

35
THIRTY-FIFTH ANNUAL

Winter Conference on Brain Research



January 26–February 2, 2002
Snowmass Village, Colorado



Office of Continuing Education

UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Toll free 877-455-2687
www.confed.uiuc.edu

Welcome to the Thirty-Fifth 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 Sunday, January 27. Our guest speaker will be Dr. Donald Kennedy, Editor-in-Chief of Science. On Tuesday, January 29, a **town meeting** will be held for the Aspen/Snowmass community at which Dr. George Ricaurte, and WCBR participants will discuss drug addiction and toxicity of addictive drugs. Also, participants in the WCBR **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.

The continued generous donations from sponsors has permitted us to continue the WCBR Fellowship Award Program. These awards are given to young neuroscientists who are on the program and who are newcomers to WCBR. Congratulations and a warm

welcome to this year's fellows: Dwight Bergles, Angela Cantrell, Ali Charara, Stephanie Cragg, Carolyn Fairbanks, Bruno Frenguelli, Christopher Lowry, Mary Lynn Mercado, James Olson, Carlos Paladini, Robia Paultler, Jochen Roeper, Yi Sun, Olga Vergun, Ruth Perez, Bill Shuttleworth , Amanda Smith, Taco de Vries.

Please plan to attend the business meeting at 6:30 p.m. on Wednesday, January 30. We will elect a Program Chair Elect and three members of the Board of Directors. Other important matters will be discussed including proposed changes in the by-laws and the selection of future conference sites.

Don't forget to visit the exhibit area.



Conference Chair

Allan I. Basbaum
Michael Levine, Conference Chair Elect

Program Committee

Elizabeth Abercrombie, Chair	Patricio O'Donnell David Perkel
Marjorie Ariano	George Richerson
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Fellowship Program

James Surmeier, Chair	Ed Hall
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Exhibits

Wendy B. Macklin

School Outreach

Kimberly Topp, Coordinator	Anita Lewin Hugh McIntyre
Krys Bankiewicz	Marsha Melnick
Paula Dore-Duffy	Mark Smith
Helene Emsellem	Brad Stokes
Janet Finlay	Tom Swanson
Beth Fischer	Kimberly Topp
Kyle Frantz	Frank Welsh
Judy Garner	Michael Zigmond
Karen Greif	

Town Meeting

Laura Peoples Patricio O'Donnell

Conference Arrangements

Scott C. Miller, Assistant Head
Conferences and Institutes
University of Illinois at Urbana-Champaign
Suite 202 Presidential Tower
302 East John Street
Champaign, IL 61820

2002 Fellowship Awardees

Dwight Bergles	Carlos Paladini
Angela Cantrell	Robia Paultler
Ali Charara	Jochen Roeper
Stephanie Cragg	Yi Sun
Carolyn Fairbanks	Olga Vergun
Bruno Frenguelli	Ruth Perez
Christopher Lowry	Bill Shuttleworth
Mary Lynn Mercado	Amanda Smith
James Olson	Taco de Vries

Winter Conference on Brain Research Fellowship Sponsors

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Don't forget to visit the exhibit area.



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Molecular and Cellular Neurosciences Research Branch

Division of Neuroscience and Basic Behavioral Science
National Institute of Mental Health
6001 Executive Blvd., Room 7168
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Tel (800) 645-8100 Box 6462 Fax (972) 625-6439
E-mail: johnsr@olympus.com

Don't forget to visit the exhibit area.



General Information

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

WCBR Information Desk and Message Center are in the conference center lobby. The desk hours are as follows:

	<i>Morning</i>	<i>Afternoon</i>	<i>Evening</i>
Saturday 1/26	9:00–11:00 AM	3:30–5:30 PM	7:30–10:00 PM
Sunday 1/27	7:00–8:00 AM	3:30–6:30 PM	
Monday 1/28– Friday 2/1	7:00–8:00 AM	3:30–4:30 PM	

The telephone number for messages is 970-923-2000 ext. 278. The Snowmass Village Conference Center FAX number is 970-923-6785. The person sending or receiving faxes is responsible for all charges.

Registration packets containing 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 did 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 throughout the week in the Anderson Room. Poster presenters will be by their posters for discussion from 3:30-4:30 PM on the first day of each of the three poster sessions: Poster Session 1 – Sunday/Monday; Poster Session 2 – Tuesday/Wednesday; and Poster Session 3 – Thursday/Friday. Presenters may put up their posters after 9:30 AM (after

2:30 PM on Sunday) on the day their session starts. Presenters should take down their posters by 10 PM on the second day of their session. Please see Poster Sessions section in program for titles and names of presenters.

Exhibits and Lounge are in the Anderson Room. Coffee is available there from 7:30–10:30 AM Monday through Friday. Refreshments are provided by the exhibitors 3:30–4:30 PM, Sunday through Friday.

Breakfast is served to all registrants on Sunday 7:30–8:20 AM, in the Anderson Ballroom, and on Monday through Friday, 6:30–7:30 AM, in the Eldorado Rooms of the Silvertree Hotel. (Social guests may breakfast until 10:00 AM). The tickets in your registration packet are required for admission. On Saturday morning (February 2) before departure, continental breakfast is available in the foyer of the Snowmass Village 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 on during desk hours.

Don't forget to visit the exhibit area.



Special Events

Saturday, January 26:

Welcome Wine and Cheese Party • 7:30–10:30 PM, Anderson Ballroom.

Sunday, January 27:

Conference Breakfast and Opening Address • 7:30 AM, Anderson Ballroom (Your required ticket is in your registration packet). Our plenary keynote speaker will be Donald Kennedy.

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

Monday, January 28:

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

Tuesday, January 29:

Town Meeting • 7:00–9:00 PM, The Aspen Elementary School District Theatre, 235 High School Road, Aspen.

Wednesday, January 30:

Smitty Stevens Memorial (NASTAR) Ski Race • 10:00 AM–11:30 AM, Spider Sabich Race Arena. NASTAR registration cards to be completed no later than Monday, January 28, 8:00 AM at WCBR Information Desk.

Mountain Lunch • 11:30 AM–2:00 PM. Spider Sabich Race Arena Picnic Area. (Required lunch ticket is in your registration packet). Non-skiers, requiring transportation, should sign up at the WCBR Information Desk.

Business Meeting• Election of Program Chair Elect and 3 Members of the Board of Directors – 6:30 PM, Hoaglund Room.

Friday, February 1:

Second Meeting Board of Directors • 6:30 PM, Max Park Room of the Wildwood Hotel.

Banquet and Dinner • 7:30 PM, Anderson Ballroom (required ticket is in your registration packet). Cash bar open at 6:30 PM in the foyer of the Snowmass Village Conference Center.

Preamble to the Program

The 2002 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 27

7:30 AM

BREAKFAST ADDRESS

Guest Speaker: Donald
Kennedy

Anderson Ballroom

3:30-4:30 PM

POSTER SESSION 1

Presenters available for
discussion.

Anderson Ballroom

4:30-6:30 PM

WORKSHOP • Modulating Mam-
malian Maps

R. Siegel, S. Kastner, L. Krubitzer,
D. O'Leary

Hoaglund

PANEL • Strengthening the Brain
against the Ravages of Time:
Implications for
Neurodegenerative Diseases of
Aging.

J. Joseph, R. Quirion, D. Ingram,
W. Greenough

Sinclair

WORKSHOP • Genetic Determi-
nants and Cellular Mechanisms
Underlying Resistance to
Excitotoxic Neurodegeneration

O. Steward, P. Schauwecker,
C. Shuttleworth, P. Sullivan

Erickson

PANEL • Moving to the "Front" of
the Class: Prefrontal Cortex,
Development and Learning

J. D. Cohen, B. J. Casey,
Y. Munakata, R. O'Reilly,
K. Koedinger

Carroll

PANEL • High Gly: Role of Glycine
Transporter in Regulation of
NMDA Receptor Function

H. Sershen, L. Harsing,
B. Lipska, P. O'Donnell

Snobble

PANEL • A New Look at an Old
Receptor: Basic and Clinical
Advances on the Brain Nico-
tinic Receptor

J. Coyle, D. Berg, S. Leonard,
R. Schwarcz

Janss

8:30-10:00 PM

PANEL • Adenosine in Brain: Sleep,
Seizures, Nerve Regeneration,
Drug Withdrawal,
Neuroprotection, and More!

R. Greene, S. Masino,
B. Frenguelli, J. Fowler

Hoaglund

PANEL • Structural Databases
Provide New Insights into
Structural/Functional Relation-
ships in the Nervous System

S. Koslow, K. Harris,
M. Ellisman, R. Williams,
S. Mori

Sinclair

Sunday, January 27, continued

WORKSHOP • Ventral Tegmental Area and Substantia Nigra Dopamine Neurons – Similar or Different?

J. Finlay, A. Charara, J. Tepper, J. Roeper, M. Wightman

Erickson

PANEL • NO and Neurodegeneration: Not Gone and Not Forgotten. Is Your Brain Protected or Is It Rotten?

S. Hewett, M. Espey, C. Colton, T. Dawson

Carroll

PANEL • Peripheral Nerve—Not Just a Cable Anymore

P. Reeh, L. Sorkin, G. Bove, H. Handwerker

Snobble

PANEL • Signaling Crosstalk and Molecular Interactions in Neuroendocrine Regulation

G. Aguilera, J. Cidlowski, D. DeFranco, J. Shepard, S. Radovick

Janss

Monday, January 28

7:30-9:30 AM

PANEL • Translational Approaches to Addiction: Novel Systems, Novel Animal Models, New Technologies Are Required?

G. Koob, B. Tabakoff, H. Gutstein, B. Mason

Hoaglund

PANEL • Do Alterations in Neuronal Membrane Properties and Synaptic Transmission Contribute to Striatal Dysfunction and Degeneration in Huntington's Disease?

A. Cantrell, M. Levine, L. Raymond, G. Rebec

Sinclair

PANEL • NO Way Nitric Oxide Is the Only Endothelium-Related Factor Regulating Cerebral Vasodilation: Redundancy and Interactions among Multiple EDRFs

D. Pelligrino, D. Harder, C. Leffler, S. Marrelli

Erickson

PANEL • Neurotransmitter/Neuropeptide Interactions in Neuroendocrine, Autonomic, and Homeostatic Systems.

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

Carroll

PANEL • Gene Therapy for Human Neurodegenerative Diseases: Scientific, Ethical and Legal Perspectives

R. Beresford, H. Federoff, J. Bernat

Snobble

PANEL • Functional Imaging of Neural Circuitry in the Retina.

M. Iuvone, R. Marc, S. Bloomfield, S. Massey

Janss

3:30-4:30 PM

POSTER SESSION 1

Posters continue to be available for viewing.

Anderson Ballroom

4:30-6:30 PM

PANEL • Perspectives on the Functional Organization of the Basal Ganglia

E. Abercrombie, P. Bolam, M. F. Chesselet, M. DeLong, H. Kita

Hoaglund

PANEL • 'Tide Life, 'Tide Death: The Genetic Control of Neuronal Survival

J. Morgan, K. Herrup, L. Parada, R. Smeyne

Sinclair

PANEL • Regulation of Ion Channels by Calcium-Calmodulin

J. Hell, W. Catterall, I. Levitan, J. Adelman

Erickson

PANEL • A New Look at the Role of Kainate Receptors in Epilepsy

G. L. Collingridge, C. Mulle, M. Rogawski, D. Lodge

Carroll

PANEL • Rho GPTases in Neuronal Development and Plasticity

T. Kuhn, J. Ng, H. Cline, P. Meberg

Snobble

PANEL • Role of CRF and Serotonergic Systems in Stress-Related Behavior

S. Lightman, L. Van de Kar, C. Lowry, S. Maier, L. Kirby

Janss

6:30-8:30 PM

MINI-COURSE • Providing Instruction in Responsible Conduct

B. Fischer, C. Atwell

Max Park Room

Wildwood Lodge

8:30-10:00 PM

PANEL • Dendritic mRNA Localization and Translation

G. Bassell & S. Zukin (co-chairs), D. Wells, O. Steward

Hoaglund

PANEL • Hol(e)y Mitochondria: the Transition from Life to Death?

I. Reynolds, E. Jonas, O. Vergun, J. Kemp

Sinclair

Monday, January 28, continued

PANEL • Voltammetric Monitoring of Behaviorally and Pharmacologically Elicited Changes in Extracellular Dopamine Levels

A. Michael, R. Wise,
D. Robinson, G. Rebec

Erickson

PANEL • Unravelling Synaptic Integration in Mammalian Central Neurons by Injection of Synthetic Conductances

H. Robinson, M. Häusser,
D. Jaeger, J. White

Carroll

PANEL • Induction of HO by WCBR-Related Activities: Good or Bad!

M. A. Smith, S. Doré, B. Dwyer,
N. Abraham

Snobble

PANEL • Selection of Candidate Genes and Candidate SNP's in Pharmacogenetic Studies of Antipsychotic Drug Response

A. Malhotra, M. Knable,
H. Van Tol, D. Goldman

Janss

Tuesday, January 29

7:30-9:30 AM

PANEL • Glutamate and Drugs of Abuse: Plasticity to Toxicity

B. Yamamoto, D. Farb,
G. Siggins, M. Wolf

Hoaglund

PANEL • Cortical Network States, Memory Formation, and the First Generation Cyborg

D. Plenz, H. Robinson, S. Potter,
S. Marom

Sinclair

PANEL • New Trends in Cellular and Gene Therapy for Neurological Disorders

C. Borlongan, L. Granholm,
M. Chopp, E. Snyder, W. Freed

Erickson

PANEL • Retinoids in the Developing, Adult and Injured CNS

M. Maden, L. Wilson, S. Smith,
J. Fawcett

Carroll

PANEL • Anatomical and Pharmacological Determinants of Relapse to Cocaine-Seeking Behavior

R. C. Pierce, J. Rowlett, R. See,
F. Weiss

Snobble

PANEL • Astrocyte Function: Back to the Future

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

Janss

3:30-4:30 PM

POSTER SESSION 2

Presenters available for discussion.

Anderson Ballroom

4:30-6:30 PM

PANEL • Dopaminergic Modulation of PFC Excitability: Is Dopamineschizoid or Are We Deluded?

D. J. Surmeier, J. Seamons, G. Barrionuovo, J. Hablitz, P. O'Donnell

Hoaglund

PANEL • Dynamic Assembly of Synapses: Lessons from the Fly and the Mouse

V. Budnik, C. Garner, L. Guosong, L. Griffith

Sinclair

PANEL • A View of the Mammalian Circadian System from the Midbrain Raphe

R. Mistlberger, M. Duncan, J.D. Glass, J. Miller

Erickson

PANEL • Have We Got Connections, Revisited: Convergent Methods for Elucidation of Connectivity in the Brain

D. Kennedy, P. Fox, R. Pautler, J. Belliveau

Carroll

PANEL • A Pivotal Role for cdk5 in Mechanisms of Neurodegeneration and Addiction

M. Ahljanian, L. Tsai, J. Bibb, J. Wang, T. Saito

Snobble

PANEL • Neurotransmitter Release without a Probe: The Wonders of Brain Imaging

J. Frost, M. Laruelle, Y. Ding, R. Rothman

Janss

8:30-10:00 PM

WORKSHOP • The Neurobiology of Viral Vectors: Neuroanatomy, Protein Targeting, Behaviour, and Therapeutics

P. Lowenstein, L. Enquist, G. Banker, B. Davidson

Hoaglund

WORKSHOP • Trials and Tribulations

K. Gale, D. Spencer, C.R. Freed, M. Walker, C. Atwell

Sinclair

PANEL • Biological Models of Basal Ganglia Networks

H. Bergman, D. Plenz, S. Haber, J. Houk

Erickson

PANEL • Metabolic Demand in Neurodegenerative Disease, Hibernation and Anoxia Tolerance: The Less You Want the More You Have.

K. Drew, J. LaManna, P. Lutz, M.A. Smith

Carroll

PANEL • GABA-A Receptors: Synaptic versus Extrasynaptic Sites of Action

S. Smith, D. Coulter, L. Overstreet, I. Mody

Snobble

Tuesday, January 29, continued

PANEL • What Are We Learning
from Microdialysis of the
Human Brain?
N.T. Maidment, M.G. Boutelle,
O. Alves, M.J. During
Janss

Wednesday, January 30

7:30-9:30 AM

PANEL • Dynamic Cyclic Nucle-
otide Signaling in Neurons
P.S. Katz, R. Gillette, F. Zufall,
D.M.F. Cooper
Hoaglund

PANEL • 2002 Census Report on
NMDA Receptor Subtypes in
Striatum: More Than One
K. Keefe, D. Standaert,
K. Wilcox, D. Lovinger
Sinclair

PANEL • No Bones about It: Roles
for Calcium in the Acute and
Chronic Actions of Drugs of
Abuse
B. Carlezon, B. Catterall,
C. Konradi, C. Pierce
Erickson

WORKSHOP • Apoptosis in
Neurological Diseases: Myth or
Reality?
R. Quirion, S. Doré, C. Cotman,
K. Jellinger
Carroll

PANEL • Alcoholism Vulnerability:
From Neurobiology to Genetics
J. Krystal, D. Goldman,
J. Lappalainen, A. Heinz
Snobble

PANEL • Cerebral Functional
Localization: Fact, Fiction or
Something Else?
E. Ross, D. Stein, A. Kertesz,
S. Small, A. Hillis
Janss

3:30-4:30 PM

POSTER SESSION 2

Posters continue to be available
for viewing.

Anderson Ballroom

4:30-6:30 PM

PANEL • Cell and Gene Therapy for
Treatment of Neurologic
Disease
C.R. Freed, K. Bankiewicz,
J. Cooper, E. Snyder
Hoaglund

PANEL • Neuroprosthetic Applications Using Brain-Machine Interface Technology

J. Chapin, M. Nicolelis,
S. Giszter, K. Moxon

Sinclair

WORKSHOP • High Times at the WCBR

K. Mackie, N. Stella,
O. Manzoni, R. Nicoll

Erickson

PANEL • Substrate-Mediated Regulation of Neurotransmitter Transporters

N. Zahniser, J. Gulley, A. Galli,
S. Apparsundaram,
M. Robinson

Carroll

PANEL • Intriguing Links between Neurons and Melanocytes

S. Roffler-Tarlov, H. Arnheiter,
S. Landis

Snobble

PANEL • Pallidal Plasticity

T.C. Napier, G. Arbuthnott,
S. Haber, G. Meredith

Janss

Thursday, January 31

7:30-9:30 AM

PANEL • AMPA and NMDA Receptor Targeting And Trafficking: Implications For Synaptic Transmission And Plasticity

P. Seeburg, R. Huganir,
R. Malenka, R.S. Zukin

Hoaglund

PANEL • Beyond Symptoms: Neuroprotective Strategies in Parkinson's Disease

M. Zigmond, M. Bohn,
V. Dawson, O. Isacson, P. Carvey

Sinclair

PANEL • The Importance of the Anterior Cingulate in Mood Regulation and Psychosis

W. Bunney, H. Mayberg,
N. McFarland, C. Tamminga,
S. Potkin

Erickson

PANEL • Black Diamonds and Black Label: Effects of Acute Stress on Responses to Drugs

H. de Wit, P. Piazza, Y. Shaham,
R. Sinha

Carroll

Thursday, January 31, continued

PANEL • GABA_A Receptors and Disease: The Delicate Balance Between Alpha 1 and Alpha 4 Subunits

S. Russek, A. Brooks-Kayal, A.L. Morrow, J. Luebke

Snobble

PANEL • Adaptation to Altitude: Brain Hypoxia and Gene Response

S. Harik, J. LaManna, J. Dunn, G. Haddad, P. Dore-Duffy

Janss

3:30-4:30 PM

POSTER SESSION 3

Presenters available for discussion.

Anderson Ballroom

4:30-6:30 PM

PANEL • Springtime for Glia

B.A. Sieber, Y. Sun, E. Anton, D. Bergles, E. Ullian

Hoaglund

PANEL • alpha-Synuclein and Parkinson's Disease: Two Entities in Search of a Connection

R. Perez, V. Lee, Y. Schmitz, M. Lee

Sinclair

PANEL • New Kidz on the Block: Novel Neurotransmission in Pain and Analgesia

C. Fairbanks, S. Carlton, J. Mogil, J. Zadina

Erickson

PANEL • Subcortical Influence on Cortical Processing

G. Tononi, M. Salbaum, F. Ghilardi, A. Schwartz
Carroll

PANEL • The Big Bad Wolf and the Three Little Pigs: Substance Abuse and the Three Monoamines

G. Ordway, D. Goldman, A. Markou, T. Svensson

Snobble

PANEL • Scientific Meetings at High Altitude: a.k.a. Ischemic Preconditioning in the Brain

E. Aizenman, V. Dawson, M. Gonzalez-Zulueta, J. Hallenbeck

Janss

8:30-10:00 PM

PANEL • Stem Cells and CNS Repair

S. Whittemore, E. Snyder, T. Hagg, M. Young

Hoaglund

PANEL • Basal Ganglia—Superior Colliculus Relationships: Novel Perspectives, New Directions

B. Stein, J. McHaffie, T. Stanford, P. Redgrave, E. Meloni

Sinclair

PANEL • Synaptic and Non-Synaptic Regulation of Dopamine Neurons

C.A. Paladini, J. Tepper, I. Mintz, A. Bonci

Erickson

PANEL • Cholinergic Mechanisms
in Reward and Arousal

J. Yeomans, P. Clarke,
S. Ikemoto, P. Rada

Carroll

WORKSHOP • Branch, Elongate, or
Retract, How Are Arbors
Defined?

R. Lane, L. Chalupa,
M. Jacquin, R. Rhoades,
F. White

Snobble

PANEL • Inhibitory Processes in
Brain Development and Repair

H. Geller, J. Fawcett, J. Raper,
H. Keirstead, M.L. Mercado

Janss

Friday, February 1

7:30-9:30 AM

PANEL • Cell Biology of
Huntington's Disease

E. Schweitzer, E. Cattaneo,
J. Olson, C. Ross

Hoaglund

PANEL • Cellular and Genetic
Coupling in the Circadian
System

C. Colwell, D. McMahon,
K. Obrietan, G. Block

Sinclair

PANEL • Cocaine Craving: Cues
and Clues

Y. Shaham, J. Grimm,
T. de Vries, C. Bradberry,
C. O'Brien

Erickson

PANEL • Extrasynaptic Neurotrans-
mission and Tonic Inhibition:
GABA-A Receptors

W. Wisden, W. Sieghart,
H. Lüddens, Z. Nusser,
E. Korpi

Carroll

PANEL • Common Processing
Themes in Rat Prefrontal
Cortex and Related Structures

G. Schoenbaum, S. Ramus,
K. Anstrom, G. Quirk

Snobble

PANEL • Mechanisms of Chronic
Central Pain: From Molecules
to Man

C. Hulsebosch, P. Dougherty,
K. Sluka, T. Morrow, C. Sang

Janss

3:30-4:30 PM

POSTER SESSION 3

Posters continue to be available
for viewing

Anderson Ballroom

Friday, February 1, continued

4:30-6:30 PM

PANEL • Dopamine Behavior in the CNS: Regulation of Release and Efficacy

M. Rice, S. Cragg, D. Sulzer,
M. Wightman
Hoaglund

PANEL • BDNF: of Mice and Men

B. Lipska, A. Morozov,
L. Mamounas, C. Weickert
Sinclair

PANEL • Does Prediction Help in Surviving the Moguls? Overcoming Performance Constraints through Prediction and Adaptation

E. Keller, S. Heinen,
A. Schwartz, J. Bloedel, L. Young
Erickson

PANEL • Manipulating CNS Myelination in Development and Repair

R. Franklin, C. French-Constant, J. Goldman,
I. Duncan
Carroll

PANEL • Electrical Synapses among Inhibitory Cortical Neurons

S. Hestrin, M. Bennett,
H. Monyer, B. Connors,
M. Galarreta

Snobble

PANEL • The Sweet Glow of Success: Applications of GFP Technology for the Study of Neural Development

K. Greif, G. Feng, M. Nonet,
M. Westerfield

Janss

Don't forget to visit the exhibit area.



Poster Sessions Schedule and Abstracts

Poster Session 1 · Sunday/Monday · Anderson Ballroom

Posters will be available for viewing from 3:30 PM Sunday to 4:30 PM Monday. Presenters will be with the posters on Sunday from 3:30 to 4:30 PM.

1. Studies on the Molecular Determinants for Alcohol Sensitivity of 5-HT₃ Receptor-Channels

FF Weight, M. Fukuzawa, M. Hosoi, X.-Q. Hu, E. Moradel, J. Schoenebeck, H. Sun & L. Zhang. Laboratory of Molecular & Cellular Neurobiology, NIAAA, NIH, Bethesda, MD 20892-8115

Ethanol potentiates the function of 5-HT₃ receptor-channels in various types of neurons and several studies have suggested that the 5-HT₃ receptor may be involved in alcohol preference and reward mechanisms. Previously, using a chimeric nicotinic-serotonergic receptor, we found evidence that alcohol and anesthetic effects on receptor function involve the extracellular N-terminal domain of the receptor (Mol. Pharmacol. 50:1010-1016, 1996; Br. J. Pharmacol. 120:353-355, 1997). We are now studying the effect of single amino acid mutations in the N-terminal domain on the function and ethanol sensitivity of the 5-HT₃ receptor. Recombinant wild-type (WT) & mutant 5-HT₃ receptors were expressed in *Xenopus* oocytes and their function was studied using two-electrode voltage-clamp. We found that substitution of the arginine at amino acid 245 (R245) in the N-terminal domain of the 5-HT₃ receptor with several other amino acids altered both the apparent agonist affinity and the ethanol sensitivity of the 5-HT₃ receptor. The order of EC₅₀ values of the 5-HT concentration-response curves was R245A < R245E < R245T < WT < R245K. On the other hand, the order of percentage potentiation by 100 or 200 mM ethanol was R245A > R245E > R245T > WT > R245K. The percentage potentiation by ethanol inversely correlates with the EC₅₀ values of the 5-HT concentration-response curves, suggesting that mutation of R245 may affect ethanol sensitivity by altering the apparent agonist affinity of the receptor. Kinetic analysis of WT and R245A receptors expressed in HEK 293 cells, using whole-cell patch-clamp recording in combination with rapid extracellular solution exchange, revealed that the mutation greatly increased the rate of channel opening (activation) but did not affect the rate of channel closing (deactivation). In addition, for mutant receptors with F, I, Q, D or G at 245, ethanol (30-200 mM) directly activated inward current and the amplitude of that current correlates with the amplitude of outward

current induced by MDL-72222 (100 nM), a 5-HT₃ receptor antagonist. The observations suggest that amino acid 245 is involved in gating the 5-HT₃ receptor-channel and thereby allosterically affects the ethanol sensitivity of the receptor.

