue that an increase in accumbal glutamate promotes cocaine craving, other findings characterize a change in accumbal glutamate as compensatory, thereby decreasing the likelihood of reinstatement. Arguments for these opposing positions will be presented in this workshop. Patricia Di Ciano (Cambridge University) will present results indicating that the direct infusion of AMPA/kainate receptor antagonists into the NAcc core attenuates discriminative control over responding by reward-paired conditioned stimuli, while NMDA receptor antagonists are without effect. Chris Pierce (Boston University School of Medicine) will outline data demonstrating that stimulation of accumbal AMPA receptors promotes cocaine seeking whereas activation of NMDA receptors in the NAcc shell promotes reinstatement. David Self (University of Texas Southwest Medical Center) will present findings showing that viral-mediated overexpression of AMPA receptors in NAcc neurons facilitates extinction of cocaine-seeking behavior. Peter Kalivas (Medical University of South Carolina) will describe experiments indicating that activation of the glutamatergic projection from the prefrontal cortex to the core of the nucleus accumbens, which is influenced by proteins such as xCT and AGS3, promotes the reinstatement of drug-seeking behavior. Collectively, these findings suggest the intriguing possibility of a role for accumbal glutamate in the relapse of drug-seeking behavior.

Workshop · Monday, January 26 · 8:30–10:00 PM · Ptarmigan A

Organization of the Vertebrate Circadian System

C. Green, J. Takahashi, G. Block, F. Davis

Remarkable progress has been made in recent years in understanding the fundamental molecular mechanisms underlying circadian rhythms. Along with notable strides in identifying the genes and proteins that compose the core oscillator mechanism, there is a growing awareness that the circadian system is multi-oscillator in composition. There is now good evidence for molecular circadian oscillations in both neural and non-neural tissues. The proposed panel discussion will explore both the issue of rhythm generation, i.e., how molecular and cellular processes interact to generate circadian periodicities, and the issue of rhythm integration, how the oscillators that comprise the mammalian timing system interact to generate a coherent unified output. Two of the proposed participants (Dr. Carla Green, Univ. Virginia; Dr. Joseph Takahashi, Northwestern Univ.) will discuss the most current information about mammalian and amphibian clock genes and how they interact to generate self-sustained oscillations. Dr. Gene Block (Univ. Virginia) will explore the integrative mechanisms by which individual oscillators within the mammalian suprachiasmatic nucleus interact to produce coherent output. Dr. Fred Davis (Northeastern Univ.) will discuss progress in the identification of the signals used by the suprachiasmatic nucleus to coordinate complex rhythmic behavior. Collectively the panel should cover two central questions about circadian regulaion of physiology and behavior and provide the audience with an up-to-date view of this rapidly advancing field.

Workshop · Monday, January 26 · 8:30–10:00 PM · Ptarmigan B

Cerebellar Function and Plasticity: A Town Hall Meeting

J. G. McElligott, V. Bracha, J. R. Bloedel, T. J. Ebner, J. L . Raymond

The cerebellum has been investigated as an area involved with sensorimotor and neuroplastic phenomena. Many labs have focused on separate paradigms and mechanisms for elucidating cerebellar function. The intent of the workshop is to explore common elements associated with cerebellar function and to address some of the more controversial issues. The investigators who work in this area will explore the different facets and seek to determine if a common unified view of cerebellar neuronal circuitry function is possible. In the true spirit and original intention of a workshop, this presentation will be organized as a town meeting or forum. Rather than having the participants bring answers or their latest results from the lab, each will come with a series of questions to be addressed by the group. For

example, possible questions to be discussed could be: "As a learning paradigm, how is conditioned eye blink related to vestibulo-ocular reflex adaptation? Do these paradigms share common cerebellar neuroplastic mechanisms? Is there a single mechanism for plasticity in the cerebellum or are there several mechanisms operating within and/or external to this structure? What actually is the function of the unique climbing fiber-Purkinje cell synapse in this regard? Is it really valid to relate cerebellar in vitro slice/culture observations to the in vivo physiology/behavior studies?" Prior to the day of the session, we invite members of our potential audience to submit their own questions for consideration by this workshop. These may be sent in advance to (<James.McElligott@temple.edu>).

Workshop · Monday, January 26 · 8:30–10:00 PM · Hasty's

Birdsong–Genes, Cells, Circuits, Behavior and Evolution

H. Karten, J. Dugas-Ford, C. Mello, S. White, D. Perkel

Many bird species learn their vocalizations. This process bears a striking resemblance to human speech learning. The study of the neurobiology of vocal learning promises to reveal mechanisms underlying this process. Understanding the evolution of vocal learning may, in turn, help clarify its mechanisms. One important approach is comparative—what information can we take from other species and apply to birds to help solve this problem? Can information about birds generalize to other vertebrate taxa? Recent work suggests startling homologies, at a number of levels of organization, that support this idea of a two-way street. Jennifer Dugas-Ford will discuss expression patterns in birds of molecular markers for specific mammalian cortical layers. Claudio Mello will discuss song behavior and brain similarities in songbirds, hummingbirds and parrots, three bird taxa that evolved vocal learning independently. David Perkel will discuss evolution of vocal learning in songbirds by way of comparing basal ganglia physiology and circuitry in songbirds and chickens. Stephanie White will present expression data in songbirds and humans for members of the FoxP subfamily of forkhead transcription factors, with particular reference to FoxP2, the recently discovered monogenetic locus for a human language disorder.

Panel · Tuesday, January 27 · 7:30–9:30 AM · Bighorn C1

Molecular and Imaging Techniques for Monitoring the Trafficking of Synaptic Proteins in Native Neuronal Preparations

R. Morrisett, D. Mayfield, J. Chandler

Major advances in our ability to label synaptic proteins and structures in intact native preparations have been coupled with the development of sophisticated imaging techniques. These advances allow questions about the

sub-cellular trafficking of proteins crucial to various aspects of neural function, plasticity and drug adaptation. The development of these approaches has three major roots: protein expression in native neural systems, fluorescence detection and analysis of dendritic structure and function in real time. In this panel presentation, the development and application of these techniques for general neurobiological analysis of synaptic proteins will be presented. The workshop will consist of three technical presentations, followed by an open, panel-type Q&A discussion. Dr. Mayfield's presentation is entitled "Viral Delivery of GFP Labeled Dopamine Transporter into Neuronal Cells". He will focus upon the dopamine transporter as a model system and discuss advances in molecular and vector technology that have led to viral systems that efficiently deliver genes of interest by ex vivo and in vivo strategies. Dr. Morrisett will present a discussion entitled "Two Photon Imaging of Receptor Trafficking in Intact Neuronal Preparations". Dr. Morrisett will describe the basic concepts and advantages underlying two-photon imaging techniques in organotypic explant preparations. Dr. Morrisett will concentrate on the technical aspects of two-photon microscopy of virally-expressed G-protein coupled receptors (dopamine D1) labeled with the fluorophore, enhanced GFP. Finally, Dr. Chandler will discuss "Imaging of Dendritic Spine Dynamics and Signaling Events". He will review techniques for the detection GFP variants to examine spine dynamics and localization. In addition, techniques for examining compartmentalized signaling events through intramolecular fluorescence resonance energy transfer (FRET) between GFP variants will be discussed.

Panel · Tuesday, January 27 · 7:30–9:30 AM · Bighorn C2

Neuroscience Meets Law: Causation, Determinism and Criminal Responsibility

R. Beresford, P. Churchland, T. Hyde, E. Ross

Central to imposing criminal liability is a judicial determination that a defendant had a criminal state of mind (mens rea). Under current law, mens rea encompasses knowing or volitional antisocial behaviors, as well as reckless disregard of consequences. Law presumes that individuals exercise free will when they commit antisocial acts. But law also permits them to escape responsibility on proof they did not appreciate that their actions were wrong or, in some jurisdictions, that they lacked volitional capacity to control conduct. The panel will explore how neuroscience can assist law to determine whether criminal defendants had the requisite mens rea. Beresford will discuss legal rules regulating use of scientific testimony about mens rea, especially testimony that purports to explain cognitive capacity to make moral judgments or volitional capacity to desist from wrongful acts. Churchland will consider the concept of causation from the perspective of neuroscience and how this perspective can be applied in adjudications of criminal responsibility. Ross will offer a behavioral neurologist's view of free will and

the capacity to distinguish moral from immoral acts, emphasizing strategies individuals deploy in forming intentions to act or refrain from acting. Hyde will review data relating focal brain dysfunction to the capacity to weigh or control behavior, and assess the potential use of such data in adjudicating mens rea. The goals are to portray actual and potential roles for neuroscience in the criminal justice system and to encourage dialogue about problems that may arise when technical and complex data are presented to legal decision-makers.

Panel · Tuesday, January 27 · 7:30–9:30 AM · Hasty's

Past, Present, and Future: Interactions Between Prefrontal Cortex and Hippocampus in Higher Cognitive Function

J. Cohen, P. O'Donnell, A. Wagner, K. Norman, R. O'Reilly

Both the prefrontal cortex (PFC) and hippocampus (HCMP) figure centrally in higher cognitive function, the one playing a critical role in executive function and cognitive control (e.g. planning future actions), and the other in longterm memory. While each has been the subject of intensive study, remarkably little work has addressed the interaction between these structures. Such interactions are likely to be critical to the functioning of each. For example, planning (PFC) relies on the retrieval of task-appropriate goals from longterm memory (HCMP). Conversely, both the encoding and retrieval of information in longterm memory (HCMP) requires the maintenance of task-appropriate cues (PFC). This Panel will explore recent work addressing such interactions, drawing upon a variety of neuroscientific methods. Wagner will present neuroimaging findings regarding PFC-HCMP interactions in human subjects performing memory tasks. O'Donnel will present neurophysiological findings from in vivo and slice recordings that provide insights into the neural circuits and neurotransmitter mechanisms that mediate interactions between PFC and HCMP. Norman will present computational modeling work, and associated behavioral findings, that address PFC-HCMP interactions in free recall. O'Reilly will present computational modeling work addressing the interaction between these structures in tasks that demand cognitive control. At the conclusion of the session, the audience should have a working knowledge both of the latest theories regarding the functions of PFC and HCMP, and how these systems interact to give rise to higher cognitive functions such as planning and free recall.

Panel · Tuesday, January 27 · 7:30–9:30 AM · Ptarmigan A

Mechanisms of Nociception: From Mice to Medicine

S. Tate, M. Costigan, J. Mogil, M. Salter

Virtually all analgesics discovered to date have been the result of empirical observation and serendipity. As we look to develop novel and improved analgesics it is important that we understand the basic mechanisms underlying nociceptive processing. Now for the first time research into the molecular mechanisms of nociceptiopn is allowing us to custom design mechanism based pain medicines. The first of these drugs, selective cyclooxygenase 2 inhibitors have met with high demand in the market place, testifying to the size of the unmet need for chronic pain treatment present within the population. The panel will provide insights into technological advances in molecular biology and genetic manipulation that allow the identification of key molecular players in the pain pathway. Ways of manipulating these molecules to provide a therapeutic outcome will also be discussed. Mike Costigan will outline the use of oligoarrays to profile gene expression within primary sensory neurons and the changes that occur within these cells as a result of neuropathic damage and chronic inflammation. Mike Salter will discuss the molecular mechanisms that generate chronic pain within the spinal cord. Jeff Mogil will discuss the genetic basis of pain and pain inhibition, with a focus on linkage mapping approaches. Simon Tate will discuss the recent advances in the ability to exploit ion channels as targets for new analgesics, with a focus on voltage-gated sodium channels.

Panel · Tuesday, January 27 · 7:30–9:30 AM · Ptarmigan B

To Eat or Not to Eat, or What to Eat for Brainsake

F. Gomez-Pinilla, M. Mattson, G. Cole, P. Sullivan, C. Greenwood

The influences of dietary factors on mental capacity have been recognized for as long as the history of mankind. Yet it is only recently that their scientific basis have started to be examined. Specific dietary components critical for development and life span of the nervous system have been identified. For example, saturated fats can have a negative influence on cognitive performance in rodents and humans, while "good fats" such as Omega 3 fatty acids can have opposite effects. The number of calories consumed over time and the time interval between feedings is another fundamental aspect that is emerging as a major factor in brain health. Mark Mattson will discuss mechanisms by which dietary restriction increases the resistance of neurons to insults associated to aging and neurodegenerative diseases. Pat Sullivan will review studies showing the involvement of mitochodrial func-

tion mediating the effects of dietary fats and dietary restriction on the outcome of brain injury. Greg Cole will discuss how the relative composition of Omega 3 and Omega 6 fatty acids in the diet can reduce neurodeneration related to Alzheimer?s disease. Carol Greenwood will review studies showing the effects of dietary fats on cognitive performance, and how this relate to the integral body physiology in rodents and humans. Fernando Gomez-Pinilla will discuss the involvement of neurotrophins on the effects of dietary factors on synaptic plasticity, and the capacity of exercise to reverse the effects of poor diets. Discussion will focus on the crucial role of lifestyle to influence the capacity of the brain for plasticity

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Panel · Tuesday, January 27 · 7:30–9:30 AM · Ptarmigan C

Ins and Outs of Salt and Water Homeostasis: New Insights into CNS Mechanisms

C. Sladek, F. Flynn, S. Bealer, A. Kim Johnson

Maintenance of fluid and electrolyte homeostasis is critical for maintenance of cardiovascular and excitable cell function. Sodium and water homeostasis is achieved by complex regulation of intake (e.g. sodium appetite and thirst) and output (e.g. renal actions of vasopressin and aldosterone). This panel will focus on new insights into the mechanisms regulating vasopressin secretion and salt appetite, the impact of salt intake on baroreflex function, and mechanisms directing the balance between salt appetite and thirst. Specifically, Francis W. Flynn will discuss the control of salt appetite and vasopressin secretion by tachykinins. His presentation will address characterization of the tachykinin receptors and ligand(s) involved, identification of the source of the tachykinin ligand, and the physiological signals that activate tachykinin receptors involved in salt appetite and vasopression secretion. Celia D. Sladek will discuss the role of estrogen receptor beta in the regulation of vasopressin secretion as well as the impact of saline drinking, hyponatremia, and AV3V lesions on estrogen receptor beta expression in vasopression neurons. Steve Bealer will describe the impact of dietary sodium on vasopressin-mediated baroreflex responses during systemic hyperosmolality. Finally, A. Kim Johnson will describe the role of the lateral parabrachial nucleus as a switch in determining salt or water preference under conditions of normal and altered sodium intake. The significance of these mechanisms to normal and pathophysiological challenges such as dehydration, hemorrhage, hyponatremia, and hypertension will be discussed.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Bighorn C1

Gene Therapy in the CNS: Novel Vectors for Imaging and Regulating Gene Expression

M. C. Bohn, B. L. Davidson, K. Bankiewicz, X. Breakefield

Two cases of leukemia occurred recently in children enrolled in a gene therapy trial for X-linked severe immunodeficiency disease (X-SCID). These adverse events resulted in many clinical trials being put on hold and further exposed gene therapy to public criticism. However, the adverse events that occurred in the X-SCID trial have little relevance to most gene therapy approaches being developed for CNS and the potential of gene therapy for diseases of the CNS remains tremendous. Bohn will introduce this workshop by discussing why the adverse events in the X-SCID trial raise different concerns from those of gene therapy approaches being developed for the CNS. The workshop will then focus on novel developments in viral vector design and means for imaging transgene expression in CNS. Davidson will present methods for rapidly generating and testing various small inhibitory RNAs (siRNA) for reduction of expression from target sequences, followed by examples of their application to dominant neurodegenerative diseases using viral based delivery methods. Bankiewicz will discuss the development of a gene therapy approach for Parkinson's disease using amino-acid decarboxylase (AADC) and PET imaging of transgene expression. Bohn will continue with vector development for Parkinson's disease in which transgene expression is under control of tetracycline-regulated promoters. Breakefield will present data showing that vector delivery and tumor cell death can be imaged in the brain using multiple luciferases and near infra-red fluorescence. Although there have been gene therapy workshops at WCBR previously, these have been educational about gene therapy approaches per se, or have focused on therapeutic strategies for specific diseases. The proposed session is unique in that it will focus on new elements that can be incorporated into gene therapy vectors for controlling and imaging gene expression and effects. Thus, the workshop promises to be interesting to neuroscientists with both clinical and basic research interests.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Bighorn C2

The Other Catecholamine: Norepinephrine and Working Memory

A. Lavin, G. Aston-Jones, B. Waterhouse, B. Ramos

It is known that the prefrontal cortex (PFC) is critically involved in cognitive processes underlying working memory. In fact, it has been proposed that one of the primary functions of the PFC is to guide behaviors based on working memory. In addition, it has been shown that neurons in the PFC actively retain an internal representation of previous information through

sustained firing modes. Numerous studies indicate norepinephrine (NE) is playing a fundamental role in modulating working memory processes. Experiments have demonstrated that depletion of NE from the PFC produces spatial working memory deficits, and these deficits are improved by the administration of NE agonists. Moreover, electrical stimulation of the locus coeruleus modulates cortical bistability and sustained activity. This panel will examine the evidence for NE modulation of the cognitive processes and cellular underpinnings of working memory. Brian Ramos will discuss the role of the alpha-2 receptor and second messenger mechanisms involved in age-related changes in cognition in the PFC of both rats and monkeys. Barry Waterhouse will discuss the role of NE in sensory motor cortex, Gary Aston-Jones will present new data from recordings of LC impulse activity in monkeys showing that phasic LC activation is strongly associated with the animal's decision to behaviorally respond to a stimulus. Finally, Antonieta Lavin will present data on NE modulation of Up states and cortical excitability.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Hasty's

Sex, Aggression, and Learning in Small Brains: Lessons from Invertebrate Systems

T. Swanson, R. Huber, R. Gillette, T. Fischer, M. Van Staaden

Aggressive, addictive, and predatory behaviors create great social dysfunction and are co-morbid factors in many psychiatric diseases. Methods for studying these behaviors in mammals are limited, and often give little insight into neurochemical and molecular mechanisms underlying both normal and maladaptive behaviors. For example, serotonergic drugs are widely used in many countries for mood alteration (serotonin selective re-uptake inhibitors or SSRI's), headache, and adjunctive therapy in several other neuroloigcal and psychiatric disorders. The "real" mechanisms of action as well as "bystander effects" of these prolifically consumed substances are obscure. More simple neuronal systems should not be overlooked as complicated and expensive high technology techniques appear. This panel will highlight innovative invertebrate model systems that continue to produce profound insights into very clinically relevant questions. Swanson will give a brief introduction, moderate the talks, and stimulate audience participation. Huber will describe a model for studying aggression in crayfish and discuss novel insights into how SSRI's effect aggression and addiction. Moira van Staaden will discuss mechanisms of hearing perception in grasshoppers and crickets and the role of hearing in sexual and other social behaviors. Fischer will describe experiments examining activity-dependent forms of synaptic plasticity in an oligosynaptic aplysia pathway, and how a few synapses can modify whole animal behavior. Rhanor Gillette will talk about the role of NO and 5HT on motivational states and feeding behavior in a

predatory snail. We will compare the "bang for the buck" of these types of experiments versus human and whole animal studies.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Ptarmigan A