2. A Novel Stimulus-Transcription Coupling Pathway Linking Dopamine to HO-1 Induction in Astroglia

J.E. Schmidt, St. Jude Children's Research Hospital

The pathology associated with Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) with evidence of iron deposition, mitochondrial dysfunction, and oxidative injury. Heme oxygenase-1 (HO-1) is an oxidative stress-inducible gene that is over-expressed in astroglia of PD patients. Furthermore, in the mouse MPTP model of PD, HO-1 is over-expressed exclusively in striatal astroglia. Since HO-1 plays a critical role in iron homeostasis and cellular responses to oxidative stress, it may contribute to PD pathology. We have investigated the mechanisms by which HO-1 expression is regulated in the MPTP paradigm as a prelude to elucidating its role in PD. Dopamine (DA) is a potent inducer of HO-1 in cultured astroglia suggesting that dopamine released from affected SNpc neurons may trigger HO-1 induction in striatal astroglia. Furthermore, in excess, the products of HO-1 activity (iron, carbon monoxide, and bilirubin) are neurotoxic. Thus, these products may represent a mechanistic link between HO-1 induction and PD pathology by producing a feed-forward cytotoxic cycle. Utilizing astroglial culture models we employed pharmacological inhibitors of candidate regulatory factors to characterize the stimulus-transcription coupling pathway by which DA induces HO-1 expression. Although dopamine induction of HO-1 is not mediated by dopamine receptors, transporters, or common dopamine metabolites, this induction is triggered by an intermediate of dopamine oxidation. Subsequent downstream signaling is mediated in part by HSP-90, tyrosine kinases, and NF- κ B family members. Our findings suggest potential molecular targets amenable to therapeutic modulation in the treatment of PD. Supported in part by NIH Cancer Center Support CORE Grant P30 CA 21765, the American Lebanese Syrian Associated Charities (ALSAC), and NIEHS ES 10772 to J.I.M.

3. Melatonin Regulation: Involvement of a cAMP Operated Protein Binding Switch

D. Klein, NICHD, NIH

A remarkably conserved feature of vertebrate physiology is a 10 to 100-fold daily rhythm in melatonin production, with highest values occurring at night. This daily rhythm in melatonin levels is controlled by cAMP through actions on the penultimate enzyme in melatonin synthesis pathway, arylalkylamine N-acetyltransferase (AANAT). cAMP regulates AANAT at the post-translational level in most vertebrates. We have found that cAMP acts

through an evolutionarily conserved cAMP-dependent protein kinase (PKA) phosphorylation site (RRHT31) located at the N-terminal region of the molecule. Phosphorylation of this site converts the region into a motif, RRHpT31LP, that binds to 14-3-3 proteins. This family is composed of 30 and 33 kDa isoforms, which exist as homo- and hetero-dimers. X-ray crystallographic analysis of the 14-3-3/AANAT complex revealed that this motif binds to an amphipathic groove of 14-3-3. Complex formation decreases the K_m of phospho-AANAT for arylalkylamine substrates (~10-fold) and hence activates AANAT; apparently by restricting the movement of a floppy loop of the enzyme. That activation of AANAT in the cell is dependent upon phosphorylation of the binding motif was also demonstrated in COS7 cells using wild type AANAT and an AANAT T31/A mutant. Complex formation also shields AANAT from dephosphorylation and proteolysis in vitro. These results suggest that the phospho-AANAT/14-3-3 regulatory complex plays a pivotal role in melatonin production in two ways. First, by rapid cAMP-dependent activation of AANAT; second, by protecting AANAT against proteasomal proteolysis. It is of interest to consider that cAMP-operated 14-3-3 binding switches, similar to that described here, may be essential elements of cAMP-mediated signal transduction in other vertebrate systems because 14-3-3 proteins are ubiquitous and putative 14-3-3 binding motifs occur in many proteins.

4. Clozapine-Induced Dopamine Release in Medial Prefrontal Cortex Depends on Local Tyrosine Availability: Studies of Tyrosine Depletion and Augmentation

G. E. Jaskiw, Louis Stokes Cleveland VAMC

Several lines of evidence suggest that PFC DA levels can be influenced by the availability of the precursor tyrosine. For instance, systemically administered tyrosine augments clozapine-induced DA release in the MPFC of the rat, as measured by in vivo microdialysis (Jaskiw et al, 2001). We now report how tyrosine depletion affects MPFC DA levels. Male Sprague-Dawley rats (200-250gr) had a unilateral cannula inserted into the MPFC. Two days after surgery, a microdialysis probe was lowered (AP +3.2, ML +0.7). Sixteen hrs later, microdialysate collection began (1.0 μ /min). Some animals were pretreated with a tyrosine and phenylalanine free neutral amino acid mixture (NAA-) two IP injections (1g/kg each) 1 hr apart. NAA- reduced MPFC microdialysate tyrosine levels by 48%. Clozapine (10mg/kg IP) increased MPFC DA release to 270% of baseline. The latter was attenuated by pretreatment with NAA- (139% of baseline, $p < 0.0001$). Pretreatment with NAA-, followed by co-administration of clozapine and tyrosine (100mg/kg IP) restored the clozapine-induced MPFC DA release, confirming that clozapine-induced MPFC DA release depends on tyrosine availability. In a separate study, we infused tyrosine locally through a microdialysis cannula. Clozapine 10mg/kg IP increased MPFC DA levels (209% of baseline). The latter was significantly ($p < 0.05$) augmented by local infusion of tyrosine (305% of baseline). The data indicate that tyrosine levels within the MPFC

affect clozapine-induced DA release and suggest that manipulation of brain tyrosine levels may be useful both in the development of research probes and in the pharmacotherapy of schizophrenia.

5. The Effects of Chronic Clozapine or Haloperidol Treatment on Rat Brain Vesicular Monoamine Transporter

M. Rehavi, Tel-Aviv University

Clozapine is an atypical antipsychotic drug, found to be effective in reducing negative symptoms of schizophrenia, depressive symptoms and suicidal behavior and has low incidence of extrapyramidal side effects. We compared the effects of chronic clozapine and haloperidol treatment on the expression of rat brain vesicular monoamine transporter (VMAT2) as well as on the membranal presynaptic transporters for serotonin, dopamine and noradrenaline. Rats were treated for 21 days with clozapine (25 mg/kg), haloperidol (0.5mg/kg) or saline. VMAT2 expression was assessed on the protein level by high affinity [³H]dihydropyridylbenzazepine binding using autoradiography, and on the RNA level by in situ hybridization. The densities of the dopamine, serotonin and noradrenaline transporters were evaluated by autoradiography using high affinity binding of [³H]GBR 12935, [³H]paroxetine and [³H]nisoxetine, respectively. Clozapine administration led to an increase in [³H]TBZOH binding in the nucleus accumbens, prefrontal cortex and striatum, whereas haloperidol had no effect on VMAT2 binding capacity. The clozapine-induced increase in VMAT2 was accompanied by a parallel increase in the membranal serotonin transporter in the prefrontal cortex and striatum, as well as a slight decrease in the norepinephrine transporter in the mediodorsal thalamic nucleus. Haloperidol induced an increase in the serotonin transporter in the striatum and the core of the nucleus accumbens. Neither clozapine nor haloperidol had an effect on the dopamine transporter or the mRNA level of VMAT2. The unique upregulatory effect of clozapine on VMAT2 density may augment the capacity of presynaptic monoaminergic neurons to store and release monoamines in the nigrostriatal and mesocortical pathways. These effects may be relevant to the unique therapeutic advantages of clozapine.

6. Reversal of Biochemical Parameters of Brain Aging by Melatonin and Acetyl-L-Carnitine

S. Bondy, University of California, Irvine

The possibility of use of dietary supplementation in order to prevent some of the oxidative and inflammatory changes occurring with age, has been studied.

Elevated basal levels of mRNA for several cytokines associated with inflammatory events such as interleukin 6 (IL-6) and TNF α , were found in the cortex of senescent (26 month-old) male B6C3F1 mice, relative to levels in younger (5 month-old) mice. However the responsiveness of mRNA levels to

an inflammatory stimulus such as lipopolysaccharide (LPS), was actually depressed in the aged mouse brain. When melatonin was fed in the diet (200 ppm) for 6 weeks to old mice, both the depressed levels of cytokine mRNAs and their impaired responsivity to LPS, were restored to levels and responses corresponding to those of younger mice.

Levels of neuronal nitric oxide synthase (nNOS) and peptide nitrotyrosine were also elevated in cortex of 27 month-old mice relative to younger (4 month-old) animals. When old mice were treated for 9 weeks with 200 ppm melatonin in the diet, these levels were partially restored to those found in younger animals. This restoration was complete when old animals received basal diet together with 300 mg/l acetyl-l-carnitine in the drinking water for a similar time period. However, the altered levels of mRNA for nNOS following these treatments did not parallel these changes.

These findings suggest that dietary supplementation can not merely arrest but indeed reverse some age-related increases in markers of oxidative and inflammatory events.

7. Different Mouse Strains Might Strain Your Experimental Design

S. Scheff, University of Kentucky

Experimental traumatic brain injury (TBI) results in a rapid and significant necrosis at the site of injury. The cell death pathways that mediate this injury process have not been elucidated. Genetically engineered strains of mice are becoming a premier tool in many avenues of neuroscience research. Recent experimental evidence has disclosed significant specific morphologic and behavioral differences in some of the commonly used background strains. The present study was undertaken to assess possible strain specific difference following TBI. Six different strains of mice (C57Bl/6, C57BL/10, 129/SvEMs, 129/SvJ, FVB/N, and BALB/c) were subjected to a moderate cortical contusion and the brains assessed for damage using an unbiased stereologic protocol at 7 days post injury. While every strain demonstrated some loss of cortical tissue, there was a significant strain-dependent cortical sparing among the groups. C57BL/6 mice demonstrated the least amount of tissue sparing, while C57BL/10 and FVB/N strains manifested the greatest neuroprotection. These results stress the necessity to fully consider background strains when designing experiments involving genetically altered mice. Care must be taken to include the appropriate strain control groups in experimental designs. The present findings also provide an avenue for exploring molecular mechanisms and genetic avenues for the development of therapies for TBI. Supported by NINDS NS39828

8. Limbic-Cortical Integration in the Nucleus Accumbens

Y. Goto and P. O'Donnell, Center for Neuropharmacology & Neuroscience, Albany Medical College

The nucleus accumbens (NAcc) is a region where limbic and prefrontal cortical (PFC) inputs converge. Despite their importance, limbic-cortical inte-

gration mechanisms in NAcc neurons are not properly understood. In this study, limbic-cortical integration in the NAcc was examined by in vivo intracellular recordings from NAcc neurons with simultaneous stimulation of the hippocampus (HPC)+PFC (n=10), the basolateral amygdala (BLA)+PFC (n=11), or the paraventricular nucleus of the thalamus (PV)+PFC (n=6). PFC stimulation evoked excitatory post synaptic potentials (EPSPs) in NAcc neurons (n=40/44; 91 %). Similar EPSPs were observed after stimulation of the HPC (n=11/16; 69 %), BLA (n=12/15; 80 %), or PV (n=7/13; 54 %). Simultaneous HPC+PFC, BLA+PFC, or PV-PFC stimulation resulted in sublinear summation of EPSPs, especially with large EPSP amplitude. EPSPs evoked by each of these afferents exhibited large trial-to-trial amplitude variability. Paired stimulation resulted in EPSPs with a lower coefficient of variation of their amplitude compared to that observed in post-hoc summation of individual EPSPs. The information gained by the more consistent EPSP amplitude in paired stimulation was examined with Shannon's information theory. Information increased by simultaneous stimulation was linear summation of information encoded by individual stimulation. Different voltage dependence between PFC- and limbic-evoked EPSP amplitudes was also observed. EPSPs evoked by HPC or BLA stimulation were linearly degraded as membrane potential was depolarized ($r=-0.712$, $P<0.0001$), whereas PFC-evoked EPSPs became larger as membrane potential was more depolarized before decreasing in amplitude, with the largest EPSP amplitude around ~ 60 mV. This suggests that synaptic inputs from the limbic structures are more effective when NAcc neurons are in their resting membrane potential (i.e. DOWN state), and PFC inputs are more effective at depolarized states (i.e. UP states). Taken together, these results suggest that near-coincident synaptic inputs from the PFC and limbic structures may contribute to establish reproducible responses that control NAcc output. The reduced variability in synaptic response in this condition may allow for an effective synchronization within a NAcc neural ensemble. Supported by MH57683, MH60131, and a NARSAD Independent Investigator Award to P.O.

9. A Lipophilic Transition Metal Chelator, DP-109, Attenuates Asymmetric Rotations in the 6-hydroxydopamine Partial Lesion Model of Parkinson's Disease in the Adult Rat

*J.E. Friedman, A. Aran, I. Shapiro, I. Angel and A. Kozak
D-Pharm, Ltd*

Over accumulation of transition metals such as copper, iron and zinc can cause oxidative stress in neurons. These metals are considered to be involved in neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Antioxidants and metal chelators have been found to be beneficial in various models of these diseases, but are problematic due to poor penetration across the blood brain barrier. To address this problem, we have developed a family of lipophilic transition metal chelators. The lead compound, DP-109 has a $K_d(\text{Ca})\sim 5\times 10^{-5}\text{M}$, whereas the $K_d(\text{Cu})\sim 10^{-9}\text{M}$ and is highly lipo-

philic, with $\log p > 2.5$ (octanol/water). DP-109 was tested in the unilateral 6-OHDA substantia nigra lesion model using adult male Wistar rats. Three to five days post-lesion animals were screened for apomorphine-induced rotations over a 5 min period. Responding animals subsequently received either DP-109 (10-500 $\mu\text{g}/\text{kg}$) or vehicle daily, p.o., for a period of up to 60 days. Animals were tested weekly or biweekly for apomorphine-induced rotations. Results were normalized and the increase in asymmetric rotations, indicating progressive neurodegeneration, was recorded. After 1 or 2 months brains were taken for morphologic analysis. Vehicle treated animals increased their rotations approximately 20-fold within 30d. DP-109 treated animals demonstrated significantly fewer rotations in a dose-dependant manner. DP-109 attenuated both the rate of increase and number of rotations by 75%. Morphologic analysis found unilateral damage along the striatum in all animals. DP-109-treated animals exhibited less neuronal loss than seen in vehicle controls. We suggest that DP-109 represents a new class of compounds that might be effective in treating neurodegenerative disorders.

10. Multiple Presynaptic Targets for General Anesthetics

H.C. Hemmings Jr., T.A. Ryan, W. OuYang, R.I. Westphalen and P. Vissavajhala. Departments of Anesthesiology, Biochemistry and Pharmacology, Weill Medical College of Cornell University, 525 E. 68th Street, New York, NY 10021 USA

The role of presynaptic actions in general anesthetic effects on synaptic transmission has been difficult to determine. The small size of most CNS nerve terminals ($<1 \mu\text{m}$ diameter) hampers direct electrophysiological analysis of presynaptic events, and direct measurement of action potential-evoked transmitter release from single CNS synapses is not possible. Novel approaches to presynaptic physiology are improving our understanding in this area; these include dual isotope studies of glutamate and GABA release, quantitative confocal microscopy employing fluorescent probes to monitor synaptic vesicle exocytosis/endocytosis, use of specialized presynaptic preparations accessible to electrophysiological techniques, and analysis of SNARE protein interactions. Volatile anesthetics and propofol inhibit endogenous glutamate release from isolated rat cortical nerve terminals at a site upstream of Ca^{2+} channel activation. Inhibition of presynaptic Na^+ channels is implicated in this action since nerve terminal Na^+ channels are sensitive to anesthetics by a number of independent neurochemical criteria. Similar effects were observed in dual isotope studies, in which isoflurane and propofol inhibited Na^+ channel-dependent release of [^3H]glutamate and [^{14}C]GABA, with minor effects on transmitter uptake or binding to transporters. Direct measurements of anesthetic effects on presynaptic ion channels by patch-clamp recording are possible in isolated rat neurohypophysial terminals. Isoflurane (0.4-0.8 mM) and propofol (10 mM) inhibited voltage-gated Na^+ and Ca^{2+} currents, and potentiated delayed rectifier K^+ currents. In each of these systems, the effects of isoflurane occurred at clinical con-

centrations, while those of propofol required relatively higher concentrations, consistent with a greater presynaptic component for volatile anesthetic action. Isoflurane reversibly inhibited synaptic vesicle exocytosis from cultured rat hippocampal neurons preloaded with the amphipathic fluorescent dye FM 1-43 or transfected with GFP-tagged synaptobrevin/VAMP (synaptobrevin). A concentration-effect relationship with a shallow phase at low concentrations, a steep phase centered around 0.8 mM, and a shallow phase approaching complete inhibition at high concentrations was observed with a stimulation frequency of 10 Hz. Anesthetic effects on SNARE protein interactions have been implicated by genetic and biochemical studies. Isoflurane affected the interaction between synaptotagmin 1, a Ca^{2+} and phospholipid binding protein, and syntaxin 1, a t-SNARE component of the fusion machinery, in crude extracts prepared from isolated rat cortical nerve terminals. Multiple molecular mechanisms involving voltage-gated ion channels and/or exocytotic protein interactions may underlie the presynaptic actions of general anesthetics on evoked neurotransmitter release depending on the agent and synapse type. Supported by NIH grants GM 58055 and GM 61925.

11. Decreased Neurogenesis Following an Alcohol Binge

*Nixon, K. * and Crews, F.T. Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, NC, 27599*

Mechanisms which regulate adult neural stem cells are also affected by ethanol (EtOH). To determine whether acute or binge EtOH exposure alters stem cell proliferation and survival, bromodeoxyuridine (BrdU), which labels dividing cells, was administered to adult male rats. For acute EtOH treatment, rats were gavaged with a 5g/kg dose of EtOH or vehicle, then administered two 100mg/kg doses of BrdU two hours apart. Animals were perfused at either 2 hours following the last dose of BrdU or 1 week later. For binge EtOH treatment, rats were infused with EtOH 3 times per day using a modified Majchrowicz model (8-12g/kg/day) or isocaloric control diet. Rats were given 50mg/kg of BrdU once a day for the 4 days of binge treatment, then perfused either immediately following the last dose of EtOH or 28 days later. After immunohistochemical processing, the granule and subgranular cell layers of the dentate gyrus were quantitated for the number of BrdU-positive cells. Acute EtOH treatment reduced BrdU positive cells 37% ($p < 0.05$). Binge EtOH exposure had profound effects on both cell proliferation (day 0) and cell survival (day 28). Immediately following the binge treatment (day 0), BrdU positive cells were decreased 57% relative to diet controls ($p < 0.05$). Cell survival at day 28 in the binge EtOH group was reduced 97% compared to diet controls ($p < 0.05$). Thus, acute EtOH administration does not appear to alter neurogenesis or early survival of neural stem cells whereas binge EtOH exposure dramatically reduces both neural stem cell proliferation and survival. (Supported by NIAAA)

12. Direct and Indirect Regulation of Striatal Acetylcholine Efflux by the Parafascicular Nucleus of the Thalamus

J. A. Zackheim and E. D. Abercrombie, CMBN, Rutgers University, Newark NJ 07102

Cholinergic interneurons play a key modulatory role in striatal function. Direct glutamatergic regulation of these neurons is primarily via afferents from the parafascicular nucleus of the thalamus (Pf). The Pf afferents also target striatal GABAergic medium spiny neurons, some of which synapse upon cholinergic interneurons via axon collaterals. Pf may thus exert both direct excitatory and indirect inhibitory control over striatal cholinergic function. This hypothesis was tested using *in vivo* microdialysis to monitor striatal acetylcholine (ACh) efflux (10 nM neostigmine present). Pharmacological inhibition or disinhibition of Pf was effected using reverse dialysis application into Pf of muscimol (200 μ M - 2 mM) or bicuculline (50 μ M - 500 μ M), respectively. In some experiments, bicuculline (10 mM) was applied via the striatal perfusate to locally antagonize GABA-A receptor-mediated inhibition of striatal ACh.

Perfusion of Pf with a high concentration of muscimol or bicuculline elicited significant decreases ($p < 0.05$) and increases ($p < 0.01$) in striatal ACh, respectively. These results are consistent with a direct facilitatory regulation of striatal ACh output by Pf. Application of lower concentrations of muscimol or bicuculline, however, produced opposite effects on striatal ACh efflux: muscimol or bicuculline application resulted in increases ($p = 0.21$) and decreases ($p < 0.05$) in striatal ACh, respectively. Moreover, the effects of the lower concentrations of muscimol or bicuculline were reversed under conditions of striatal GABA-A receptor blockade (comparison between conditions with and without bicuculline in striatal probe: muscimol: $p = 0.06$; bicuculline: $p = 0.07$). These latter observations indicate the additional contribution of an indirect inhibitory influence of Pf on striatal ACh efflux, perhaps involving collaterals of GABAergic medium spiny neurons.

13. Inducible, Brain Region-Specific Expression of a Dominant Negative Mutant of c-Jun In Transgenic Mice Decreases Sensitivity to Cocaine

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¹Departments of Exploratory Medicinal Sciences and CNS Discovery, Pfizer Global Research and Development, ²Laboratory of Molecular Psychiatry, Yale University School of Medicine, ³Department of Psychiatry and Center for Basic Neuroscience, The University of Texas Southwestern Medical Center

Chronic administration of cocaine induces stable isoforms of fosB in the striatum, including the nucleus accumbens (NAc), a brain region impor-

tant for the reinforcing effects of addictive drugs. Transgenic mice which inducibly overexpress *fosB* in the NAc and other striatal regions show increased sensitivity to the rewarding and locomotor-activating effects of cocaine. *fosB* is a member of the *fos* family of transcription factors which heterodimerize with members of the Jun family to form active AP-1 transcription factor complexes. In the present study, we generated transgenic mice, using the tetracycline gene regulation system, that support the inducible, brain region-specific expression of a dominant negative mutant form of *c-Jun* (*c-Jun*), which can antagonize *fosB* action. To assess the effects of *c-Jun* expression on the rewarding properties of cocaine, transgenic male mice were tested for the development of cocaine-induced conditioned place preference. After conditioning with 10 mg/kg cocaine, mice maintained on the tetracycline derivative, doxycycline, to repress transgene expression, acquired place conditioning, with a mean increase of 266 ± 96 s spent in the drug-paired environment (n=12, t=2.774, 0.02 > p > 0.01). In contrast, littermate mice expressing *c-Jun* showed no significant increase in time spent in the drug-paired environment suggesting a marked decrease in their sensitivity to cocaine (n=11, t=0.903, 0.4 > p > 0.3). This effect of *c-Jun* may be mediated in part via decreased expression in the NAc of the AMPA glutamate receptor subunit, GluR2, a known target for *fosB*. These results further support a role for *fosB* and AP-1-mediated transcription in the molecular mechanisms of drug addiction.

14. The Role of Corticosterone in Food Deprivation-Induced Reinstatement of Cocaine Seeking

U. Shalev, M. Marinelli, P. Piazza and Y. Shaham, NIDA-IRP

We have previously shown that acute 24-hr food deprivation stress potently reinstates heroin seeking in rats. Here we studied (1) whether food deprivation would reinstate cocaine seeking and (2) whether the stress hormone, corticosterone, is involved in this effect. The levels of corticosterone are increased by food deprivation and previous studies have shown that corticosterone modulates cocaine-taking behavior in rats.

Rats were trained to press a lever for cocaine for 10-12 days (two, 2-hr session/day, 0.5-1.0 mg/kg/infusion, IV). The schedule requirement was fixed-ratio-1 (FR-1, each lever press is reinforced). At the end of the training phase rats were divided to 3 groups, which received one of the following treatments: (1) bilateral adrenalectomy (ADX) surgery+placebo pellets (SC), (2) ADX surgery+50-mg corticosterone pellets (ADX+CORT) or (3) sham surgery. Next, rats were given 8-12 days of extinction training during which lever presses were not reinforced with cocaine. Subsequently, tests for reinstatement were conducted after exposure to 0 (baseline condition) and 21 hr of food deprivation.

Acute 21-hr food deprivation reliably reinstated cocaine-seeking behavior in sham-operated rats. The removal of circulating corticosterone by ADX significantly attenuated this effect of food deprivation. Finally, maintaining

basal levels of the hormone by providing ADX rats with corticosterone pellets also significantly attenuated food deprivation-induced reinstatement. The present data suggest that food deprivation-induced rise in the level of circulating corticosterone plays a critical role in relapse to cocaine seeking induced by this stressor.

15. Human Neural Stem Cells are More Sensitive to Ethanol than Astrocytes

W. Lyman, Wayne State University

The embryonic central nervous system (CNS) is extremely vulnerable to the toxic effect of ethanol. However, the mechanisms of neural cell degeneration and aberrant intellectual function associated with ethanol exposure in utero remain unclear. Although ethanol toxicity for neurons, astrocytes and oligodendrocytes has been studied in a number of animal species, there are little data, which are, at best, inconclusive to address whether human neural stem cells are susceptible to ethanol. In this study, we used two populations of cells: CD133/nestin-positive fetal human brain cells; and, GFAP+ human astrocytes to assess alcohol-induced neural cytotoxicity. The cytotoxic potential of alcohol for both neural stem cell (NSC) and astrocytes in tissue culture was monitored using morphological and biochemical methods. The results of these studies revealed that astrocytes are different from NSC in their reaction to ethanol exposure and that alterations in protein kinase C signal transduction may play a critical role in this ethanol-induced pathological process. Morphological and biochemical cytotoxicity analyses showed that astrocytes are more resistant to the cytotoxic effect of ethanol than NSC. This study suggests that NSC may be the most susceptible CNS cell to the effects of prenatal ethanol exposure and may also be the most suitable in vitro model for fetal alcohol syndrome. Part of this basis for this reasoning is that NSC are the predominate CNS cell type in early embryonic brain development.

16. The Timescale of Predictability of Cortical Synaptic Responses

I. Kleppe and H. Robinson, University of Cambridge

Cortical synaptic responses show both high variability and strong short-term plasticity. Facilitation and depression of ensemble average responses are well described by models with time constants of around 1 s, but the dependence of response variability on the input history is still poorly understood. We address this question in synapses between layer 2/3 neurons, by driving presynaptic cells with spike trains of natural statistics for over 30 minutes, at an average rate of 1-3 Hz. We then measure how well postsynaptic EPSP amplitudes are forecast by nonlinear prediction: matching of recent input and response history to similar sequences arising at other times. This approach leads to much better predictability of individual EPSP amplitude than using average responses of existing kinetic models of short-term plasticity. Therefore, there is more information in the EPSP sequence

about the input spike train than would be supposed from assuming independent fluctuations about a mean response. Synapses are shown to remember several minutes of their activation history in a measurable way during natural stimulation, and specific types of pattern are transmitted more reliably than others. Supported by the BBSRC (UK).

Poster Session 2 · Tuesday/Wednesday · Anderson Ballroom

Posters will be available for viewing from 3:30 PM Tuesday to 4:30 PM Wednesday. Presenters will be with the posters on Tuesday from 3:30 to 4:30 PM.

1. Stages of Spike Time Variability During Responses of Cortical Neurons to Transient Inputs

A. Harsch and H.P. C. Robinson, University of Cambridge

The reliability of spike generation in a neuron depends in a complex way on its input history and on intrinsic noise. Previous studies have characterized spike reliability using measures of variability averaged over time. In functioning cortex, however, evidence suggests that cells fire repetitively in response to strong input fluctuations, which reset the precision of firing, erasing correlations between prior and future spike times. Here, the variance of successive spike times is measured in cortical neurons during decaying transient stimuli, of current or conductance. All such responses go through distinct stages. When the stimulus is high, variance is low, while at low stimulus levels, near threshold, variance rises dramatically, approaching a Poisson limit. This behaviour was reproduced in simulations of FitzHugh-Nagumo and Morris-Lecar models incorporating Ornstein-Uhlenbeck noise, or of a stochastic Hodgkin-Huxley model. Early stage variance represents perturbation of uniform limit-cycle motion of the dynamical variables. It is more sensitive to the timescale and amplitude of noise than is late stage variance, which reflects random motion of the dynamical variables captured within the “basin” of the resting potential. At intermediate stages, complex behaviour depends on the type of excitable dynamics. These effects are related to the phenomenon of coherence resonance. Cortical neurons thus respond to transient, decaying inputs with a rapid breakdown in reliability, which may restrict precise signalling by spike times to brief time windows, and limit the duration of coherent synchronous responses in the cortex.