Sodium Channels: From Normal Function to Disease

T. Scheuer, D. Carr, P. Ruben, R. Wallace

Current through sodium channels underlies action potential depolarization in neurons as well as contributing current controlling synaptic integration, dendritic activity and repetitive firing. This panel will consider how sodium channels contribute to modulation of these properties and how improper sodium channel function results in disease. Sodium channels in neurons are modulated by activation of protein kinases subsequent to activation of G protein coupled receptors. David Carr will provide evidence that this modulation occurs by facilitation of a process with the properties of slow inactivation. Regulation of Na current via this slow process, in turn, tightly controls neuronal activity, providing a potent mode of neuronal modulation. Mutations in sodium channels are also linked to an ever-increasing number of disease syndromes. Peter Ruben will discuss mutations leading to paramyotonia congenita in skeletal muscle. The resultant changes in channel gating provide important clues to the role of the affected regions in normal sodium channel function. In the brain, mutations in the alpha1, alpha2 and beta1 subunits cause a variety of forms of epilepsy. Robyn Wallace will discuss the frequency of particular sodium channel mutations and the correlation between particular sodium channel genotypes, their effects at the cellular level and the associated epilepsy phenotype. Some of the mutations causing severe epilepsy result in the de facto deletion of sodium channel subunits. Todd Scheuer will discuss the cellular and organismal phenotypes of mice lacking sodium channel subunits that are potential models for these forms of epilepsy.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Ptarmigan B

Regulation of Neural Precursor Cell Proliferation and Differentiation During Development and Disease

M. Mayer-Proschel, S. Davies, S. Haber, M. Mehler

One of the important challenges in the development of the CNS is to obtain a complete identification of all the sequential steps required to proceed from a totipotent embryonic stem cell to a defined differentiated cell type. To understand such a complex program it is critical to identify the cellular components that are involved during this process. Once the cellular targets are identified, their progressive development is regulated not only in a region

specific way but also along a precise time axis. This regulation involves signaling molecules and transcriptional modulators that act in concert to determine the fate of specific target cells. This panel will provide insight into (i) the mechanisms by which the generation and differentiation of CNS precursor cell populations are regulated (ii) the pathological consequences of factors that disturb normal precursor cell function and (iii) possible therapeutic approaches that involve precursor cells as tools for repair. Margot Mayer-Proschel will begin by discussing modulation of the proliferation and differentiation of CNS precursor cell populations by nutritional components and their role in disease manifestation. Stephen Davies will then address how transplanted precursor cell population and their progeny affect glial scar tissue in spinal cord injury. Suzanne Haber will show the extensive cell proliferation in the primate brain as a result of MPTP treatment. This will be compared that seen in both young and normal adult animals. Mark Mehler will address the role of alterations in neurodevelopment signaling pathways in the pathogenesis of neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's Diseases.

Panel · Tuesday, January 27 · 4:30–6:30 PM · Ptarmigan C

Pick Complex, FTD, and the Tauopathies

A. Kertesz, D. Dickson, M. Hutton, D. Geschwind

Pick Complex is an integrative term for a number of conditions that have been considered to have a common biology. Originally described as Pick's disease and lately renamed as frontotemporal dementia (FTD). The autosomal dominant familial variety was discovered to have linkage to chromosome 17. Half of those families have various tau mutations. However, tau negative pathology is common and possible heterogeneity in the genetics is postulated. Kertesz will describe the clinical nosology and highlight the controversy whether corticobasal degeneration and progressive supranuclear palsy should be considered part of the entity. The relatedness of disinhibition dementia and primary progressive aphasia (PPA) is important in the recognition of this relatively frequent presenile degenerative disease. Dickson will discuss the pathological variations of FTD/Pick Complex in both sporadic and genetic varieties (FTDP-17) and will present his experiments with the mouse model. Hutton will describe the exonic and intronic mutations that give rise to predominantly four repeat and three repeat tau, and outline the evidence of their relationship to clinical phenotypes. He will also discuss current genetic research in the field concerning other chromosomal sites and polymorphisms. Geschwind will discuss using a drosophila model of tau induced neurodegeneration to identify genetic modifiers that could serve as potential therapeutic targets for FTD and Alzheimer's disease. This work includes the demonstration of neurofibrillary tangle formation of the fly. Taoists will find this panel particularly interesting, but Baptists, Synners and Apostates are welcome too.

Town Meeting · 7:00 PM · Summit Middle School, Frisco, CO

Exercise and the Brain

On Tuesday, January 27, a town meeting will be held for the Copper-Frisco-Breckenridge-Dillon area community at which Michael Zigmond will speak on exercise and the brain. His presentation will focus on the evidence that exercise can help reduce the vulnerability of the brain to such conditions as Alzheimer's disease, stroke, and Parkinson's disease. Zigmond is the director of the newly formed Morris K. Udall Research Center for Parkinson's disease at the University of Pittsburgh. The center focuses on exercise as a treatment for Parkinsonson's disease, and is doing clinical research as well as research with animal and cellular models of the disease. Zigmond will be joined by a panel of individuals with epxerience in exercise, physical therapy, and neurology, who will answer questions from the audience. The town meeting is open to anyone interested in the benefits of exercise no matter what their level of exertise in the brain sciences. It will be followed by a reception during which Zigmond and members of the panel will be available for additional discussion.

Panel · Tuesday, January 27 · 8:30–10:00 PM · Bighorn C1

Neuroscience Perspectives on LTD: Potential Implications for Medication-resistant Symptoms of Schizophrenia

I. Cavus and J. Krystal, T. Teyler, J. Daskalakis, R. Hoffman

Long-term depression (LTD), a form of synaptic plasticity characterized by enduring decrease in the synaptic activity in response to low-frequency stimulation (LFS), has been now demonstrated in numerous animal models. LFS of already potentiated pathways could also induce a long-lasting depression, i.e. a depotentiation. It has been proposed that LTD and depotentiation may underlie the changes in synaptic transmission associated with learning. However, LTD and depotentiation may also be utilized to depress/inhibit the inappropriately potentiated pathways in the brain. Recent evidence from evoked response potential (ERP) and repetitive transcranial stimulation (rTMS) studies indicates that schizophrenia is a disorder associated with deficits in the cortical inhibitory mechanisms. Further, rTMS application at LFS to the auditory cortex in schizophrenics could decrease their auditory hallucinations. In this panel, we will extend the observations of LTD in animals to humans, describing human LFS studies in health and disease, and its potential utilization for treatment. First, Tim Teyler will discuss the sensory stimulus ˆ induced LTP and LTD ˆ like phenomena of the visual cortex ERPs in healthy humans. Second, Idil Cavus will present data on the spike and intracranial EEG activity changes with

intrahippocampal and intracortical LFS in neurosurgical epileptic patients. Third, Jeff Daskalakis will present data relating to the possible therapeutic mechanisms of action of rTMS on the cortical inhibition in schizophrenic patients. Fourth, Ralph Hoffman will discuss clinical trial data using 1 Hz rTMS for treatment of the auditory hallucinations in schizophrenia.

Panel · Tuesday, January 27 · 8:30–10:00 PM · Bighorn C2

The Role of DBH and Norepinephrine in Addictive Processes

V. Olson, R. Malison, D. Weinshenker, C. Zabetian

While the importance of dopamine in addiction is well known, the role of norepinephrine has largely been overlooked. However, a growing body of evidence suggests that norepinephrine plays a significant role in withdrawal, sensitization, and reward. For example, noradrenergic neurons become hyperactive during opiate withdrawal, though it is unclear which noradrenergic nuclei, and which brain regions innervated by these nuclei, contribute to withdrawal behaviors. Preliminary findings suggest that norepinephrine modulates opiate reward and locomotion, as well as behavioral sensitization to psychomotor stimulants in rodent models. Several components of the noradrenergic signaling pathway are potential targets for treatment of addictive disorders, including dopamine beta hydroxylase (DBH), the enzyme responsible for conversion of dopamine to norepinephrine. Recently, putative functional polymorphisms have been identified within the human DBH gene that might influence behavioral responses to drugs of abuse. This panel will discuss new findings that illustrate how norepinephrine and DBH might contribute to addictive processes. Valerie Olson will discuss the functional neuroanatomy of norepinephrine in opiate withdrawal, locomotion, and reward in animal models of addiction. David Weinshenker will present evidence for the role of norepinephrine in behavioral sensitization. Cyrus Zabetian will review current knowledge of functional variation in the DBH gene and how this impacts noradrenergic transmission in humans. Robert Malison will present preliminary data that suggest a common functional polymorphism in the DBH gene might modify responses to acute psychostimulant administration, and discuss the noradrenergic system as a therapeutic target for treatment of drug addiction.

Workshop · Tuesday, January 27 · 8:30–10:00 PM · Hasty's

Necrosis: The Forgotten Giant

C. Wasterlain, D. Fujikawa, A. Kondratyev, K. Thompson

Necrosis has received little attention, but it is a mode of neuronal death far more common than apoptosis in the adult brain. Recent evidence suggests

that some forms of necrosis, far from being the haphazard bursting of a cell overwhelmed by ionic fluxes, can be an organized form of death, which requires the activation of a highly organized cell death program. Fujikawa will show that necrosis is far more common than apoptosis as a result of brain disease in the adult, and will suggest that caspase-independent programmed mechanisms may be involved. Wasterlain will show that hypoxic neuronal necrosis requires the protein synthesis-independent release of cytochrome c and caspase 3 and 9 activation, and will discuss potential implications for the treatment of necrotic neuronal death. Valina Dawson will discuss AIF-mediated neuronal death, and will take the position that the necrotic morphology is not important, and we should focus on mechanisms. Kondratyev will discuss the mechanisms by which necrosis can "override" apoptosis in the aftermath of seizure-induced neuronal death. An open discussion will consider these mechanisms in the overall picture of neuronal death, and of its most common form—necrosis.

Workshop · Tuesday, January 27 · 8:30–10:00 PM · Ptarmigan A

Be the "Best" That You Can Be: Examining Models of Parkinson's Disease

T. Hastings, J. T. Greenamyre, S. Przedborski, T. Dawson

One of the biggest challenges in the study of all neurodegenerative diseases is finding the "best" models to mimic the pathological conditions of the disease. Parkinson disease is characterized by the loss of dopamine neurons in the nigrostriatal pathway and the presence of proteinaceous inclusions known as Lewy bodies. The mechanisms associated with the degenerative process are unknown, although contributing factors such as oxidative stress, dopamine, mitochondrial dysfunction, proteosome dysfunction, environmental toxins, and genetics have been proposed to play a role. To examine the contribution of these factors to the vulnerability of dopaminergic neurons, investigators have utilized a variety of different models. Over the years, we have firmly established that we can damage or destroy dopaminergic neurons in both cellular and animal models. The question remains however as to how relevant these models are to the disease process itself? In this workshop, our panel of investigators, Tim Greenamyre, Serge Przedborski, and Ted Dawson will discuss/debate the pros and cons of utilizing various toxin-induced and transgenic animals models. We will also evaluate the utility of cellular models such as dopaminergic cell lines and primary mesencephalic cultures. The goal is to define the "best" model for mimicking cell death in Parkinson disease and identifying therapeutic targets. Terri Hastings will serve as the master of ceremonies and "devil's advocate" to promote lively debate amongst the participants and the audience.

Workshop · Tuesday, January 27 · 8:30–10:00 PM · Ptarmigan B

Novel Forms of Communication by Astrocytes

B. MacVicar, B. Ransom, M. Nedergaard, H. Sontheimer, T. Chan-Ling

Astrocytes are poised between the vasculature and neurons yet their functions in the regulation of either are not fully understood. This workshop will discuss recent evidence for novel forms of communication between astrocytes and both neurons and the vasculature. It is recognized that astrocytes are responsible for the release of numerous neuroactive agents. We will discuss the novel mechanisms for the release of neurotransmitters such as ATP and glutamate. For example, the opening of gap junctions to the extracellular space (hemichannels) has been found to be responsible for glutamate release from astrocytes (Ransom). The response of neurons to glutamate can also be regulated by the glutamate uptake in surrounding glia (Sontheimer). Chan-Ling will discuss the development of the cellular relationships between astrocytes, pericytes and the vasculature. The close and distinct anatomical relationship suggests functional interactions. Nedergaard will present evidence for signaling at the gliovascular interface. The work presented helps validate the emerging concept that 'information molecules' mediate wide spread functional interactions between glia and the brain's other cells.

Workshop · Tuesday, January 27 · 8:30–10:00 PM · Ptarmigan C

How Cells Navigate from the Ventricular Zone to the Cortical Plate

S. Juliano, M. Frotscher, S. Noctor, J. LoTurco

Birth and migration of cells during corticogenesis is a complex process requiring numerous factors that include proper signaling, the proper substrate and scaffold, and orchestrated gene expression. Interruption of any of these processes results in developmental disorders ranging from severe cortical dysplasias associated with mental retardation and seizures to milder disorders such as dyslexia. Recent work has not only demonstrated novel and distinct modes of migration, but also discovered that cortical neurons are generated from the radial glial scaffold and arise from the subcortical ganglionic eminence. The participants of this workshop will comment on novel aspects of neuronal migration, including differing views on the signaling properties of reelin, the mechanisms of neuronal locomotion, and genes that influence migration pattern. M. Frotscher (Freiburg) will provide evidence that the protein reelin signals information to the radial glial scaffold in mouse hippocampus, which results in improved migration of granule

cells. In contrast, S. Juliano (Bethesda) will show that reelin is not required to realign disrupted radial glia and improve neuronal migration in the neocortex of newborn ferrets. S. Noctor (New York) will reveal that neurons generated from radial glia demonstrate distinct phases and modes of migration involving specific movement patterns that appear to correlate with the cell cycle of the mother radial glial cell. J. LoTurco (Storrs) will specify that the Doublecortin gene (DCX) is essential for radial migration. Both cellular locomotion and nuclear translocation require DCX, and disruption of this gene in rodents results in cortical dysplasias similar to those in humans.

Minicourse · Wednesday, January 28 · 7:30–9:30 AM · Bighorn C1

Mass Spectrometry, Proteomics, and Peptidomics in Neuroscience Research

L. Fricker, D. Desiderio, J. Sweedler

Mass spectrometry is a powerful tool that can be used to identify, quantify and determine the chemical state of proteins and peptides. Many universities have mass spectrometry centers but often neuroscientists don't know how to use them effectively for their own projects, especially many of the newer capabilities offered by such facilities. This session provides a general introduction to mass spectrometry and proteomics/ peptidomics techniques, with examples of the types of questions that can be readily addressed using both basic and advanced techniques. The overall goal is to educate the audience so that they can incorporate these techniques into their own research, as well as highlight the current state-of-the-art in neuroproteomics/peptidomics. This session includes presentations from three neuroscientists who have been using mass spectrometry for a number of years. Dominic Desiderio will introduce the basic types of mass spectrometers and the general concept of proteomics/peptidomics. A number of key terms will also be defined (monoisotopic versus average molecular mass, m/z and others). Next, Lloyd Fricker will describe the general approaches for quantitation of proteins and peptides using differential isotopic labeling. Then, Jonathan Sweedler will present the technique of neuroimaging and single cell mass spectrometry. All three lecturers will present specific examples of mass spectrometry techniques answering different types of questions in neuroscience-related research. Ample time will be allowed for questions from the audience.

Panel · Wednesday, January 28 · 7:30–9:30 AM · Bighorn C2

The Enchanted Loom of Spatial Perception in the Dorsal Stream of Monkey

R. Siegel, H. Karten, J. Bisley, B. Krekelberg

The dorsal stream has often been considered a monolithic entity of visual processing with information about "where" an object is dominating. This concept arose from the simple dichotomy of the what and where pathways, initially proposed on human and monkey lesion studies. Detailed examination of the where pathway in behaving primates has shown that, rather than there being a straightforward progression of visual processing towards some Platonic ideal of location, there are multiple stops, digressions and turns yielding, as one always finds, a more complex and ultimately more flexible representation of visual space around us. Bart Krekelberg will show that the first stop in dorsal stream, area MT, is not simply a classical motion analyzer. So-called Glass patterns, which contain no coherent motion information but imply motion by virtue of their global form, are unexpectedly represented in area MT. This early neural representation is closely related to both human and non-human primates' perception. By way of a counter-example, Harvey Karten shows how the processing of motion is not limited to the dorsal stream, but distributed elsewhere. Indeed novel inputs to MT can be seen from out of the dogmatically expected anatomical sources. James Bisley will discuss how the visual world is spatially represented in the lateral intraparietal area, creating a salience map that may be used in the allocation of visual attention. Ralph Siegel using optical imaging will provide examples of how so many properties are interwoven at the crown of the inferior parietal lobule- areas 7a and DP. The early onset of cognitive processes in the dorsal stream and the difficulty in keeping all of these mixed signals organized presents great challenges, yet at the same time provides a modern example of James' Enchanted Loom for us to unravel.

Panel · Wednesday, January 28 · 7:30–9:30 AM · Hasty's

Do Dopamine and Glutamate Alterations in Schizophrenia Form a Vicious Circle?

A. Abi-Dargham, H. Tsukada, J. Seamans, J. Krystal

The prefrontal cortex (PFC) in schizophrenia is believed to be associated with two neurochemical imbalances involving glutamate transmission at the NMDA receptors and dopamine transmission at D1 receptors. Given the intimate relationships between NMDA and D1 receptors, these alterations are likely to be related in a complex and circular manner. This symposium will present new data supporting the hypothesis that, in

schizophrenia, a deficit in D1 transmission in the cortex might be secondary to sustained NMDA hypofunction, and may further weaken NMDA function.

Hideo Tsukada will present PET studies in primates chronically exposed to MK-801. Compared to control monkeys, MK-801 treated monkeys showed decreased dopamine levels in the PFC, measured with microdialysis, and increased availability of D1 receptors measured with PET and the selective D1 receptor radiotracer [11C]NNC 112. Anissa Abi-Dargham will present results of a D1 receptor PET imaging study in severe and chronic recreational ketamine abusers, with a history of at least one ketamine-induced psychotic episode. These subjects exhibit a regionally selective increase in [11C]NNC 112 binding potential in the DLPFC similar to the one observed in MK801 treated monkeys by Tsukada, and to the one previously reported in schizophrenia (Abi-Dargham et al., J Neuroscience, 2002, 9:3708-19). Together, these data suggest that abnormalities of D1 receptor function in schizophrenia might be secondary to sustained NMDA impairment. Jeremy Seamans will discuss cellular network models of PFC function that seek to explain aspects of these PET data. John Krystal will discuss the therapeutic consequences of this model, contrasting the effects of DA blockade and DA augmentation on the cognitive deficits induced by NMDA antagonism in humans.

Panel · Wednesday, January 28 · 7:30–9:30 AM · Ptarmigan A

Huntington's Disease: From Models to the Clinic

P. H. Reinhart, R. Wetzel, M-F. Chesselet, K. Marder

Currently there are no treatments for Huntington's disease (HD), and the largest unmet need is to develop therapeutics to prevent the neuronal dysfunction and neurodegeneration associated the progression of this invariably fatal disease. The development of such therapeutics requires information about cellular targets whose activity is to be altered by potential drugs, and information about relevant cell types at which such drugs should be directed. Information relevant for effective preclinical and clinical trials requires the utilization of model systems that closely recapitulate inclusion formation, neuronal dysfunction and eventually neurodegeneration. Models that can faithfully recapitulate specific aspects of disease progression are most likely to provide information about early cellular Œbiomarkers, for disease initiation/progression, and about the temporal progression of functional changes important for identifying relevant loci of intervention useful for presymptomatic patients. This panel will provide an overview of recent progress in translational research for new HD therapeutics. Ron Wetzel will describe our current understanding of the most defining process in HD, the aggregation of human mutant huntingtin into

protein inclusions, and discuss functional subtypes of inclusions. Peter Reinhart will describe the use of intact brain slices to study both morphological and functional alterations in cortical and striatal neurons during disease progression. This model utilizes the biolistic co-transfection of neurons with human huntingtin constructs together with fluorescent reporters. Marie-Françoise Chesselet will discuss the use of mouse models that enable the exploration of early pathological, molecular and cellular abnormalities produced by the mutation within huntingtin. Currently many different types of transgenic and knock-in mice have been generated and allow the testing of new pharmacological approaches to delay the onset or slow the progression of HD. Karen Marder will provide a current snapshot of clinical treatments and critical factors in the design of clinical trials for new HD drug candidates.

Panel · Wednesday, January 28 · 7:30–9:30 AM · Ptarmigan B

The Role of Retinal Neuronal Circuits in the Encoding and Propagation of Visual Signals

S. Bloomfield, S. Massey, P. Lukasiewicz, M. Iuvone

The vertebrate retina has served for many years as a model system for studying CNS structure and function. The retina offers several advances over other CNS loci in that it is a relatively simple and accessible portion of the brain that can be isolated in an in vitro preparation and still be stimulated physiologically. As the subtypes of neurons in the retina and their synaptic connections have been well documented, we are now able, at the single cell level, to determine the circuitry involved in the extraction and encoding of different cues within a visual scene. This panel will detail recent advances in our understanding of how specific retinal circuits compute and propagate visual signals. Discussion will focus on: (1) communication via chemical synapses using classic neurotransmitters, (2) electrical synaptic transmission, and (3) how intrinsic neuronal properties, in the form of cellular circadian clocks, provide global changes in neuronal responsiveness. Peter Lukasiewicz will discuss how bipolar cell outputs are modulated by a unique GABA receptor, the GABAc receptor, to alter ganglion cell light sensitivity. Stephen Massey will discuss the different connexins expressed in the mammalian retina, including the role of connexin36-based gap junctions in the transmission of rod signals. Stewart Bloomfield will discuss the electrical and chemical synapses responsible for the three different types of spike synchrony found between neighboring ganglion cells in mammalian retina. Finally, Mike Iuvone will discuss emerging evidence for networks of circadian clocks in multiple cell types in the retina that regulate the daily rhythms of visual sensitivity.

Panel · Wednesday, January 28 · 7:30–9:30 AM · Ptarmigan C

Mechanisms of Developmental Synaptic Plasticity

A. El-Husseini, T. Benke, G. Collingridge, T. Taira

Synaptic plasticity is a fundamental process necessary for the correct wiring of the nervous system during development and is also critical for learning and memory. Considerable information has been obtained by studying synaptic plasticity, in particular long-term potentiation (LTP) and long-term depression (LTD), in the hippocampus. It is known, for example, that the various types of glutamate receptor (AMPA, NMDA, mGlu and kainate) are involved in the induction and expression of various forms of LTP and LTD. Here we address recent aspects of mechanisms of hippocampal synaptic plasticity, with a focus on how these mechanisms vary dramatically during development. The highly multidisciplinary nature of the field is represented by talks on mathematical modelling, molecular biology and cellular anatomy, molecular mechanisms of synaptic plasticity and neuronal network properties. Alaa El-Husseini will describe the role of the postsynaptic density protein (PSD95) and its associated synaptic signalling molecules, neuroligin, in the assembly of elements critical for synapse development and proper neuronal function. Tim Benke will describe the use of mathematical modelling to predict how synaptic transmission and synaptic plasticity may alter during development. Graham Collingridge will describe several distinct forms of LTP that can be observed at CA1 synapses during the second week of life. Tomi Taira will describe a novel, developmentally regulated mechanism that regulates synaptic transmission and network activity in the hippocampus during the first week of life.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Bighorn C1

Before and After: Regulation of Neurotransmission on the Presynaptic and Postsynaptic Sides of the Synapse

W. Catterall, J. Rettig, R. Huganir, R. Nicoll

Synaptic plasticity results from modulation of neurotransmission on the presynaptic and postsynaptic sides of the synapse, ranging from facilitation in msec to long-term potentiation (LTP) for hours. This panel will discuss and integrate molecular mechanisms that contribute to these regulatory events. Bill Catterall will give an overview of synaptic transmission and present recent work on modulation of presynaptic calcium channels by calcium-binding proteins, which cause calcium-dependent facilitation and inactivation. Assembly of the SNARE complex of synaptobrevin, syntaxin and SNAP-25 is a fundamental step in neurotrans-

mitter release. Jens Rettig will show that mutations in the SNARE complex alter calcium cooperativity and that exocytosis is modulated by PKA- and PKC-mediated phosphorylation of SNARE proteins. On the postsynaptic side of the synapse, Rick Huganir will discuss the role of glutamate receptor phosphorylation during synaptic plasticity. His work shows that phosphorylation of AMPA receptors is modulated during LTP and long-term depression. Recent studies indicate that phosphorylation of AMPA receptors is required for these forms of neuroplasticity and for certain forms of memory retention. Roger Nicoll will focus on the role of the tetra-membrane-spanning protein stargazin and the scaffolding protein PSD-95 in control of synaptic AMPA receptor number at synapses. Stargazin is a member of a large protein family, whose members have distinctive patterns of expression in the CNS. These proteins bind to AMPA receptors and PSD-95 to target and anchor AMPA receptors at synapses. A final discussion period will integrate the information from the talks to give a unified picture of regulation of neurotransmission.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Bighorn C2

Promiscuity in Neuroendocrinology

J. Becker, K. Olsen, D. Dorsa, S. Mani, R. Handa

Our understanding of how reproductive hormones act in the brain has changed dramatically. It was originally thought that the steroid hormones acted only at intracellular receptors to initiate gene transcription. But, we now know that steroid hormone receptors are acting in novel, and sometimes promiscuous, ways to modulate central nervous system activity. In this panel, moderated by Kathie Olsen, the latest research on steroid hormone actions in the brain will be discussed. Becker will give an overview of what is new in the field. She will also discuss evidence that estradiol receptor (ER)-alpha can act at the membrane to mediate rapid responses to estradiol. Handa will discuss new perspectives on the role of ERß in the brain. He has evidence that ERß can act as an androgen receptor in hypothalamic-pituitary-adrenal regulation and furthermore, that some variants of ERß can be activated by second messenger pathways. Dorsa will discuss his data indicating that ERalpha and ER-ß can modulate a variety of signal transduction cascades in target cells. In neurons in culture, estradiol activation of MAP kinase signaling systems has been found after transfection with ERa or ERß. These membrane-initiated actions lead ultimately to Estrogen response element-independent gene transcription, and mediate the neuroprotective actions of estrogens. Mani has shown that both dopamine and progesterone can activate the intracellular progestin receptors, and she will present evidence that there is cross talk between dopamine and progesterone in activation of progesterone receptors to induce sexual behavior.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Hasty's

Susceptibility Genes for Schizophrenia: Neurobiology and Pathophysiology

J. Kleinman, D. Weinberger, S. Leonard, D. Lewis

The discovery of several genes that increase the risk for schizophrenia has changed the landscape of psychiatric research. Susceptibility genes for schizophrenia have improved our understanding of cognition, altered our approach to neuroimaging studies and allowed for a new perspective in neuropathological studies of the human brain. This panel will review the basis for the notion that these genes have been identified, examine their effects on cognition and neuroimaging, and review their effects on the neuropathology of schizophrenia. An overview of the association of susceptibility genes (DISC1, dysbindin(DTNBP1), metabotropic glutamate receptor-3(GRM3), neuregulin(NRG1), G72 and COMT) with schizophrenia will be presented by Daniel Weinberger. He will also review the data linking these genes to cognition as well as their utility in neuroimaging studies that utilize cognitive trials. Sherry Leonard will follow with data linking the alpha-7 nicotinic receptor (CHRNA7) to schizophrenia and to P50 auditory evoked responses as well as postmortem expression studies in several brain regions of schizophrenics and controls. David Lewis will continue with this theme, but focus on RGS4 as another susceptibility gene with abnormal expression in dorsolateral prefrontal (DLPFC) cortex of schizophrenics. He will also present data on the effect of BDNF genotype on GABA neuronal markers. Lastly, Joel Kleinman will present expression data on mRNA and protein in DLPFC focusing on DTNBP1, GRM3, NRG1 and COMT. In addition, he will present data showing how genotypes associated with schizophrenia have dramatic effects on susceptibility genes as well other genes downstream neuroanatomically and biochemically.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Ptarmigan A

From Cage to Clinic: The Painful Truth About Diabetic Neuropathy

D. Wright, N. Calcutt, T. Morrow, J. Christianson

The occurrence of diabetes is increasing in epidemic proportions and the associated neural damage contributes significantly to the mortality and morbidity affiliated with this condition. Sensory complications include abnormal or reduced cutaneous sensation in the distal limbs, which in some cases may be accompanied by chronic pain. Both naturally-occurring and experimentally-induced rodent models of diabetic neuropathy have proven useful to study aspects of the human disease but fail to fully mimic human neural symptoms and pathology. The goal of this panel is to highlight re-

cent advances in this field and bring to light strengths and weaknesses of rodent models. Dr. Doug Wright will introduce the participants and provide a brief background on diabetes-induced deficits in cutaneous sensation and pain. Dr. Nigel Calcutt will address the validity of current animal models in relation to current behavioral tests, underlying mechanisms and sites of neural dysfunction. Included will be a discussion of the value of animal models for developing targeted therapeutics and predicting clinical efficacy. Dr. Tom Morrow will describe experiments in streptozotocin-induced diabetic rats using brain imaging to correlate the development of painful diabetic neuropathy with regional activation of discrete supraspinal systems. Finally, Dr. Julie Christianson will present anatomical and behavioral data demonstrating that in contrast to rats, streptozotocin-induced mice developed significantly reduced cutaneous innervation and hypoalgesia to cutaneous stimuli. Also, Dr. Christianson will illustrate how treatment of diabetic mice with neurotrophins such as NGF, GDNF, or NT-3 can restore selective aspects of cutaneous sensory loss in diabetic mice.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Ptarmigan B

Understanding and Preventing Suicide: A National Imperative

W. E. Bunney, A. Roy, D. A. Brent, J. J. Mann, S. G. Potkin

31,000 individuals in the United States and an estimated one million worldwide kill themselves each year. Suicide outnumbers total homicides per year by one-third in the United States. The NIMH-supported Institute of Medicine, National Academy of Sciences recent report recommended the development of new strategies to advance our fundamental understanding of suicide. Recent genetic studies, newly discovered biochemical abnormalities, and new pharmaceutical treatments of suicidality in adolescents and adults will be addressed by the panel. Dr. Roy will review genetic investigations on suicide, presenting data that genetic influences may be independent of psychiatric illness. Aggressive and impulsive traits appear to be one mechanism by which genetic factors can influence suicidal behavior, either directly or through the early onset of mood disorders. Dr. Brent will present data from a high risk study of offspring of mood-disordered suicide attempters. These offspring are at a five-fold increased risk for suicide. Parental sexual abuse also substantially increases its risk. Dr. Mann will discuss in vivo and in vitro cortical receptor binding evidence for lowered serotonin input to the ventral prefrontal cortex and for serotonergic and noradrenergic brain stem abnormalities resulting in decreased input to ventral prefrontal cortex in post-mortem studies of suicidal patients. Mood disorders are associated with fewer cortical and limbic target neurons for ascending brain stem monoamine fibers. The combination of these two abnormalities distinguishes individuals at risk for suicide. The 9% risk for suicide in schizophrenia approaches that of mood disorders. Dr. Potkin will

present new data concerning the risk factors associated with suicide and schizophrenia, and the recent perspective evidence demonstrating the antipsychotic clozapine's ability to significantly reduce suicidality in schizophrenia.

Panel · Wednesday, January 28 · 4:30–6:30 PM · Ptarmigan C

ERKed by Neurodegeneration: MAP Kinase Signaling in Neurodegenerative Diseases

J. Cavanaugh, J. Joseph, Z. Xia, and R. Perez

The mitogen activated protein kinase (MAPKs) family, which includes extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinase (JNK) and p38, are highly conserved signaling cascades that have been implicated in neuronal survival and apoptosis, differentiation, and learning and memory. As the cellular functions mediated by the MAPKs are affected in neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, the role of the MAPK pathways in the neuropathology of these diseases is being elucidated. Interestingly, recent evidence suggests that ERK, JNK and p38 are activated in the cortex and hippocampus of Alzheimer disease patients. This panel will discuss the role of MAPKs in neuronal apoptosis and survival and how these processes contribute to neurodegenerative diseases. Jane Cavanaugh will present an introduction including her work on the role of MAP kinase activation in GDNF-mediated neuroprotection from 6-hydroxydopamine (6-OHDA) induced cell death in the substantia nigra. Jim Joseph will discuss his work on the effects of berryfruit flavonids on MAPK signaling and learning and memory. Zhengui Xia will discuss the MAPK signaling pathways that regulate neuronal apoptosis. Ruth Perez will discuss her work on neuronal APP as a modulator of MAPK signaling. Together these data provide evidence that the MAPK pathways may be important targets for the development of new therapeutic approaches for the treatment of neurodegenerative diseases.

Panel · Thursday, January 29 · 7:30–9:30 AM · Bighorn C1

Dynamic Control of Transmitter Uptake: New Views of Transporter Function

G. Richerson, M. Quick, H. Lester, M. Kavanaugh

The traditional view of neurotransmitter transporters is that their location is static, and that they function solely to scavenge their substrate after vesicular release. The speakers will introduce a much different view. Michael Quick will show that GABA transporters can be rapidly inserted into the presynaptic membrane from a unique population of synaptic vesicles. This

calcium-dependent increase in functional GABA transporters occurs in response to presynaptic firing, permitting dynamic control of GABA transport. Henry Lester will present data from knock-in mice that express a fusion of GAT1 and GFP in place of the WT GAT1 gene. This has permitted direct measurements of the membrane density of GAT1 on different types of neurons. A strain of GAT1 deficient mice was also generated, in which there is a large increase in extracellular GABA levels resulting in a tonic GABAA-receptor mediated conductance in hippocampal neurons. Mike Kavanaugh will discuss new work using fluorescent probes of glutamate transporters. Functional transporters created by cysteine mutagenesis and incorporation of covalent fluorophores allow realtime monitoring of conformational changes during transport. TIRF studies of GFP-EAAT fusion proteins reveal subtype-specific trafficking differences. George Richerson will show that GABA transporters reverse and release GABA in response to physiological levels of depolarization, and spontaneously after treatment with the anticonvulsant vigabatrin. These transporters also regulate the level of tonic inhibition in the hippocampus. These data dictate a new view of transporters as highly dynamic and as playing a much more active role in neurotransmission than is generally believed.

Panel · Thursday, January 29 · 7:30–9:30 AM · Bighorn C2

Regional Patterning and Cell Specification in the Developing Vertebrate Nervous System

E. Carpenter, A. LaMantia, E. Jacobs, M. Goulding

This panel will consider the local and regional events that regulate early nervous system patterning by focusing on patterning in the developing forebrain and spinal cord. Initially, Dr. Anthony Lamantia will discuss forebrain induction and will demonstrate that olfactory epithelium and bulb induction is an adaptation of the non-axial mesenchymal/epithelial induction that also guides morphogenesis in the limb buds, brachial arches, and heart. He will show in the context of this mechanism that there are specific signals that constrain the molecular and functional phenotype of at least two distinct cell types during initial forebrain differentiation: the olfactory bulb granule cell and the olfactory receptor neuron. Dr. Erin Jacobs will describe recent work using a promoter element of the myelin basic protein gene that targets expression of transgenes to cortical preplate neurons. Her work shows that expression from this promoter begins early in development and continues into postnatal life. Subplate neurons expressing the transgenes initially pioneer the corticothalamic pathway. These subplate neurons also survive to adulthood and maintain their projections to both the thalamus and layer I of the neocortex. Her results suggest the existence of functional interactions between subplate neurons and cortical and subcortical regions that continue well into adult life. Dr. Ellen Carpenter will describe early

events in the regional differentiation of the spinal cord. Her presentation will focus on the roles of three paralogous Hox genes, Hoxa10, Hoxc10, and Hoxd10 and their combinatorial activity in the development of the lumbar spinal cord. Dr. Martyn Goulding will conclude the panel with a description of the formation of sensorimotor circuits in the spinal cord. He will demonstrate that transcription factors play a central role in regulating the specification of sensorimotor neurons in the spinal cord and in controlling the expression of downstream molecules that control the wiring of neurons into functional networks. Together these presentations will describe several different mechanisms at play in the specification of regional and cellular identity in the developing nervous system.