2. Corticostriatal Changes in Transgenic Models of Huntington's Disease: Physiological and Morphological Correlations

M. Ariano, C. Cepeda, C.R. Calvert, M.S. Levine, The Chicago Medical School

Huntington's disease is an autosomal dominant, lethal disorder produced by polyglutamine expansion in the encoded protein, huntingtin. The function of huntingtin is unknown, however the mutation produces a constellation of neuropsychological abnormalities including selective degeneration random splicing within efferent systems of the striatum and cortex. We have investigated the time course of physiological changes detected within visually identified, medium-sized spiny striatal neurons (MSNs) in a transgenic model of HD (R6/2 mouse), and compared the findings to age-matched controls. The frequency of spontaneous excitatory postsynaptic currents (EPSC) was reduced in MSNs in early stages of the disease (30-40 days of age), and very large amplitude events also were detected, indicative of dysregulation of the excitatory corticostriatal afferents. As the disease progresses and R6/2 begin to exhibit more severe motor symptoms, and further reductions in spontaneous EPSC frequency occurred. We have shown in previous studies that spines are lost and the dendritic tree of MSN retracts at this later stage of experimental HD in the R6/2 (Klapstein et al, 2001). We have now detected losses in the striatal expression of PSD-95 and synaptophysin, key proteins of the synaptic complex. Losses in PSD-95 expression also have been detected in two other HD transgenic models that carry longer constructs of the human HD gene with fewer polyglutamine repeats. These data indicate that early and progressive alterations in cortical neurons and/or the corticostriatal system accompany or may precede striatal malfunctions that include substantial cytoarchitectural reshaping of the postsynaptic terminations in experimental HD.

Supported by the Hereditary Disease Foundation, Los Angeles.

3. Modulation of Prefrontal Cortex-Nucleus Accumbens Synaptic Responses by Stimulation of the Ventral Tegmental Area In Vivo

A.M. Himmelheber and P. O'Donnell, Center for Neuropharmacology & Neuroscience, Albany Med Coll, Albany, NY, USA

Dopamine (DA) in the nucleus accumbens (NAcc) has been postulated to modulate the effects of other afferent inputs rather than act in a strictly excitatory or inhibitory fashion. Accordingly, DA has been shown to dampen the responses of NAcc neurons to stimulation of the hippocampus or amygdala in vivo, as well as to prefrontal cortex (PFC) stimulation in vitro. In the current study, the effect of evoked DA release in the NAcc on synaptic responses elicited by PFC stimulation was investigated using in vivo intracellular recording in anesthetized adult male rats. Most NAcc neurons exhibited slow (<1 Hz) transitions between two steady state membrane

potential values, a hyperpolarized down state (-85 mV) and a more depolarized up state (-71 mV) during which spontaneous firing could be observed. Single pulse stimulation of the PFC (0.6 to 1.0 mA, 0.5 ms) evoked EPSPs in most NAcc neurons, with amplitudes ranging from 7 to 28 mV. In NAcc neurons that exhibited up and down states, PFC stimulation elicited spike firing only during the depolarized up states. Train stimulation of the ventral tegmental area (VTA) in a pattern designed to mimic burst firing of DA neurons (5 pulses, 20 Hz, 1.0 mA) evoked a sustained depolarization (range 6 to 17 mV) that lasted 370 to 2310 ms. A second PFC stimulation delivered during this VTA-evoked depolarization elicited an EPSP that was significantly smaller in amplitude ($p < 0.001$) than the response to the first PFC stimulation. The amplitude of EPSPs evoked following VTA stimulation were also smaller than those evoked during similar periods of membrane depolarization during spontaneously occurring up events ($p = 0.019$). In some cells, the VTA was not stimulated but positive current (0.1 to 0.18 nA, 500 ms) was injected through the recording electrode to mimic the level of membrane depolarization produced by VTA stimulation. PFC-evoked EPSPs during this current-induced plateau were not different in amplitude than EPSPs evoked at resting membrane potential, suggesting that the ability of VTA stimulation to dampen PFC-NAcc responses cannot be explained by membrane depolarization alone. The results suggest that DA can modulate the effects of PFC input to the NAcc, and provide support for the hypothesis that VTA activity may affect information processing by both depolarizing the membrane and reducing signal transmission in the NAcc. It can be speculated that these combined effects may allow only strong or synchronous inputs to elicit action potential firing in the NAcc. Thus, DA release in the NAcc may serve as a filtering mechanism which could underlie the hypothesized role of mesolimbic DA in attributing salience to environmental stimuli.

Supported by: MH57683, MH60131, DA14020, DA14821

4. Neuroplasticity by the Antipsychotic Drugs Haloperidol and Clozapine

M. E. Eaton, J. T. Dudman and C. Konradi, McLean Hospital, Harvard Medical School

One approach to understanding the mechanisms by which psychiatric disorders occur in the brain is to look at effective therapies and to determine their mechanisms of action. Several antipsychotic agents have been determined to be effective in treating schizophrenia. Neuronal adaptations such as synaptic plasticity and neurogenesis are thought to underlie their mechanisms of therapeutic action. It has been proposed that the plastic changes generated by antipsychotic drugs lead to the formation and stabilization of synaptic connections, thus counteracting the inadequate synaptic organization that has been associated with schizophrenia. We focus on the conventional antipsychotic drug, haloperidol, and the atypical antipsychotic, clozapine. We will present new evidence of neuronal plasticity in response

to treatment with these agents. We will show how exposure to antipsychotic drugs leads to the activation of signal transduction pathways and transcription factors. In addition, we will show gene array analyses of the effects of chronic antipsychotic treatment on gene expression. Finally, we have used BrdU labeling of hippocampal neurons to assess neurogenesis by antipsychotic drugs.

This work is supported by NIDA (DA07134) and by NARSAD.

5. Repeated Cocaine Administration Produces a Persistent Sensitization of Psychomotor Activation which Correlates with Fos-Immunoreactivity in Accumbens, But Not in Caudate

B. Hope and H. Crombag, NIDA/IRP

Repeated administrations of psychomotor stimulant drugs, such as cocaine, produce a progressive and persistent increase, or sensitization, of psychomotor activity. These sensitization-related behavioral changes are thought to reflect differences in neural activity within target regions of the mesolimbic dopamine system, particularly within accumbens and caudate. We examined this hypothesis by investigating the effects of repeated cocaine treatment on psychomotor activation and neural activity within the caudate and accumbens. Rats received 7 once daily injections of cocaine (15 mg/kg, ip) and their locomotor activity was monitored. Eight days following the last injection, independent groups received an injection of either saline or cocaine (7.5, 10, 15, 20, or 30 mg/kg) to test for expression of sensitization. After monitoring locomotor activity for 2 hours, the animals were perfused with paraformaldehyde and the brains were processed for Fos immunohistochemistry. There was a leftward shift in the dose-response curve for locomotor activity of cocaine-sensitized animals relative to that of saline-pretreated animals. More importantly, there was a corresponding leftward-shift in the dose-response curve for the induction of Fos-immunoreactive nuclei in accumbens, but not in caudate, of cocaine-sensitized animals. These results provide the first demonstration of persistent sensitization of neural activity in the accumbens as a consequence of prior cocaine experience. (supported by NIDA/IRP/NIH)

6. Membrane Potential States of Prefrontal Cortical Pyramidal Neurons Correlate with Local Field Potentials in the Ventral Tegmental Area

Y. Peters, Albany Medical College

Pyramidal neurons in the prefrontal cortex (PFC) spontaneously oscillate between two membrane potential states: a down state with a negative resting membrane potential and a depolarized up state. Up states are dependent on synchronous excitatory inputs, most likely cortico-cortical in nature. Activation of the mesocortical projection by electrical stimulation of the ventral tegmental area (VTA) mimicking dopamine (DA) cell burst firing resulted in a prolonged up state in PFC pyramidal neurons. This effect was

blocked with systemic administration of the D1 antagonist SCH 23390 (Lewis and O'Donnell, 2000). These results indicated that DA in the PFC may contribute to the maintenance of the depolarized state in pyramidal neurons. It is conceivable that spontaneous PFC up states are also sustained by VTA activity. In that case, membrane potential fluctuations in PFC pyramidal neurons should be correlated with VTA electrical activity. Simultaneous intracellular and extracellular recordings were performed in the PFC and VTA, respectively, in chloral hydrate-anesthetized rats. PFC pyramidal neurons exhibited the characteristic bistable membrane potential oscillating at 0.75 ± 0.31 Hz ($n = 14$) while VTA local field potentials (LFP) showed spontaneous oscillations of 0.70 ± 0.24 Hz ($n = 12$). Spectral analyses of waveforms recorded simultaneously revealed similar peaks in 12 of 14 pairs. Co-spectral density analysis indicated a coherence (measured as r^2) of 0.89 ± 0.09 between PFC intracellular waveforms and VTA LFP at the frequency of the coincident slow peaks. These results indicate that spontaneous up states in PFC pyramidal neurons are synchronous with population neural activity in the VTA. Whether this is a reflection of VTA driving up states in the PFC or of PFC control of VTA activity remains to be elucidated. Since PFC neurons fire action potentials during up states, a dopaminergic control of membrane potential states in the PFC would be a very effective way of affecting PFC function. Supported by MH57683, MH60131 and DA14020

7. A Millisecond Timescale for Unblock of NMDA Receptors and Its Implications for the Excitability of Cortical Pyramidal Neurons

M. Vargas-Caballero and H. Robinson, University of Cambridge, UK

Synaptic NMDA receptors (NMDARs) provide a long-lasting component of elevated conductance at glutamatergic synapses, but experience a voltage-dependent block by extracellular Mg at the resting potential. The timing of unblock is potentially critical for determining the nonlinear contribution of NMDARs to excitability. To assess its role in the excitability of cortical neurons we have measured the kinetics of unblock and block of NMDAR current in nucleated patches of rat cortical pyramidal neurons during depolarising voltage steps. The observed kinetics of unblock showed two components: one very fast, and one slower component lasting for tens of milliseconds, which accounts for approximately half of the current (for example $\tau_{\text{fast}} = 0.7$ ms and $\tau_{\text{slow}} = 20$ ms for steps to +40mV). In contrast, after repolarisation block is effectively instantaneous. We found that existing models – open channel block (Ascher and Nowak, 1988, Jahr and Stevens, 1990) and trapping block (Sovolebsky and Yelshansky, 2000) – of NMDA receptor kinetics were not able to predict the observed asymmetric kinetics of unblock and block. The asymmetry of the current responses would be explained if unblock involves a return to the open state along two or more Mg-bound blocked states, while block would only require the passage to the first of these states. Our results can be fitted by adding an extra blocked state to the open channel block mechanism. This model predicts that the

slow unblock after depolarisation reduces the ability for NMDAR channels to drive spike generation in neurons, and at the same time protects the channels from passing to desensitized states or from losing bound glutamates, prolonging the silent activation of NMDARs. Numerical simulations of this mechanism in a simple cable model of a cortical cell showed that these properties can radically alter the number and timing of spikes in burst responses. Therefore the kinetics of unblocking of NMDARs are potentially very important in shaping spike generation driven by glutamatergic synaptic input. Supported by the EC and the BBSRC. MVC is funded by the Oliver Gatty Studentship, University of Cambridge.

8. In Vivo Detection of Neuropathology in an Animal Model of Alzheimer's Disease by Magnetic Resonance Imaging

*J. Helpern, T. Wisniewski, K. Duff, V. Dyakin, M. de Leon, B. Ardekani, O. Wolf, C. Branch, J. O'Shea, J. Wegiel, and R. A. Nixon. * Nathan Kline Institute/New York University School of Medicine, Orangeburg, NY 10962; IIR, Staten Island, NY 10314.*

The cerebral deposition of amyloid β -peptide, a central event in Alzheimer's disease (AD) pathogenesis, begins several years before the onset of clinical symptoms. Non-invasive detection of AD pathology at this initial stage would facilitate intervention and enhance treatment success. Using MRI at 7 Tesla, we studied PS-APP transgenic mice expressing the human genes for amyloid precursor protein (APP) and presenilin-1 (PS), which harbor mutations, APPK670N, M671L and PSM146V known to cause AD in humans. In these mice, β -amyloid begins to deposit at 10-12 weeks of age and progressively accumulates as plaque-like lesions throughout the life span. Although some neurofibrillary tangle formation and neuronal cell loss are not detected. These mice, therefore, represent a model of β -amyloidosis with a level of tissue injury corresponding most closely to the early stages of AD. In mice 16-23 months old, we observed that the transverse relaxation time T2, an intrinsic MR parameter thought to reflect impaired cell physiology, was reduced (21-28% $p < 0.0001$) in cortical regions containing β -amyloid but only slightly in cerebellum, which contains little β -amyloid. T2 relaxation times were not prolonged in 6-8 weeks old mice, which have not begun to deposit β -amyloid. MR measures were also minimally altered in mice expressing mutant presenilin-1, which do not deposit amyloid β -peptide. These findings support the view that the MR abnormalities in PS-APP mice are partly related to amyloid β -peptide deposition. We also detected reduced volumes of the cingulate gyrus (21% $p < 0.001$) and corpus callosum (32% $p < 0.0002$) and a comparable extent of ventricular enlargement. These changes were detected more sensitively by MR than histopathologic analysis in the same mice using unbiased stereology. These results set the stage for MRI to aid in the evaluation of potential therapies for AD and other neurodegenerative diseases in transgenic animal models and, ultimately, in patients.

Supported by: NIA (AG17617)

9. Dopamine Targets in Human Amygdala are Abnormal in Major Depression: Postmortem Study

V. Klimek, University of Mississippi Medical Center

A deficiency of mesolimbic dopamine is a leading candidate for the etiology of certain symptoms of depression, e.g. difficulty in experiencing pleasure (anhedonia) and loss of motivation (lack of interest). In fact, there is a considerable amount of preclinical and clinical pharmacological data implicating an involvement of dopamine in the pathophysiology of major depression. However, there is a striking lack of neurochemical and neuroanatomical studies of dopaminergic systems in postmortem brain tissue from subjects diagnosed with major depression. The aim of this study was to compare amounts of dopaminergic proteins in the amygdala, a key brain structure involved in the integration of emotions and stress, in subjects with Axis I diagnoses of major depression and in psychiatrically normal control subjects. The amygdala receives dopaminergic projections from the ventral tegmental area, noradrenergic projections from the locus coeruleus, and serotonergic innervation from the dorsal and median raphe nuclei. Nissl staining and acetylcholinesterase histochemical staining were used to identify anatomical boundaries of amygdaloid nuclei. The specific binding of [125I]RTI 55 to the DA transporter, [3H]SCH 23390 to the D1 receptor and [125I]epidepride to D2/D3 receptors were measured in the right amygdaloid complex in postmortem brains from 11 subjects with major depression and 11 age and postmortem delay matched control subjects that were psychiatrically normal. The binding of [125I]RTI 55 to DA transporter was significantly lower in the basal and central amygdaloid nuclei, while the binding of [125I]epidepride to D2/D3 receptors was significantly higher in the basal, central and lateral amygdaloid nuclei comparing subjects diagnosed with major depression to control subjects. In contrast, there was no difference in the binding of [3H]SCH 23390 to D1 receptors in the amygdala comparing subjects diagnosed with major depression and control subjects. Given that DA depletion in rats can induce a reduction in the DA transporter and an up-regulation of D2/D3 receptors, the present data are consistent with the hypothesis that major depression is associated with a deficiency of mesolimbic DA.

10. Overexpression of Alpha-Synuclein Decreases Depolarization-Induced Dopamine Release

K. E. Larsen, Columbia University

Alpha-synuclein (SYN) is a protein of unknown function that is involved in Parkinson's disease. A role for SYN in stimulation-dependent regulation of neurotransmitter release has been suggested, as null mice were found to have a faster recovery of dopamine (DA) release in a paired pulse protocol. We recently tested human SYN-overexpressing PC12 cell lines for depolarization-induced DA release and intracellular DA levels via HPLC-EC. Cell

lines expressing mutant SYN (A53T) had lower intra-cellular DA levels than either empty vector or wild-type SYN (WT) overexpressors. Moreover, evoked DA release was impaired in WT lines and completely suppressed in A53T lines. Electron microscopy (EM) analyses demonstrated a total absence of dense core granules (DCGs; catecholamine-secreting vesicles) in the A53T lines, suggesting that DA sequestration is severely disabled. In contrast, empty vector and WT lines displayed normal ultrastructural morphology. In order to study the effect of WT SYN on DA release in more detail, we have generated additional PC12 cell lines expressing WT SYN (tet-SYN) or empty vector based on the Tet-on system (Clontech). tet-SYN lines also showed an impairment of evoked DA release that is not evident in empty vector lines. EM studies revealed that there was an accumulation of DCGs in a “docked” position very close to the plasma membrane in the tet-SYN lines following depolarization. Preliminary data suggest that the impairment of DA release is not due to an alteration in calcium triggering of vesicular fusion, as tet-SYN and empty vector lines have identical Hill coefficients. Moreover, a similar SYN-dependent decrease in evoked DA release occurs in response to stimulation with the calcium ionophore, A23187. We conclude that SYN acts as a negative regulator of evoked DA release and that this effect appears to be mediated at a point downstream of docking and calcium entry.

11. Neuronal Apoptosis from NMDA-Receptor Blockade in Neonatal Rats Occurs without Caspase-3 Activation

D. G. Fujikawa, M.D., VA GLAHS/UCLA

Blockade of NMDA receptors during the first postnatal week in rats results in neocortical neuronal apoptosis, but whether programmed cell death mechanisms are involved is not known. We determined if internucleosomal DNA cleavage and caspase-3 activation occur in this apoptotic model. Postnatal day 7 (P7) rats were given MK-801, 1 mg/kg, or saline i.p., and 6 h or 24 h later they either underwent (1) in situ brain perfusion-fixation for light-microscopic (LM) H & E, TUNEL and active caspase-3 immunocytochemical evaluation of the left retrosplenial cortex and electron-microscopic (EM) evaluation of the contralateral cortex, or (2) rapid dissection of the neocortex for DNA gel electrophoresis, DEVD-AFC assays for caspase-3-like activity and Western blot analysis for the presence or absence of the active p17 subunit of caspase-3. Thymuses of adult rats given methylamphetamine (MAP), to produce apoptotic thymocytes, or saline were used as controls for active caspase-3 immunoreactivity and biochemical assays. Apoptotic neurons, identifiable by LM with the H & E stain, were shrunken, with large, round, basophilic chromatin clumps and eosinophilic cytoplasm. Surprisingly, the chromatin clumps were TUNEL-negative, but the cytoplasm was TUNEL-positive. Nuclear membranes of apoptotic neurons were fragmented or absent by EM. 6.5 h after MAP treatment, thymocytes showed DNA laddering, active caspase-3 immunoreactivity, the presence of the active p17 subunit of caspase-3 on Western blots, and a 25-fold increase of

DEVD-AFC cleavage (1.13 ± 0.20 vs. 0.05 ± 0.01 units/mg protein, mean \pm SD of three experiments). In contrast, neocortices of MK-801 treated P7 rats had no evidence of active caspase-3 immunoreactivity, absence of the p17 subunit on Western blots, and no increase of DEVD-AFC cleavage at either 6 or 24 h, despite DNA laddering at 24 h. Neuronal apoptosis with DNA laddering in neonatal rats may be a caspase-independent process.

12. Fine Mapping of an Alcohol Withdrawal QTL to a < 1 cM Region of Mouse Chromosome 4: Identification of the Mpdz Gene as a Promising Candidate

K. J. Buck, Oregon Health & Science University

Risk for onset of alcoholism is related to genetic differences in acute alcohol withdrawal liability. We previously mapped a quantitative trait locus (QTL) responsible for 26% of the genetic variance in acute alcohol withdrawal convulsion liability on mouse chromosome 4. We have now narrowed the map position of this QTL to a < 1 cM interval using a combination of novel, interval-specific congenic strains and recombinant progeny testing. We report the development of a small donor segment (SDS) congenic strain, which confirms "capture" of a gene affecting alcohol withdrawal within the < 1 cM interval. We have also confirmed a pentobarbital withdrawal locus within this < 1 cM interval, suggesting that the same gene may influence predisposition to physiological dependence on alcohol and a barbiturate. This congenic strain will be invaluable for determining whether this interval also harbors a gene(s) underlying other QTLs mapped to the mid-distal region of chromosome 4, including loci affecting voluntary alcohol consumption and alcohol-induced ataxia, and seizure response to pentylenetetrazol and audiogenic stimuli. Sequence analysis of candidate genes within the QTL interval identifies the *Mpdz* gene, which encodes the multiple PDZ domain protein (MPDZ), as a promising candidate gene for this QTL. Sequence analysis of 15 standard inbred mouse strains identifies 6 *Mpdz* haplotypes that predict 3 MPDZ protein variants. Evidence using interval-specific congenic lines and inbred strain analyses shows that alcohol withdrawal severity is genetically correlated with MPDZ status, indicating that *Mpdz*, or a closely linked gene, influences alcohol withdrawal liability.

13. Diversity and Stability of Elementary Activity Patterns that Spontaneously Form in Isolated Cortex

J. Beggs and D. Plenz, Unit of Neural Network Physiology, LSN, NIMH, NIH*

Networks of cultured cortical neurons become spontaneously active during maturation, typically showing periods of brief activity separated by long pauses of inactivity. This firing pattern has been previously described as random. Here we show that such activity is in fact highly structured, containing diverse spatio-temporal sequences lasting from 4-80 ms that consistently recur up to many hours later.

We cultured slices of rat cortex, striatum and substantia nigra for over 4 weeks on a 60-channel microelectrode array (MCS). Field potentials were recorded, thresholded (± 3 sd), low-pass filtered (50 Hz), and peak amplitudes were binned at 4 ms. A frame was defined as the pattern of suprathreshold electrodes during a bin. A consecutive sequence of frames was defined as a run. Similarity between runs was defined as the intersection of their active electrodes normalized by their union. Similar runs were clustered into families using a simulated annealing algorithm. Significance was based on 20 sets of spatially or temporally shuffled data. The cultures ($n = 2$) produced over 1,500 runs/hr. Runs from actual data were significantly more diverse in length (275%) and clustered into families significantly more often (90%) than runs from shuffled data. Up to 44% of clustering was found between files separated by 1, 2, 5 and 10 hours, which indicated that runs were stable over time. Our results indicate that highly diverse and stable spatio-temporal activity patterns emerge spontaneously in isolated cortex. Their diversity and persistence implies that they could form basic elements of cortical memory.

Support from DIRP & NIMH

14. Acquisition of Conditioned Defeat in Syrian Hamsters: Molecular Mechanisms

K. L. Huhman, C. Shi, M. Davis and A. M. Jasnow, Georgia State University

Conditioned defeat is a prolonged behavioral response exhibited by Syrian hamsters following exposure to a social defeat stressor. This response occurs after a single, 15 min defeat in the home cage of a larger, more aggressive hamster. Subsequently, the defeated hamster fails to produce normal territorial aggression in its own home cage even when it is paired with a docile, smaller opponent. We have hypothesized that conditioned defeat represents an ethologically relevant form of fear conditioning, and we have produced data indicating that similar neural circuits may mediate conditioned defeat and fear-potentiated startle. Increasing cAMP response element binding (CREB) protein in the basolateral amygdala of rats using herpes simplex viral (HSV) vector-mediated gene transfer dramatically facilitates the acquisition of fear-potentiated startle following massed fear training, a procedure that normally induces only a weak facilitation. In the present experiment, we tested the hypothesis that overexpression of CREB in the basolateral amygdala of hamsters would facilitate the acquisition of conditioned defeat following a submaximal, 5 min defeat trial. We found that defeated hamsters infused with HSV-CREB in the basolateral amygdala displayed significantly more submissive/defensive behaviors when tested with a non-aggressive opponent than did hamsters infused with HSV- β -galactosidase. These data suggest that CREB activity in the amygdala may serve as a molecular switch for the formation of a variety of longterm fear memories. (Supported by the STC Program of the NSF under Agreement No. IBN-9876754)

15. 5-HT_{2A} Receptors on Rat Substantia Nigra Pars Reticulata Projections to Thalamus: A Double Immunofluorescence Study

W. A. Wolf Hines VA/Loyola University Chicago

Serotonin (5-hydroxytryptamine; 5-HT) 5-HT_{2A} receptors have been implicated in mediating extrapyramidal motor side effects of high potency dopamine blocking antipsychotics. In the rat, 5-HT_{2A} receptors can be found in moderate density in basal ganglia regions, such as the striatum and substantia nigra pars reticulata (SNr). As a major output nucleus of the basal ganglia, the SNr sends inhibitory projections to regions involved in motor control, such as the thalamus. It is believed that abnormal activity of SNr efferents contributes to a variety of motor disturbances. In order to further our understanding of the role of 5-HT_{2A} receptors in modulating basal ganglia output, the present study was designed to determine whether 5-HT_{2A} receptors reside directly on SNr neurons projecting to the thalamus. Rats received an intrathalamic injection of rhodamine-labeled microspheres (1 ul) while under anesthesia. After 3 days recovery, rats were anesthetized and perfused with saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Following cryopreservation and sectioning, 30 um sections were processed for 5-HT_{2A}-like immunoreactivity (5-HT_{2A}-LI) using a monoclonal primary antibody (ms x 5-HT_{2A}; BD-Pharmingen), biotinylated secondary antibody and Cy2-labeled streptavidin (Jackson ImmunoResearch). The results demonstrate that 5-HT_{2A}-LI co-localizes with retrogradely-labeled cell bodies in the SNr. Preliminary analysis indicates that approximately 70% of retrogradely-labeled neurons co-expressed 5-HT_{2A}-LI. By comparison, approximately 40% of 5-HT_{2A}-LI expressing neurons in SNr were retrogradely-labeled. Taken together, these results suggest that a substantial proportion of nigrothalamic projection neurons express 5-HT_{2A} receptors. This raises the possibility that drugs which act at 5-HT_{2A} sites can directly modulate activity of SNr efferents involved in motor control. The significance of these results with respect to pharmacological treatment of motor disorders will be discussed.

16. Differential Regulation of Somatodendritic and Nerve Terminal Dopamine Release by Nigral Serotonin

W. S. Cobb, Rutgers University

Substantia nigra dopamine neurons release dopamine from nerve terminals in striatum as well as from the soma and dendrites. It is unclear whether dopamine release at the two sites always occurs in parallel or whether dendritic dopamine release may be regulated independently of nerve terminal release under some conditions. Previous studies have shown that stimulation of dorsal raphe can decrease somatodendritic excitability of nigral dopamine neurons, presumably via increased dendritic dopamine release, without altering the overall spontaneous firing rate of the cell (Trent and

Tepper, 1991). In this situation, it is hypothesized that nerve terminal dopamine release in striatum would be unaltered. We sought to examine this issue using in vivo microdialysis to simultaneously measure dendritic dopamine release and nerve terminal dopamine release in the nigrostriatal dopamine system. Fenfluramine (100 uM) was infused locally in substantia nigra via reverse dialysis to stimulate serotonin release. Nigral fenfluramine application significantly increased dendritic dopamine efflux, but had no effect on extracellular dopamine in striatum. In contrast, nigral application of the D2 receptor agonist quinpirole (100 uM) significantly decreased dopamine efflux in both striatum and substantia nigra. These data suggest that serotonin afferents to substantia nigra may selectively evoke dendritic dopamine release in distal regions of the dopamine neuron and that this regulation of dendritic dopamine release can take place independent of changes in neuronal firing rate and nerve terminal dopamine release.

Poster Session 3 · Thursday/Friday · Anderson Ballroom

Posters will be available for viewing from 3:30 PM Thursday to 4:30 PM Friday. Presenters will be with the posters on Thursday from 3:30 to 4:30 PM.

1. Neurite Regeneration of the Adult Mammalian Spinal Cord Explants Mediated by a Retinoid-Signaling Mechanism

P. So, J. Corcoran, M. Maden, Centre for Developmental Neurobiology, New Hunt's House, King's College London, Guy's Campus, London SE1 9RT, United Kingdom*

Retinoic acid (RA) has been shown to be required for neurite outgrowth. We have recently demonstrated that the mechanism of its action in peripheral nerve regeneration requires activation of the retinoic acid receptor (RAR) b2. In adults, the central nervous system does not regenerate. Therefore, we have investigated if regenerative failure in the adult spinal cord is related to the expression of RARb2. Using an in vitro assay system, we show that in embryonic mouse spinal cord, which has regenerative properties, RARb2 was up-regulated at concentrations that maximally stimulated neurite outgrowth. This was in contrast to the adult mouse spinal cord, in which RARb2 expression was not detected nor induced by RA and no neurite outgrowth was observed. However, when the adult cord was transfected with RARb2, neurite regeneration was induced. There was no neurite outgrowth when the spinal cord was transfected with another isoform of RARb, RARb4, indicating that receptor specificity is important for neurite regeneration.

2. Absence of Retinoids Can Induce Motoneuron Disease in the Adult Rat and a Retinoid Defect Is Present in Motoneuron Disease Patients

J. Corcoran, P. So, M. Maden, MRC Centre for Developmental Neurobiology, New Hunt's House, King's College London, Guy's Campus, London SE1 9RT, United Kingdom.*

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the loss of motoneurons in the motor cortex, brain stem and spinal cord, leading to muscle weakness and atrophy. ALS occurs in both sporadic (90 % of all cases) and familial forms (10 % of all cases). Genes involved in the sporadic cases have yet to be identified. We have generated retinoid-deficient adult rats, which display motoneuron pathology. The muscles showed atrophy and when held by the tail, their hindlimbs retract. More detailed analysis showed that the motoneurons had degenerated and that there was an accumulation of neurofilaments as well as an increase in astrocytosis. These effects were associated with loss of the retinoic acid receptor (RAR) expression in these motoneurons. The same receptor deficit was found in motoneurons from patients suffering from spontaneous ALS. Furthermore, we show that there was also a loss of expression of the retinaldehyde dehydrogenase enzyme (RALDH) II in their motoneurons. We therefore propose that a defect in the retinoid-signaling may in part be responsible for some types of motoneuron disease.

3. Regulation of Striatal Neural Activity by the Orbital Prefrontal Cortex In Vivo: Modulation by Nitric Oxide

A.R. West, University of Pittsburgh

The role of the orbital prefrontal cortex (oPFC) and tonic nitric oxide (NO) in modulating the activity of medium spiny striatal neurons was investigated using intracellular recordings performed concurrently with reverse microdialysis in chloral hydrate-anesthetized rats. The basal and evoked activity of a subpopulation of neurons in the ventromedial striatum was examined during separate intra-striatal infusions of artificial CSF and the NO chelator carboxy PT-10 (CPT-10). In neurons responding to oPFC stimulation, intra-striatal infusion of CPT-10 (1mM) decreased membrane excitability as evidenced by: 1) an increase in the intracellular current injection amplitude required to elicit an action potential and 2) a decrease in the maximal depolarized membrane potential. Similar effects were observed following intra-striatal infusion of the neuronal NO synthase inhibitor, 7-nitroindazole (300 μ M), indicating the involvement of neuronal sources of NO in modulating striatal neuron activity. Local infusion of CPT-10 did not alter the bistable membrane potential characteristics or input resistance of striatal neurons. However, a decrease in maximal EPSP amplitude and duration evoked by electrical stimulation of the oPFC was observed following CPT-10 infusion indicating that these neurons are under a tonic excitatory influence by NO. In contrast to the above observations, a minority of neu-

rons which did not respond to oPFC stimulation were activated by local NO antagonist infusions. Together, these findings reveal that NO containing interneurons modulate the activity of striatal neuronal networks differentially and that NO signaling plays a significant role in the integration of corticostriatal information within striatal medium spiny neurons.

4. Orexin A in the Lateral Hypothalamus Influences Peripheral Uncoupling Proteins

C. Kotz, Minneapolis VA Medical Center and University of Minnesota

Orexin A is a recently characterized neuropeptide that enhances feeding behavior and plays a role in sleep disorders. Orexin A is predominant in the lateral hypothalamus (LH) and LH-injected orexin A dose-dependently stimulates feeding and activates neurons in several feeding-regulatory brain areas. Neural systems regulating food intake are often coordinately associated with processes involved in energy expenditure. One portion of energy expenditure is that due to non-shivering thermogenesis (NST), which may be attributed to activity of uncoupling protein(s) (UCPs). UCPs uncouple mitochondrial electron transport from ATP production, resulting in the dissipation of energy as heat. UCP1 in brown adipose tissue has an established role in NST, and other recently identified UCPs, in particular UCP2 in white adipose tissue and UCP3 in muscle tissue, may also be involved. In the current study, we tested the effect of LH-injected orexin A on gene expression of UCP1 in brown adipose tissue, UCP2 in white adipose tissue and UCP3 in muscle tissue. To do this, male Sprague Dawley rats were injected with either artificial cerebrospinal fluid or orexin A (500 pmol) at 0800 h, 1000 h and 1200 h. Food was not allowed during or after the injections so that differences in caloric intake would not confound results. Animals were sacrificed at 1400 h and tissues taken for gene expression analysis. Orexin A in the LH significantly decreased gene expression of UCP1 in perirenal brown adipose tissue whereas gene expression of UCP3 in biceps femoris muscle was significantly decreased. Orexin A had no significant effect on UCP1 in interscapular brown adipose tissue, UCP2 in white adipose tissue or UCP3 in acromiotrapius muscle. These results indicate that orexin A in the LH has differential effects on gene expression of uncoupling proteins in peripheral tissues, and provide evidence that orexin A in the LH may have an important impact on processes governing energy expenditure. This work was supported by the Department of Veterans Affairs and the National Institute of Health (DK 57573).

5. Chronic Stress-Evoked Sensitization of Noradrenergic Neurons of the Locus Coeruleus: Electrophysiological Studies in Rat

H. P. Jedema and A.A. Grace, University of Pittsburgh

Previous studies have indicated that chronic exposure to stress alters the response of noradrenergic neurons of the locus coeruleus (LC) to excitatory inputs. Specifically, we demonstrated that the LC neuron spike activity and

norepinephrine (NE) release in response to noxious stimuli or central corticotropin releasing hormone (CRH) administration is enhanced following chronic cold exposure without alteration of basal LC activity or NE release. We wished to determine whether the sensitized responsivity was a result of changes in the afferents to the LC or changes in the intrinsic properties of the LC neurons. Therefore, we performed intracellular recordings of LC neurons in horizontal slices from control or previously cold-exposed rats. We determined 1) the site of action of CRH 2) the electrophysiological properties and excitability of LC neurons in response to depolarizing current injection and CRH administration.

Pressure ejection of CRH dose-dependently increased the activity of spontaneously active LC neurons in the slice by increasing the rate of repolarization following spike discharge. The CRH-evoked activation persisted after blockade of synaptic transmission by TTX (2 μ M) suggesting that CRH acts directly on LC neurons. We found no difference in average membrane potential, input resistance, or spike waveform characteristics between LC neurons obtained from control and cold-exposed rats. However, the response of LC neurons to depolarizing current injection was enhanced in slices obtained from cold-exposed rats. In addition, the accommodation of current-evoked spike discharge was decreased, and the typically observed post-activation inhibition period appeared to be decreased in slices from cold-exposed rats.

The present results demonstrate that 1) CRH can activate LC neurons in vitro directly, 2) the alterations underlying the sensitized response of LC neurons previously observed in vivo, are at least in part localized to the LC and are maintained in vitro. Furthermore, the decreased accommodation suggests that a decreased feedback inhibition may underlie the enhanced responsivity of LC neurons following chronic cold exposure.

6. Effects of MDMA on Cocaine-Related Behavior and Neurochemistry in Periadolescent and Adult Rats

K. J. Frantz, A. A. Rowinski, and L. H. Parsons, The Scripps Research Institute, Department of Neuropharmacology, La Jolla, CA 92037

Although long-term depression, anxiety and paranoia may result from MDMA use by human adolescents, the long-term effects of MDMA on reward-related behaviors and forebrain neurotransmitter levels have not been thoroughly investigated in the laboratory. In the present study, MDMA was administered (s.c., 0, 15 or 20 mg/kg, 2x daily, 4 days) to male Wistar rats starting at postnatal day 38 (periadolescent age group) or postnatal day 63 (young adult age group). Under the present environmental conditions, the 20 mg/kg MDMA treatment regimen was lethal to over 60% of the adult subjects but none of the periadolescents. Two weeks after MDMA, subjects were either sacrificed and post-mortem tissue levels of serotonin were measured, or spontaneous acquisition of cocaine self-administration was investigated (0.35 mg/kg/infusion, Fixed-Ratio 1, Time Out 20, 2 hr sessions, 18 sessions total). Depletions of serotonin induced by MDMA were less se-

vere in periadolescent than young adult rats, and such resistance to MDMA-induced neurotoxicity extended to the behavioral effects of MDMA. In periadolescent rats, MDMA treatment did not alter cocaine self-administration. In young adult rats, pretreatment with 15 mg/kg MDMA resulted in a higher proportion of subjects acquiring cocaine self-administration early in the 18-day testing period, compared with saline treated controls. Pretreatment with 20 mg/kg MDMA produced a similar trend. These results may be related to serotonin depletion or sensitization of dopaminergic responses to cocaine after exposure to MDMA. Experiments are ongoing to probe the combined effects of MDMA treatment and cocaine self-administration on tissue levels of serotonin and dopamine in the forebrain.

7. Prefrontal and Amygdalar Regulation of Locus Coeruleus Neurons: Effects of Chronic Stress

H. Moore, University of Pittsburgh

Efferents from the prefrontal cortex (PFC) and central amygdala (CEA) are two of the few forebrain regions that innervate locus coeruleus (LC) noradrenergic neurons. Moreover, neurotransmitter release and neuron spike activity in each of these regions respond to acute and/or chronic stressors. In particular, the LC and NE release in its terminal regions appear to be sensitized following chronic stress. However, whether this sensitization involves changes in the PFC or CEA regulation of LC neurons is unknown. In this context, the aims of the present study were 1) to characterize the responses of LC neurons to stimulation of the PFC and CEA and determine how they are changed after chronic stress and 3) determine how long the changes in LC neuron responsiveness persist after termination of a chronic stressor (cold exposure). Male Fischer 344 rats were partially shaved and single-housed at 5 deg C for 17 days. We have previously reported that rats adapt to this cold environment, for example, showing normal body temperature and weight gain after being housed in the cold for at least one week, and maintaining normal body temperature after being removed from the cold. Following the 17-day continuous exposure to cold, rats were removed and single-housed under standard housing conditions for 24-48 hrs (1-day post-stress) or 10-12 days (10-day post-stress). In control, 1-day post-stress and 10-day post-stress groups, fear-potentiated startle was measured as one index of amygdala function. Following behavioral testing, rats were anesthetized with halothane and stereotaxic surgery was performed to place stimulating electrodes in the PFC and CEA and a recording electrode in the LC. Extracellular, single-unit recordings of LC neurons were used to measure spontaneous spike firing, as well as responses evoked by single-pulse or burst stimulation of the PFC and CEA. In control rats, single-pulse or burst stimulation of the PFC evoked either an excitatory/inhibitory pattern or a late inhibition in LC neurons. This inhibition has previously been shown to involve noradrenergic negative feedback mechanisms. On the other hand, single pulse or burst stimulation of the CEA resulted in a marked and long-lasting suppression of spike firing in LC neurons in control animals. In ani-

mals that had been removed from the chronic cold stress for 1 or 10 days, the size of PFC-evoked responses in LC neurons was reduced. Surprisingly, burst stimulation of the CEA produced an excitation, followed by inhibition, in LC neurons of 1-day or 10-day post-stress animals. CEA-evoked excitation was not observed in control rats. Thus, following the termination of a chronic stressor to which the animal has adapted, changes in the PFC and CEA regulation of the LC persist for at least 10 days. These persistent changes are consistent with changes in the response of LC neurons to footshock as well as deficits in fear-potentiated startle, both of which also persist for at least 10 days following termination of a chronic stressor.

8. Tyrosine Nitration from the Simultaneous Generation of Nitric Oxide and Superoxide Does Not Require Formation of Peroxynitrite

D.D. Thomas, National Cancer Institute

Nitrotyrosine is found in many tissues associated with various disease conditions. It is often considered as a marker for peroxynitrite formation, and its presence is consistent with oxidative stress. Peroxynitrite is formed from the reaction between nitric oxide and superoxide and its reactivity is favored when these reactants are present in approximately equal molar ratios. Using the nitric oxide donor SPER/NO and a superoxide generating system (hypoxanthine/xanthine oxidase), we were able to produce peroxynitrite under physiologically relevant fluxes of NO and O₂⁻. Optimal peroxynitrite formation was verified by DHR oxidation however exposure of BSA to these conditions did not result in detectable nitrotyrosine formation. It is well known that peroxidases are able to catalyze nitrotyrosine formation from nitrite and peroxide. We found that hemin, which can be formed from degradation of heme-containing proteins, was also able to catalyze nitrotyrosine formation in a similar manner. Although the reaction of NO and O₂⁻ did not nitrate BSA, nitrotyrosine was observed upon addition of both SOD and hemin or peroxidases. We propose a new mechanism for NO/O₂⁻ mediated nitration whereby SOD promotes formation of nitrite and peroxide, both of which are ideal substrates for hemin and peroxidase.

9. Modeling and Mutational Analysis of a Putative Sodium-Binding Pocket on the Dopamine D2 Receptor

K. A. Neve, Portland VA Medical Center

A homology model of the dopamine D2 receptor was constructed based on the crystal structure of rhodopsin. A putative sodium-binding pocket identified in an earlier model (PDB 1I15) was revised. It is now defined by Asn-419 backbone oxygen at the apex of a pyramid and Asp-80, Ser-121, Asn-419, and Ser-420 at each vertex of the planar base. Asn-423 stabilizes this pocket through hydrogen bonds to two of these residues. Highly conserved Asn-52 is positioned close to the sodium pocket where it hydrogen bonds with Asp-80 and the backbone carbonyl of Ser-420. Mutation of three of these residues, Asn-52 in helix 1, Ser-121 in helix 3, and Ser-420 in helix 7, profoundly

altered the properties of the receptor. Mutants in which Asn-52 was replaced with Ala or Leu or Ser-121 was replaced with Leu exhibited no detectable binding of radioligands, although receptor immunoreactivity in the membrane was similar to that in cells expressing the wildtype D2L receptor. A mutant in which Asn-52 was replaced with Gln, preserving hydrogen-bonding capability, was similar to D2L in affinity for ligands and ability to inhibit cyclic AMP accumulation. Mutants in which either Ser-121 or Ser-420 was replaced with Ala or Asn had decreased affinity for agonists (Ser-121), but increased affinity for the antagonists haloperidol and clozapine. Interestingly, the affinity of these Ser-121 and Ser-420 mutants for substituted benzamide antagonists showed little or no dependence on sodium, consistent with our hypothesis that Ser-121 and Ser-420 contribute to the formation of a sodium-binding pocket.

10. New Neurons May Be Involved in Functional Compensation in Healthy Tissue after Unilateral Injury

L. Wilbrecht and F. Nottebohm, Rockefeller University

The high vocal center (HVC) in songbirds controls the ipsilateral half of the vocal organ (syrinx) via the tracheosyringeal (TS) nerve. We cut the left or right TS nerve in juvenile zebra finches before song learning commenced, forcing birds to imitate a tutor song using the intact syringeal half. The cell birth marker BrdU was given at various times during and after the sensitive period for song learning and the birds were killed 30 days later. The number of new HVC neurons on the intact side was nearly double that seen in controls and on the denervated side. This effect was only seen during the last 30 days of the sensitive period, and it did not occur when nerve section was combined with deafening or a bilateral anterior forebrain lesion that disrupts song learning. Deafening or bilateral anterior forebrain lesions by themselves had no effect on new HVC neuron number during this same period. We infer that the dynamics of new neuron recruitment in HVC can be affected by song learning during the sensitive period, though basal levels of recruitment and the total count of HVC neurons at adulthood are unaffected by early disruptions of learning. We suggest that new neurons may be useful for functional recovery in healthy tissue burdened with compensation after injury.

11. Effect of BDNF Val66met Genotype on Hippocampal Function and Risk for Schizophrenia

M.F. Egan, T.E. Goldberg, B. Kolachana, J.H. Callicott, A. Bertolino, V.S. Mattay, R. Vakkalanka, A. Malhotra, R. Straub, M. Dean, D. Goldman and D.R. Weinberger. Clinical Brain Disorders Branch, National Institute of Mental Health, NIH

Brain derived neurotrophic factor (BDNF) is a neurotrophin involved in long term potentiation and hippocampus-mediated memory. Patients with schizophrenia have a variety of deficits referable to the hippocampus, including impaired episodic memory and reduced hippocampal N-

acetylaspartate (NAA), a measure of neuronal integrity assayed with MR spectroscopy. Both abnormalities are also seen in their unaffected siblings, suggesting they are genetic traits related to schizophrenia. We examined the effects of functional genetic variation in the gene for BDNF on episodic memory, in vivo hippocampal NAA measures, and risk for schizophrenia in a cohort of 217 patients, 311 of their siblings, and 130 controls. The coding region for BDNF was sequenced for 50 subjects. Only one nonconservative variant (val66met) was detected. High throughput genotyping was then performed on all subjects using a "Taqman" 5' exonuclease assay. Allele frequencies were similar between patients, siblings and controls (val=.81, met=.19) and confirmed in two additional control samples (N=303 and 299).

BDNF genotype had a significant relationship to episodic memory scores from the Wechsler Memory Scale (genotype effect, $F=4.34$, $p=.01$). Homozygotes for the met allele performed significantly worse than val/met and val/val subjects. Similarly, BDNF genotype accounted for 1.8% of the variance in NAA measures ($p<.02$); met/met homozygotes had lower hippocampal NAA, compared to other genotype groups. Using the transmission disequilibrium test (TDT) of association, there was no excess of transmissions of the met allele from heterozygote parents to probands in over 200 trios.

These data suggest that BDNF val66met affects human episodic memory as well as hippocampal neuronal integrity. While the met allele did not appear increase risk for schizophrenia, a weak effect cannot be excluded. This is the first data demonstrating an effect of BDNF on episodic memory in humans. Furthermore, the results with BDNF and hippocampal NAA measures suggest this effect is mediated by the hippocampus.

12. Untangling Agonist Binding and Channel Gating

R.A. Pearce and A. Saad, Department of Anesthesiology, University of Wisconsin, Madison

In defining the mechanisms by which drugs or mutations alter channel kinetics, a basic distinction must be made between changes in binding vs. gating. Despite an apparent conceptual simplicity, this has proved to be a difficult problem. It is difficult because when agonist binding leads to conformational changes such as gating, the affinity of the receptor for agonist (and drug) is altered by that gating; and conversely, gating is altered when drug-induced changes in microscopic agonist affinity lead to changes in binding site occupancy. To develop a method by which binding and gating may be separated experimentally, we have explored the use of permeating, non-conducting anions to suppress conformational changes that are induced by agonist binding.

Whole cell voltage clamp recordings were obtained from HEK293 cells expressing GABA_A receptors composed of rat $\alpha 1$ and $\alpha 2$ subunits. Solutions with and without GABA, and containing different anions, were applied ($t_{\text{exchange}} \sim 2$ ms) using a three-barrel pipette connected to a piezoelectric stacked translator (Physik Instrumente). For experiments with an-

ion exchange, chloride ions in standard HEPES-buffered saline or pipette solution were replaced by equimolar amounts of gluconate or propionate. Permeabilities (relative to chloride, assessed by reversal potential shift of anion mixtures) were low for the large organic anions gluconate ($P=0.30$) and propionate (0.07), as observed previously. Neither anion was able to conduct through the channel, and both anions prevented the development of rapid desensitization despite the continued presence of a saturating concentration of GABA. In the presence of nonconducting anions, the unbinding rate for GABA was assessed by applying a brief pulse of GABA in the absence of chloride, allowing GABA to unbind for a variable “unbinding interval”, and then reapplying chloride to estimate the number of channels to which transmitter remained bound. In the presence of intracellular gluconate and extracellular propionate, the unbinding rate for GABA was greatly accelerated (unbinding ~ 8 ms) compared to deactivation (decay ~ 30 and 200 ms), indicating that a majority of receptors were unable to remain open under these conditions.

Desensitization and opening are suppressed sufficiently by low permeability, non-conducting anions that it appears possible to dissociate binding from gating. This will permit direct examination of the effects of drugs and mutations on microscopic binding and unbinding rates.

This work was supported by NIH GM55719 and the UW Department of Anesthesiology.

13. Cocaine-Associated Environmental Cues Lower Electrical Brain-Reward Thresholds and Augment Nucleus Accumbens Dopamine in Rats – Evidence for Cue-Induced Proponent Processes in the Neurobiological Substrates of Addiction

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The ability of drug-paired environmental cues to trigger drug craving and relapse to drug-taking behavior in both humans and laboratory animals is well established. The involvement of deep temporal lobe loci, including the basolateral amygdala, in cue-triggered craving and relapse has been established by neuroimaging studies at the human level and inactivation of amygdaloid nuclei by microinjections of tetrodotoxin (TTX) during cue-triggered “reinstatement” of drug-seeking behavior in animals. While such experiments have shown the importance of deep temporal lobe structures to

cue-evoked drug craving and relapse, they have also suggested (e.g., by double-dissociation TTX inactivation of amygdala versus nucleus accumbens) that cue-evoked relapse to drug-seeking does not involve the meso-accumbens dopamine (DA) circuit, long suggested to be a crucial substrate in the neurobiology of drug addiction. However, we and others have shown that activation of deep temporal lobe loci - hippocampus and amygdala - profoundly influences electrophysiological and neurochemical functions of the meso-accumbens DA circuit. Therefore, the present experiments were undertaken to see if drug-paired environmental cues could similarly alter meso-accumbens DA functions - using both meso-accumbens electrical brain-stimulation reward (BSR) and *in vivo* microdialysis measurements of accumbens DA overflow as dependent measures. We found that cocaine-paired environmental cues significantly lowered BSR thresholds and significantly elevated extracellular accumbens DA overflow, i.e., in the same direction as cocaine itself. These data suggest that drug-paired environmental cues acquire the ability to modulate meso-accumbens reward-related functions, in proponent rather than opponent fashion. These data may help explain the profound ability of drug-paired environmental stimuli to provoke relapse to drug-taking behavior in abstinent and recovering addicts, and guide the development of novel therapeutic approaches. (Supported by the Julia Sullivan Medical Research Fund, the U.S. Department of Energy Office of Biological and Environmental Research, and by NIMH grants MH49165 and MH55155).

14. Light-Induced Alteration in NMDA Receptor Function Are Mediated via the Redox Modulatory Site

D. Leszkiewicz and E. Aizenman, University of Pittsburgh School of Medicine

NMDA-induced whole-cell responses in rat cortical neurons are potentiated by a brief focal light pulse directed at the cell body and proximal dendrites via an optical fiber (Leszkiewicz et al. *J. Physiol* 524:365, 2000). Our current studies use recombinant NMDA receptors transfected into CHO cells in order to elucidate the potential light sensitive moiety within the NMDA receptor. Whole cell responses from CHO cells transfected with wildtype NMDA receptors potentiate in response to brief light pulses. Exposure to the reducing agent dithiothreitol (DTT, 4 mM) for six minutes enhanced NMDA-evoked currents in these cells via a modification of the redox modulatory site. Under these conditions, light induced potentiation of NMDA-mediated whole-cell responses of recombinant NR1b/NR2A NMDA receptors was substantially attenuated. In addition, exposure to light during incubation with an oxidizing agent (5,5'-dithio-bis[2-nitrobenzoic acid], 500 mM) also decreased the effects of light. Furthermore, the redox-insensitive NR1a(C744A, C798A)/NR2B and NR1b(C765A, C819A)/NR2B receptor combinations were virtually insensitive to light, indicating that the elimination of the redox site on NR1 also abolishes light-induced potentiation. NR1a(C744A, C798A)/NR2A and NR1b(C765A, C819A)/NR2A still retain some degree of light induced potentiation suggesting that additional

redox sites may confer light sensitivity in these receptor configurations. These results suggest that redox sensitivity modulates the effects of light on the NMDA receptor.

15. Characterization of Dopaminergic Phenotype in the hNT-DA Neurons

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The major limitations of neural transplantation of human embryonic dopamine neurons for treatment of Parkinson's disease are: insufficient supply of tissue, ethical concerns, and poor graft survival. Human NT2 cells have been considered an alternative source and in the presence of retinoic acid express dopaminergic markers. In the present study, NT2 cells were differentiated by retinoic acid (4wk) and examined for dopaminergic phenotype and response to toxic stimuli. The differentiated cultures (hNT-DA) contained 42% dopamine neurons as assessed by tyrosine hydroxylase (TH) and dopamine transporter, but produced only marginal amounts of homovanillic acid, a metabolite of DA. The DA neurons in these cultures were totally resistant to cell death induced by serum withdrawal (20hr) and were markedly insensitive to MPP+ (LD₅₀ 2mM). This was in sharp contrast to the primary DA neurons from rat ventral mesencephalon where 32% of the DA neurons were apoptotic after 20hr of serum withdrawal and the LD₅₀ for MPP+ was 23mM. The hNT's resistance to MPP+ correlated with low DA uptake. Observed resistance of hNT-DA neurons to cellular stresses is beneficial for cell transplantation. However, further enhancement of dopaminergic phenotype in the hNT-DA neurons will be required prior to their consideration for transplantation in Parkinson's disease. Supported by NS38619.

16. Dopaminergic Stimulants Strengthen and Synchronize Oscillations in Hippocampal Theta Power and Globus Pallidus Firing Rates

D.N. Ruskin, D.A. Bergstrom, P.L. Tierney, and J.R. Walters, National Institutes of Health

Multisecond oscillations (mean: ~25 s) in neuronal firing rates are present in several basal ganglia nuclei in awake, immobilized rats. These oscillations are robustly modulated by dopaminergic agonists and catecholaminergic stimulants, and are not present in systemically-anesthetized rats. Spectral and wavelet analyses of transcortical EEG (tEEG) signals taken during globus pallidus extracellular single unit recording sessions in awake rats indicated that periodic bursts of tEEG theta rhythm (4-7 Hz) accompanied multisecond firing rate oscillations in the globus pallidus (n=33). This cor-

related activity was present in 36% of baseline recordings and the incidence significantly increased to 76% after systemic injection of catecholaminergic stimulants (tested drugs: cocaine, methylphenidate, GBR-12909, all at 3.2 mg/kg i.v.). The incidence of correlated oscillations dropped dramatically after subsequent injection of the dopamine antagonist haloperidol. Phase relationships between globus pallidus and tEEG theta differed widely between cases in baseline, but became synchronized (concentrated around zero degrees) after stimulant injection ($p < .001$). Also, stimulant injection increased the regularity of bursts in tEEG theta (over 50%, $p < .02$) and shifted the interburst period from 19 s to 9 s ($p < .01$). Localized field potential recordings revealed that theta rhythm bursts originated in the hippocampus ($n=23$): hippocampal theta bursts in baseline and after stimulant injection shared essentially all the characteristics of those recorded in the tEEG. These data indicate that multisecond periodicities in electrical activity are present in both the motor and limbic systems, and are strengthened and synchronized by stimulants via the dopamine system. In general terms, multisecond oscillations have been shown to modulate the propagation of information through sensory systems and spinal motor circuits; the presently-described oscillations could perform this function in the basal ganglia and hippocampus in an ultraslow time range. Specifically regarding the effects of stimulants, given a recent report that theta-frequency electrical stimulation of the hippocampus reinstates cocaine-seeking behavior in addicted rats, these data suggest that the dopaminergic modulation of multisecond patterning of hippocampal theta might strengthen the learned association of self-administration context with self-administered drug.