Panel · Thursday, January 29 · 7:30–9:30 AM · Hasty's

Translational Genomics: How DISC1, GRM3, and Neuregulin Increase Risk for Schizophrenia

M. Egan, J. H. Callicott, J. Morris, D. Falls

Recent advances in clinical genetics are rapidly transforming schizophrenia research and now point to specific genes that increase risk. These include DISC1, neuregulin (NRG-1), and the metabotropic glutamate receptor 3, (GRM3). This workshop will bring together clinical and basic perspectives to examine how these genes do so. Joe Callicott will begin by describing linkage and association studies of DISC1 and neuregulin. He will report the effects of a specific missense mutation in DISC1 on cognition and hippocampal physiological responses during memory tasks. Jill Morris will review the molecular biology of DISC1, including its structure, function, and expression in mesial temporal lobe structures, including hippocampus. Next, Doug Falls will discuss the molecular biology of the extraordinarily large NRG1. He will describe its complex alternative splicing, its role in neurodevelopment and cell signaling through ErbB receptors, and how knockouts exhibit many neurobiological abnormalities related to schizophrenia. Finally, Michael Egan will describe clinical results suggesting that GRM3 increases risk for schizophrenia through its effects on prefrontal physiology and cognition. He will also describe molecular changes in post mortem tissue indicating that genetic variants in GRM3 produce surprisingly robust alterations on indices of synaptic glutamate. Together, these findings point to new directions for translational studies of the molecular neurobiology of schizophrenia.

Panel · Thursday, January 29 · 7:30–9:30 AM · Ptarmigan A

Living Without in Hibernation

K. Drew, M. Harris, W. Milsom

Patiently count the breaths of a cold, lifeless, furry mammal, if it breathes at all in 30 min, and imagine how this state of suspended animation could be achieved in humans. Metabolic arrest experienced by hibernating mammals would provide a novel, neuroprotective, emergency response for stroke and trauma patients if comparable decreases in O2 and nutrient demand could be achieved in humans. Along with metabolic arrest, hibernation is characterized by a unique state of consciousness distinguishable from coma, in part, by the ability of external stimuli to initiate arousal. Autonomic nervous system (ANS) responses such as decreases in heart rate (HR) and respiration rate (RR) are the first indicators of entrance into this state of suspended animation (termed "torpor"). Likewise, increases in HR and RR are the earliest indicators of subsequent arousal; suggesting an active and regulatory role for the ANS in hibernation. However, while critical for the maintenance of homeostasis, the role of the autonomic nervous system during entrance and exit from torpor (heterothermy) is enigmatic. In this panel discussion, Dr. Harris will discuss at least two contradicting theories proposed to account for autonomic nervous system regulation of hibernation. Then, in light of hypoxia-induced metabolic arrest in turtles, Dr. Milsom and Drew will present data supporting and refuting hypoxic metabolic suppression in hibernation.

Panel · Thursday, January 29 · 7:30–9:30 AM · Ptarmigan B

When Good Guys Go Bad: Amyloid Precursor Protein and Non-Amyloidogenic Routes to Neurodegeneration

S. Barger, T. Ikezu, L. DeGiorgio, S. Griffin

A prevailing hypothesis in Alzheimer's disease research is that elevation of amyloid ß -peptide (Aß) causes the observed neurodegeneration. The neurotoxicity of Aß has been invoked as evidence, whereas the Aß precursor (ßAPP) has been connected to neurotrophism and neuroprotection. However, recent research reveals means by which domains of ßAPP outside of Aß can contribute to neurodegeneration. ßAPP, a type-I membrane protein, is processed to yield a secreted form (sAPP) that includes most of the protein's aminoterminal, extracellular portion; evidence indicates that sAPP can act as a cytokine. In addition, emerging data suggest roles for the carboxyterminal, intracellular portion of ßAPP acting similarly to the analogous portion of Notch. Under certain conditions, both of these portions of ßAPP could have neurodegenerative consequences. Lorraine DeGiorgio will

present results of lesion models in ßAPP-knockout mice. Knockout animals demonstrate sparing that suggests contributions of ßAPP and/or its carboxyterminal domain to neuronal damage and neuroinflammation. Sue Griffin will address an in vitro model of neuroinflammation in which microglia are cocultured with neurons. Through immunodepletion studies, this model indicates a role for endogenous sAPP in activation of microglia by stressed neurons, resulting in an interleukin-1-dependent feedback loop. Tsuneya Ikezu has taken such a coculture model a step further through viral transduction of neurons with ßAPP, generating evidence that sAPP may cooperate with Aß to elicit an excitotoxin from monocytic cells. Steve Barger will emphasize this link between excitotoxicity and neuroinflammation mechanistically, with demonstrations that sAPP and Aß stimulate microglial production of two specific glutamate receptor agonists.

Panel · Thursday, January 29 · 7:30–9:30 AM · Ptarmigan C

Nontraditional Synthesis and Actions of Progesterone on Neural Development, Sexual Differentiation, Remyelination and Reproduction

K. Sinchak, P. Micevych, S. Mellon, C. Wagner, C. Ibanez

Although progesterone is primarily thought of as a steroid hormone of ovarian or placental origin that regulates reproduction, progesterone is also a neurosteroid, synthesized de novo in the CNS and has wide ranging effects in both males and females. This panel will discuss the synthesis of progesterone in the brain and the effects of progesterone on neuronal development, sexual differentiation, myelination and estrogen positive feedback. Synthia Mellon will discuss neurosteroid synthesis and the potential role of neurosteroids in neural development using a mouse model of a human neurodegenerative disease, Niemann-Pick Type C (NP-C), to study the normal function of neurosteroids during development. Her data suggest that appropriately timed synthesis of neurosteroids may be required for normal neural development. Christine Wagner will discuss the mechanisms regulating sexually dimorphic expression of progesterone receptors (PR) in the medial preoptic area and ventromedial nucleus of the hypothalamus of neonatal rats and their role in sexual differentiation. Chrystelle Ibanez will discuss the role of neuroprogesterone in promoting the myelination and remyelination of neurons in cerebellar organotypic cultures and aging male rats, respectively. These effects of progesterone are differentially mediated via nuclear PR and the GABAA receptor. Paul Micevych will discuss the estrogenic regulation of neuroprogesterone synthesis throughout the lifespan of the female rat and how neuroprogesterone initiates the LH surge mediating the estrogen positive feedback stimulation of the LH surge.

Minicourse · Thursday, January 29 · 4:30–6:30 PM · Bighorn C1

Catch Me If You Can: Second-by-Second Measures of Glutamatergic and Cholinergic Neurotransmission

G. A. Gerhardt, N. T. Maidment, J. P. Bruno, A. C. Michael

The rapid dynamics of glutamatergic and cholinergic neurotransmitter systems have resulted in the struggle to measure these neurotransmitter systems in the brain and relate them to behavior, effects of drugs of abuse and damage to the CNS. Over the last decade, there have been significant advancements in the development of microelectrode technologies to measure glutamatergic and cholinergic neurotransmission. The purpose of this session is to discuss the current capabilities of microelectrode technologies to measure *second-by-second* changes of glutamatergic and cholinergic neuronal activity in the CNS. Greg Gerhardt will present data obtained with newly designed ceramic- and glass-based microelectrode arrays to measure glutamate or choline in brain areas of freely moving rats. Adrian Michael will report on redox polymer technology, which can be used to further improve the selectivity of microelectrode recordings for measurements of glutamate and choline. Nigel Maidment will discuss the use of microelectrode arrays for measurements of glutamate in a mouse model of Huntington's disease and recent data collected with a fiber optic based system to measure rapid changes in glutamate. Finally, John Bruno, will present data from recent studies with a choline recording microarray and attempts to use changes in choline as an indicator of acetylcholine release in anesthetized animals. All presenters will strive to bring forth a consensus of the current technologies that give the most rapid, sensitive, and reliable measures of glutamatergic and cholinergic neurotransmission. Participants should gain a wealth of information regarding the practical applicability of these technologies for CNS recordings in laboratory animals.

Panel · Thursday, January 29 · 4:30–6:30 PM · Bighorn C2

Immunoneuroendocrine Interactions in Brain Inflammation

G. Aguilera, C. Cunningham, S. Lightman, F. Tilders

Peripheral inflammation is associated with central nervous system effects, including activation of the hypothalamic pituitary adrenal (HPA) axis and central production of proinflammatory cytokines. This panel will address possible mechanisms of central effects of peripheral immune activation, and the role of HPA axis responsiveness on this process. After a brief introduction, Greti Aguilera will show evidence of exacerbated immune reaction in the brain following an acute immune challenge in a rat model of adjuvant-induced arthritis, in spite of marked activation of the HPA axis. Colm

Cunningham will show data on exacerbation of LPS-induced acute sickness behaviour and local production of cytokines by prior activation with prion disease. He will discuss mechanisms involved in central immune hyperresponsiveness including iNOS, increased protease activity and oxidative damage, as well as the hypothesis that infection accelerates the course of neurodegeneration. Stafford Lightman will address mechanisms through which peripheral inflammation can influence CNS pathways and in particular the activation of both catecholaminergic and serotonergic cell groups within the brain stem. Finally, Fred Tilders will present data from experimental models of multiple sclerosis and chronic relapsing experimental encephalomyelitis as basis for discussion on how peripheral inflammation and some of its mediators induce functional remodeling of neuroendocrine pathways between brainstem noradrenergic neurons, hypothalamic CRH neurons and pituitary corticotrophs. Discussion of these topics will provide new insight on the multiple mechanisms by which peripheral immune activation may impact on the central nervous system and set up basis for future investigation in the field.

Panel · Thursday, January 29 · 4:30–6:30 PM · Hasty's

Drug Discovery for Huntington's Disease and Other Neurologic Diseases

G. Bates, R. Hughes, C. Johnson, J. Olson

The identification of the mutation that causes Huntington's disease (HD), as a CAG/polyglutamine (polyQ) repeat expansion, dramatically increased our understanding of the early molecular events that underlie the pathogenesis of this disease. As the molecular targets for intervention are better understood, they will be incorporated into a comprehensive approach to Huntington's disease drug discovery. High-throughput screens are being conducted in existing and modified yeast and mammalian cell based assays and in vitro aggregation assays (RH). The hits arising from these screens are validated in multiple cell and simple organismal HD models and lead compounds optimized through chemi-informatics and medicinal chemistry (CJ). The pharmacokinetics, toxicity, and efficacy of compounds are assessed prior to the evaluation in preclinical mouse trials. Thus far aggregation inhibitors arising from high-throughput screens or otherwise have been assessed in secondary screens and have progressed to evaluation in preclinical mouse trials (GB, JO). Similarly, histone deacetylase (HDAC) inhibitors intended to target transcriptional repression, have shown beneficial effects in both Drosophila models and mouse models of HD (GB). These results have validated the use of this series of assays as a drug development pipeline that will feed novel compounds into preclinical trials. We will discuss partnership strategies for academic investigators and biotech companies to establish ultra-high throughput screens of chemical libraries in combination with chemi-informatics, medicinal chemistry and the optimization of lead compounds for neurologic diseases.

Panel · Thursday, January 29 · 4:30–6:30 PM · Ptarmigan A

Role of BDNF in Addiction and Fear: An Update

G. Meredith, J. McGinty, Y. Shaham, D. Ron, K. Thomas

Brain-derived neurotrophic factor (BDNF) is found in brain areas involved in drug reward and fear conditioning. Additionally, BDNF plays a role in synaptic plasticity, a neuronal correlate of learning and memory. We will present new data suggesting that BDNF plays important roles in addictive behavior for different classes of abused drugs, and in fear memory. After a brief introduction by Meredith (Chicago Med Sch) on the role of BDNF and its tyrosine kinase receptor in functional plasticity, McGinty (MUSC) will present the effects of methamphetamine binge on BDNF+/- mice with decreased neuropeptide mRNA in their striatal medium spiny neurons. These findings will be related to methamphetamine-induced exacerbation of tyrosine hydroxylase depletion in GDNF+/- mice. Shaham (NIDA) will present data on alterations in mesolimbic dopamine BDNF levels over the first months of cocaine withdrawal and on the enhancement of cue-controlled cocaine seeking by intra-VTA infusions of BDNF. The potential relevance of these data to the phenomenon of "incubation of cocaine craving" will be discussed. Ron (UCSF) will present data indicating that the signaling pathway consisting of the scaffolding protein RACK1, BDNF and downstream genes is part of a homeostatic pathway that attenuates the behavioral effects of alcohol. Thomas (Cambridge) will present data demonstrating that local inhibition of BDNF translation using an antisense oligonucleotide impairs the consolidation, but not reconsolidation, of hippocampal- and amygdala-dependent fear memories. At the end, we will discuss the implications of our data for neuronal plasticity processes underlying conditioned and unconditioned drug- and fear-induced behaviors.

Panel · Thursday, January 29 · 4:30–6:30 PM · Ptarmigan B

Role of Activity in the Formation of the Visual Connections: Reassessment from Recent Evidence

R. Meyer, J. Crowley, L. Chalupa, C. Riegle

Evidence accumulated over 40 years (reviewed by Meyer) has led to the widely accepted idea that impulse activity plays a critical role in the formation of the visual system. Physiological studies showed that abnormal visual experience during development results in abnormal visual responses in adult cortex suggesting activity *instructs* receptive field properties. Anatomical studies on the formation ocular dominance columns and lamination in geniculate indicated fibers corresponding to each eye were initially intermixed and then segregated into eye-specific domains. Segregation was

thought to be generated by locally correlated activity in retina, particularly, by developmentally regulated waves of activity. Parallel studies in lower vertebrates led to similar conclusions. *Ocular dominance columns* could be induced in frog or fish by making two eyes innervate the same tectum but only if there was impulse activity in optic fibers. Recent studies have led to a reevaluation of some of these ideas. Crowley will present evidence that ocular dominance columns form much earlier than previously thought and can do so without retinal input suggesting activity might not be required for their initial formation. Chalupa will describe studies showing that while activity may be required for eye-specific lamination in geniculate, this activity need not be locally correlated and so may not be instructive. Riegle will describe studies in the goldfish retinotectal system indicating that retinal waves do not exist and spontaneous optic activity does not drive tectal cells during *activity-dependent* refinement. Instead, activity may play a role in the non-Hebbian homeostatic regulation of synaptic strength.

Panel · Thursday, January 29 · 4:30–6:30 PM · Ptarmigan C

Exitatory Amino Acids in Neonatal Brain Injury

S. Levison, J. Nunez, T. Wood, P. Follett

The human infant encounters numerous situations that may induce brain injury. Insults related to pregnancy or birth include: pre-eclampsia, cytokine-mediated inflammation, umbilical cord dysfunction, asphyxia; postnatal events include seizures, cardiac arrest, sepsis and anemia. The immature status of the premature infant predisposes it to traumatic events. These insults lead to anatomical and behavioral deficits that persist into adulthood. In this panel we will focus on one stimulus that is common to numerous pathologies ˆ the excessive release of amino acid neurotransmitters. Studies on the effects of amino acid neurotransmitters reveal that GABA and glutamate have different actions in the immature brain than the mature brain. We will address the consequences of normal and abnormal glutamate and GABA signaling in the developing brain, with an emphasis on how these neurotransmitters affect brain injury and repair. Joseph Nuñez will provide a brief overview on glutamate and GABA signaling in the immature brain, then talk about his work suppoting the emerging idea that GABAA receptor activation in immature cells increases calcium influx, which can damage neurons when overstimulated. Next, Terri Wood will discuss her work on the excitotoxic effects of glutamate on oligodendrocyte precursors and long-term protection from glutamate afforded by IGF-1 stimulation. Pamela Follett will discuss her data on the neuroprotection afforded by antagonizing AMPA/kainate receptors in a neonatal rat model of brain injury. Finally, Steve Levison will provide data demonstrating that in contrast to the deleterious effects that glutamatergic stimulation has on neural progenitors, glutamate can stimulate a regenerative response from neural stem cells.

Panel · Thursday, January 29 · 8:30–10:00 PM · Bighorn C1

Rounding Up Molecular Suspects in Schizophrenia; Strategies for Postmortem Studies

B. Lipska, M. Webster, W. Honer, S. Bahn

New gene and protein profiling techniques provide a powerful approach to explore molecular changes associated with complex psychiatric disorders, such as schizophrenia and mood disorders. Many symptoms of schizophrenia appear to involve dysfunction of the cognitive processes mediated by the neural circuitry of the prefrontal cortex and the hippocampus. These brain regions have been the subject of extensive molecular surveys with often mixed and confusing results. Part of the problem may lie in an inadequate quality of the tissue and/or methodological pitfalls. In this session, we will discuss the process of acquisition and characterization of high quality postmortem brain tissue, RNA and protein extraction and preparation and use for gene and protein assessment in schizophrenia research. M. Webster will present the approaches of tissue acquisition and quality assessment of brain tissue used by the Stanley Foundation and discuss methods of data analysis obtained through multicenter collaborative research. W. Honer will talk about the assessment of synapse-associated proteins in in schizophrenia using an enzyme-linked immunoadsorbent assay (ELISA) and discuss the normalization methods and the inclusion of controls. S. Bahn will talk about tissue preparation and RNA quality control for laser-capture dissection combined with microarray technology. B. Lipska will present data on gene expression using a real-time RT-PCR technique and show data from animal studies on the effects of postmortem interval and antipsychotic treatment to address the issue of medication and PMI in post-mortem human studies. In this panel, we will show that brain tissue can yield good quality RNA and intact protein antigens, which allow the successful application of traditional molecular biology methods as well as novel profiling techniques.

Panel · Thursday, January 29 · 8:30–10:00 PM · Bighorn C2

Drug-Induced Neurochemical and Neurophysiological Plasticity: Contributions to Drug Addiction and Implications for Current Theories of Addiction

C. O'Brien, G. Koob, P. Kalivas, L. Peoples

Drug addiction is believed to be attributable to drug-induced and long-lasting changes in brain. It is hypothesized that these drug effects contribute to a dysregulation of primary reward mechanisms and, alternatively or additionally, to aberrant drug-reward-related learning. The present panel will discuss neurochemical and neurophysiological changes associated with

extended drug exposure that could contribute to either or both of these functional abnormalities. Koob will address changes in the reward system associated with the transition from drug use to drug dependence. Extended exposure to cocaine, opiates, and alcohol is associated with escalation in drug intake and neuropharmacological studies implicate dysregulation of dopamine, opioid peptides and GABA in the extended amygdala. Kalivas will describe long-term changes in biochemistry and physiology of cells in the nucleus accumbens following withdrawal from cocaine administration. Notable are changes in postsynaptic signaling molecules and protein scaffolds affecting signaling. Peoples will describe complimentary findings from chronic extracellular recordings made in animals with varying histories of drug self-administration. These studies show that across repeated drug sessions there is a progressive decline in basal accumbal neural activity and phasic accumbal responses to drug-reward-related events. Finally, O'Brien will discuss evidence of neuroplasticity in the reward system of human cocaine addicts as manifested by changes in neural activation and DA release in response to drug cues in drug free former users. He will also show data on the effects of modafinil in potentially reversing the glutamate deficit reported in animal studies after chronic cocaine.

Panel · Thursday, January 29 · 8:30–10:00 PM · Hasty's

Allosteric Modulation of AMPA Receptors: A Novel Therapeutic Approach to Neurological and Psychiatric Disorder

E. Nisenbaum, P. Skolnick, G. Lynch, J. Witkin

An accumulating body of evidence suggests that dysfunction of glutamatergic signaling in the CNS may contribute to deficits associated with a variety of neurological and psychiatric disorders. As such, ongoing efforts are exploring therapeutic approaches to these disorders all of which share the common goal of enhancing glutamatergic synaptic transmission. One novel strategy has focused on compounds that allosterically regulate glutamate AMPA receptors which mediate the majority of rapid excitatory neurotransmission in the CNS. Several consequences of allosteric regulation have been described, including direct enhancement of AMPA receptor signaling, secondary recruitment of voltage-dependent NMDA synaptic transmission, and facilitation of the induction of long-term potentiation. Positive modulators of AMPA receptors also have been shown to mobilize intracellular signaling pathways and augment expression of neurotrophins such as BDNF. Collectively, these data have prompted experimental and clinical studies on the therapeutic utility of AMPA receptor modulators in a variety of neurological and psychiatric diseases that may benefit from enhanced glutamatergic transmission per se and/or upregulation of neurotrophin expression. In this panel session, E. Nisenbaum initially will review the molecular, pharmacological, and functional properties of AMPA receptors, as well as the structural determinants of allosteric regulation by different modulators. J. Witkin will discuss evidence for the therapeutic po-

tential of AMPA receptor potentiators in depression. P. Skolnick will present data demonstrating activity of positive modulators in animal models of Parkinson's disease. G. Lynch will describe preclinical and clinical data supporting a role for allosteric modulation of AMPA receptors in the treatment of cognitive disorders

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Workshop · Thursday, January 29 · 8:30–10:00 PM · Ptarmigan A

The Tao of Tyrosine and Catecholamines for Non-Believers

G. Jaskiw, T. Maher, F-A. Wiesel, B. Yamamoto

Although increasing data suggest that tyrosine availability can affect catecholaminergic transmission, many neuroscientists deny the latter and remain faithful to the tenets of classical pharmacology. Their skepticism is not unfounded. Tyrosine effects have varied depending on the dose of tyrosine, the activation state of catecholaminergic neurons and the assay technique used. The skeptics demand definitive proof that tyrosine availability affects not just catecholamine metabolism but catecholamine-mediated neurotransmission and has functional effects. Some of the less orthodox concede that tyrosine's influence can be demonstrated experimentally, but question whether it has any physiological or therapeutic implications. What are we to do with all these people? We propose a forum in which they can air their concerns and join in a critical examination of the evidence from several points of view. Heretical ideas will be par for the course. George Jaskiw will claim that much of the inconsistency in the data is due to non-linear tyrosine dose-response effects. Tim Maher will propose that many tyrosine-sensitive catecholaminergic responses are mediated primarily through norepinephrine rather than dopamine systems. Bryan Yamamoto will speculate on underlying neurochemical mechanisms and will introduce the concept of tyrosine-mediated toxicity. Frits-Axel Wiesel will argue that schizophrenia is associated with abnormal tyrosine kinetics implicating membrane dysfunction and thereby influencing brain function. The presenters will challenge members of the audience to consider the role of tyrosine in their own work and to propose studies that would address outstanding questions. We promise that there will be no forced conversions.

Panel · Thursday, January 29 · 8:30–10:00 PM · Ptarmigan B

Stress, Drug Abuse and Synaptic Plasticity

Y. Shaham, K. Anstrom, P. V. Piazza, K. McFarland, A. Bonci

In humans, exposure to stress is associated with compulsive drug use and relapse to drugs during abstinence periods. The cellular and neuroanatomical mechanisms involved in the stress-drugs of abuse interaction, however,

are to a large degree not known. Here, we will present recent progress in this research area, with a particular emphasis on the impact of stress on synaptic plasticity within the mesocorticolimbic dopamine reward system. Piazza (INSERM, France) will present data from mice studies on the effect of chronic stress on the transcription of genes relevant to drug addiction. He also will present data on the effect of tissue-specific conditional knockout of the glucocorticoid receptor on cocaine reward. Anstrom (Wake Forest) will present data from electrophysiological studies in awake rats on the effect of restraint stress on basal firing properties and electrophysiological sensory gating responses of individual neurons of the midbrain ventral tegmental area, the cell body region of mesocorticolimbic dopamine neurons. McFarland (MUSC) will discuss the role of cortical, striatal and limbic circuitry in stress-induced reinstatement of cocaine self-administration behavior after withdrawal. Her data suggest that glutamate-dopamine interactions in these circuits are involved in footshock-induced reinstatement of cocaine seeking. Bonci (UCSF) will present data indicating that several drugs of abuse, as well as acute stress and administration of the stress neuropeptide, corticotropin-releasing factor (CRF), increase the strength of excitatory synapses within the ventral tegmental area. The panel (and the audience) will discuss the implications of these recent data for the understanding of the role of stress in drug addiction.

Panel · Thursday, January 29 · 8:30–10:00 PM · Ptarmigan C

Inflammatory Modulators are Key Factors in Amyloidosis and Neurodegeneration

S. Richardson, D. Mousseau, S. Frautschy, T. Golde, T. Wyss-Coray

Considerable evidence suggests that the neurodegenerative process in Alzheimer's disease involves a destructive multifaceted inflammatory cascade induced by ß-amyloid peptides. However, a clinical trial of a vaccination strategy aimed at reducing ß-amyloid burden was stopped because of evidence of increased inflammation of the brain meninges of the test subjects. And NSAIDs did not alter the cognitive deterioration over 1 year in patients with existing Alzheimer's disease in a recent clinical study. These inconsistent observations may reflect the multifunctionality of cytokines such as transforming growth factor-ß (TGF-ß). Generally considered to be a pro-inflammatory cytokine in models of Alzheimer's disease / ß-amyloid toxicity, TGF-ß exerts both beneficial (neurotrophic effects and inflammatory clearance of ß-amyloid) and detrimental (exacerbation of neurotoxicity and incomplete inflammation) actions. This panel will present new data and novel interpretations of evidence in the context of the inflammation hypothesis of Alzheimer's disease. Discussions will focus on three of the many systems implicated. Tony Wyss-Coray will discuss how his genetically engineered mice reveal a non-redundant function for TGF-ß in maintain-

ing neuronal integrity and in regulating microglial activation. Sally Frautschy will discuss the pathogenic relevance of the TGF-ß2 isoform in the cellular delivery of ß-amyloid, and the pros and cons of complement activation. Darrell Mousseau will present evidence for a unique, receptor-independent mechanism underlying the amyloidogenic actions of TGF-ß. And Todd Golde will discuss how NSAIDs lower ß-amyloid(1-42) via a mechanism that is independent of the inhibition of cyclo-oxygenase enzymes. These new and exciting observations will help to redefine our understanding of the etiology of Alzheimer's disease and will provide the seeds for treatment strategies beyond our current limited and often ineffectual, pharmacopoeia.

Panel · Friday, January 30 · 7:30–9:30 AM · Bighorn C1

Hallucinogens: What a Trip from Single Neurons to Behaving Brains

R. Andrade, M. Geyer, F. Vollenweider, G. Williams, J-C. Beique

The search for a mechanistic understanding of hallucinogen actions lies at the origins of neuropharmacology. While it was realized very early that classic hallucinogens were serotoninergic agents, it was not until the 1980's that 5-HT2A receptors were identified as the targets for indoleamine hallucinogens such as LSD and psilocybin. The identification of the molecular target for classic hallucinogens was an important step in our understanding of their mechanism of action. However, it only deferred the key question, namely how does the interaction of these compounds with 5-HT2A receptors induces the altered state of consciousness that characterize their effects in humans. Understanding how hallucinogens act clearly requires the synthesis of coordinated, multi-level, approaches covering a broad continuum ranging from single cells to neuronal circuits to behaving animals and humans. Sixty years after Hoffman's discovery of the hallucinogenic properties of LSD, the realization of such a task no longer looks like an unattainable goal. This session will bring together different perspectives on the mechanism of action of hallucinogens, each based upon a different level of analysis. Franz Vollenweider will present brain imaging and behavioral data on psilocybin in humans, while Mark Geyer will present parallel work on animals. Graham Williams will present his work on the effect of 5-HT2A receptors on neuronal activity in prefrontal cortex in awake animals, while Jean-Claude Béïque will present recent in vitro electrophysiological results on the cellular effects of 5-HT2A receptors in prefrontal cortex.

Panel · Friday, January 30 · 7:30–9:30 AM · Bighorn C2

Improved Experimentation through Modeling.

S.H. Koslow. G. Ascoli, G. Jacobs, G. Shepherd, D. Mountain

Recent approaches to modeling neuronal process afford new ways to quantitatively express experimental results. These approaches also allow for the

integration of vast amount of data collected with different experimental techniques and spanning multiple scales and levels of analysis. This process provides a medium for the discovery of new principles of neural function and a clear and precise mechanism for communicating a theory with other scientists. Giorgio Ascoli will present on the L-Neuron project, in which dendritic structure is described algorithmically: measurements taken from real cells are used to synthesize anatomically plausible virtual neurons. Gwen Jacobs has as a goal the study of the mechanisms of information processing in sensory systems. She will describe how anatomical and physiological data can be combined to build realistic models of neural circuits and to test hypotheses about system functions. Gordon Shepherd will demonstrate how his laboratory uses experimental membrane property data to construct realistic compartmental models of soma and dendrites. These models allow one to test hypotheses of neuronal function in a rigorous manner. He will also describe ModelDB which is a web accessible database designed to permit and encourage widespread testing, validation, and enhancement of neuronal models, in the olfactory and other systems. Lastly, David Mountain will present his work toward developing "EarLab" models and tools. The objective of the EarLab project is to develop large-scale models of auditory function and disease using distributed computing techniques.

Panel · Friday, January 30 · 7:30–9:30 AM · Hasty's

Cholecystokinin (CCK) the Quintessential Neuromodulator

M. Beinfeld, E. Pothos, P. Micevych, N. Geary, S. Simasko

CCK is one of the most ubiquitous and abundant neuropeptides. It is colocalized with a number of classic neurotransmitters in central and peripheral neurons and is secreted by endocrine cells of the intestinal mucosa. Some of CCK's most intriguing neural effects are manifested in concert with other neuroactive agents. Recent investigations are apprehending and integrating these interactive effects of CCK at the subcellular, cellular and organismic levels in several neural systems. This panel will examine the interaction of CCK with other neurotransmitters and modulators. The discussion will focus on defining common and unique mechanisms of CCK modulation of these signaling pathways. After a brief introduction by Margery Beinfeld, Emmanuel Pothos will discuss his novel observation of the direct regulation of catecholamine quantal size (the number of molecules released by a single vesicle) by CCK receptors from wild type and CCK receptor knockout mouse cell cultures. Paul Micevych will discuss reciprocal modulatory interactions between CCK, endogenous opioids and estrogen that regulate reproduction and nociception. Nori Geary will discuss the behavioral and molecular analysis of the interaction of CCK, estradiol and NMDA receptors in the NTS in the control of feeding. Steve Simasko will discuss behavioral and cellular studies defining the integration of CCK and leptin signaling by vagal afferent neurons, which represents a mechanism for control of feeding and energy balance by CCK.

Panel · Friday, January 30 · 7:30–9:30 AM · Ptarmigan A

Pathogenic Mechanisms and Therapeutic Implications in Models of Alzheimer's and Huntington's Disease

L. Ellerby, S. Sinha, J. Buxbaum, C. Ross

Huntington's disease (HD) and Alzheimer's disease (AD) cause neuronal dysfunction and cell death in specific areas of the brain. In this session we will present some of the common features and mechanisms thought to underlie AD and HD pathology and disease progression, with emphasis on altered protein conformation and proteolytic processing. Both diseases involve abnormal protein conformation, and deposition of protein aggregates in brain. AD is well known to involve proteolytic processing, and HD has been postulated recently to have a comparable phenomenon. Joseph Buxbaum will discuss the pathology of AD, and regulation of proteolytic processing of APP, suggesting therapeutic strategies to reduce the production of β-amyloid. Sukanto Sinha will describe the role of BACE in the cleavage of APP to generate Ab, strategies to inhibit this protease for AD therapy, and the evidence for non-plaque Ab aggregates as possible mediators of AD pathology. Christopher Ross will describe pathology of HD, altered conformational states of mutant huntingtin, and mouse model and human data suggesting a role for proteolytic processing. Lisa Ellerby will discuss the role of caspases, calpains, and possibly other proteolytic enzymes, in the cleavage of huntingtin in cell culture and transgenic models, and whether these cleavage events precede or occur simultaneously with other proteolytic pathways involved in HD. Discussion will focus on common pathogenic mechanisms in AD and HD, particularly whether any of the proteolytic mechanisms and pathways in HD and AD overlap. Comparison of the common molecular pathways, may provide therapeutic strategies for both AD and HD.

Panel · Friday, January 30 · 7:30–9:30 AM · Ptarmigan B

Man-Made Marijuana: Endogenous Cannabinoid Roles in Plasticity and Reward

D. Lovinger, C. Lupica, O. Manzoni, A. Hoffman

Abused drugs alter synaptic transmission within addiction-related brain circuits. Both short and long-term synaptic plasticity occur in this circuitry, and there is evidence that such plasticity can be initiated by in vitro and in vivo exposure to drugs of abuse. Cannabinoid drugs modulate synaptic transmission at many synapses in the CNS. Endocannabinoids are endogenous lipid metabolites that activate cannabinoid receptors and also play critical roles in both short-term synaptic depression and a form of long-term synaptic depression (eLTD). eLTD is initiated by postsynaptic mechanisms and subsequent release of an endocannabinoid that activates

presynaptic CB1 cannabinoid receptors. Interestingly, eLTD occurs in addiction and habit-formation-related nuclei including amygdala, dorsal striatum and nucleus accumbens (NAc). Panel participants will compare mechanisms of cannabinoid-mediated synaptic modulation and plasticity across brain regions, and will discuss potential roles in addiction and habit formation. Dr. Lovinger will describe cannabinoid effects on glutamatergic transmission, as well as the mechanisms involved in eLTD at corticostriatal synapses. Dr. Hoffman will present exciting new evidence that chronic Delta-9-THC exposure produces tolerance to cannabinoid-induced synaptic depression and eLTD in NAc. Dr. Manzoni will discuss mechanisms underlying eLTD in the NAc and will present intriguing evidence showing how a single in vivo exposure to cocaine or Delta-9-THC disrupts eLTD. Finally, Dr. Lupica will present new findings on synaptic modulation by cannabinoids and endocannabinoids in the ventral tegmental area and discuss how this may contribute to the release of dopamine, a neurotransmitter implicated in addiction.

Panel · Friday, January 30 · 7:30–9:30 AM · Ptarmigan C

The Exciting Complexities of Excitotoxicity

I. Reynolds, J. Kemp, S. Hewett, K. Hoyt

Excitotoxicity used to be simple: effective activation of NMDA receptors caused a cellular flood of calcium causing neurons to disappear into a puff of necrotic smoke. Time and the failure of numerous glutamate antagonists to be neuroprotective in real life have resulted in the re-evaluation of this simple scheme. The more complex reality of excitotoxic neuronal injury will be the focus of this panel, and we will discuss sources of injurious stimuli, the targets, and factors that modify the sensitivity of the targets to injury. Dr Kemp will critically evaluate the contribution of synaptic and non-synaptic NMDA receptors to neuronal injury. Dr Hewett will discuss observations suggesting that the secondary release of glutamate may be at least an equal if not a more important determinant of neuronal injury than initial NMDA receptor activation. Dr Hoyt will present an evaluation of glutamate receptor-mediated signaling in a chronic model of neurodegeneration, Huntington's disease, with a focus on the modulation of excitotoxicity by huntingtin. Dr Reynolds will focus on the relationship between mitochondrial location, morphology and function in the response of cells to excitotoxic injury. While not promising an answer to the question of how to protect neurons from excitotoxic injury in neurological disease, this panel will effectively highlight important additional variables that need to be considered when keeping this goal in mind.

Panel · Friday, January 30 · 4:30–6:30 PM · Bighorn C1

Stressing in the Bed Nucleus

J. Williams, D. Rainnie, E. Dumont, G. Aston-Jones, G. Koob

The bed nucleus of the stria terminalis is a forebrain cluster of nuclei that surrounds the caudal part of the anterior comissure. It has a very high content of CRF and receives dense noradrenergic and serotoninergic inputs from the brainstem and the midbrain. It is also innervated by glutamatergic connections from the hippocampus and the cortex as well as GABAergic inputs from the central nucleus of the amygdala. Efferents include the paraventricular nucleus of the hypothalamus and the ventral tegmental area. Because of this strategic localization, the BNST is an important integrating structure involved in stress related phenomena such as depression and drug abuse. This panel will review recent advances in understanding of local synaptic regulation and behavioral consequences of that control. Donald Rainnie will present work on the interaction between 5-HT and CRF on the regulation of activity of neurons in the lateral BNST. Eric Dumont will present work on the synaptic regulation of projection cells in the lateral BNST during acute opioid withdrawal with specific attention to the role of noradrenergic mechanisms. Gary Aston-Jones will present recent behavioral experiments showing that the activity in the ventral BNST is proportional to enhanced morphine seeking in previously morphine-dependent (5 weeks withdrawn) rats. George Koob will discuss recent evidence suggesting that the motivational effects of drug dependence may involve sensitization of elements of the brain stress systems in the BNST.