Sessions Abstracts

Workshop · Sunday, January 27 · 4:30-6:30 PM ·
Hoaglund

Modulating Mammalian Maps

R. Siegel, S. Kastner, L. Krubitzer, D. O'Leary

It is a central dogma in our understanding of central nervous system organization that there are static functional architectures. Functions are mapped to neurons whose placement on the cortex progresses in an orderly fashion. The spatial ordering is fixed in time. This idea permeates our thinking of CNS function. For example, after the critical period, in primary visual cortex, orientation and ocular dominance columns are thought to be locked in place providing a substrate for the generation of secondary and tertiary visual representations.

Yet maps cannot be so static. Maps need to change. During development, not only are the neural structures themselves, the very substrates, being modified but the animal is growing and changing the relationship between sensory input and motor outflow. Across phyla there are changes in maps of sensory and motor function that are driven by natural selection as well as the demands of the individual. The internal state of an animal can alter the tuning properties of an individual neuron and presumably the overlying architecture. Indeed even at the highest level of the network, it can be expected that different collections of regions may be exploited as a function of the animal's behavioral state for similar visual and behavioral tasks.

This workshop will examine evidence for the modulation of maps and question the unchanging static view of central nervous system organization. Dennis O'Leary will discuss the role of molecular gradients in map development and their deliberate alteration. Evolution provides a different model of pressures to change maps as will be described by Leah Krubitzer. Ralph Siegel will discuss the shifts in cortical maps in the parietal lobe as a function of attended and intended behaviors in monkey. Sabine Kastner will discuss the modulation of cortical networks in humans by attention.

Panel · Sunday, January 27 · 4:30-6:30 PM · Sinclair

Strengthening the Brain Against the Ravages of Time: Implications for Neurodegenerative Diseases of Aging

J. Joseph, R. Quirion, D. Ingram, W. Greenough

"By the year 2050, 30% of the total population will exceed 65 years of age, and there is a high probability that they will be exhibiting the most common motor and cognitive behavioral changes that occur in aging with asso-

ciated increases in age-related neurodegenerative diseases (eg., Alzheimer's disease, AD). In fact, there is accumulating evidence that with increasing age the brain may provide a fertile environment for the development of AD and other related disorders such as vascular dementia. The aged brain exhibits increased sensitivity to oxidative stress and inflammation, that ultimately could affect such parameters as neuronal signaling, cognition, and vulnerability to stroke (among others). Thus, there is growing research interest in pharmacological, dietary, or behavioral interventions that would reduce these age-related increases in vulnerability. The aim of this panel is to discuss the salient aspects of this work. To this end, Remi Quirion will present findings on the possible beneficial effects and mechanisms of action of trophic factors, Ginkgo Biloba and resveratrol. Jim Joseph will describe the putative benefits of a diet containing fruits and vegetables that are high in antioxidant activity on age-related declines in neuronal and behavioral function. Don Ingram will discuss the effectiveness of dietary supplementation with agents that mimic caloric restriction (a long-known method for altering the course of aging) on preventing neuronal and related deficits in aging. Bill Greenough, will present data on the "use it or lose it" concept of brain aging by describing the effects of physical and mental exercise on cognition and neurogenesis in senescence."

Workshop · Sunday, January 27 · 4:30-6:30 PM ·
Erickson

**Genetic Determinants and Cellular Mechanisms Underlying
Resistance to Excitotoxic Neurodegeneration**

O. Steward, P. Schauwecker, C. Shuttleworth, P. Sullivan

It has recently become clear that certain strains of mice carry gene(s) that confer resistance against excitotoxic neurodegeneration (Schauwecker and Steward, 1997). This panel will discuss recent findings regarding the genetic and cellular basis of the resistance. P.E. Schauwecker will discuss the experiments that established the difference in sensitivity to excitotoxic neurodegeneration, and will summarize new information regarding the genetic basis of the resistance. C. Shuttleworth will describe experiments involving Ca²⁺ imaging in living neurons in hippocampal slices that demonstrate substantial differences in Ca²⁺ dynamics in neurons from sensitive vs. resistant strains. P. Sullivan will summarize evidence demonstrating that isolated mitochondria from strains that are resistant to excitotoxic neurodegeneration have a dramatically increased threshold for induction of the mitochondrial permeability transition in comparison to mitochondria from sensitive strains or from rats. These intrinsic differences in mitochondria predict the sorts of differences in Ca²⁺ dynamics that are actually seen in the Ca²⁺ imaging studies. The greater capacity to buffer Ca²⁺ as levels increase enables neurons to survive levels of Ca²⁺ that would otherwise be lethal. Together, these observations provide a plausible cell biologi-

cal mechanism for the difference in sensitivity to excitotoxic neurodegeneration. O. Steward will discuss how these differences in background genes affect responses to injury, and may explain some of the current paradoxes in studies involving murine models of neurodegenerative disorders. In particular, strain differences in sensitivity to excitotoxic neurodegeneration may explain some of the differences that have been seen in the onset and severity of striatal neurodegeneration in different murine models of Huntington's Disease.

Panel · Sunday, January 27 · 4:30-6:30 PM · Carroll

Moving to the “Front” of the Class: Prefrontal Cortex, Development and Learning

J. D. Cohen, B. J. Casey, Y. Munakata, R. O'Reilly, K. Koedinger

The frontal cortex has long been recognized as a critical brain structure in executive function. It is also well accepted that this structure undergoes a protracted course of development, extending well into adolescence in humans, which parallels the development of uniquely human abilities, such as planning, and reasoning. This panel will discuss the relationship between executive function and prefrontal cortex, as assessed through neuroimaging, behavioral, and computational studies of their development, and the utility of these insights in designing better educational tools. The overarching goal of the panel will be to survey what is presently known about the organization of prefrontal cortex function, how this relates learning during development and in maturity. B. J. Casey will review neuroimaging studies of frontal maturation, and its relationship to the development of fundamental mechanisms of cognitive control. Yuko Munakata will describe behavioral and computational studies of the development of executive functions, focusing on basic computational functions thought to be supported by prefrontal cortex, such as active maintenance of information in working memory. Randy O'Reilly will describe computational modeling studies that examine the ability of basic learning algorithms to simulate the development of representations in frontal cortex, that are necessary for task generalization. Ken Koedinger will describe studies making combined use of fMRI, eye tracking, and computational modeling to identify the neural processes underlying the acquisition of complex skills such as algebraic reasoning. This work is being conducted in conjunction with an extensive program of research using computer-based tutors to augment classroom instruction in formal skills, such as algebra and geometry. Thus, this work ties basic research on executive function — at both the neural and cognitive levels — together with real world educational applications. We anticipate that the findings presented will provoke questions and a lively discussion about existing theories of frontal function and its role in the acquisition of executive function, as well as new directions that should be taken in this important, but under-represented area of cognitive neuroscience research.

Panel · Sunday, January 27 · 4:30-6:30 PM · Snobble

High Gly: Role of Glycine Transporter in Regulation of NMDA Receptor Function

H. Sershen, L. Harsing, B. Lipska, P. O'Donnell

Glycine (Gly) has been shown to augment the response of NMDA receptors, acting as an obligatory co-agonist at the Gly modulatory site of the NMDA receptor. It has also been shown that Gly administration reduces PCP-induced activity in rodents and in humans has been reported to reduce the negative symptoms of schizophrenia. In these studies very high amounts of Gly must be administered, suggesting that local Gly concentration is regulated by an efficient Gly uptake transporter (GlyT) that possibly governs Gly site occupancy of the NMDA receptors. Recent studies have examined the role of GlyT inhibitors as a means to enhance NMDA function. Dr. Sershen will show effects of GlyT inhibitors on NMDA-mediated dopamine release and reversal of PCP-induced effects by Gly and GlyT inhibitors. Dr. Harsing will discuss issues of occupancy of the NMDA receptor by endogenous Gly, whether or not they are saturated, and the contribution of the Gly binding site and GlyT in the regulation of Gly and GABA efflux. Dr. Lipska will demonstrate that NMDA antagonists (PCP and MK-801) produce delayed emergence of motor hyperactivity, and that Gly and GlyT inhibitors reverse behavioral abnormalities in a neonatal hippocampal rat model of glutamatergic dysfunction. Dr. O'Donnell will report on electrophysiological activity in the prefrontal cortex and nucleus accumbens showing GlyT inhibitors can effectively enhance NMDA function. The use of GlyT inhibitors may prove to be a novel approach for enhancing NMDA function and may prove beneficial in treatment of schizophrenia.

Panel · Sunday, January 27 · 4:30-6:30 PM · Janiss

A New Look at an Old Receptor: Basic and Clinical Advances on the Brain Nicotinic Receptor

J. Coyle, D. Berg, S. Leonard, R. Schwarcz

Darwin Berg will review recent evidence that alpha 7 nicotinic receptors (nAChRs) mediate Ca²⁺ influx in an activity dependent fashion. Alpha 7nAChR stimulation at low levels causes calcium transients independent of voltage gated channels. High frequency stimulation produces Ca²⁺ dependent activation of CREB and downstream changes in gene expression that may mediate trophic and neuroprotective effects. Robert Schwarcz will present recent findings that nAChRs, especially the alpha 7 subtype, are inhibited by kynurenic acid, the tryptophan metabolite that also inhibits NMDA receptors. Furthermore, prolonged nicotine treatment increases selectively brain kynurenate levels. Post-mortem studies have revealed elevations of kynurenic acid in the brains of schizophrenics. Sherry Leonard will

discuss evidence of impaired nAChR function in schizophrenics associated with an abnormality in the auditory evoked potential, P50. A linkage site at 15q14 has been associated with an increased risk for schizophrenia and P50 abnormalities in certain pedigrees. This site contains the gene for the alpha 7nAChR which in affected individuals has a mutation in the promoter region that reduces receptor expression. Joseph Coyle will review the therapeutic effects of galantamine, an acetylcholinesterase inhibitor and a positive allosteric modulator of nAChRs, in Alzheimer's disease (AD). Galantamine increases the duration of nAChR channel opening and sensitivity to acetylcholine. Galantamine not only significantly enhances cognition but appears to slow progression in AD.

Panel · Sunday, January 27 · 8:30-1000 PM ·
Hoaglund

Adenosine in Brain: Sleep, Seizures, Nerve Regeneration, Drug Withdrawal, Neuroprotection, and More!

R. Greene, S. Masino, B. Frenguelli, J. Fowler

Adenosine receptors in brain have profound effects upon many neural systems, yet many aspects of their role remain obscure. Caffeine, which is an adenosine receptor antagonist, has been reported to both protect the brain, as well as to exacerbate neuropathology under different experimental conditions. Participants in this panel will discuss alterations in brain function produced by adenosine receptor antagonists such as caffeine, as well as by knockouts of adenosine receptors, as ways to identify the functions subserved by adenosine. Mechanisms that regulate extracellular adenosine will be discussed, including via cAMP transport, NMDA receptor activation, and nitric oxide release, as will the mechanisms underlying the stimulation of adenosine release during hypoxia, both in vivo and in vitro. In terms of the role of adenosine in non-pathological conditions, there is evidence that adenosine may function as an endogenous regulator of excitability, and may be important in the initiation of sleep. Adenosine A1 receptor knockout mice have been found to be relatively insomniac (more than 10% less sleep), and to have overall changes in sleep patterns that are consistent with a disruption of sleep homeostatic process as indicated by deficits in the generation of delta wave power. The panelists will discuss some of the multiple roles that have been proposed for adenosine, and address possible reasons for some of the differences that have been reported between studies in vivo and in vitro.

Panel · Sunday, January 27 · 8:30-10:00 PM · Sinclair

**Structural Databases Provide New Insight into Structural/
Functional Relationships in the Nervous System**

S. Koslow, K. Harris, M. Ellisman, R. Williams, S. Mori

Within the field of Neuroscience understanding the relationship between structure and function is a continuing pursuit. Some of the more recent analytical tools and databases emerging from the field of Neuroinformatics, through funding from the Human Brain Project, offer new insights into structure/function relationships as well as demonstrating the advantages of creating and applying these informatics initiatives toward the understanding of nervous system function. Kristen Harris will present and discuss automated methods for visualizing the nervous system at the EM level and the novel tools that have been developed to unravel the complex connections within the neuropil. Utilizing the EM tomographic approach Mark Ellisman will build on this approach using data from his 3D Cell Centered database, which contains information about neuronal structure and protein distribution, and demonstrates how this data from his database can be linked with other distinct data sources. Ellisman and colleagues have developed a novel XML wrapper-based mediator integration paradigm to assist the users by providing them with integrated views of data regardless of the source. The mediator is responsible for selecting, restructuring, and merging information from autonomous sources and for providing an integrated XML view of the information. Abnormalities in structure or connectivity of different structures may be key to understanding nervous system structural abnormalities in mutant mice as well as nervous system disorders in Humans. To facilitate collaborative efforts to map genes affecting brain and behavior Robert Williams will presentation will detail the web informatics tools and resources under developments that includes an Internet-accessible slide collection, a motorized microscope interfaced to the web using a Java applet, and special gene mapping software. Users of this site will be able to parse out heritable variation in CNS traits into sets of well-mapped quantitative trait loci (QTLs). By crossing mice with distinct phenotypes (e.g., high and low neuron number) they are mapping a growing number of QTLs associated with marked variation in CNS traits and specific neuron populations (hippocampus, striatum, cerebellum, olfactory bulb, retina). Finally Susumu Mori is establishing a web-based database using Diffusion tensor imaging (DTI), a new MRI technique, which uses water diffusion properties as a probe to study brain white matter anatomy. Previous studies indicated that it could reveal trajectories of axonal tracts in the white matter non-invasively. This technique is being applied to postmortem human brains to establish a high-resolution, electronic white matter atlas of healthy human brains. In this presentation, the data will be compared to conventional MR images as well

as in vivo results to demonstrate the usefulness of the postmortem DTI studies. The synergy of this panel will demonstrate the powerful new tools and approaches available through Neuroinformatics for understanding functional/structural relationships and the enhanced efficiency of science attainable through their development and utilization.

Workshop · Sunday, January 27 · 8:30-10:00 PM ·
Erickson

**Ventral Tegmental Area and Substantia Nigra Dopamine
Neurons—Similar or Different?**

J. Finlay, A. Charara, J. Tepper, J. Roeper, M. Wightman

Ventral tegmental area (VTA) and substantia nigra (SN) dopamine (DA) neurons may be somewhat discrete neuronal populations. Initially, this distinction was based on the observation that axons of VTA DA neurons terminate largely in the cortex and ventral striatum, whereas those of SN DA neurons terminate in the dorsal striatum. Differences in VTA and SN DA neuron function were first postulated ~25 yrs ago based on evidence of differential regulation of these neurons by release and impulse modulating autoreceptors. Numerous studies have now evaluated the structure and function of VTA and SN DA neurons. Some investigators have concluded that the functional capacities of VTA and SN DA neurons are qualitatively different under, for example, conditions of stress, psychoactive drug administration, and injury. Mechanisms postulated to contribute to the apparent functional differences have ranged from differences in afferent regulation to intrinsic cellular proteins. The purpose of the present workshop is to discuss whether the evidence that has accumulated in the last 25 yrs supports or refutes the view that there are fundamental qualitative differences between VTA and SN DA neurons. Differences and similarities in the regulation of electrophysiological activity (Roeper & Tepper) and neurotransmitter release and uptake (Wightman & Finlay) will be discussed. Both intrinsic regulatory mechanisms and extrinsic influences such as afferent glutamatergic projections will be debated (Charara).

Panel · Sunday, January 27 & 8:30-10:00 PM & Carroll

**NO and Neurodegeneration: Not Gone and Not Forgotten. Is Your
Brain Protected or Is It Rotten?**

S. Hewett, M. Espey, C. Colton, T. Dawson

Many cellular functions are regulated by the direct interactions of NO with target biomolecules. In addition, NO can react with oxygen, superoxide or other nitrogen oxides with subsequent pathophysiological consequences. It is now apparent that the balance between nitrosative and oxidative chem-

istry within specific biological compartments determines whether the presence of NO will be ultimately deleterious or beneficial. With this in mind, Dr. Michael Graham Espey (NIH) will begin this panel by describing his provocative theory on “supernitrosation.” He will explain to the audience how oxidative or nitrosative stress can be focused into microdomains depending upon the rates of NO/O₂- production, diffusion and compartmentalization of scavenger substances. This provides a wonderful back drop for the following three speakers who will collectively bring the audience up to date on the current thinking with regards to the sometimes paradoxical, but always interesting, role of NO in acute and chronic neurodegenerative disease processes. Drs. Sandra Hewett (Univ. CT Health Ctr.), Ted Dawson (Johns Hopkins Univ.) and Carol Colton (Duke Univ.) will provide a broad overview of the current knowledge of both the protective and deleterious roles of NO in stroke, Parkinson’s disease and Alzheimer’s disease, respectively.

Panel · Sunday, January 27 · 8:30-10:00 PM · Snobble

Peripheral Nerve—Not Just a Cable Anymore

P. Reeh, L. Sorkin, G. Bove, H. Handwerker

“Do axons only ax?” No - they also sense, and this may essentially contribute to syndromes of neuropathic pain, hyperalgesia and dysesthesia. Linda Sorkin (UC San Diego) will report on the inflammatory cytokine TNF α which applied to an intact peripheral nerve induced ectopic discharge in nociceptive C-fibers. In awake animals, TNF on the nerve also led to an acute allodynia, an aversive response to light touch, but no change in response to thermal stimulation. Geoffrey Bove (Harvard) induced a “natural” inflammation of a peripheral nerve by application of Complete Freund’s Adjuvant and will describe the slow development of graded mechanosensitivity at the inflamed site that led to encoding discharge in nociceptive fibers innervating musculoskeletal but not cutaneous tissue. Neuropathic pain attacks are often triggered by movements stretching nerves. Other sensory transduction mechanisms present in normal unmyelinated axons are specifically activated by noxious heat, capsaicin and protons and lead to vesicular exocytosis of the pro-inflammatory calcitonin-gene related peptide (CGRP). Related work will be reviewed by Peter Reeh (Univ. Erlangen, Ger.), and limited effects of capsaicin antagonists as well as of deletion of the capsaicin receptor gene VR1 will be reported. Sensitization of stimulus transduction in inflamed or ischemic (acidotic) nerves may lead to ongoing discharge, e.g. in case of diabetic neuropathy. Finally, Hermann Handwerker (Univ. Erlangen, Ger.) will give an overview of differential peripheral mechanisms for heat and mechanical hyperalgesia as derived from human microneurography and microdialysis studies that also included neuropathic patients.

Panel · Sunday, January 27 · 8:30-10:00 PM · Janiss

Signaling Crosstalk and Molecular Interactions in Neuroendocrine Regulation

G. Aguilera, J. Cidlowski, D. DeFranco, J. Shepard, S. Radovick

Neuroendocrine mechanisms involving neuropeptide secretion as well as central regulatory action of hormones are critical for most physiological functions, including reproduction, growth, behavior and adaptation to changing environment. This regulation requires multiple modulatory mechanisms, which coordinate appropriate neuroendocrine cell responsiveness to meet physiological demands. This panel will explore recent progress in the molecular mechanisms which underlie precise regulation of neuroendocrine function at the transcriptional level. John Cidlowski will discuss how differential activation of signaling pathways depending on the physiological condition can modulate the regulatory action of glucocorticoids either by receptor phosphorylation, differential regulation of glucocorticoid receptor subtype or induction of transcription factors able to interact with the glucocorticoid receptor. Don DeFranco will describe mechanisms by which the signal transduction capacity of steroid hormone receptors is influenced by the efficiency of receptor trafficking between cytoplasm and nucleus, and within the nuclear compartment, and will discuss the role of cellular chaperone proteins, such as heat shock proteins in this regulation. Jack Shepard will show how activation of cAMP dependent pathways by regulatory neurotransmitters leads to sequential induction of stimulatory and inhibitory transcription factors resulting in self-limitation of transcriptional responses of the corticotropin releasing hormone gene in hypothalamic parvocellular neurons. Finally, Sally Radovick will describe effects of growth factor signaling pathways, known to regulate development and metabolism, in the transactivation of pituitary-specific genes. The mechanism of recruitment of the co-activator, CREB-binding protein (CBP), to the pituitary specific POU-homeodomain protein, Pit-1, on the transcription complex will be highlighted. Discussion of these topics will provide new insight on the multiple mechanisms capable of modulating the action of transcriptional regulators, as well as opening novel perspectives for the development of diagnostic and therapeutic tools for neuroendocrine disorders.

Panel · Monday, January 28 · 7:30-9:30 AM ·
Hoaglund

**Translational Approaches to Addiction: Novel Systems, Novel
Animal Models, New Technologies are Required**

G. Koob, B. Tabakoff, H. Gutstein, B. Mason

The purpose of this panel is to explore novel approaches to the study of addiction that incorporate recent advances in animal models of drug addiction and alcoholism, novel technologies at the molecular level of analysis, and recent developments in medication development in the clinic that impact on the direct and indirect utility of such basic research. The panel will explore a hypothetical framework for how such studies can be planned with each domain, the strengths of each domain, and how they translate across domains. George Koob will discuss animal models of excessive drug and alcohol intake that serve as animal models of dependence and as animal models for the transition from nondependence to dependence. Boris Tabakoff will discuss the application of gene array technology to the study of addictive disorders. The use of high-throughput gene expression assays (cDNA and oligonucleotide microarrays) allow delineation of changes in expression of genes encoding neuronal components (e.g. receptors, ion channels, intracellular signaling apparatus, cell adhesion molecules) that may be at the basis of long-term changes in the physiological properties of neurons and the circuits in which they function. New developments in the field of neuroinformatics will be required to assimilate and provide retrieval tools for the integration of the enormous amount of data generated by such gene arrays and databases. Howard Gutstein will discuss the application of proteomics—the “differential display” of proteins from cells in different physiological conditions—to the study of addictive disorders. Barbara Mason will integrate the clinical outcome literature to identify a potential set of primary and secondary outcome criteria that may better identify drug actions and potential neurobiological targets in humans. Such characterization will serve to identify the human model appropriate for detecting a positive treatment effect in the treatment of drug abuse and the prevention of relapse; further, it will provide the rationale for pharmacogenetic and neuroimaging studies. This panel will provide a basis for the development of translational research in the addiction field linking animal models, molecular events, and clinical significance.

Panel · Monday, January 28 · 7:30-9:30 AM · Sinclair

Do Alterations in Neuronal Membrane Properties and Synaptic Transmission Contribute to Striatal Dysfunction and Degeneration in Huntington's Disease?

A. Cantrell, M. Levine, L. Raymond, G. Rebec

Huntington's disease (HD) is an inherited, progressive, neurodegenerative disorder that has devastating consequences for patients and their families. Abnormal involuntary movements characterize this neurodegenerative disease, along with dystonia, intellectual impairments and emotional disturbances. Affected individuals suffer from a diminished ability to walk, talk, think, reason and maintain emotional balance. Unfortunately, no cure is available and treatment options designed to slow progression of the disease are highly limited at the present time. Significant progress has been made in defining the underlying causes of Huntington's disease (HD) and it is thought that the clinical manifestations of HD result from the selective loss of medium spiny projection neurons in the neostriatum. However, the mechanisms underlying the striatal degeneration are still unclear. Recent reports have indicated that electrophysiological abnormalities occur in the brains of HD transgenic animals. These abnormalities include altered somatic discharge, broadening of the excitatory postsynaptic potential (EPSP) and failure to induce long term potentiation (LTP) following high frequency stimulation. These abnormalities precede neurobehavioral and neuropathological alterations suggesting to some researchers that cytoplasmic functions including neurotransmitter regulation of ion channels and regulation of intracellular Ca^{2+} may play a role in this disease. In support of this hypothesis, alterations in the membrane properties of post-synaptic medium spiny striatal neurons have recently been reported in mice in which expression of mutant huntington has been induced transgenically. First, Mike Levine and Lynn Raymond will discuss their respective findings in R6/2 and YAC72 transgenic mice. In the R6/2 mice, medium spiny striatal neurons have more depolarized resting membrane potentials, increased input resistance and decreased membrane time constant along with an enhanced sensitivity to NMDA correlated with increased expression of the NMDAR1 subunits and a subsequent increase in intracellular Ca^{2+} flux possibly through NMDA receptors and alterations in K^+ channel function. In YAC72 mice, medium spiny neurons have increased NMDA current amplitude, higher intracellular Ca^{2+} levels and increased vulnerability to cell death. Angela Cantrell will discuss observations from her laboratory suggesting that alterations in the membrane properties of pre-synaptic corticostriatal projection neurons also occur in R6/2 mice. Her data suggest that voltage-gated Ca^{2+} currents are altered in identified corticostriatal projection neurons from R6/2 transgenic mice. Finally, George Rebec will discuss behavior-related deficits in striatal ascorbate release in R6/2 mice that may represent a dysfunction of corticostriatal glutamate. Restoration of ascorbate ameliorates the HD behavioral phenotype.

Panel · Monday, January 28 · 7:30-9:30 AM · Erickson

**NO Way Nitric Oxide is the Only Endothelium-Related Factor
Regulating Cerebral Vasodilation: Redundancy and Interactions
among Multiple EDRFs**

D. Pelligrino, D. Harder, C. Leffler, S. Marrelli

Cerebral vasodilation occurs in response to multiple stimuli. The general purpose is to increase blood flow and improve the delivery of vital energy substrates (O₂ and glucose), as well as removal of metabolic wastes (e.g., CO₂), under conditions of enhanced neuronal activity or diminished circulating levels of O₂ or glucose. The endothelium plays a vital role in the regulation of vascular smooth muscle tone. Over the past decade, nitric oxide (NO) has received most of the attention regarding endothelium-related cerebral vasodilation. However, NO is not the only endothelium-derived relaxing factor (EDRF). Others include vasodilator prostanoids and the rather elusive paracrine factors collectively labeled as endothelium-derived hyperpolarizing factor (EDHF). The latter may involve products of arachidonate metabolism (epoxides), agonists of cannabinoid receptors, or carbon monoxide (CO). Non-paracrine factors, that operate via cell-to-cell communication pathways (i.e., the connexin-related gap junctions) may also be involved in endothelial regulation of cerebral vasodilation. Crosstalk among the NO, prostanoid, and/or EDHF pathways may occur, to the extent that blocking one pathway may lead to an increase in the contribution from another of the aforementioned factors. The end result of this is a maintained vasodilating response to a given stimulus (vasodilatory redundancy). Dave Harder will discuss recent findings concerning EDHF in the cerebral circulation. Charles Leffler will cover the contributions from prostanoids and their interactions with other EDRFs, with some emphasis on differences between neonates and adults. Dale Pelligrino will discuss endothelium-dependent cerebral vasodilation, with respect to estrogen's influence on eNOS function and the balance between eNOS-derived NO and EDHF contributions. Sean Marrelli will introduce the concept of cell-to-cell communication (gap junctions) and EDHF in the regulation of cerebral vasodilation.