Panel · Friday, January 30 · 4:30–6:30 PM · Bighorn C2

Reversing Consciousness

A. Jenkins, G. E. Homanics, R. A. Pearce, L. E. Nelson, M. B. MacIver

The conscious brain strives to maintain the limbic control of awareness, learning and memory throughout the diencephalon and brainstem. When these systems fail or when their functions are modulated by drug action, we slide rapidly into unconsciousness. It is well known that many hypnotic drugs enhance GABA(A) receptor function, but the behavioral importance of this enhancement is unknown. This panel will discuss molecular, synaptic and network events that underpin the conscious state. Gregg Homanics will discuss the role the GABA(A) receptor plays in generating the anesthetized state by describing the effects of alcohol and anesthetics on a gene-knockin mouse line containing two amino acid substitutions in the alpha1 subunit that ablate anesthetic action in vitro. Bob Pearce will ask the question do ion-channel kinetics hold the key to memory modulation by anesthetics? He will explore two mechanisms by which changes in inhibitory synaptic function may modulate memory formation: “direct” control of LTP

via hyperpolarization and "indirect" control via changes in brain oscillations. Laura Nelson will describe a GABAergic pathway in the histaminergic tuberomammillary nucleus of the anterior hypothalamus implicated in sleep, sedation and anesthesia. Finally, Bruce MacIver will discuss the mechanisms underpinning G-force loss of consciousness (G-LOC), a major physical limitation experienced by fighter pilots (and the occasional snowboarder). In rats, EEG magnitude and spectral content are closely correlated with acceleration and are predictive of G-LOC onset.

Panel · Friday, January 30 · 4:30–6:30 PM · Hasty's

Regulation of Gene Expression in Psychiatry

J.P. Quinn, G. Breen, R. Maier, H. Marston

Genetic factors have been implicated in the aetiology of mental illness and many studies have determined that changes in protein correlate with predisposition to specific conditions. However there are an increasing number of polymorphic areas that are outside coding regions and still risk factors for a disorder. We predict that many of these regions act at the level of gene expression or mRNA processing and are mechanistically correlated with the disorder. Breen is constructing a global map of genetic variation using a microsatellite and minisatellite database of the human genome. These satellites are a common and highly informative class of polymorphism. They account for around 25% of genetic variation in humans and one can argue that they have a more likely functional effect of gene expression or function than a single nucleotide polymorphism(SNP). Quinn will demonstrate that certain classes of microsatellite DNA (found within monoamine transporter genes) correlated with predisposition to a variety of neurological disorders act as neuronal tissue specific and differential regulators of gene expression indicating a direct route for modulation of gene expression being associated a genetic predisposition to psychiatric disorders. This raises the question of function for many of the elements identified by Breen. Maier will demonstrate the changes in gene expression in schizophrenia. Finally, Marson will demonstrate how clinical validations of potential targets establish how these can be used in preclinical drug development . Linking the polymorphic and microarray data to systems neuroscience will be invaluable in developing novel therapeutic intervention

Panel · Friday, January 30 · 4:30–6:30 PM · Ptarmigan A

What Makes Parkinsonian's Parkinsonian?

T. Boraud, H. Bergman, M. Gluck, S. Haber

It is now well established that parkinsonian symptoms are caused by basal ganglia (BG) dopamine depletion and accompanied by severe modifications of dynamic properties of BG network. The most prominent features are

modification of firing frequency and pattern of the neurons at rest and emergence of synchronized oscillation at 4-15 Hz in the whole network. But, it still to be defined if those electrophysiological disruptions are causes or consequences of the clinical symptoms observed. In this panel symposium we propose an up to date statement of what has been collected about this topic. S Haber will provide new data on the relative impact various inputs to the midbrain are likely to have on dopamine cells. T Boraud backed by a model of the dynamic properties of the cortical-basal-ganglia motor loop will show that there is no clear cut correlation between the evolution of the motor symptoms and the disruptions of the dynamic properties of the BG neurons (GP and STN), in progressive parkinsonian syndrom induced by daily injections of low-dose of MPTP in primates. M Gluck and H Bergman will propose a new approach of parkinsonian motor symptoms enlighten by learning theories, respectively in rodents and primates.

Panel · Friday, January 30 · 4:30-6:30 PM · Ptarmigan B

Symposium on Neuregulin and Schizophrenia: From humans to animals

D. Brunner, G. Corfas, J. D. Buxbaum, M. O'Donovan, D. Talmage, H. Stefansson.

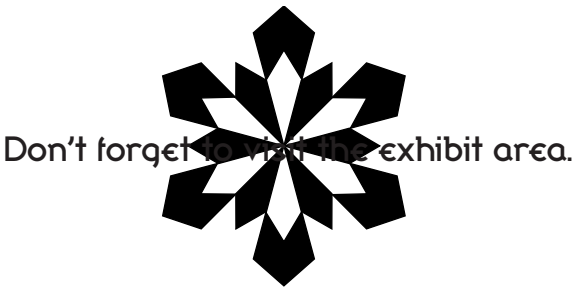
Dr. Brunner, the symposium organizer, will open the panel with a brief introduction and will present the speakers. Speakers will discuss data providing support for a role of neuregulin 1 (NRG1) in schizophrenia and discuss the newly discovered association between NRG1 and schizophrenia. Evidence implicating deficits in glia formation/maintenance in schizophrenic patients has lead to the proposal that a functional deficiency of glial growth factors and of growth factors produced by glial cells are among the distal causes in processes leading to schizophrenia. Dr. Corfas will review the literature on NRG and will speak about cell-specific approaches as tools to explore the role of NRG in brain development and function. Drs. Buxbaum and O'Donovan, in their talks "*Microarray analysis implicates oligodendrocyte abnormalities in schizophrenia*" and "*Genetic analysis of neuregulin and related genes in schizophrenia*", respectively, will present results from the analysis of human tissue pointing to defects in myelination of the forebrain as an early factor in schizophrenia. Concerning the role of NRG in neuron-glia interactions, Dr. Talmage will address new evidence in his talk "*Bidirectional signaling in the NRG system and its role in synaptic maintenance*". NRG1 is a growth and differentiation factor with three recognized gene products, types I, II and II, which differ in the domains present. Dr. Stefansson, will present new data regarding new gene variants in his talk "*New NRG1 subtypes and LD structure for Neuregulin*".

Panel · Friday, January 30 · 4:30–6:30 PM · Ptarmigan C

Dopamine Neurotransmission: A Functional Mystery Tour

P. Phillips, W. Schultz, M. Beckstead, W. Hopf

It was only relatively recently that the rapid nature of dopamine neurons for encoding reward and their compliance with formal learning theory were revealed, raising many mechanistic questions on this rapidly modulating system. In order to address these issues successfully investigators need to study the system at multiple levels from behaving animals to preparations that are more accessible to the fine tuning. This panel provides a slice of multidisciplinary research from some of the most influential labs working in this field. It progresses through the stages of dopamine transmission from the initial activation to the passage of information onto the next cell in the circuit. Wolfram Schultz will open the session by presenting single-unit electrophysiological recordings from alert monkeys, demonstrating how dopamine neurons are activated by reward-related stimuli and the computations they encode. Mike Beckstead will then discuss his work from John Williams, lab using patch-clamp electrophysiology in brain slices to explore some of the features of the D2 receptors that regulate impulse flow in these neurons. Next, Paul Phillips will present his studies that utilize electrochemical dopamine detection in awake rats to reveal the multiple short-term adaptive processes involved in the transformation of impulse activity to dopamine release at the terminal and how this signaling influences reward-seeking behavior. Finally, Woody Hopf will show data from Antonello Bonci's lab where he has demonstrated the co-operative interaction of D1 and D2 receptors in transduction of dopamine signaling in medium spiny neurons of the nucleus accumbens.



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Neurotechnology, ***Michael F. Huerta, Ph.D.***
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Small Business Technology Transfer, ***Margaret C. Grabb, Ph.D.***
Basic Neuroscience Centers, ***Laurie S. Nadler, Ph.D.***

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Director, Office of Special Populations, ***Ernest D. Márquez, Ph.D.***
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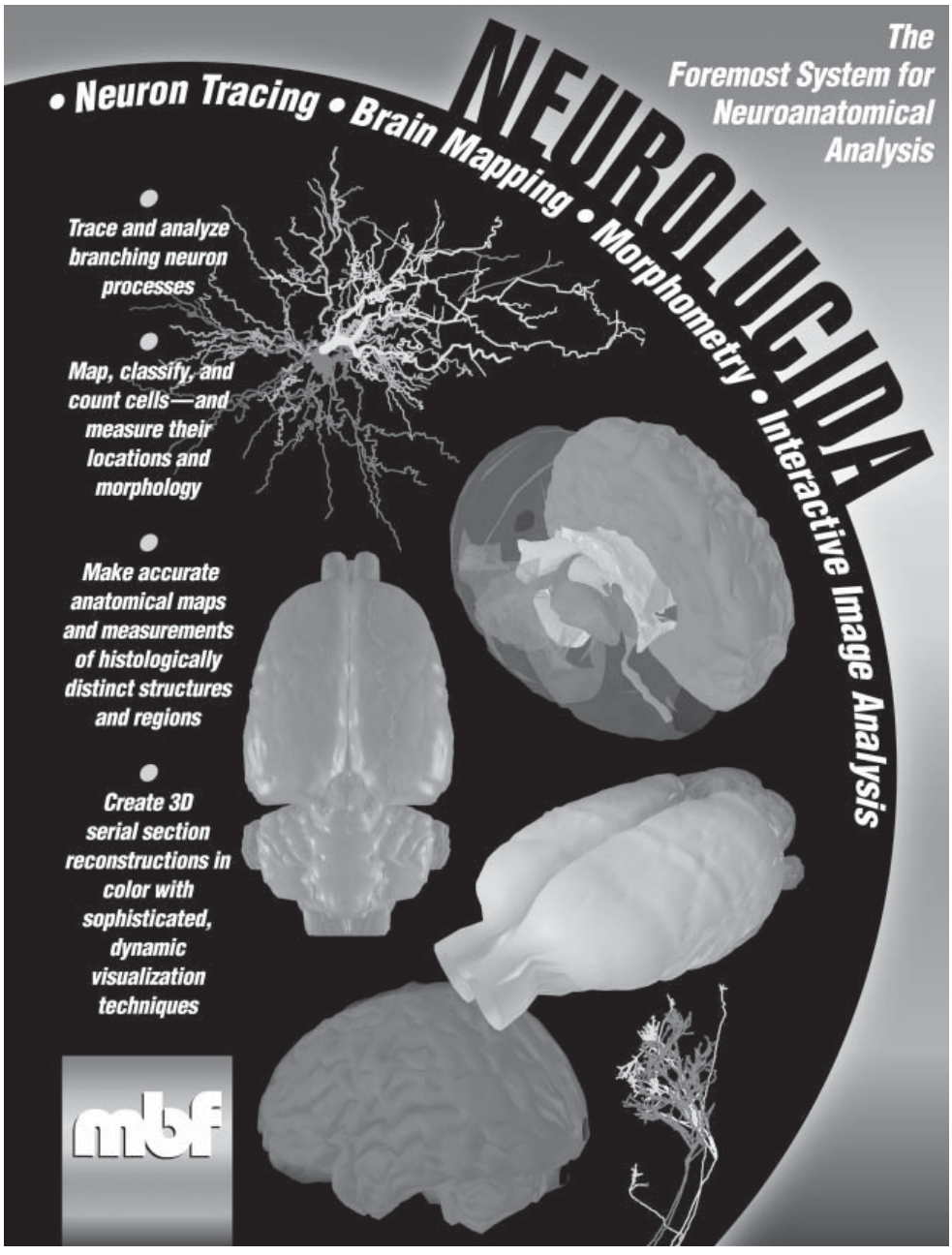
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Participant List/Index

Elizabeth Abercrombie
Rutgers University
abercrombie@axon.rutgers.edu

Anissa Abi-Dargham
Columbia University
aa324@columbia.edu

Anissa Abi-Dargham, 87
NYSPI
aa324@columbia.edu

Tunrayo Esther Adelusi
Jubril Matins High School
tunrayoadelusi@yahoo.com

Greti Aguilera
National Institute of Child Health and Human Development
Greti_Aguilera@nih.gov

Michael Ahlijanian
Pfizer, Inc.
michael_k_ahlijanian@groton.pfizer.com

Elliott Albers
Georgia State University
biohea@panther.gsu.edu

Charles Allen, 61
Oregon Health & Science University
allenc@ohsu.edu

Brenda Anderson, 39
State University of New York Stony Brook
banderson@notes.cc.sunysb.edu

Rodrigo Andrade, 107
Wayne State University School of Medicine
randrade@med.wayne.edu

Veronique Andre
University of California Los Angeles
vandre@mednet.ucla.edu

Glenn Andrews, 25
Medical University of South Carolina
andrewsg@musc.edu

Kristin Anstrom, 105
Wake Forest Health Sciences
kanstrom@wfubmc.edu

Margie Ariano, 57
The Chicago Medical School
arianom@finchcms.edu

Giorgio Ascoli, 107
George Mason University
ascoli@gmu.edu

Gary Aston-Jones, 78, 111
University of Pennsylvania
gaj@mail.med.upenn.edu

Constance Atwell
National Institutes of Health
ca23c@nih.gov

Sabine Bahn, 103
University of Cambridge/Babraham Institute
sabine.bahn@bbsrc.ac.uk

Vaishali Bakshi, 53
University of Wisconsin at Madison
vbakshi@wisc.edu

Krys Bankiewicz, 78
University of California San Francisco
kbank@itsa.ucsf.edu

Steve Barger, 97
University of Arkansas Medical School
sbarger@uams.edu

Allan Basbaum
W.M. Keck Foundation Center for Integrative Neuroscience
aib@phy.ucsf.edu

Anthony Basile
DOV Pharmaceuticals
abasile@dovpharm.com

Gary Bassell
Albert Einstein College of Medicine
bassell@aecom.yu.edu

Gillian Bates, 100
King's College London
gillian.bates@kcl.ac.uk

Steven L. Bealer, 77
University of Utah
steve.bealer@deans.pharm.utah.edu

Jill Becker, 91
University of Michigan
jbbecker@umich.edu

Mike Beckstead, 114
Oregon Health Sciences University
beckstem@ohsu.edu

Margery Beinfeld, 108
Tufts University School of Medicine
Margery.Beinfeld@tufts.edu

Jean-Claude Beique, 107
Wayne Sate University
jbeique@med.wayne.edu

Tim Benke, 90
University Colorado Health Science Center
tim.benke@uchsc.edu

Richard Beresford
University of Rochester School of Medicine
richard.beresford@med.va.gov

Will Berglind
Medical University of South Carolina
berglind@musc.edu

Hagai Bergman, 112
Hebrew University
hagaib@md.huji.ac.il

Craig Berridge
University of Wisconsin
berridge@wisc.edu

Anne Kjorsvik Bertelsen
Haukeland University Hospital
anne.kjorsvik@fys.uib.no

Isadora Bielsky
Emory University
irapopo@emory.edu

Llewellyn Bigelow
National Institute of Mental Health
bigelowl@intra.nimh.nih.gov

Graeme Bilbe
Novartis Institutes for Biomedical Research
graeme.bilbe@pharma.novartis.com

Charles Billington, 63
Minneapolis Veterans Administration Medical Center
billi005@umn.edu

James Bisley, 87
Columbia University
jwb2003@columbia.edu

Gene Block, 72
University of Virginia
gdb@virginia.edu

James Bloedel, 72
Iowa State University
jbloedel@iastate.edu

Stewart Bloomfield, 89
New York University School of Medicine
blooms01@med.nyu.edu

Martha Bohn, 78
Northwestern University
m-bohn@northwestern.edu

Antonello Bonci, 105
Gallo Center/UCSF
bonci@itsa.ucsf.edu

Stephen Bondy
University of California, Irvine
scbondy@uci.edu

Thomas Boraud, 112
CNRS
thomas.boraud@umr5543.u-bordeaux2.fr

Vlastislav Bracha, 72
Iowa State University
vbracha@iastate.edu

Xandra Breakefield, 78
Massachusetts General Hospital
breakefield@hms.harvard.edu

David Bredt, 62, 65
University California San Francisco
bredt@itsa.ucsf.edu

Gerome Breen, 112
Institute of Psychiatry
g.breen@iop.kcl.ac.uk

Michael Brenner, 26
UAB
aaron@nrc.uab.edu

David Brent, 93
University of Pittsburgh
sughrueb@upmc.edu

Christine Brown
Research!America
brownc@researchamerica.org

Daniela Brunner, 26, 113
PsychoGenics Inc. /Columbia University
daniela.brunner@psychogenics.com

John Bruno, 99
The Ohio State University
bruno.1@osu.edu

Marcy Bubar
University of Texas Medical Branch
mjbubar@utmb.edu

William Bunney, 93
University of California, Irvine
webunney@uci.edu

Gully Burns, 60
University of Southern California
gully@usc.edu

Joseph Buxbaum, 109, 113
Mt Sinai School of Medicine
joseph.buxbaum@mssm.edu

Nigel Calcutt, 92
University of California San Diego
ncalcutt@ucsd.edu

Joseph Callicott, 96
National Institutes of Mental Health, National Institutes of Health
callicoj@intra.nimh.nih.gov

Robert Cannon, 60
Edinburgh University
robert.cannon@ed.ac.uk

Angela Cantrell, 66
University of Tennessee Health Science Center
acantrell@utmem.edu

Bill Carlezon
Harvard Medical School
carlezon@mclean.harvard.edu

Ellen Carpenter, 95
University of California Los Angeles School of Medicine
ecarpenter@mednet.ucla.edu

David Carr, 80
Northwestern University
d-carr2@northwestern.edu

Stacy Castner, 41
University of Illinois at Chicago / MIICRO, Inc.
scastner@uic.edu and scastner@miicro.com

William Catterall, 90
University of Washington
wcatt@u.washington.edu

Jane Cavanaugh, 94
University of Pittsburgh
jec21@pitt.edu

Idil Cavus, 82
Yale University
idil.cavus@yale.edu

Leo Chalupa, 101
University of California Davis
LMCHALUPA@UCDAVIS.edu

Judson Chandler, 73
Medical University of South Carolina
chandj@mucs.edu

Jingyu Chang, 59
Wake Forest University
jchag@wfubmc.edu

John Chapin, 59
State University of New York Downstate
School of Medicine
john_chapin@downstate.edu

Marie-Francoise Chesselet, 88
University of California, Los Angeles
mchesselet@mednet.ucla.edu

Michael Chopp, 65
Henry Ford Hospital
chopp@neuro.hfh.edu

Julie Christianson, 92
University of Pittsburgh Medical Center
jcc26@pitt.edu

Patricia Churchland, 74
University of California San Diego
pschurchland@ucsd.edu

Paul Clarke
McGill University
pclarke@pharma.mcgill.ca

Jonathan Cohen, 75
Princeton University
jdc@princeton.edu

Carlo Colantuoni
National Institutes of Mental Health
colantuc@intra.nimh.nih.gov

Greg Cole, 76
University of California Los Angeles/
Veterans Administration
gmcole@ucla.edu

Graham Collingridge, 90
University of Bristol
g.l.collingridge@bristol.ac.uk

Carol Colton
Duke University Medical Center
glia01@aol.com

Christopher Colwell, 61
University of California, Los Angeles
ccolwell@mednet.ucla.edu

David Cook, 66
VA Medical Center, GRECC
dgcook@u.washington.edu

Gabriel Corfas, 113
Childrens Hospital Boston
gabriel.corfas@pch.harvard.edu

Michael Costigan, 76
MGH and Harvard
costigan@helix.mgh.harvard.edu

Carl Cotman
University California Irvine
cwcotman@uci.edu

Joseph Coyle, 61
Harvard Medical School
joseph_coyle@hms.harvard.edu

Fulton Crews, 42
UNC-Chapel Hill
ftcrews@med.unc.edu

Tara Crowder
Ernest Gallo Clinic and Research Center
UCSF
tarac@egcrc.net

Justin Crowley, 101
Carnegie Mellon University
jcrowley@neuro.duke.edu

Colm Cunningham
University of Southampton
cc7@soton.ac.uk

Kathryn Cunningham, 27, 58
University of Texas Medical Branch
kcunning@utmb.edu

Zafiris Daskalakis, 82
Centre for Addiction and Mental Health
Jeff_Daskalakis@camh.net

Beverly Davidson, 78
University of Iowa
beverly-davidson@uiowa.edu

Stephen Davies, 80
Baylor College of Medicine
sdavies@bcm.tmc.edu

Duff Davis, 28
Pfizer Inc.
duff.davis@pfizer.com

Fred Davis, 72
Northeastern University
f.davis@neu.edu

Ted Dawson, 84
Johns Hopkins University
tdawson@jhmi.edu

Valina Dawson
Johns Hopkins University School Of Medicine
VDAWSON@JHMI.EDU

Harriet de Wit
University of Chicago
hdew@midway.uchicago.edu

Lorraine DeGiorgio, 97
Burke Medical Research Institute
Ldegiorg@burke.org

Dominic Desiderio, 86
University Tenn. Health Science Center
ddesiderio@utmem.edu

Patricia Di Ciano, 71
University of Cambridge
pd241@cus.cam.ac.uk

Dennis Dickson, 81
Mayo Clinic
dickson.dennis@mayo.edu

Sylvain Dore
Johns Hopkins University / School of Medicine
sdore@jhmi.edu

Paula Dore-Duffy
Wayne State University
pdduffy@med.wayne.edu

Daniel Dorsa, 91
Oregon Health & Science University
dorsad@ohsu.edu

Kelly Drew, 97
University of Alaska Fairbanks
ffkld@uaf.edu

Fritz Drury, 63
Rhode Island School of Design
fdrury@risd.edu

Laura Dugan
Washington University
duganl@neuro.wustl.edu

Jennifer Dugas-Ford, 73
University of Chicago
jbdugas@uchicago.edu

Eric Dumont, 111
Vollum Institute
dumonte@ohsu.edu

Michael Egan, 96
National Institutes of Mental Health
eganm@intra.nimh.nih.gov

Burr Eichelman
University of Wisconsin
bseichelman@wisc.edu

Alaa El-Husseini, 29, 90
University of British Columbia
alaa@interchange.ubc.ca

Lisa Ellerby, 109
Buck Instititute for Age Research
lellerby@buckinstitute.org

Helene Emsellem
The Center for Sleep & Wake Disorders
sleepdoc@sleepdoc.com

Alan Faden, 55
Georgetown University Medical Center
fadena@georgetown.edu

Doug Falls, 96
Emory University
dfalls@emory.edu

James Fawcett, 67
University of Cambridge
jf108@cam.ac.uk

Elizabeth (Beth) Finch, 67
Emory University School of Medicine
finch@cellbio.emory.edu

Janet Finlay
Western Washington University
janet.finlay@wwu.edu

Beth Fischer
University of Pittsburgh
bfischer@pitt.edu

Thomas Fischer, 79
Wayne State University
Thomas.Fischer@wayne.edu

Colin Fletcher, 69
GNF/TSRI
fletcher@gnf.org

Francis Flynn, 77
University of Wyoming
flynn@uwyo.edu

Bob Foehring
University of Tennessee
foehring@nb.utmem.edu

Pamela Follett, 102
Children's Hospital
pamela.follett@tch.harvard.edu

Peter Fox
UTHSCSA
fox@uthscsa.edu

Donald Franz
University of Utah
sheila.merril@pharm.utah.edu

Sally Frautschy, 106
University of California Los Angeles
frautsch@ucla.edu

Lloyd Fricker, 59, 86
Albert Einstein College of Medicine
fricker@aecom.yu.edu

James Frost, 43
Johns Hopkins University SOM
jfrost@jhmi.edu

Michael Frotscher, 85
University of Freiburg
Michael.Frotscher@anat.uni-freiburg.de

Denson Fujikawa, 64, 83
VA University of California Los Angeles
dfujikaw@ucla.edu

Kathleen Ganley
University of California, San Francisco
kganley@usc.edu

Don Gash
University of Kentucky Medical Center
dongash@uky.edu cc: lizj@uky.edu

Volker Gauck, 67
University Tuebingen
volker.gauck@uni-tuebingen.de

Nori Geary, 108
Weill Medical College of Cornell Univ
ndgeary@med.cornell.edu

Jerry Gebhart
The University of Iowa
gf-gebhart@uiowal.edu

Herbert Geller
NHLBI
geller@umdnj.edu

Greg Gerhardt, 99
University of Kentucky, Chandler Medical Center
gregg@uky.edu

Kimberly Gerrow, 29
University of British Columbia
gerrow@interchange.ubc.ca

Dan Geschwind, 81
UCLA School of Medicine
dhg@ucla.edu

Mark Geyer, 107
University California San Diego
mgeyer@ucsd.edu

Martha Gillette, 61
University of Illinois
mgillett@life.uiuc.edu

Rhanor Gillette, 79
University of Illinois at Urbana
rhanor@uiuc.edu

Jay Gingrich, 30
Columbia University
jag46@columbia.edu

Mark Gluck, 112
Rutgers, The State University of New Jersey
gluck@pavlov.rutgers.edu

Todd Golde, 106
Mayo Clinic Jacksonville
tgolde@mayo.edu

David Goldman
National Institutes of Health, Park Building/Alcoholism & Abuse
dgneuro@box-d.nih.gov

Timothy Gomez
University of Wisconsin
tmgomez@facstaff.wisc.edu

Fernando Gomez-Pinilla, 76
University of California Los Angeles
fgomezpi@ucla.edu

Todd Gould, 56
National Institute of Mental Health
gouldt@intra.nimh.nih.gov

Gunnar Gouras, 66
Weill Medical College of Cornell University
gkgouras@med.cornell.edu

Bill Green, 70
University of Chicago
wgreen@midway.uchicago.edu

Carla Green, 72
University of Virginia
cbg8b@virginia.edu

J Timothy Greenamyre, 84
Emory University
jgreena@emory.edu

David Greenberg, 65
Buck Institute for Age Research
dgreenberg@buckinstitute.org

Carol Greenwood, 76
University of Toronto
carol.greenwood@utoronto.ca

Karen Greif
Bryn Mawr College
kgreif@brynmawr.edu

Sue Griffin, 97
University of Arkansas Medical School
stgriffin@uams.edu

Suzanne Haber, 80, 112
University of Rochester
suzanne_haber@urmc.rochester.edu

Edward Hall, 55
University of Kentucky Medical Center
edhall@uky.edu

Robert Handa, 53, 91
Colorado State University
robert.handa@colostate.edu

Sami Harik, 63
University of Arkansas College of Medicine
SIHarik@uams.edu

Michael Harris, 97
University of Alaska Fairbanks
ffmbh@uaf.edu

Ronald Harris-Warrick
Cornell University
rmh4@cornell.edu

Teresa Hastings, 84
University Pittsburgh School of Medicine
hastings@bns.pitt.edu

Johannes Hell
University of Iowa
johannes-hell@uiowa.edu

Hugh Hemmings, 30
Weill Cornell Medical College
hchemmi@med.cornell.edu

Fritz Henn
Central Institute of Mental Health
henn@zi-manneim.de

Ellen Hess, 69
Johns Hopkins University
ehess@jhmi.edu

Sandra Hewett, 110
University of Connecticut Health Center
shewett@neuron.uchc.edu

Bart Hoebel
Princeton University
hoebel@Princeton.EDU

Alexander Hoffman, 109
National Institute of Health/National Institute of Drug Abuse
ahoffman@intra.nida.nih.gov

Beth Hoffman, 54
Eli Lilly and Company
beth.hoffman@lilly.com

Ralph Hoffman, 82
Yale University School of Medicine
ralph.hoffman@yale.edu

Gregg E. Homanics, 111
University of Pittsburgh
homanicsge@anes.upmc.edu

William Honer, 103
University of British Columbia
honer@interchg.ubc.ca

Woody Hopf, 114
University of California San Francisco
woody@egcrc.net

Kristen Ashley Horner, 58
University of Utah
kristen.horner@pharm.utah.edu

Kari Hoyt, 110
Ohio State University
hoyt.31@osu.edu

Paul Huang, 65
Massachusetts General Hospital, East
phuang1@partners.org

Robert Huber, 79
Bowling Green State University
lobsterman@caspar.bgsu.edu

Richard Huganir, 90
HHMI/Johns Hopkins University
rhuganir@jhmi.edu

Robert Hughes, 100
Myriad Proteomics
rhughes@myriadproteomics.com

Patricia Hurn, 65
Oregon Health & Science University
hurnp@ohsu.edu

Michael Hutton, 81
Mayo Clinic
hutton.michael@mayo.edu

Thomas Hyde, 74
National Institute of Mental Health, NIH
HYDET@intra.nimh.nih.gov

Chrystelle Ibanez, 98
INSERM U488, Steroides et Système Nerveux
ukcambridge@hotmail.com

Donald Ingram, 53
National Institute on Aging
IngramD@grc.nia.nih.gov

John Isaac, 65
University of Bristol
j.t.r.isaac@bris.ac.uk

Amaal Islam
University of California, Los Angeles
aislam@mednet.ucla.edu

Michael Iuvone, 89
Emory University
miuvone@pharm.emory.edu

Erin Jacobs, 95
University of California, Los Angeles
ejacobs@mednet.ucla.edu

Gwen Jacobs, 107
Montana State University
gwen@cns.montana.edu

Russell Jacobs, 63
California Institute of Technology
rjacobs@caltech.edu

Mark Jacquin
Washington University School of Medicine
jacquinm@neuro.wustl.edu

Dieter Jaeger, 67
Emory University
djaeger@emory.edu

George Jaskiw, 105
Louis Stokes Cleveland VAMC
gxj5@po.cwru.edu

Andrew Jenkins, 111
Emory University School of Medicine
andrew_jenkins@emoryhealthcare.org

Emily Jocoy
University of California Los Angeles
ejocoy@ucla.edu

Alan Kim Johnson, 77
University of Iowa
alan-johnson@uiowa.edu

Carl Johnson, 100
Hereditary Disease Foundation
carljohnson@hdfoundation.org

Rolf Joho, 69
University of Texas Southwestern Medical Center
Rolf.Joho@utsouthwestern.edu

Elizabeth Jonas
Yale University School of Medicine
elizabeth.jonas@yale.edu

Carrie Jones, 54
Eli Lilly & Co
jones_carrie_k@lilly.com

Katalin Juhasz-Pocsine, 63
University of Arkansas Medical Sciences
pocsinekatalinj@uams.edu

Sharon Juliano, 85
Uniformed Services University of the Health Sciences
sjuliano@usuhs.mil

Leonard Kaczmarek
Yale University School of Medicine
leonard.kaczmarek@yale.edu

Peter Kalivas, 71, 103
Medical University of South Carolina
kalivasp@musc.edu

Rolf Karlstrom, 68
UMass Amherst
karlstrom@bio.umass.edu

Harvey Karten, 73, 87
University of California, San Diego
hjkarten@ucsd.edu

Paul Katz
Georgia State University
pkatz@gsu.edu

Michael Kavanaugh, 94
32 Campus Dr
kavanaug@selway.umt.edu

Kristen Keefe
University of Utah
k.keefe@m.cc.utah.edu

Ken Kellar, 70
Georgetown University School of Medicine
kellark@georgetown.edu

Edward Keller
Smith-Kettlewell Institute
elk@ski.org

John Kelsoe
University of California, San Diego
jkelsoe@ucsd.edu

Anna Kenney, 31
Dana-Farber Cancer Institute
Anna_Marie_Kenney@DFCI.harvard.edu

Andrew Kertesz, 81
University of Western Ontario
andrew.kertesz@sjhc.london.on.ca

Alane Kimes, 31
NIDA IRP
akimes@intra.nida.nih.gov

Sergei Kirov, 43
Medical College of Georgia
skirov@mail.mcg.edu

David Klein
NICHD,NIH
klein@helix.nin.gov

Joel Kleinman, 92
National Institutes of Mental Health
kleinmaj@intra.nimh.nih.gov

Jeffery Kocsis, 69
Yale University School of Medicine
jeffery.kocsis@yale.edu

Vassilis Koliatsos, 64
Johns Hopkins University School of Medicine
koliat@jhmi.edu

Alexei Kondratyev, 83
Georgetown University
kondrata@georgetown.edu

George Koob, 103, 111
The Scripps Research Institute
gkoob@scripps.edu

Stephen Koslow, 107
NIMH, NIH
koz@helix.nih.gov

Catherine Kotz, 53
Minneapolis Veterans Administration Medical Center
kotzx004@umn.edu

Scott Krahl, 69
University of California Los Angeles/VA Greater Los Angeles
scott.krahl@med.va.gov

Bart Krekelberg, 87
The Salk Institute
bart@salk.edu

David Kremers, 63
Caltech
davidkremers@caltech.edu

John Krystal, 82, 87
Yale School of Medicine
john.krystal@yale.edu

David Laidlaw, 63
Brown University
dhl@cs.brown.edu

Joseph LaManna, 65
Case Western Reserve University
JCL4@po.cwru.edu

Anthony LaMantia, 95
The University of North Carolina, Chapel Hill
anthony_lamantia@med.unc.edu

Richard Lane
Medical College of Ohio
rlane@mco.edu

Christopher Lapish, 44
Medical Univeristy of South Carolina
lapishc@musc.edu

Sari Lauri
University of Helsinki
sari.lauri@helsinki.fi

Antonieta Lavin, 78
Medical University of South Carolina
lavina@musc.edu

Charles Leffler
University of Tennessee
cleffler@physio1.utmem.edu

Sarah Leibowitz
The Rockefeller University
leibow@rockefeller.edu

Sherry Leonard, 92
University of Colorado Health Sciences Center
sherry.leonard@uchsc.edu

Henry Lester, 94
California Institute of Technology
lester@caltech.edu

Paul Letourneau
University of Minnesota
letour@lenti.med.umn.edu

Barry Levin, 63
East Orange Veterans Administration Medical Center
levin@umdnj.edu

Joel Levine, 67
State University of New York at Stony Brook
Joel.Levine@sunysb.edu

Michael Levine, 57
University of California Los Angeles
mlevine@mednet.ucla.edu

Steve Levison, 102
Penn State College of Medicine
slevison@psu.edu

Irwin Levitan
University of Pennsylvania School of Medicine
levitani@mail.med.upenn.edu

Anita Lewin
Research Triangle Institute
ahl@rti.org

David Lewis, 92
University of Pittsburgh
lewisda@upmc.edu

Stafford Lightman
University of Bristol UK
stafford.lightman@bristol.ac.uk

Iris Lindberg, 59
Louisiana State University Health Sciences Center
ilindb@lsuhsc.edu

Jon Lindstrom, 70
University of Pennsylvania Medical School
jslkk@mail.med.upenn.edu

Barbara Lipska, 103
National Institute of Mental Health
lipskab@intra.nimh.nih.gov

Marguerite Littleton-Keareny, 32
Johns Hopkins Medical Institutions
mkearney@jhmi.edu

Donald Lo, 33
Duke University Medical Center
lo@neuro.duke.edu

Joe LoTurco, 85
University of Connecticut
loturco@uconn.edu

David Lovinger, 109
National Institute on Alcohol Abuse and Alcoholism
lovindav@mail.nih.gov

Ronald Lukas, 70
Barrow Neurological Institute
rlukas@chw.edu

Peter Lukasiewicz, 89
Washingtion University School of Medicine
Lukasiewicz@vision.wustl.edu

Carl Lupica, 109
National Institutes of Health/National Institutes of Drug Abuse
clupica@intra.nida.nih.gov

Gary Lynch, 104
University of California, Irvine
glynch@uci.edu

Minda Lynch, 71
National Institutes of Health/National Institute on Drug Abuse
mlynch1@nida.nih.gov

Ernest Lyons
NIH/NINDS
lyonse@ninds.nih.gov

Bruce MacIver, 111
Stanford University
maciver@stanford.edu

Ken Mackie
University of Washington
kmackie@u.washington.edu

Wendy Macklin
Cleveland Clinic Foundatin
mackliw@ccf.org

Jeffrey Macklis, 57
Harvard Medical School
jeffrey_macklis@hms.harvard.edu

Carol MacLeod, 61
University of California, San Diego
cmacleod@ucsd.edu

Brian MacVicar, 85
University of British Columbia
bmacvica@interchange.ubc.ca

Timothy Maher, 105
Massachusetts College of Pharmacy & HS
tmaher@mcp.edu

Nigel Maidment, 99
University of California, Los Angeles
nmaidmen@ucla.edu

Rainer Maier, 112
Novartis Pharma AG
rainer.maier@pharma.novartis.com

Regina Maldve, 33
University of Texas at Austin
rmaldve@mail.utexas.edu

Roberto Malinow, 66
Cold Spring Harbor Laboratory
malinow@cshl.org

Robert Malison, 83
Yale School of Medicine
robert.malison@yale.edu

Laura Mamounas
NIH
rl230z@nih.gov

Shaila Mani, 91
Baylor College of Medicine
smani@bcm.tmc.edu

J John Mann, 93
Columbia University
jjm@columbia.edu

Olivier Manzoni, 109
Inserm
manzoni@bordeaux.inserm.fr

David Marcus, 34
New York University School of Medicine
DAVID.MARCUS@MED.NYU.EDU

Andres Maricq, 65
University of Utah
maricq@biology.utah.edu

Athina Markou
The Scripps Research Institute
amarkou@scripps.edu

Michael Marks, 70
University of Colorado
marksm@colorado.edu

Neville Marks
Nathan Kline Institute and NYU
marks@nki.rfmh.org

Hugh Marston
Organon Laboratories Ltd
h.marston@organon.co.uk

Maryann Martone, 60
University of California, San Diego
mmartone@ucsd.edu

Stephen Massey, 89
University of Texas Medical School at Houston
steve.massey@uth.tmc.edu