Panel · Monday, January 28 · 7:30-9:30 AM · Carroll

**Neurotransmitter/Neuropeptide Interactions in Neuroendocrine,
Autonomic, and Homeostatic Systems**

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

Neurons receive extensive and diverse afferents utilizing a broad spectrum of neurotransmitters and neuropeptides as chemical signals. In many cases, a single afferent neuron releases multiple transmitters and/or peptides at a single synapse. An important challenge for neuroscientists in the 21st century is to understand how neurons integrate these complex chemical sig-

nals into appropriate responses. The focus of this panel will be on interactions between neuroactive agents in neuroendocrine, autonomic and behavioral systems reliant on visceral sensory information. Specifically, Celia Sladek will describe selective potentiation of vasopressin and oxytocin release by chemicals co-released from the A1 catecholamine nerve terminals. These include ATP, norepinephrine, substance P, and neuropeptide Y. Steve Bealer will discuss the interactive roles of norepinephrine and histamine in suckling-induced oxytocin release. A. Kim Johnson will focus on the interactions of aminergic (serotonin) and peptidergic (cholecystokinin) systems in the lateral parabrachial nucleus of the hindbrain in the control of body salt and water balance. Francis W. Flynn will present evidence for modulation of tachykinin receptors during stimulation of salt appetite and vasopressin and oxytocin release. Mechanisms underlying the observed interactions ranging from convergence of second messenger signaling cascades to modulation of receptor recruitment/internalization, and presynaptic facilitation/inhibition of transmitter release will be discussed. Since corelease of these and other agents occurs throughout the CNS, the information presented has broad functional implications and will further understanding of neuronal integration of afferent signals at all levels of the CNS.

Panel · Monday, January 28 · 7:30-9:30 AM · Snobble

Gene Therapy for Human Neurodegenerative Diseases: Scientific, Ethical and Legal Perspectives

R. Beresford, H. Federoff, J. Bernat

Improved methodologies for delivery of therapeutic genes and growing understanding of the molecular basis of several human neurodegenerative diseases have evoked considerable interest in gene therapy for these disorders. However, achieving safe and effective gene therapy poses major challenges. Among the scientific challenges are choice of vector, choice of target cell or tissue, achieving internalization and regulation of transferred genes, and monitoring for gene expression and adverse effects. Ethical challenges include assuring adequate disclosure of risks, protecting vulnerable subjects from therapeutic misconceptions, and avoiding conflicts of interest on the part of clinical investigators. Legal challenges include achieving regulation that will rigorously protect research subjects without unduly burdening promising research, assuring accountability, and developing sensible approaches to protecting the intellectual property involved in developing gene therapy. Howard Federoff will portray the “state of the art” with respect to gene therapy for human neurodegenerative disorders, indicating promises and pitfalls of existing and anticipated strategies. James Bernat will identify the central ethical issues in gene therapy for human diseases and consider how these problems can be resolved or minimized. Richard

Beresford will discuss the evolving regulatory structure with respect to gene therapy and consider relevant intellectual property issues. The goals of the panel are to offer diverse perspectives on the present and future of gene therapy for human neurodegenerative diseases. Questions and discussion will be encouraged.

Panel · Monday, January 28 · 7:30-9:30 AM · Janss

Functional Imaging of Neural Circuitry in the Retina

M. Iuvone, R. Marc, S. Bloomfield, S. Massey

Advances in imaging techniques have made it possible to functionally image neural circuitry and correlate anatomy and physiology under different physiological conditions. Robert Marc will describe how glutamate receptor-coupled channel activation can be quantitatively mapped in all retinal cell populations using channel permeant organic cations (e.g. 1-amino-4-guanidobutane), allowing excitatory glutamate signaling in the mammalian retina to be parsed into functional modules. These modules preferentially decode synaptic glutamate signals with (1) mGluR6 receptors (ON-center bipolar cells), (2) kainate receptors (OFF-center bipolar cells), (3) AMPA receptors (horizontal cells and amacrine cells), and (4) combined AMPA/NMDA receptor signaling (amacrine and ganglion cells). Steve Massey and Stewart Bloomfield will focus on the inner retinal circuitry of the rod pathway that mediates vision under scotopic conditions. This pathway involves glutamatergic synapses of rod bipolar cells onto AII amacrine cells and wide-field GABAergic S1/S2 amacrine cells. Both the AII and S1/S2 amacrine cells form coupled networks via gap junctions, some of which are subject to regulation by neuromodulators (dopamine and NO). Massey will describe the relative distribution of synaptic ribbons, GABA and glutamate receptor subunits and connexins at this synaptic complex. Bloomfield will present recent data showing that light-induced changes in the conductance of gap junctions between AII amacrine cells support rod signaling under different scotopic light conditions. Abnormalities in the scotopic light responses of a connexin36-knockout mouse, which lack AII cell junctions, will also be described. Bill Eldred will describe the imaging of nitric oxide production in retina and how NO production is modulated by excitatory or inhibitory receptors in specific cell types. In addition, he will focus on the production of NO in specific subcellular locations providing evidence that it is not always freely diffusible. Experiments examining potential mechanisms for its subcellular retention will also be described. These approaches are leading to significant advances in our understanding of signal processing through neural networks.

Panel · Monday, January 28 · 4:30-6:30 PM ·
Hoaglund

Perspectives on the Functional Organization of the Basal Ganglia

E. Abercrombie, P. Bolam, M. F. Chesselet, M. DeLong, H. Kita

The participants in this Interactive Panel have each played a dominant role in the development of the current functional model of the basal ganglia circuitry. We will explore with each of them their own “cognitive map” of the basal ganglia. Recall the famous New Yorker cover by Saul Steinberg presenting a map of the United States as seen by a New Yorker. Manhattan dominates the map with points west of the Hudson River minimally displayed. What is true of maps of places – that they differ according to the perspective of the mapmaker – is true of conceptual maps as well. Our eminent basal ganglia researchers will provide us with their basal ganglia “maps”. Each will review past findings that he/she considers to have been most critical to advances in our understanding of the network function of this system. What’s more, they will identify what they consider to be the most important issues that remain for future research on the basal ganglia. The goal of the panelists is to encourage discussion on how to go about unravelling the complex functioning of the basal ganglia in health and disease.

Panel · Monday, January 28 · 4:30-6:30 PM · Sinclair

‘Tide Life, ‘Tide Death: The Genetic Control of Neuronal Survival

J. Morgan, K. Herrup, L. Parada, R. Smeyne

Neurons are eliminated both as a component of normal development and as a result of pathological processes and aging in the adult. In both situations the decision to die or survive is determined by the interplay of genetic and epigenetic factors. This panel will describe new insights into the genetic basis of neuronal survival and outline strategies for investigating this phenomenon.

James Morgan will describe the biochemical and biological properties of a new class of secreted neuronal survival factor that functions in the adult nervous system. This presentation will also introduce the concept of using somatic nuclear cloning of mice to identify genes involved in neuronal survival and to develop new in vivo paradigms to investigate this process.

Luis Parada will discuss the role of the NGF family of neurotrophic factors in neural development and death. The TrkB and TrkC genes encode two receptor isoforms, one bearing a tyrosine kinase domain and the other bearing a truncated membrane bound receptor. The role of the truncated isoforms in sensory neuron pruning will be discussed. This presentation will also highlight the use of genetically modified mice.

Karl Herrup will discuss the role of ectopic re-entrance into the cell cycle as a trigger for cell death both in development and disease. The use of natu-

rally occurring and engineered genetic mutations as well as post-mortem material from human brain illustrates the broad applicability of this principle to neurons at all stages of their 'life-cycle'. It will also emphasize the importance of cell cycle regulation in the homeostasis of a neuron.

Richard Smeyne will discuss the genetic mechanisms that contribute to sensitivity to MPTP toxicity and outline the implications for the pathogenesis and treatment of Parkinson's Disease. This presentation will introduce chimeric culture systems and genetic mapping methods that can be used to identify the genes and cell types that contribute to neuronal survival.

Panel · Monday, January 28 · 4:30-6:30 PM · Erickson

Regulation of Ion Channels by Calcium-Calmodulin

J. Hell, W. Catterall, I. Levitan, J. Adelman

Ca is a potent second messenger that controls a variety of neuronal functions including neuronal excitability, neurotransmitter release, synaptic plasticity, and gene expression. Crucial sources of Ca influx are voltage-gated Ca channels (VOCC) and NMDA-type glutamate receptors. Negative feedback by Ca keeps the activity of these ion channels in check. The incoming Ca also activates Ca-activated K channels, which reduce neuronal excitability. These effects are mediated by calmodulin (CaM), which interacts in various complex ways with these ion channels. Adelman will present results showing that the mechanism of gating for small-conductance Ca-activated K channels (SK channels) is mediated through a constitutive association between CaM and a defined region in the intracellular C-terminus of the SK channels (CaMBD). Binding of Ca to CaM induces conformational alterations in the channel alpha subunits that open the pore; Ca release closes the pore. The crystal structure of the CaMBD complexed with Ca-CaM will be described. Structure-function experiments based upon information from the crystal dissected the constitutive and Ca-dependent interactions between CaM and the SK channels. Catterall will present recent results showing that presynaptic P/Q-type Ca channels are modulated by Ca, CaM, and other Ca-binding proteins. His work shows that Ca and CaM bind to a specific site in the C-terminal domain and cause facilitation and inactivation of these channels, allowing them to respond to the level of Ca in the nerve terminal as well as to membrane depolarization. Other Ca-binding proteins can interact with the same site on P/Q-type Ca channels and cause different forms of regulation. The results provide a mechanism, by which the regulation of P/Q-type Ca channels in nerve terminals can be tuned by expression of specific Ca-binding proteins. Levitan will talk about CaM interactions with the KCNQ K channel, which is responsible for the ubiquitous M current present in most or all neurons. The M current is especially interesting because it is an important determinant of neuronal excitability near the resting potential, and is regulated by a wide variety of neuromodulators. Levitan et al. have identified two sites on the KCNQ chan-

nel that are necessary for CaM binding and have found that channel activity is abolished when CaM binding is disrupted, suggesting that CaM may be an obligatory subunit for channel function. Hell will present findings on the interaction site of CaM with the membrane-proximal C0 region of the NMDA receptor NR1 subunit. NMDA receptor-mediated Ca influx is a critical step in induction of various forms of synaptic plasticity. Upon Ca influx, CaM binds to the NMDA receptor and inhibits its activity. The very same site also binds CaMKII and alpha-actinin. Biochemical, structural, and functional studies will be presented and discussed that elucidate the interplay of CaM, CaMKII, and alpha-actinin with the NMDA receptor and the physiological relevance.

Panel · Monday, January 28 · 4:30-6:30 PM · Carroll

A New Look at the Role of Kainate Receptors in Epilepsy

G. L. Collingridge, C. Mulle, M. Rogawski, D. Lodge

It has been known for many years that application of kainic acid leads to seizures and cell death. However, the role of kainate receptors in the mediation of epilepsy has been difficult to establish due to the lack of specific tools. The aim of this panel is to summarize how recent advances in the molecular biology and pharmacology of kainate receptors is helping the elucidation of the roles of kainate receptors in epilepsy. Christophe Mulle will summarise work on the different kainate receptor knockouts that relates to epilepsy and underlying synaptic mechanisms. David Lodge will provide an update of the different pharmacological tools that are available to study kainate receptors and will present new data on how receptors comprised of specific kainate receptor subunits might be involved in the induction and expression of epileptiform activity in the hippocampus. Graham Collingridge will describe the various roles of kainate receptors in synaptic transmission and synaptic plasticity in the hippocampus and will provide a theoretical framework for their role in the genesis of epilepsy in the hippocampus. Mike Rogawski will describe the role of kainate receptors in synaptic transmission, synaptic plasticity and epilepsy in the amygdala. We anticipate that this highly topical panel will generate lots of interest and provide a useful discussion regarding the roles of kainate receptors in epilepsy in the brain.

Panel · Monday, January 28 · 4:30-6:30 PM · Snobble

Rho GTPases in Neuronal Development and Plasticity

T. Kuhn, J. Ng, H. Cline, P. Meberg

Small GTPases of the rho-subfamily have emerged as pivotal regulators of processes fundamental to cellular homeostasis including actin filament dynamics, cell division, stress kinase activation and, only recently, redox signaling. This family consists of rac1A, rac1B, rac2, cdc42, rhoA and some

distant members. Rho GTPases act as molecular switches that cycle between an active, GTP-bound conformation and an inactive, GDP-bound conformation after GTP hydrolysis. Both the rates of GDP/GTP exchange and GTP hydrolysis are accelerated by a number of different factors with varying specificity for each small GTPase. Due to this complex regulation of their activity, Rho GTPases function as critical points of convergence for multiple extrinsic signals.

This panel will focus on the cellular functions of the Rho GTPases during development and in adult plasticity of the nervous system in several organisms (Mouse, Rat, Xenopus, Chicken, and Drosophila). Dr. Ng (Stanford University) will address the roles of Rho GTPases as regulators of dendritic and axonal development and plasticity in mammalian hippocampus and Drosophila mushroom body neurons. Dr. Cline (Cold Spring Harbor Laboratories) will focus on how Rho GTPases affect neuronal architecture and NMDA receptor activity in the Xenopus optic tectum. Dr. Meberg (University of North Dakota) will emphasize downstream targets of Rho GTPases, in particular ADF/Cofilin and Lim Kinases, and their effects on actin filament dynamics with respect to neurite outgrowth of mammalian cortical neurons. Finally, Dr. Kuhn will concentrate on the role of the small GTPase rac1A in redox signaling in motor neurons via the stimulation of reactive oxygen species and its implication for neurite outgrowth and neuronal survival.

Panel · Monday, January 28 · 4:30-6:30 PM · Janss

Role of CRF and Serotonergic Systems in Stress-Related Behavior

S. Lightman, L. Van de Kar, C. Lowry, S. Maier, L. Kirby

Although serotonergic neurones were first described in the brain in 1964, the role of serotonergic systems in stress-related behavior and neuroendocrine function remains a controversial and unresolved question. For example, studies using in vivo electrophysiology in behaving animals suggest that the neuronal firing rates of serotonergic neurones within various brainstem raphe nuclei are tightly coupled to sleep-wake cycles and the level of behavioural arousal. Furthermore, in the presence of various stress-related stimuli (even those that induce a strong sympathetic activation), there is little or no change in the neuronal activity of serotonergic neurones that cannot be accounted for by changes in the level of motor activity. These findings argue that serotonergic systems respond to stress-related stimuli, but that changes in activity are simply correlated with the increase in behavioural activity and arousal associated with the stress response. However, recent studies are shedding new light on 1) how stress and stress-related neuromodulatory systems, including corticotropin-releasing factor (CRF), may directly modulate serotonergic systems, and 2) how serotonergic systems may contribute to the expression of stress-related behaviour

and neuroendocrine function. Research led by Christopher Lowry suggests that serotonergic neurones may respond differently to stress or stress-related neuromodulators, e.g. corticotropin-releasing factor (CRF), depending on their topographical location (and, by inference, their functional properties) within the raphe complex. Differential responses of topographically and functionally distinct subpopulations of serotonergic neurones may account for some of the confusion that has arisen with respect to the role of serotonergic systems in stress-related behaviour, e.g. anxiety and fear, and the role of serotonergic systems in stress-related neuropsychiatric disorders. Steven Maier and colleagues have demonstrated a role for inescapable stress in activation and sensitisation of serotonergic neurones located in the caudal part of the dorsal raphe nucleus, a process thought to play an important role in behavioural sensitisation and learned helplessness. These studies by Maier and colleagues highlight the dynamic nature of serotonergic systems and may provide insight into the neural basis of chronic states of anxiety or fear. Rita Valentino and colleagues have demonstrated interactions between stress, CRF and serotonergic systems using anatomical, pharmacological, behavioural, electrophysiological, and neurochemical approaches; these findings have implications for our understanding of the neural basis of major depression and other stress-related neuropsychiatric disorders. Louis van de Kar and colleagues have characterised the effects of serotonergic systems on CRF synthesising neurones within the hypothalamic paraventricular nucleus and associated activation of the hypothalamo-pituitary-adrenal (HPA) axis. These findings point toward reciprocal interactions between CRF and serotonergic systems and have important implications for understanding the neuroendocrine/behaviour interface during stress responses. It is hoped that bringing these researchers together will stimulate a lively discussion and will promote an appreciation for the complexity of the role of serotonergic neuronal systems in stress responses in vertebrate brain.

Mini-Course · Monday, January 28 · 6:30-8:30 PM ·
Max Park Room, Wildwood Lodge

Providing Instruction in Responsible Conduct

B. Fischer, C. Atwell

Over the past several years, there has been an increased emphasis within funding agencies, academic institutions, and professional societies on the topic of providing instruction in the responsible conduct of research. In this mini-course, Connie Atwell will discuss current federal regulations for providing ethics training, including answering the questions of what, how, and how much. She also will provide the latest information on any anticipated changes. Beth Fischer will then present an overview of several models for instituting instruction in the responsible conduct of research, focusing on ways to incorporate ethics instruction into the existing curriculum, as well

as methods for expanding instruction to include staff. Participants will then have an opportunity discuss an ethics case relevant to neuroscience. Individuals also will be encouraged to comment on their own experiences teaching research ethics, and may wish to bring multiple copies of syllabi and other relevant materials to share with the audience. Dinner will be provided for those who register for the session on-site at WCBR by Sunday evening.

Panel · Monday, January 28 · 8:30-10:00 PM ·
Hoaglund

Dendritic mRNA Localization and Translation

G. Bassell & S. Zukin (co-chairs), D. Wells, O. Steward

The localization of polyribosomes to subsynaptic sites in dendrites may be an important mechanism to influence synaptic architecture and plasticity. Recent studies have begun to identify the specific proteins that are locally synthesized and elucidate mechanisms of mRNA localization and translational regulation at synapses. This session will highlight the broad spectrum of research on this topic and include physiological, cellular and molecular approaches to this question. Oswald Steward will summarize evidence regarding the selective localization of polyribosomes at synapses, and new evidence regarding the mechanisms that mediate the targeting of mRNA to synapses. Suzanne Zukin will discuss the role of protein kinases in trafficking of glutamate receptor subunits, in particular the NR1 subunit of NMDA receptors. More recent work has investigated the dendritic localization of mRNAs encoding glutamate receptor subunits using fluorescence in situ hybridization on cultured hippocampal neurons. Gary Bassell will discuss work on the mRNA binding proteins, Zipcode Binding Protein (ZBP1) and Fragile X Mental Retardation Protein (FMRP) that may be involved in the activity-dependent regulation of mRNA trafficking in dendrites. Research on the mechanism of function of ZBP1 mediated trafficking of b-actin mRNA in developing neurons will also be discussed. David Wells will then describe a mechanism for the translational regulation of mRNA located at synapses. Here, mRNA polyadenylation regulates translation, a process mediated by the mRNA binding protein CPEB (cytoplasmic polyadenylation element binding). The role of CPEB in regulating α -CaMKII synthesis in the visual cortex following visual experience will be discussed. These studies underscore the importance for regulated mRNA localization and translation as a means to influence the protein composition at post-synaptic sites and achieve synapse-specific modification of synaptic strength.

Panel · Monday, January 28 · 8:30-10:00 PM · Sinclair

Hol(e)y Mitochondria: the Transition from Life to Death?

I. Reynolds, E. Jonas, O. Vergun, J. Kemp

Mitochondria are correctly respected as the major generators of ATP in neurons, and the disruption of oxidative phosphorylation that occurs in ischemic injury undoubtedly contributes greatly to neuronal death. However, there is a growing appreciation of the direct role that mitochondria play in both necrotic and apoptotic injury. For example, mitochondrial calcium accumulation appears to be a critical process in excitotoxic neuronal death, while the release of proteins from the intermembrane space (such as cytochrome c) has emerged as a critical step in many forms of apoptosis. These revelations have returned mitochondria to the limelight, and have provoked many questions about both the normal function of mitochondria as well as the specific alterations in these functions that contribute to the death of neurons. This panel will provide a review of some of the key properties of neuronal mitochondria that may arbitrate life and death decisions. Ian Reynolds will discuss issues of mitochondrial synthesis and turnover in neurons, and will also present recent observations of spontaneous changes in membrane potential in neuronal mitochondria. Elizabeth Jonas will address the issue of the control of outer membrane permeability by Bcl-2 and related proteins, and the relationships between this permeability, synaptic transmission and apoptotic injury. Olga Vergun will describe the impact of ischemic injury on the ability of mitochondria to manage glutamate-induced calcium loads. Finally, John Kemp will provide insight into the properties of the permeability transition pore and a critical evaluation of its potential role in the death of neurons. Collectively, this panel will provide a broad overview of the critical questions that need to be resolved to determine the contribution of mitochondria to the life and death of neurons, and in doing so illustrate the wealth of novel therapeutic targets offered by this "born again" organelle.

Panel · Monday, January 28 · 8:30-10:00 PM ·
Erickson

Voltammetric Monitoring of Behaviorally and Pharmacologically Elicited Changes in Extracellular Dopamine Levels

A. Michael, R. Wise, D. Robinson, G. Rebec

Voltammetric techniques enable dynamic changes in extracellular dopamine levels to be monitored in vivo in both anesthetized and awake animals. Most often, voltammetry has been used to monitor dopamine release evoked by electrical stimulation of dopaminergic neurons or axonal pathways. Recently, however, voltammetry has been increasingly applied to monitor behaviorally and pharmacologically elicited changes in extracellular dopamine

levels. The objective of this panel is to present recent findings and to place those findings in context with results obtained by other methods, such as microdialysis.

Roy Wise will describe conflicting data from voltammetry and microdialysis studies of intravenous drug self-administration, suggesting several potential interpretations of each technique that might contribute to explaining the observed differences.

Donita Robinson will present transient, naturally occurring changes in extracellular dopamine that can now be detected in the brain of freely moving animals. Such changes are most likely to accompany stimuli that are alerting to the animal. These large (>500 nM) changes in dopamine have a lifetime of less than a second.

George Rebec will show that voltammetry can be combined with iontophoresis to assess the mechanisms by which drugs of abuse alter dopamine transmission in behaving animals. This combination has been used to confirm dopamine uptake blockade by cocaine, but the time course of this effect appears unrelated to the motor-activating and reinforcing effects of the drug.

Adrian Michael will describe measurements of extracellular dopamine performed by voltammetry alone and in combination with microdialysis under basal conditions and during systemic drug administration. These studies provide new information about basal extracellular dopamine levels in the rat striatum and provide evidence for the role of autoreceptors in the homeostasis of dopamine levels as measured by voltammetry following uptake inhibition with nomifensine.

Panel · Monday, January 28 · 8:30-10:00 PM · Carroll

Unravelling Synaptic Integration in Mammalian Central Neurons by Injection of Synthetic Conductances

H. Robinson, M. Häusser, D. Jaeger, J. White

The technique of synthesizing a membrane conductance electronically, or “dynamic clamp” (Robinson, 1991; Robinson & Kawai 1993; Sharp et al., 1993), is beginning to transform our understanding of postsynaptic integration in mammalian central neurons. The method offers many advantages. It allows the experimenter to mimic precisely the electrical effects of a point-conductance input, for example a synapse, and to test how the characteristics and location of the conductance control spike generation in the neuron. Because exactly the same conductance stimulus can be applied repeatedly, one can determine the variability of spike-generating mechanisms due to postsynaptic noise. Stochastic conductance stimuli can be injected, to study the sensitivity of firing to synaptic and channel noise of known properties. Using dendritic recording, the spatial integration of synaptic conductance inputs can be measured. In addition, the role of active

conductances in spike generation and reliability can be studied by introducing additional conductance, or by electronically cancelling the contribution of native conductances. In this session, some recent results obtained with this approach are presented. Hugh Robinson will describe how correlated bursts of unitary synaptic conductance inputs, which lead to natural firing statistics, induce two modes of spike variability in cortical neurons, and how variability is amplified by voltage-dependent NMDA receptor conductance. Dieter Jaeger will discuss the control of spike pattern and firing precision in Purkinje cells and in deep cerebellar nucleus neurons by synaptic conductance patterns simulating in-vivo like input conditions. Michael Häusser will describe how the threshold and spatial propagation of synaptically-triggered dendritic calcium spikes is controlled by inhibition. John White will address the role of active conductances in stellate cells of the entorhinal cortex in shaping the reliability of firing, and in generating the hippocampal theta rhythm.

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Panel · Monday, January 28 · 8:30-10:00 PM
· Snobble

Induction of HO by WCBR-Related Activities: Good or Bad!

M. A. Smith, S. Doré, B. Dwyer, N. Abraham

Whether you're a skier, snowboarder or simply a sauna goer, you will be affected by the importance of heme oxygenase (HO). Altitude, hypoxia and head injury have all been associated with increase in HO levels. HO levels/activities are also modulated in relation of cognitive performance and acute and chronic neurological disorders, the former is hopefully more relevant to WCBR attendees. HO degrades heme (a prooxidant) originated from heme-containing proteins to generate iron, carbon monoxide (a vasodilator) and biliverdin which is immediately converted into bilirubin (an antioxidant). HO is now being recognized as a critical antioxidant enzyme. As Paracelsus (1493-1541) once said: "All substances are poisonous. Only the dose differentiates a poison from a remedy." All of these biologically active end-products have dual actions, good and bad, mostly depending on physiological or pharmacological concentrations. Mark Smith will review data on the potential role of HO in AD brains and its relation to tau protein. Sylvain Doré will present evidence obtained from knockout mice supporting the neuroprotective role of HO in heart and cerebral ischemia. Barney Dwyer will discuss HO implications in hypoxia and cerebral edema using HO inhibitors. And Nader Abraham will present recent findings, using retrovirus mediated HO-1 gene and its interaction with nitric oxide synthase and cyclooxygenase. Using different technical approaches, the participants will engage an open discussion about all the different physiological actions of HO and will evaluate potential applications for the development of new therapeutic avenues.

Panel · Monday, January 28 · 8:30-10:00 PM · Janss

Selection of Candidate Genes and Candidate SNP's in Pharmacogenetic Studies of Antipsychotic Drug Response

A. Malhotra, M. Knable, H. Van Tol, D. Goldman

The sequencing of the human genome and rapid progress in the identification of single nucleotide polymorphisms (SNP's) has provided a massive number of candidate genes and candidate SNP's for use in molecular genetic studies. Pharmacogenetic studies of antipsychotic drug response have primarily focused on SNP's within genes that code for neurotransmitter re-

ceptor subtypes, with inconsistent results. In this panel, we will discuss alternative methods for candidate gene identification and new methods to identify the SNP's within those genes with the highest apriori probabilities of influencing antipsychotic drug action. Dr. Anil Malhotra will discuss the first generation of antipsychotic drug pharmacogenetic studies, including methods of candidate gene selection, data from several groups examining the dopamine and serotonin system genetic variation, and current methodological advances to handle the increased availability of genomic sequence and sequence variation information. Dr. Michael Knable will present data from the post-mortem brain collection of the Stanley Foundation utilizing an array of molecular markers within the prefrontal cortex of antipsychotic drug-treated subjects as a method to identify novel candidates for pharmacogenetic studies. Dr. Hubert Van Tol will present data assessing the acute effects of antipsychotic drug administration on gene expression as well as data providing direct evidence for functional differences associated with polymorphisms in key dopamine receptor genes. Finally, Dr. David Goldman will provide an update on the identification and functional characterization of SNP's within central nervous system genes, with an emphasis on those genes and SNP's that represent the best candidates for pharmacogenetic studies. Overall, this panel should provide a critical assessment of novel strategies to identify candidate genes and candidate SNP's for pharmacogenetic studies, as well as provide insight into the next generation of genes and SNP's that will be examined in antipsychotic drug pharmacogenetic studies.