Mark Mattson, 76
National Institute on Aging
mattsonm@grc.nia.nih.gov

Margot Mayer-Proschel, 80
University of Rochester
margot_mayer-proschel@urmc.rochester.edu

Dayne Mayfield, 72
University of Texas at Austin
dayne.mayfield@mail.utexas.edu

A. Kimberley McAllister, 62
University of California Davis
kmcallister@ucdavis.edu

James G. McElligott, 72
Temple University School of Medicine
James.McElligott@temple.edu

Krista McFarland, 105
Medical University of South Carolina
mcfarlk@musc.edu

Jacqueline McGinty, 101
Medical University of South Carolina
mcginty@musc.edu

Hugh McIntyre
Harbor-UCLA Medical Center
hbmcintyre@pol.net

Mark Mehler, 80
Albert Einstein College of Medicine
mehler@aecom.yu.edu

Claudio Mello, 73
Oregon Health and Science University
melloc@ohsu.edu

Synthia Mellon, 98
University of California San Francisco
mellon@cgl.ucsf.edu

Marsha Melnick
NeuroClin2
marsha@neuroclin2.com

John Mendelson
UCSF
jemmd@itsa.ucsf.edu

Istvan Merchenthaler, 53
Wyeth Research
merchei@wyeth.com

Gloria Meredith, 101
Chicago Medical School
gloria.meredith@finchcms.edu

Ronald Meyer, 101
University of California Irvine
rlmeyer@uci.edu

Paul Micevych, 98, 108
David Geffen School of Medicine
pmicevych@mednet.ucla.edu

Adrian Michael, 99
University of Pittsburgh
amichael@pitt.edu

Bill Milsom, 97
University of British Columbia
milsom@zoology.ubc.ca

Dinah Misner, 35
Roche Palo Alto
dinah.misner@roche.com

Ralph Mistlberger
Simon Fraser University
mistlber@sfu.ca

Jeffrey Mogil, 76
McGill University
jeffrey.mogil@mcgill.ca

Holly Moore
Columbia University
hm2035@columbia.edu

Jill Morris, 96
Northwestern University and CMIER
j-morris4@northwestern.edu

Richard Morrisett, 73
University Texas-Austin
ramorris@mail.utexas.edu

Thomas Morrow, 92
University of Michigan
rufcat@umich.edu

David Mountain, 107
Boston University
dcm@bu.edu

Darrell Mousseau, 106
University of Saskatchewan
darrell.mousseau@usask.ca

Kerry Murphy, 57
Open University
k.murphy@open.ac.uk

N. Eric Naftchi
New York University
ericnaftchi@aol.com

Maiken Nedergaard, 85
Rochester University
maiken_nedergaard@nymc.edu

Laura Nelson, 111
Merck Sharp & Dohme
laura_nelson2@merck.com

Kim Neve, 45
Portland VA Medical Center
nevek@ohsu.edu

Roger Nicoll, 70
University of California, San Francisco
nicoll@cmp.ucsf.edu

Eric Nisenbaum, 104
Eli Lilly and Company
ESN@lilly.com

Laura Nisenbaum, 56
Eli Lilly and Company
l.nisenbaum@lilly.com

Akiko Nishiyama, 67
University of Connecticut
akiko.nishiyama@uconn.edu

Stephen Noctor, 85
Columbia University
scn8@columbia.edu

Lourdes Nogueira, 45
Medical University of south Carolina
nogueira@musc.edu

Kenneth Norman, 75
Princeton University
knorman@princeton.edu

Joseph Nunez, 102
University of Maryland, Baltimore
jnune001@umaryland.edu

Charles O'Brien, 103
University of Pennsylvania
obrien@mail.trc.upenn.edu

Patricio O'Donnell, 75
Albany Medical College
odonnep@mail.amc.edu

Michael O'Donovan, 113
University of Wales College of Medicine
ODonovanMC@Cardiff.ac.uk

Randall O'Reilly, 75
University of Colorado Boulder
oreilly@psych.colorado.edu

Kathie Olsen, 91
Executive Office of the President
kolsen@ostp.eop.gov

James Olson, 100
Fred Hutchinson Cancer Center
jolson@fhcrc.org

Valerie Olson, 83
University of Washington
vgolson@u.washington.edu

Gregory Ordway
University of Mississippi Medical Center
gordway@psychiatry.umsmed.edu

Mary Ann Ottinger, 53
University of Maryland
m020@umail.umd.edu

Ron Paletzki, 46
National Institute of Mental Health
paletzkr@intra.nimh.nih.gov

Sarah Pallas
Georgia State University
spallas@gsu.edu

Vladimir Parpura, 46
University of California
vlad@citrus.ucr.edu

Larry Parsons, 58
The Scripps Research Institute
lparsons@scripps.edu

Robert Pearce, 111
University of Wisconsin
rapearce@wisc.edu

Laura Peoples, 103
University of Pennsylvania
lpeoples@psych.upenn.edu

Ruth Perez, 94
University of Pittsburgh
ilto:perezrg@pitt.edu" perezrg@pitt.edu

Regino Perez-Polo
University of Texas Medical Branch
regino.perez-polo@utmb.edu

David Perkel, 73
University of Washington
perkel@u.washington.edu

Candace Pert, 55
Georgetown University School of Medicine
pertc@georgetown.edu

Phuong Pham
National Institutes of Health
pp64n@nih.gov

Paul Phillips, 114
University of North Carolina
pemp@unc.edu

Piazza Pier Vincenzo
University of Bordeaux 2
piazza@bordeaux.inserm.fr

Chris Pierce, 71
Boston University School of Medicine
rcpierce@bu.edu

Magistretti Pierre
University of Lausanne
pierre.magistrettiiphysiol.unil.ch

John Pintar, 59
Robert Wood Johnson Medical School
pintar@cabm.rutgers.edu

Stacey Poloskey, 36
University of Rochester School of Medicine
sp006k@mail.rochester.edu

The Honorable John Edward Porter

Emmanuel Pothos, 108
Tufts University School of Medicine
Emmanuel.Pothos@tufts.edu

Piotr Popik, 47
Polish Academy of Sciences
nfpopik@cyf-kr.euu.p

Steven Potkin, 93
University of California, Irvine
sgpotkin@uci.edu

John Povlishock, 55
Virginia Commonwealth University
jpovlish@mail2.vcu.edu

Christoph Proschel, 47
University of Rochester, Medical School
chris_proschel@urmc.rochester.edu

Serge Przedborski, 84
Columbia university
sp30@columbia.edu

Michael Quick, 94
University of Southern California
mquick@usc.edu

John Quinn, 112
University of Liverpool
JQUINN@LIV.AC.UK

Rémi Quirion
Douglas Hospital Research Centre
quirem@douglas.mcgill.ca

Don Rainnie, 111
Emory University
drainni@emory.edu

Brian Ramos, 78
Yale University
brian.ramos@yale.edu

Bruce Ransom, 69, 85
University of Washington
bransom@u.washington.edu

Judith Rapoport, 56
National Institutes of Health/National Institute of Mental Health
rapoport@helix.nih.gov

Jennifer Raymond, 72
Stanford University
jenr@stanford.edu

Lynn Raymond, 57
University of British Columbia
lynnr@interchange.ubc.ca

Wade Regehr, 67
Harvard Medical School
wade_regehr@hms.harvard.edu

Jens Rettig, 90
Saarland University
jrettig@uniklinik-saarland.de

Ian Reynolds, 110
University of Pittsburgh
iannmda@pitt.edu

Robert Rhoades
Medical College of Ohio
rrhoades@mco.edu

Denis Richard, 53
Laval University
denis.richard@phs.ulaval.ca

Steve Richardson, 106
University of Saskatchewan
richardson@sask.usask.ca

George Richerson, 94
Yale University
George.Richerson@Yale.Edu

Christopher Riegle, 101
University of California, Irvine
criegle@ivc.edu

Katherine Roche, 65
National Institutes of Health
rochek@ninds.nih.gov

Suzanne Roffler-Tarlov
Tufts University
suzanne.tarlov@tufts.edu

Dorit Ron, 101
Gallo Center/University California San Francisco
dorit@itsa.ucsf.edu

Jane Roskams, 64
University of British Columbia
roskams@zoology.ubc.ca

Christopher Ross, 109
Johns Hopkins School of Medicine
caross@jhu.edu

Elliott Ross, 74
University Oklahoma Health Science Center
elliott-ross@ouhsc.edu

Alec Roy, 93
Veterans Administration Medical Center
alec.roy@med.va.gov

Peter Ruben, 80
Utah State University
pruben@biology.usu.edu

Michael Ruff, 55
Georgetown University School of Medicine
ruffm@georgetown.edu

Amelia Russo-Neustadt, 48
California State University, Los Angeles
arusson@calstatela.edu

Jean Saint-Cyr, 59
University of Toronto
jean@uhnres.utoronto.ca

Michael Salter, 76
Hospital for Sick Children
mike.salter@utoronto.ca

Stephen Scheff, 55
University of Kentucky
sscheff@email.uky.edu

Todd Scheuer, 80
University of Washington
scheuer@u.washington.edu

Wolfram Schultz, 114
University of Cambridge
ws234@cam.ac.uk

Robert Schwarcz, 61
University of Maryland
rschwarc@mprc.umaryland.edu

Roy Schwarz
Pfizer Global Research & Development
roy.schwarz@pfizer.com

Erik Schweitzer, 37
University of California Los Angeles
schweitzer@mednet.ucla.edu

Jeremy Seamans, 87
Medical University South Carolina
seamans@musc.edu

Ronald See
Medical University of South Carolina
seere@musc.edu

David Self, 71
University of Texas Southwestern Medical Center
david.self@utsouthwestern.edu

Henry Sershen
Nathan Kline Institute
sershen@nki.rfmh.org

Susan Sesack
University of Pittsburgh
sesack@bns.pitt.edu

Yavin Shaham, 101, 105
National Institute on Drug Abuse
yshaham@intra.nida.nih.gov

Kent Shellenberger
Neuroclin2
Kent@neuroclin2.com

Gordon Shepherd, 107
Yale Medical School
gordon.shepherd@yale.edu

David Sibley, 49
NINDS/NIH
sibley@helix.nih.gov

Beth-Anne Sieber
National Institute of Mental Health
bseiber@mail.nih.gov

Ralph Siegel, 87
Rutgers
axon@cortex.rutgers.edu

Larry Siever, 49
Mount Sinai School of Medicine
Larry.Siever@med.va.gov

Rae Silver, 61
Columbia Unviersity
QR@columbia.edu

Steven Simasko, 108
Washington State Univ
simasko@vetmed.wsu.edu

James Simpkins, 53
University of North Texas Health Science Center
jsimpkin@hsc.unt.edu

Kevin Sinchak, 98
David Geffen School of Medicine
sinchak@mednet.ucla.edu

Sukanto Sinha, 109
Elan Pharmaceuticals
sukanto.sinha@elan.com

Phil Skolnick, 104
DOV Pharmaceutical, Inc.
pskolnick@dovpharm.com

Celia Sladek, 53, 77
University of Colorado Health Sciences Center
celia.sladek@uchcs.edu

Michelle Smeyne, 38
Saint Jude Children's Research Hospital
michelle.smeyne@stjude.org

Richard Smeyne
Saint Jude Children's Research Hospital
richard.smeyne@stjude.org

Chris Snell
Carl Zeiss Microimaging, Inc
jzellar@zeiss.com

Gretchen Snyder
Intra-Cellular Therapies, Inc.
gsnyder@intracellulartherapies.com

Adu Solomon
adu_solomon@yahoo.co.uk

Harald Sontheimer, 85
The University of Alabama at Birmingham
sontheimer@uab.edu

Madalina Stanciu
University of pittsburgh
madalina@pitt.edu

Amaal Starling, 50
University of California Los Angeles
aislam@mednet.ucla.edu

Hreinn Stefansson, 113
Decode Genetics

Donald Stein
Emory University
dstein04@emory.edu

Nephi Stella
University of Washington
nstella@u.washington.edu

Oswald Steward
University of California at Irvine
osteward@uci.edu

Bradford Stokes
The Ohio State University
stokes.1@osu.edu

Patrick Sullivan, 76
University of Kentucky Chandler
Medical Center
patsull@uky.edu

D. James Surmeier
Northwestern University
J-SURMEIER@NORTHWESTERN.EDU

Thomas Swanson, 69, 79
Midwest Neuroscience Inc.
domino@wcnet.org

Jonathan Sweedler, 86
University of Illinois
jsweedle@uiuc.edu

Tomi Taira, 90
University of Helsinki
tomi.taira@helsinki.fi

Joseph Takahashi, 72
Northwestern University
j-takahashi@northwestern.edu

David Talmage, 113
Columbia University
dat1@columbia.edu

Simon Tate, 76
GlaxoSmithKline
Simon.N.Tate@gsk.com

Timothy Teyler, 82
University of Idaho
tteyler@earthlink.net

Kerrie Thomas, 101
University of Cambridge
klt25@cus.cam.ac.uk

Fred Tilders
VU University Medical Center
fjh.tilders@vumc.nl

Arthur Toga, 60, 63
University of California Los Angeles
toga@loni.ucla.edu

Gary Tollefson, 56
Eli Lilly and Company
tollefson_gary_d@lilly.com

Kimberly Topp
University of California San Francisco
kstopp@itsa.ucsf.edu

Heather Trantham-Davidson
Medical University of South Carolina
tranthah@musc.edu

Mark Trocchi
Association Book Exhibit
info@bookexhibit.com

Ramon Trullas, 51
IIBB/CSIC
rtonbi@iibb.csic.es

Hideo Tsukada, 87
Hamamatsu Photonics K.K.
tsukada@crl.hpk.co.jp

Ikezu Tsuneya
University of Nebraska Medical Center
tikezu@unmc.edu,ningraham@unmc.edu

Wylie Vale, 53
Salk Institute
vale@salk.edu or guerra@salk.edu

Derek van der Kooy, 57
University of Toronto
derek.van.der.kooy@utoronto.ca

Moira van Staaden, 79
Bowling Green State University
mvs@caspar.bgsu.edu

Zoltan M. Varga, 68
University Freiburg
zoltan.varga@biologie.uni-freiburg.de

Michael Vitek, 55
Cognosci
mikevitek@cognosci.com

Franz X. Vollenweider, 107
Psychiatric University Hospital Zurich
vollen@bli.unizh.ch

Anthony Wagner, 75
Stanford University
wagner@psych.stanford.edu

Christine Wagner, 98
University at Albany
cwagner@albany.edu

Claes Wahlestedt, 54
Karolinska Institute
claes.wahlestedt@cgb.ki.se

Robyn Wallace, 80
University of Tennessee
rhwallace@utmem.edu

Claude Wasterlain, 83
University of California Los Angeles
wasterla@ucla.edu

Barry Waterhouse, 78
Drexel University College of Medicine
b.waterhouse@drexel.edu

Maree Webster, 103
SMRI, Uniformed Serv, 103ices
University of the Health
websterm@stanleyresearch.org

Daniel Weinberger, 92
National Institutes of Mental Health
weinberd@intra. nimh.nih.gov

David Weinshenker, 83
Emory University
dweinshenker@genetics.emory.edu

Friedbert Weiss
The Scripps Research Institute
bweiss@scripps.edu

Frank Welsh
University of Pennsylvania
fwelsh@mail.med.upenn.edu

John Welsh, 69
Oregon Health and Science University
welshj@ohsu.edu

Gary Westbrook, 62
Oregon Health Science University
westbroo@ohsu.edu

Monte Westerfield, 68
University of Oregon
monte@uoneuro.uoregon.edu

William Wetsel, 59
Duke University Medical Center
wetse001@mc.duke.edu

Stephanie White, 73
University of California Los Angeles
swhite@physci.ucla.edu

Scott Whittemore, 57
University of Louisville
swhittemore@louisville.edu

Frits-Axel Wiesel, 105
Uppsala University
Frits-Axel.Wiesel@neuro.uu.se

George Wilcox
University of Minnesota
george@umn.edu

Graham Williams, 107
University of Illinois / MIICRO, Inc.
gvw@uic.edu

John Williams, 111
Oregon Health Sciences University
williamj@ohsu.edu

Susan Wilt, 55
Bronx VA Medical Center
swilt@aaahawk.com

Roy Wise
National Institute on Drug Abuse
rwise@intra.nida.nih.gov

Jeff Witkin, 104
Lilly Research Labs
jwitkin@lilly.com

Terri Wood, 102
Penn State College of Medicine
twood@psu.edu

Donald Woodward, 59
Wake Forest University School of Medicine
dwoodwar@wfubmc.edu

Mary Woolley
Research!America
mwoolley@researchamerica.org

Doug Wright, 92
Kansas University Medical Center
dwright@kumc.edu

Tony Wyss-Coray, 106
Stanford University
twc@stanford.edu

Zhengui Xia, 94
University of Washington
zxia@u.wasington.edu

Bryan Yamamoto, 58, 105
Boston University School of Medicine
bkyam@bu.edu

F. Eugene Yates
University of California Los Angeles
gyates@ix.netcom.com

Michael Young
Harvard, Schepens Eye Research Institute
mikey@vision.eri.harvard.edu

Elmer Yu
University of Pennsylvania/ Philadedlphia VAMC
yu_e@mail.trc.upenn.edu

Cyrus Zabetian, 83
VA Puget Sound Health Care System
zabetian@u.washington.edu

Michael Zawada
University of Colorado Health Sciences Center
mike.zawada@uchsc.edu

Xiongwei Zhu
Case Western Reserve University
xxz12@po.cwru.edu

Michael Zigmond, 82
University of Pittsburgh
zigmond@pitt.edu

R. Suzanne Zukin, 62
Albert Einstein College of Medicine
zukin@aecom.yu.edu

Karl Zurn
Med Associates, Inc
karl@med-associates.com

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