Panel · Tuesday, January 29 · 7:30-9:30 AM ·
Hooglund

Glutamate and Drugs of Abuse: Plasticity to Toxicity

B. Yamamoto, D. Farb, G. Siggins, M. Wolf

Several convergent lines of evidence point to the important role of glutamate in mediating the pharmacological actions of drugs of abuse. Past and recent findings indicate that glutamate may be involved in a variety of these actions ranging from plasticity responses to excitotoxicity. George Siggins will present findings indicating acute mu agonist administration and chronic morphine treatment alters NMDA receptor mediated transmission in the nucleus accumbens. Changes in the pharmacological properties of the NMDA receptor and single-cell rt-PCR analysis of isolated accumbens neurons are suggestive of a recombination of NMDA receptor subunits following chronic morphine. Marina Wolf will present neurochemical data showing that repeated injections of amphetamine produce an increase in AMPA receptor responsiveness in the ventral tegmental area, possibly triggered by long-lasting increases in extracellular glutamate levels that resemble those associated with neurotoxic amphetamine regimens. She will discuss these findings in light of growing evidence that changes in synaptic localization

of AMPA receptors underlie the expression of most forms of activity-dependent plasticity. David Farb will expand the scope of the role of glutamate in behavioral sensitization and discuss the potential role of endogenous neurosteroids as glutamatergic modulators acting at the NMDA receptor. He also will address the possibility that neurosteroids can function as antagonists at the NMDA receptor and may be neuroprotective against the toxic effects of psychostimulants. Along these lines, Bryan Yamamoto will discuss the role of excitotoxicity in the pharmacological actions of high doses of methamphetamine. Through discussion of these data from studies examining various abused drugs, the participants will encourage discussion on the potentially critical role of glutamate in mediating the acute and long-term effects of drug abuse, and consider possible mechanistic overlap between glutamate-dependent mechanisms mediating plasticity and toxicity.

Panel · Tuesday, January 29 · 7:30-9:30 AM · Sinclair

Cortical Network States, Memory Formation, and the First Generation Cyborg

D. Plenz, H. Robinson, S. Potter, S. Marom

A central goal of neuroscience is to understand the mechanisms of cortical memory storage/retrieval and the formation of new cortical memories by association. While tremendous effort has been directed towards pursuing this issue at the synaptic level and the large scale systems level, e.g. fMRI, very little work has been done to investigate how small groups of cortical neurons might act collectively to perform these memory functions. Many theories have been proposed on neuronal group formation, however, experimental in vitro models that allow for thorough testing of these ideas have only recently emerged.

Combining cortical cultures with multi-electrode array chips (MEAs) linked to new generation computers for rapid data acquisition and feedback, allows for an exploration of memory function at the network level. This new field of research identifies cortical network states and studies the manipulation of these states through a computer controlled – virtual – environment.

Dietmar Plenz will present data indicating that highly diverse and stable spatio-temporal activity patterns emerge spontaneously in reduced cortical networks. Their diversity and persistence implies that they represent network states that could form basic elements of cortical memory. Hugh Robinson will talk about the mechanism and dynamics of spontaneous synchronous burst firing in cortex cultured on MEAs. Statistical and nonlinear analysis of long time series of synchronous firing demonstrates that it is well-described by Markov process models, which identify distinct states of the cortical network. Tetanic stimulation is shown to produce complex patterns of long-term potentiation and depression in different pathways in the network, and their effects on spontaneous synchronous firing are analysed.

Steve Potter will describe a project in which neuronal cultures grown on MEAs are interfaced in a closed-loop with a computer. Rat cortical neurons will be given a simulated body which together form an 'Animat' that can move in a computer generated virtual world. The effect of the interaction between the Animat's movements and the environment are then fed back into the dish in the form of electrical stimulation.

Shimon Marom will present thoughts and results on closed loop learning experiments in cortical networks using MEA in which a large random neuronal network interacts with a computer-controlled environment. He will show that such a network forms a large space of connectivity configurations that are stable over many hours and that the connectivity can be modulated by external focal stimulation in an activity-dependent manner.

Panel - Tuesday, January 29 - 7:30-9:30 AM -
Erickson

New Trends in Cellular and Gene Therapy for Neurological Disorders

C. Borlongan, L. Granholm, M. Chopp, E. Snyder, W. Freed

This symposium will present important preclinical research advances on the use of novel cellular and gene therapies for neural reconstruction in animal models of human neurological diseases. The presentations will cover four types of cell-based and gene strategies, namely 1) human neuroteratocarcinoma cells; 2) bone marrow stromal cells; 3) human neural stem cells, and; 4) immortalized neuronal cells. These strategies have recently been demonstrated to promote protection and repair of the central nervous system, as well as functional recovery in a variety of animal models of brain disorders. Each presentation is devoted to one putative therapeutic strategy and will briefly discuss the techniques in preparation of the cell products, then offer views on how the cells themselves can be used as platforms for investigation of cell survival/death mechanisms, and finally focusing on the transplantation of the cells or delivery of vectors and their potential therapeutic effects on neurological disorders. We envision that this symposium will provide insights into the new transplantation technologies that have been proven efficacious in delivering gene products or specific neurotransmitters into the degenerating or aging brain. We believe that these four cell-based strategies have become the frontier of cell replacement and gene therapies. Since these strategies have been developed only in recent years, this symposium is very timely. The broad appeal of this symposium is that it targets not only those working in the field of transplantation, but should also attract cell biologists, behavioral neuroscientists and

clinical researchers. Recently, some of these cells have been introduced in the clinic, and thus the symposium should appeal also to biotechnology representatives. The speakers are either the pioneers or leading scientists of these cell-based strategies and therefore they will be able to provide the best authoritative scientific knowledge in this field. Overall, we believe that the symposium will be very informative and should further advance our understanding of brain degeneration and regeneration mechanisms.

Michael Chopp, PhD • Bone marrow stromal cells for transplantation in neurological disease and injury. Bone marrow stromal cells are a great source of stem-like and progenitor cells, as well as an array of trophic/growth factors. Bone marrow stromal cells when administered intravenously specifically target the injured rodent brain and atrophic muscle and they provide significant functional recovery from stroke, traumatic brain injury, spinal cord injury and Parkinson's disease models. Thus, the use of bone marrow stromal cells for transplantation therapy promises to be a potential treatment strategy for neural injury and neurodegenerative disease. Dr. Chopp will present data on the functional effects of bone marrow cells delivered intravenously in animal models of traumatic brain injury and stroke. The ability for bone marrow stromal cells to provide a safe, potent, and site-specific delivery of trophic/growth factors into the brain will be the main focus of the talk. Cellular mechanisms underlying the therapeutic benefits of the transplanted bone marrow stromal cells will also be discussed.

Evan Y. Snyder, MD, PhD • Neural stem cells as source of cells & therapeutic factors for repair of the central nervous system. Transplants of multipotent neural progenitors and stem cells have been demonstrated to integrate appropriately into the developing and degenerating central nervous system. These cells may act as vehicles for the delivery of genes, cells, and nondiffusible factors either globally or locally in the brain. Laboratory studies have shown that genetically modified neural stem cells, acting as both a source of replacement cells & of therapeutic molecules, have the potential to participate in brain & spinal cord repair. While Dr. Snyder will talk primarily on the manipulation of multipotent neural stem cells for therapeutic applications in neurological disorders, he will also discuss recent investigations into the proliferation, fate commitment, and differentiation of pluripotent neural progenitors to mature CNS cells. Both these methods of examining neural stem cells are essential tools in further understanding brain plasticity and development, as well as in designing treatment strategies for neurological disorders.

William J. Freed, PhD • Immortalized cells with enhanced GABA production for use in neural transplantation. Genetically engineered cells can be used as alternative graft source for neural transplantation. Immortal cell lines can be produced from neural cell cultures, providing an unlimited number of identical cells from a single cell. Dr. Freed will describe CNS cell immortalization strategies and the biochemistry of cell immortalization. Further genetic alterations can be introduced into immortal cell lines to optimize their use for neural transplantation. One example of the use of immortal cell lines for transplantation will be presented. Using immortalized fetal rat striatal GABAergic cells as a starting material, GABA production was enhanced as much as 50-fold by introducing the gene for the human form of the enzyme that the brain uses to produce GABA (GAD67). Transplantation of these cells into animal models of Huntington's disease and epilepsy has been demonstrated to promote functional recovery.

Panel • Tuesday, January 29 • 7:30-9:30 AM • Carroll

Retinoids in the Developing, Adult and Injured CNS

M. Maden, L. Wilson, S. Smith, J. Fawcett

Retinoids are vitamin A metabolites and obtained from dietary sources. They are powerful modulators of developmental and differentiative events acting at the level of the genome by binding to and activating a particular family of nuclear transcription factors. Thus these low molecular weight lipophilic molecules can have direct effects on the pattern of gene activity in cells. The role of retinoids on the developing CNS is gradually being elucidated by studying the neuroanatomy of the brain and spinal cord in quail embryos which have been deprived of vitamin A. The result is that the posterior hindbrain is missing, the AP and DV organisation of the spinal cord is abnormal and neurite outgrowth fails. The gene pathways which are abnormal in the CNS of these embryos will be described (Wilson). Similar experiments on adults involving the deprivation of vitamin A and studying the effects on CNS functioning and maintenance have never been done. The first results of two such studies will be reported here. In one case (Maden) using vitamin A deprived adult rats the effects on behavioural characteristics, CNS functioning and the expression of known genes will be described. Remarkably such rats show many of the characteristics of neurodegenerative diseases suggesting a role for retinoids in the maintenance of the CNS. In the second study (Smith) also using vitamin A-deprived adult rats a cDNA microarray analysis has identified many CNS genes which are regulated by retinoids. The value of this technique as well as the type of genes which have been picked up in this screen will be discussed. Finally, it may also be the case that retinoids are involved in the repair of damage in the adult CNS. Meningeal cells are unique among glia in expressing very high levels of an

enzyme which synthesises retinoic acid, namely RALDH2. But they have a poorly defined role in the CNS injury response, mostly because they have been difficult to identify up to now. We (Fawcett) will discuss experiments in which the behaviour of meningeal cells is tracked following a variety of injuries to the CNS.

This discussion will therefore provide a valuable overview of the role of these powerful molecules (retinoids) in CNS development, maintenance and injury. It will also highlight how research in the basic sciences can lead to clinical discoveries.

Panel · Tuesday, January 29 · 7:30-9:30 AM · Snobble

Anatomical and Pharmacological Determinants of Relapse to Cocaine-Seeking Behavior

R. C. Pierce, J. Rowlett, R. See, F. Weiss

Following cocaine detoxification, the relapse rate among human addicts is discouragingly high. Although many factors contribute to the reinstatement of cocaine-seeking behavior, it is clear that acute re-exposure to cocaine and/or cocaine-associated cues is a major determinant of relapse. This panel will focus on the anatomical and pharmacological bases of reinstatement of cocaine-seeking behavior using non-human primate and rodent models of relapse. James Rowlett (Harvard University) will present data obtained from squirrel monkeys indicating that dopamine transporter blockers both mimic and enhance the priming effects of cocaine, whereas serotonin and norepinephrine transporter blockers have few effects on cocaine priming-induced reinstatement. Dr. Rowlett also will describe results indicating that D2 receptor agonists mimic while, surprisingly, D1 receptor agonists inhibit the priming effects of cocaine. Chris Pierce (Boston University) will outline the role of dopamine receptor activation in the rat medial prefrontal cortex and nucleus accumbens as well as interactions between these nuclei in cocaine priming-induced reinstatement. Ron See (Medical University of South Carolina) will describe how both the acquisition and the expression of conditioned-cued reinstatement of drug-seeking behavior are uniquely dependent on discrete nuclei of the amygdala. Dr. See also will present data showing that cholinergic and dopaminergic inputs to the amygdala play a critical role in regulating cocaine-seeking behavior maintained by drug-paired stimuli in rats. Bert Weiss (The Scripps Research Institute) will present findings from rats demonstrating that cocaine-seeking induced by drug-related stimuli is highly resistant to extinction and that the motivating effects of cocaine cues recruit D1-dependent neural mechanisms within the medial prefrontal cortex and basolateral amygdala. Collectively, these presentations will describe the current status of research aimed at identifying the neurotransmitter changes in the limbic circuitry responsible for both cocaine- and cue-induced reinstatement of cocaine-seeking behavior.

Panel · Tuesday, January 29 · 7:30-9:30 AM · Janss

Astrocyte Function: Back to the Future

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

Insights about astrocyte function have come slowly. Historically they have been viewed as plastic cells capable of division in adults, providing nutrition to neurons, prone to neoplastic transformation leading to neuronal damage, and the cell most likely to swell in the CNS. The panel members will present new findings that provide fresh credibility for these old concepts. Tailoi Chan-Ling has characterized astrocyte precursor cells in human and rodent retina and studied their proliferative potential from birth to adulthood. Bruce Ransom will discuss the capacity of astrocytic glycogen to support and protect CNS axons in the absence of glucose. Harry Sontheimer has found abnormal glutamate uptake in neoplastic astrocytes (and in reactive astrocytes) with important clinical implications. Brian MacVicar has used intrinsic optical signals and two-photon laser scanning microscopy to monitor CNS swelling during neural activity, and verify its cellular origin and mechanisms

Panel · Tuesday, January 29 · 4:30-6:30 PM ·
Hooglund

**Dopaminergic Modulation of PFC Excitability: Is
Dopamineschizoid or Are We Deluded?**

D.J. Surmeier, J. Seamans, G. Barrionuevo, J. Hablitz, P. O'Donnell

Alterations in dopaminergic signaling in the prefrontal cortex (PFC) have long been hypothesized to be at the root of the pathophysiology of schizophrenia. As a consequence, there has been a concerted effort to understand how dopamine shapes the excitability of PFC pyramidal neurons and GABAergic interneurons. In spite of years of effort, a consensus has yet to emerge about the actions of dopamine. There are several potential reasons why controversy remains. This panel brings together leaders in the field of PFC cellular physiology to discuss the most important of these issues in an attempt to plot a course toward calmer waters. Jim Surmeier will moderate the session after giving brief introductory remarks about the major issues facing the field. Jeremy Seamans will discuss *in vitro* studies of rodent PFC pyramidal neurons showing a temporal dissociation of dopaminergic effects mediated by D1 and D2 class receptors. John Hablitz will discuss *in vitro* rodent studies revealing differences in the dopaminergic modulation GABAergic interneurons and pyramidal neurons. German Barrionuevo will discuss *in vitro* studies of connectivity and dopaminergic modulation of pyramidal neurons and GABAergic interneurons in the primate PFC and

how differences in the organization of rodent and primate PFC might lead to differences in dopaminergic regulation. Patricio O'Donnell will conclude by presenting in vivo rodent studies arguing that dopamine modulates state-transitions in PFC pyramidal neurons.

Panel · Tuesday, January 29 · 4:30-6:30 PM · Sinclair

Dynamic Assembly of Synapses: Lessons from the Fly and the Mouse

V. Budnik, C. Garner, L. Guosong, L. Griffith

A pivotal issue in neuroscience has been the elucidation of the mechanisms by which synapses are assembled and mature. In recent years, major advances have come forth in two areas: synaptic scaffolding proteins have been identified that assemble multi-protein synaptic complexes, and the functional significance of these complexes for synaptogenesis and synapse maturation is becoming apparent. Strikingly, many of these proteins and processes are conserved across species, allowing one to cross the boundaries of model systems and to use each to their greatest advantage to unravel the fundamental principles behind synapse development. This panel will summarize recent work using both the mouse and the fly on the molecules that organize synapses, on the mechanisms by which synaptic complexes are transported and inserted at developing synapses, and on the significance of these processes for synaptic function. Dr. Garner will briefly summarize our current understanding of synapse organization in mammals and will describe exciting observations derived both from biochemical approaches and real time imaging showing that components of the presynaptic active zone are recruited and inserted into nascent synapses via prefabricated vesicular intermediates. In contrast, postsynaptic proteins are recruited sequentially from a combination of both vesicular and cytosolic intermediates. Dr. Liu will then describe his studies of synapse formation and functional maturation by discussing the dynamic localization of AMPA receptors during synaptogenesis, and switch in presynaptic transmitter release mechanisms at individually visualized synapses. These studies portray a dynamic picture of functional maturation of synapses during the development of synaptic transmission. Dr. Budnik will then switch to work on the molecular mechanisms of synapse maturation obtained from genetic studies in the fly with particular emphasis on the role of PDZ containing-proteins during glutamatergic synapse assembly and growth. Finally, Dr. Griffith will examine the role of CaMKII activity on synaptic transmission and activity dependent plasticity at fly synapses. This study defines a new role for autophosphorylation of CaMKII and suggests a molecular mechanism for the regulation of the intrinsic properties of synapses by activity.

Panel · Tuesday, January 29 · 4:30-6:30 PM · Erickson

A View of the Mammalian Circadian System from the Midbrain Raphe

R. Mistlberger, M. Duncan, J.D. Glass, J. Miller

Circadian rhythms in mammals are regulated by a master circadian pacemaker comprised of a population of coupled but cell-autonomous clock cells in the hypothalamic suprachiasmatic nucleus (SCN). The SCN is richly innervated by serotonergic (5-HT) fibers from the median raphe nucleus, and is secondarily modulated by 5-HT inputs from the dorsal raphe by way of another major source of SCN afferents, the thalamic intergeniculate leaflet. Midbrain 5-HT neurons are most active when animals are awake and aroused, and are quiescent during the sleep states. 5-HT inputs to the clock are therefore believed to convey information concerning behavioral state. However, the significance of this state-dependent influence for circadian function in health and disease (e.g., depression) remains to be fully clarified. This panel will provide a comprehensive review of the mechanisms and functions of 5-HT within the circadian system, from research programs utilizing behavioral pharmacology, microdialysis, receptor binding and autoradiography, immunocytochemical and electrophysiological approaches. Ralph Mistlberger will begin with an overview of the phenomenological evidence that light and manipulations of behavioral state (e.g., exercise and sleep deprivation; *J Neurosci* 20:9326-32, 2000) regulate the timing of circadian rhythms in mammals. Dave Glass will then describe his work delineating the mechanisms by which the midbrain raphe regulate behaviorally-induced 5-HT release in the SCN, and the effects of 5-HT on the phase of the clock and its response to light in vivo (e.g., *J Neurophysiol* 81:1469-77, 1999). Marilyn Duncan will review the phenomenology of age-related changes in circadian rhythms and recent evidence from her laboratory that these reflect changes in 5-HT transmission to the clock (e.g., *Brain Res* 856:213-9, 2000). Finally, Joe Miller will discuss signal transduction mechanisms for 5-HT from his studies of the SCN clock in vitro and of 5-HT receptor-transfected cell lines (e.g., *Neuron* 11:449-58, 1993), and will provide commentary on controversial evidence for age, species and strain differences in the function of 5-HT within the circadian system. These presentations should be of special interest to those working on the neurobiology of circadian rhythms, aging or affective disorders.

Panel · Tuesday, January 29 · 4:30-6:30 PM · Carroll

Have We Got Connections, Revisited: Convergent Methods for Elucidation of Connectivity in the Brain

D. Kennedy, P. Fox, R. Pautler, J. Belliveau

As the methods available for the structural and functional mapping of brain function advance in terms of spatial and temporal resolution, the field is faced with the complex task of going beyond the 'spotology' of describing what loci are required for specific brain functions to the description of the underlying circuitry of the distributed neural system which subserves each of the inter-related processes which comprise a specific behavioral task. To this end, neural system modeling is concerned with both the functional properties of ensembles of coherently firing neurons and the connections these neurons make to other discrete systems. The purpose of this session is to present progress in four evolving techniques which ostensibly relate to anatomical pathways, in vivo, thereby providing a basis for advances in neural system modeling.

First, David Kennedy will present the use of MR diffusion tensor imaging to observe fiber pathways in vivo. This will be followed by a presentation by Robia Pautler related to the use of manganese (Mn) in MRI as a fiber tract-specific contrast agent for track tracing in experimental animals. Next, Peter Fox will describe the use of transcranial magnetic stimulation as a non-invasive method to modulate effective connectivity in humans. Finally, Jack Belliveau will describe the spatio-temporal characteristics of integrated MEG/EEG and fMRI to assess the temporal sequencing of brain activation as an functional expression of connectivity. Discussion will be encouraged regarding these methods and their prospect for substantively advancing efforts at neural-system modeling and the challenges faced by these techniques in terms of sensitivity, specificity, spatial and temporal resolution.

Panel · Tuesday, January 29 · 4:30-6:30 PM · Snobble

A Pivotal Role for cdk5 in Mechanisms of Neurodegeneration and Addiction

M. Ahljanian, L. Tsai, J. Bibb, J. Wang, T. Saito

Cyclin-dependent kinase 5 (cdk5) is a serine-threonine protein kinase that requires association of an activating protein partner, p35, for catalytic activity. Detection of p35, amino-terminal proteolytic fragments of p35 such as p25, and a p35 isoform p39, in brain and muscle initially suggested that cdk5 might play a key role in neuronal function. Early genetic studies supported this potential role as cdk5 knock out mice display abnormal corticogenesis and perinatal lethality while abnormal neuronal migration and and early death are evident in p35 knock out mice. In addition, it was

demonstrated recently that cdk5/p35 plays a key developmental role at the neuromuscular junction. These studies confirm the central role of cdk5 in neuronal development. One of the initial substrates identified for cdk5 was the microtubule binding protein tau. In a series of recent studies, it was shown that amyloid beta-induced, calpain-dependent conversion of p35 to p25 leads to dysregulation of cdk5 activity, resulting in hyperphosphorylation of tau and apoptotic neuronal death. Overexpression of human p25 in transgenic mice also results in hyperphosphorylation of tau and neurofilament and ultrastructural abnormalities of the cytoskeleton. These data support a key role for cdk5 in neurodegenerative diseases including Alzheimer's disease. In the last year, Dopamine and cyclic-AMP regulated protein (DARP-32) has been identified as a substrate for cdk5. Phosphorylation of DARP-32 by cdk5 results in modulation of both cAMP-dependent protein kinase activity and dopaminergic neurotransmission. Furthermore, expression of cdk5 was up-regulated following repeated administration of cocaine to rats. These results suggest that cdk5 plays a role in dopaminergic transmission and addictive processes suggesting potential utility as a therapeutic target for schizophrenia, Parkinson's disease and addiction. Taken together, this body of work confirms that cdk5 activity plays a broad and pivotal role in neuronal function and dysfunction. This panel will review the cell and developmental biology of cdk5 as well as more deeply explore the role of cdk5 and substrates in neurodegenerative and psychiatric diseases.

Panel · Tuesday, January 29 · 4:30-6:30 PM · Janss

Neurotransmitter Release Without a Probe: The Wonders of Brain Imaging

J. Frost, M. Laruelle, Y. Ding, R. Rothman

Recent advances in brain imaging have led to methods that permit measurement of changes in intrasynaptic neurotransmitter concentration in vivo. The methods use PET and SPECT receptor binding radioligands whose binding is affected by the interaction of neurotransmitter and receptor. These methods have the ability to map the distribution of endogenous neurotransmitter release noninvasively and thus represent a powerful extension of brain imaging in humans and in experimental animals. The increasing availability of small animal PET scanners in research institutions contributes to the appeal of this approach for basic science investigators. The method is also being applied to human subjects, including those with neurological and psychiatric disorders.

The original models for detecting and measuring neurotransmitter-neuroreceptor interactions were based on simple competitive binding between radioligand and neurotransmitter. Thus, increased receptor occupancy by neurotransmitter would result in decreased binding of the PET or SPECT ligand. However, recent results have suggested that the mechanisms are more complex. Several studies have detected increased receptor binding following stimuli that increase neurotransmitter levels in the synapse. These changes are difficult to explain by competitive binding and may involve other mechanisms, such as receptor internalization or changes in receptor affinity. Thus, elucidation of the mechanisms by which increased synaptic concentration of neurotransmitter leads to a change in receptor binding requires knowledge of the normal and pathological processes that involve receptors.

The purpose of this panel is to bring the participants up to date on recent advances in the measurement of intrasynaptic neurotransmitter content using PET and SPECT imaging. The panel members will focus not only on new results, but also on unsolved issues relating to relevant receptor mechanisms that play a role in leading to a change in receptor binding. The panel will be of interest to basic and clinical investigators to wish to learn more about this technique and possibly use it in their own research. It is anticipated that results from the imaging studies will stimulate both discussion and new experiments by basic science investigators that will help clarify relevant receptor mechanisms that mediate changes in in vivo receptor binding.

Richard Rothman will first present an overview of our current knowledge of receptor mechanisms that could play role in causing changes in in vivo receptor binding. These will include competitive binding, affinity changes, and receptor internalization and intracellular trafficking. Marc Laruelle will then review the current state of measurement of changes in dopamine D1 and D2 receptor binding in response to changes in intrasynaptic dopamine content. He will also review the results of recent efforts to measure changes in serotonin receptor binding in response to altered synaptic serotonin levels. Yu-Shin Ding will discuss the cholinergic system and approaches to stimulating acetylcholine release and measuring its effect on cholinergic receptor binding. James Frost will review studies of mu opioid receptors, including mechanistic studies in animal models and the results of human imaging studies in cocaine addicts and in experimental pain.

Workshop · Tuesday, January 29 · 8:30-10:00 PM ·
Hooglund

The Neurobiology of Viral Vectors: Neuroanatomy, Protein Targeting, Behaviour, and Therapeutics

P. Lowenstein, L. Enquist, G. Banker, B. Davidson

“This workshop will discuss recent advances in the use of viral vectors to explore the structure, function, behaviour, and pathology of the CNS. This is an incredibly rapidly moving field. Developments in viral vector technology occur at a fast rate, and it can be bewildering to decide which vector to use and how to use it. What are viral vectors used for? Can I use them in my particular system? Where do I get hold of them? Are they really so toxic? Can I use them to modify behaviour in whole animals? Can they be combined with transgenics and knockouts? Why are there so many different opinions on which vector to use?! Viral vectors can be used to explore multisynaptic pathways, explore how neuronal proteins are targeted to various compartments, analyze behaviour, explore neuro-immune interactions, and develop new treatments for brain diseases.

This workshop will explore from the basic aspects of working with viral vectors to a vast range of their applications in neurobiology from cellular to whole animal experiments. Participants will be encouraged to bring their own experience to the workshops and will have an ideal opportunity to discuss the potential as well as the shortcomings of this powerful new technologies to explore the molecular basis of nervous function. Bring your problems, your criticisms, your questions, your doubts, your models, your unanswered challenges... and together we will explore how the use of viral vectors can transform the way you can address your own experiments in very new powerful and exciting ways.”

Workshop · Tuesday, January 29 · 8:30-10:00 PM ·
Sindair

Trials and Tribulations

K. Gale, D. Spencer, C.R. Freed, M. Walker, C. Atwell

The frontiers of basic research have been steadily advancing into the clinical arena. Technological progress has brought a wealth of interventions that allow us to experimentally probe brain function and/or treat neuropsychiatric disorders in human patients. Experimentation on human patients in some areas is more extensive and far-reaching than analogous studies in animals; these include cases in which the research conducted on humans has no animal counterpart. This raises the question of whether and how it is possible to conduct rigorous scientific studies with appropriate controls in human patients without introducing unacceptable risks. Is it always possible to conform to good experimental design without violating good clinical

cal practice? Are there cases in which the advantages to interpretation of results offset risk to the patient? What is an appropriate 'null hypothesis'? In this workshop, we will have an animated debate on this issue and its highly controversial ramifications, including the role of "sham" or "placebo" controls in clinical experiments. Examples of dilemmas, conflicts and challenges for the conduct of well-controlled invasive experiments in human patients will be drawn from the fields of epilepsy research and research on movement disorders. Studies involving neural tissue transplantation, implantation of intracerebral stimulating and/or recording electrodes, and other devices for manipulating or monitoring the function of selected brain circuits in humans will be critiqued from both the scientific and patient care perspectives. It is hoped that by airing disagreements it will be possible to raise consciousness regarding the obstacles and controversies that may be faced in pursuing experimental neuroscience in patient populations.

Panel · Tuesday, January 29 · 8:30-1000 PM ·
Erickson

Biological Models of Basal Ganglia Networks

H. Bergman, D. Plenz, S. Haber, J. Houk

While the current physiological model of the basal ganglia circuitry has been invaluable for the development of neurosurgical therapies of Parkinson' disease, it has become the target of much criticism in recent years. The anatomical connections between cortex and basal ganglia set up a complicated structure of coupled neuronal networks. It is now clear that this complex neuronal network is involved in motor, cognitive and limbic processing, and that understanding of this neuronal loop requires more than a "box and arrow" model of its main connections. This panel reviews new findings on the anatomy and temporal organization of neuronal activity in the cortex - basal ganglia loops, and will discuss the possible implications of this results to the global understanding of the role of basal ganglia in reinforcements and motivational aspects of behavior.

Suzanne Haber will present her anatomical studies of the basal ganglia cortical loop, with emphasis on her spiral theory of motivation to cognitive to motor information flow in the basal ganglia-cortical loops. Ditemar Plenz will present his competitive models of basal ganglia circuitry, in light of his experiment with organo typical cultures of basal ganglia neurons. Hagai Bergman will present his data regarding functional connectivity within basal ganglia neurons during learning and after dopamine depletion by MPTP. Finally, James Houk will elaborate on his findings on how primate basal ganglia neurons are modulated by the probability of subsequent reward in light of his cellular model of striatal spiny neurons

Panel · Tuesday, January 29 · 8:30-10:00 PM · Carroll

Metabolic Demand in Neurodegenerative Disease, Hibernation and Anoxia Tolerance: The Less You Want the More You Have

K. Drew, J. LaManna, P. Lutz, M.A. Smith

A fine line appears to distinguish life from death for a hibernating ground squirrel that has dropped its oxygen consumption 10 fold along with heart rate, blood flow, body temperature and protein synthesis. Nevertheless, this furry animal will survive up to 8 months without food or water, a feat far from attainable in an animal near death. Similarly, anoxia tolerant turtles survive without oxygen for 4-5 months underwater during winter dormancy. Hibernating mammals and anoxic turtles masterfully down regulate demand for oxygen and nutrients. How they achieve this is unclear, however, central nervous system control as well as profound suppression of CNS activity appears to be involved. In this panel discussion, Joseph LaManna will provide background information on mammalian response to hypoxia including hypoxia-regulated expression of hypoxia-inducible factor 1; the transcription factor responsible for many cellular adaptations to hypoxia. Anoxia tolerant turtles, in contrast to most mammals respond to anoxia by dramatically suppressing CNS metabolic demand. Peter Lutz will highlight how turtles tolerate anoxia through maintenance of adenosine A1 receptor and KATP channel function. Hibernating species of mammals are also known to suppress metabolism in response to hypoxia and during winter torpor. Kelly Drew will show ¹⁴C]-Leu autoradiographs of ground squirrel brain providing evidence that neuronal activity continues during hibernation in discrete brain nuclei including median eminence and nucleus of the solitary tract. These relative hot spots of activity may orchestrate metabolic suppression while regulating respiration, heart rate, postural control, and endocrine function during hibernation. Finally, Mark Smith will present evidence that metabolic abnormalities or metabolic deficiencies are essential mediators in Alzheimer disease and dementia. Failure to meet metabolic demands in humans is likely a common factor in neurodegenerative disease, stroke and central nervous system trauma. Decreasing demand may therefore be the most effective means of avoiding the consequences of diminished supply. Better understanding of metabolic suppression in hibernating mammals and anoxia-tolerant turtles may thus lead to novel approaches for the treatment of neurodegenerative disease and CNS injury.

Panel · Tuesday, January 29 · 8:30-1000 PM ·
Snobble

GABA-A Receptors: Synaptic Versus Extrasynaptic Sites of Action

S. Smith, D. Coulter, L. Overstreet, I. Mody

The GABA-A receptor (GABAR) is comprised of varying subunit combinations which impart unique pharmacological and kinetic properties to these receptors. Additional diversity of function for receptor action is provided by the specific location of the receptors at either synaptic or extrasynaptic sites. Recent models of GABAR kinetics suggest that desensitization influences receptor deactivation, an intrinsic property especially demonstrated by delta-containing GABAR, which may form more of the abundant extrasynaptic pool of GABAR. Heretofore, little information has been available to allow comparisons between these two separate receptor populations, which may subservise different roles in mediating neuronal excitability. Istvan Mody will describe changes in both the synaptic and extrasynaptic GABA-mediated conductances in the delta knock-out mouse. Sheryl Smith will describe altered GABAR kinetics correlated with alpha-4 and delta subunit upregulation following withdrawal from the neurosteroid allopregnanolone. Doug Coulter will describe similar changes in GABAR subunit composition in dentate gyrus, and will contrast these changes with those observed in CA1 hippocampus in his rat model of temporal lobe epilepsy. Linda Overstreet will talk about a shift in phasic versus tonic inhibition following inhibition of GABA transaminase. We will conclude with a discussion of the functional implications of these various changes in the synaptic versus the extrasynaptic GABAR domain in terms of the physiology of the intact circuit.

Panel · Tuesday, January 29 · 8:30-1000 PM · Janss

What Are We Learning from Microdialysis of the Human Brain?

N.T. Maidment, M.G. Boutelle, O. Alves, M.J. During

Intracerebral microdialysis has been used for several years in animal research to sample the extraneuronal environment of the brain in studies of basic physiology/pharmacology and in models of human disease. More recently, investigators have implanted microdialysis probes in the human brain. This panel will highlight what we have learned from such human studies and discuss the future potential of human microdialysis, both as a clinical and experimental tool. Oscar Alves will discuss his experience using microdialysis to measure extracellular excitatory amino acids in brain trauma patients and the extent to which such measurements can be used to predict clinical outcome. Martyn Boutelle will describe the application of on-line enzyme sensors in conjunction with microdialysis to monitor

rapid fluctuations in glucose and lactate concentration as a measure of cerebral metabolism in the intensive care unit. Nigel Maidment will present data collected from epilepsy patients recovering from neurosurgery to isolate the focus of their seizures. Changes in monoamine transmitter levels in response to cognitive challenge and during stages of sleep and wakefulness will be described. Matthew During will describe his extensive experiences monitoring amino acid and monoamine transmitters in epilepsy patients during seizures and during cognitive activity, in addition to his recent microdialysis studies in Parkinsonian patients undergoing deep brain stimulation.

Panel · Wednesday, January 30 · 7:30-9:30 AM ·
Hoaglund

Dynamic Cyclic Nucleotide Signaling in Neurons

P.S. Katz, R. Gillette, F. Zufall, D.M.F. Cooper

It is well known that the cyclic nucleotides, cAMP and cGMP, convey signals in neurons. But it is not generally appreciated how rapid and localized those signals can be. This panel will discuss the generation of cyclic nucleotide signals, some functions of cyclic nucleotide signaling, and why this is important for neurons and for behavior. Dermot Cooper will discuss the calcium sensitivity and localization of adenylyl cyclases. Microdomains of calcium and cAMP in the vicinity of cyclic nucleotide-gated (CNG) channels may produce emergent properties such as oscillations. Frank Zufall will discuss the diversity of CNG channels and their subunits. He will explain their relationship to olfactory transduction and sensory adaptation. Rhanor Gillette will discuss the effects of serotonin, nitric oxide, calcium, and pH on the currents generated by CNG channels. He will relate this to the arousal of a neural network controlling behaviors in the mollusc, Pleurobranchaea. Paul Katz will discuss the role that cAMP plays in the dynamic generation of motor patterns in a related mollusc, Tritonia. We hope that the audience will gain a greater appreciation for this type of biochemical signaling and how it enriches the computational properties of neurons and neuronal circuits.

Panel · Wednesday, January 30 · 7:30-9:30 AM ·
Sinclair

**2002 Census Report on NMDA Receptor Subtypes in Striatum:
More than One**

K. Keefe, D. Standaert, K. Wilcox, D. Lovinger

The 2001 Census Report indicates that the U.S. population is becoming increasingly diverse. As goes the U.S., so goes the C.S. ^ the corpus striatum. Over the past decades, perception of the striatum as a homogeneous struc-

ture has yielded to an appreciation of its rich cellular and molecular diversity. Over this time, the role of the NMDA subtype of glutamate receptor in many processes in striatum has been recognized. However, only recently has evidence emerged for diversity in NMDA receptor subtypes in the basal ganglia and the potential importance of such diversity for treatment of basal ganglia-related disorders. This panel will review the evidence for NMDA receptor diversity in the striatum, as well as some of the possible implications of such diversity for striatal and organismal function. Dr. Keefe will present data collected from in vivo pharmacological studies suggesting selective involvement of distinct NMDA receptor subtypes in the effects of dopamine receptor agents on striatal immediate early gene expression. Dr. Standaert will discuss the acute and long-term effects of dopamine receptor manipulations on the subcellular localization and phosphorylation state of NR2 subunits in striatum and the possible implications of these changes for the long-term consequences of dopaminergic treatment in Parkinson's Disease. Dr. Wilcox will present electrophysiological evidence based on kinetic and pharmacological analysis for the presence of distinct subtypes of NMDA receptors in striatal efferent neurons in different regions of the striatum in adult animals and also across development. Finally, Dr. Lovinger will review his work on LTP, an NMDA receptor-dependent process, in striatum. He will present data demonstrating regional and developmental differences in the extent to which LTP can be induced and will comment on the implication of these differences for learning and memory processes mediated by the basal ganglia. It is the goal of this panel to highlight the molecular and functional diversity of NMDA receptors in the striatum, providing a basis for discussion, among those interested in the basal ganglia as well as NMDA receptors, regarding the implications of such diversity for neuronal and organismal function.

Panel · Wednesday, January 30 · 7:30-9:30 AM ·
Erickson

**No Bones about It: Roles for Calcium in the Acute and Chronic
Actions of Drugs of Abuse**

B. Carlezon, B. Catterall, C. Konradi, C. Pierce

Calcium (Ca^{2+}) is a metallic element that is a critical constituent of plants and animals. In the brain, Ca^{2+} enters cells through specialized channels and some types of receptors. The entry of Ca^{2+} into neurons can regulate membrane potential, neurotransmitter release, intracellular signal transduction, and neuroplasticity. For example, dopamine and glutamate stimulate membrane receptors that can initiate Ca^{2+} -mediated intracellular signal transduction pathways, leading to activation of transcription factors and increased gene expression. Altered gene expression within groups of neurons such as midbrain dopamine neurons or striatal medium spiny neurons can affect the function of entire brain circuits and, in turn, behavior.

Despite these important actions, the relevance of Ca^{2+} in addiction and other neuropsychiatric disorders is only beginning to be appreciated. This panel will focus on how L-type Ca^{2+} channels located within midbrain dopamine systems affect the acute and chronic actions of drugs of abuse such as cocaine. Bill Catterall (University of Washington) will review the different types of Ca^{2+} channels and describe data indicating that L-type channels are located on dendrites and cell bodies. Christine Konradi (McLean Hospital) will show that L-type channels play a critical role in the regulation of dopamine receptor-mediated gene expression within striatal tissue. Chris Pierce (Boston University) will show that L-type channels and Ca^{2+} -stimulated second messengers within midbrain dopamine systems play a role in the development of behavioral sensitization to cocaine. Bill Carlezon (McLean Hospital) will present evidence that Ca^{2+} flux in the nucleus accumbens is directly involved in the rewarding effects of psychostimulant drugs such as cocaine and phencyclidine. Together these presentations may elucidate the mechanisms by which this simple element can contribute to complex changes in motivated behaviors, and more importantly, lead to a new appreciation that Ca^{2+} can play a role in disorders other than those involving bones.

Workshop · Wednesday, January 30 · 7:30-9:30 AM · Carroll

Apoptosis in Neurological Diseases: Myth or Reality?

R. Quirion, S. Doré, C. Cotman, K. Jellinger

Cell death by apoptotic mechanisms is a real “buzz” word these days. Cell death by necrosis is clearly out-of-fashion. This workshop will review current evidence suggesting that while apoptosis may occur in neurodegenerative diseases, it may not be as universal a phenomenon as some would like to believe. S. Doré will review evidence for a role for apoptotic processes in animal models of stroke and contrast these data with better established necrotic mechanisms focusing on the role of HO. G. Robertson will review recent data using caspase inhibitors that will challenge the relevance of apoptotic mechanisms in stroke. C. Cotman will review data on the possible role and relevance of neuronal apoptosis in the etiology of Alzheimer’s Disease (AD) while R. Quirion will provide views challenging the involvement of apoptosis in diseases such as AD and Parkinson’s Disease. A Summary discussion will then close the workshop.

Panel · Wednesday, January 30 · 7:30-9:30 AM ·
Snobble

Alcoholism Vulnerability: From Neurobiology to Genetics

J. Krystal, D. Goldman, J. Lappalainen, A. Heinz

There is an ongoing effort to link the emerging neurobiology of ethanol abuse and dependence to the parallel growth in the study of the genetics of alcoholism. This panel will present four new perspectives on the bridges that are emerging between the neurobiology and genetics of alcoholism. The first speaker, Dr. Jaakko Lappalainen, will review preclinical and clinical evidence linking neuropeptide Y (NPY) in reward mechanisms. He will link these findings to new data from two independently collected samples that indicates that the Pro7 allele of a functional NPY polymorphism is associated with ethanol dependence vulnerability. The second speaker, Dr. Andreas Heinz, will present neuroimaging data describing alterations in 5-HT transporter binding associated with subgroups of alcohol dependent patients. He will link these findings to molecular genetic studies of 5-HT-related genes in alcohol dependent populations. Dr. David Goldman, the third speaker, will review biochemical and neuroimaging studies of GABA alterations in alcohol dependence and present new data on the relationship between GABA-associated genes and alcohol dependence. Lastly, Dr. John Krystal will present new data implicating altered N-methyl-D-aspartate glutamate receptor function in the vulnerability to alcoholism. He will present findings from psychopharmacologic studies indicating that individuals at increased familial risk for developing alcoholism show alterations in the reward valence of NMDA antagonists (reduced dysphoria/increased euphoria) that are similar to changes in ethanol dependent patients, regardless of their family history. He will also present data describing the effects of pharmacologic pretreatments in "family history negative" individuals that alter the reward valence of NMDA antagonists in a manner similar to that seen in "family history positive" individuals. Together, these studies provide insights into current efforts to link the pathophysiology and genetics of alcoholism

Panel · Wednesday, January 30 · 7:30-9:30 AM ·
Janss

Cerebral Functional Localization: Fact, Fiction or Something Else?

E. Ross, D. Stein, A. Kertesz, S. Small, A. Hillis

Cerebral localization of function has had a checkered history. Initially, it was formalized as part of phrenology, but quickly fell into disrepute. It was then resurrected by the discoveries of Broca and Wernicke regarding localization and lateralization of propositional language functions. It then fell back into disrepute under the influence of Lashley and others but has again made a

strong comeback with the emergence of various clinical imaging techniques. The panel will explore functional localization in the context of learning, reorganization after brain lesions, changes with aging, and as emergent functions of neural networks. Issues of processing versus disconnection effects will be discussed and whether the new functional imaging techniques of fMRI, PET and diffusion/perfusion MRI are just another form of "neurophrenology." The aim of the panel is to give localization of function a dynamic basis that changes under natural conditions, e.g. development, aging and attention, and by acquired lesions. This will, hopefully, give the audience a deeper understanding of localization of function that will be useful when interpreting neuroimaging and other related research.

Panel · Wednesday, January 30 · 4:30-6:30 PM ·
Hoaglund

Cell and Gene Therapy for Treatment of Neurologic Disease

C.R. Freed, K. Bankiewicz, J. Cooper, E. Snyder

Repair of the human brain has become possible as shown by transplants of human embryonic dopamine cells for Parkinson's disease. Gene therapy offers an alternative approach for treating Parkinson's and other neurodegenerative diseases. This panel will describe human and non-human primate experiments using gene and cell therapy approaches. Curt Freed will show results of a double-blind study of fetal dopamine cell transplants for Parkinson's disease, emphasizing the importance of patient selection and the possible limitations of cell transplantation. Krys Bankiewicz will describe a gene therapy strategy for restoring dopamine production to the Parkinsonian brain. In MPTP-lesioned monkeys, the dopa decarboxylase gene is expressed in striatum using an AAV vector followed by treatment with L-dopa. James Cooper will present efforts to reverse cholinergic cell degeneration in Alzheimer's patients with transplants of autologous fibroblasts which have been transfected in vitro with the nerve growth factor gene. Repairing the developing brain in utero could have a profound impact in patients with inborn errors of metabolism or congenital structural defects. Evan Snyder will describe the survival and migration of human neural progenitor cells transplanted in utero to the cerebral ventricles of the developing non-human primate brain. These presentations will demonstrate the range of therapeutic application of cell and gene therapy.

Panel · Wednesday, January 30 · 4:30-6:30 PM ·
Sinclair

**Neuroprosthetic Applications Using Brain-Machine Interface
Technology**

J. Chapin, M. Nicolelis, S. Giszter, K. Moxon

Recent advances in multi-electrode recording and stimulation techniques provide an unprecedented ability to directly transfer information into and out of the brain. For example, single electrode neural recordings typically require multi-trial averaging, but multi-electrode recordings allow information in neural populations to be accurately measured in single trials. This ability to extract brain information in real time may one day allow paralysis patients to use their brain activity alone to control external robotic devices. Parallel developments in patterned multi-electrode stimulation in the CNS may improve our ability to accurately introduce information into neural tissue, either to provide a sensory prosthesis, or to control the motor output of the spinal cord. This panel will discuss important recent advances in brain interface technology and its use for neuroprosthetic applications. John Chapin will introduce the overall topic, including showing the feasibility of neurorobotic control and discussing current work on brain-stimulation sensory prostheses for „closed-loop“ neurorobotic control. Miguel Nicolelis will report on his successful use of simultaneously recorded motor cortex neurons in monkeys to accurately control robot arm movements in 3D. Simon Giszter will discuss issues relating to using functional electrical stimulation (FES) in the PNS or CNS to drive motor prostheses, focusing on his investigations into the possibility of stimulating force field primitives in the spinal cord. Karen Moxon will discuss her work in development of multi-contact electrodes and future electrode designs based on emerging nanofabrication technology. A concluding discussion will speculate on possible future directions, in particular the possibilities for transferring this technology to the clinic.

Workshop · Wednesday, January 30 · 4:30-6:30 PM ·
Erickson

High Times at the WCBR

K. Mackie, N. Stella, O. Manzoni, R. Nicoll

The psychoactive effects of delta-9-THC, the principal active component in cannabis, are primarily mediated by a G protein-coupled receptor, the CB1 receptor. During the past ten years, it has become clear that an endogenous cannabinoid system exists, consisting of the receptor, endogenous cannabinoids, as well as synthetic and degradative pathways for endocannabinoids. More recently, several studies have shown that both

endogenous and exogenous cannabinoids modulate neurotransmission and neural plasticity.

In this workshop several of the controversies in these recent findings will be introduced, and with the participation of the audience, perhaps reconciled. Nephi Stella (University of Washington) will discuss how different endocannabinoids are produced by distinct cell types and pathways and the implications of this for neural plasticity. Olivier Manzoni (University of Arizona) will consider controversies in cannabinoid modulation of plasticity in the nucleus accumbens. Roger Nicoll (University of San Francisco) will argue that endogenous cannabinoids can be released during neuronal activity and are responsible for a form of plasticity in the hippocampus.

Panel · Wednesday, January 30 · 4:30-6:30 PM ·
Carroll

Substrate-Mediated Regulation of Neurotransmitter Transporters

N. Zahniser, J. Gulley, A. Galli, S. Apparsundaram, M. Robinson

It is becoming increasingly evident that uptake of neurotransmitters by their respective transporters results not only in removal of the neurotransmitter from the extracellular space, but also in regulation of the transporter(s). Since uptake is crucial in determining neurotransmitter “tone”, it is important to understand this substrate-mediated regulation. Josh Gulley has used high-speed chronoamperometry in the dorsal striatum of anesthetized rats to investigate whether a brief exposure to dopamine (DA) alters DA transporter (DAT) function in vivo. His results are consistent with either a rapid DA-induced inhibition or loss of DAT function. Aurelio Galli has previously shown that amphetamine, another DAT substrate, reduces [3H]DA uptake by altering DAT trafficking. He will discuss the time- and dose-dependence of this amphetamine-induced internalization, determined using “real time” confocal microscopy. Although in most instances regulation of neurotransmitter transporters has been shown to involve altered cell surface expression of the transporter, this is not always the case. Subbu Apparsundaram has found both trafficking-dependent and -independent mechanisms for controlling norepinephrine transporter (NET) activity. Regulation by PI3 kinase involves changes in NET cell surface expression whereas regulation by p38 MAP kinase does not. Mike Robinson will discuss substrate-dependent regulation of the neuronal glutamate transporter, EAAC1. Glutamate, through its interaction with EAAC1, blocks protein kinase C- and platelet-derived growth factor-dependent redistribution of the transporter. This blockade appears to involve activation of protein phosphatase 2A. Since these kinase pathways are activated by hypoxia, this substrate-mediated regulation has both physiological and pathological implications.

Panel · Wednesday, January 30 · 4:30-6:30 PM ·
Snobble

Intriguing Links Between Neurons and Melanocytes

S. Roffler-Tarlov, H. Arnheiter, S. Landis

Neurons and melanocytes, the predominant pigment cells in vertebrates, share not only common precursors in the neural crest and the optic neuroepithelium but also the ability to catalyze the conversion of tyrosine to dopa. Focusing on the developmental aspects, Heinz Arnheiter will describe genetic models in which signaling and transcription regulation in developing melanocytes is perturbed and which result in eye abnormalities and sensory hearing deficiencies. In particular, he will highlight the distinction between the consequences of shared gene expression in pigment cells and neurons, and the roles pigment cells play indirectly in neuronal development and function.

Suzanne Roffler-Tarlov will present evidence that dopa made in melanocytes can be converted to catecholamines in sympathetic neurons and elsewhere. Pigmented mice without TH make small amounts of catecholamine: mice with neither TH nor tyrosinase do not form catecholamines. Story Landis will compare these mutants which reveal that even a little norepinephrine present in the developing sympathetic innervation to sweat glands permits sweating later in response to a cholinergic agonist. In contrast, catecholamine deficient mice that lack tyrosinase do not sweat. Gland morphogenesis proceeds normally and cholinergic properties appear in the sweat gland innervation of both types of mutants. Therefore catecholamines are required to trigger the functional maturation of the glands and appear to regulate one or more steps in stimulus-secretion coupling.

Panel · Wednesday, January 30 · 4:30-6:30 PM · Janss

Pallidal Plasticity

T.C. Napier, G. Arbuthnott, S. Haber, G. Meredith

Neuroplasticity following chronic perturbations within the brain's dopaminergic system has been well documented for the midbrain-striatal system. However, pallidal neurons are directly innervated by ascending dopaminergic projections, and both basal ganglia and limbic system output via their pallidal counterparts (e.g., the globus pallidus/entopeduncular nucleus and ventral pallidum, respectively). This circuitry suggests that pallidal regions likely contribute to the alterations that occur following dopamine removal.

In consideration of this important topic, participants in this panel will discuss the role of pallidal structures in information processing in the normal brain state and following long-term alterations in dopamine neurotransmission. Dr. Gordon Arbuthnott will talk about the actions of globus pallidus

damage in rats. He will discuss his new studies indicating how globus pallidus lesions can lead to damage of dopaminergic neurons. Dr. Suzanne Haber will present new experiments that demonstrate a profound pallidal response to MPTP-induced partial dopaminergic lesions in monkeys. Her new work reveals that lesion-induced cell proliferation can be found throughout the brain, e.g., increases occur in the rostral striatum and substantia nigra, but is particularly profuse in the internal pallidal segment. Dr. Gloria Meredith will present her novel evaluations in rats chronically treated with neuroleptics. Her results reveal unique profiles in the bed nucleus and the ventral pallidum with regard to terminal degeneration and staining for tyrosine hydroxylase and BDNF. Dr. Celeste Napier will compare and contrast transmission in the globus pallidus and ventral pallidum for both classical and peptide transmitter systems. She also will present her new work on the robust adaptations that occur in the function of these transmitters in rats lesioned with 6-OHDA or following repeated neuroleptic treatment.

Panel · Thursday, January 31 · 7:30-9:30 AM ·
Hooglund

**AMPA and NMDA Receptor Targeting and Trafficking:
Implications for Synaptic Transmission and Plasticity**

P. Seeburg, R. Huganir, R. Malenka, R.S. Zukin

Dynamic regulation of synaptic efficacy is thought to play a critical role in the formation of neuronal circuitry during development and in experience-dependent modification of neural circuitry. The molecular and cellular mechanisms by which synaptic changes are triggered and expressed has been the focus of intense interest in the past several years. This panel will review recent evidence that physical transport of AMPA and NMDA receptors in and out of the synaptic membrane provides an important mechanism underlying several long-lasting forms of synaptic plasticity including NMDA-dependent long term potentiation (LTP) and long term depression (LTD). Dr. Rick Huganir will review the molecular organization of excitatory synapses. He will discuss evidence that PSD-95, GRIP and other PDZ domain-containing proteins play a critical role in trafficking of AMPARs at synapses and in spatially organizing them within a complex lattice of signaling and scaffolding proteins at the postsynaptic density. AMPARs interact via short amino-acid sequences in their carboxy terminal tails with PDZ domain-containing proteins and with trafficking proteins required for insertion and removal of AMPA receptors from the postsynaptic membrane. Dr. Rob Malenka will present recent studies implicating rapid recycling of AMPA receptors in activity dependent changes in synaptic strength. Activation of AMPARs, NMDARs and insulin receptors trigger the rapid loss of AMPARs from synapses as a result of regulated endocytosis. Moreover, block of key proteins involved in endocytosis impairs LTD at hippocampal synapses. Dr.

Suzanne Zukin will present recent evidence that protein kinase C modulates NMDA receptor trafficking and gating in hippocampal neurons. PKC-induced potentiation of NMDA receptor currents occurs by an increase in channel opening rate and by rapid delivery of new channel molecules to the cell surface of dendritic shafts and spines. These mechanisms are expected to play a critical role in the regulation of synaptic strength in the developing and mature central nervous system.

Panel · Thursday, January 31 · 7:30-9:30 AM ·
Sindair

Beyond Symptoms: Neuroprotective Strategies in Parkinson's Disease

M. Zigmond, M. Bohn, V. Dawson, O. Isacson, P. Carvey

Parkinson's disease (PD) is associated with the degeneration of dopamine (DA) neurons, resulting in a marked reduction of DA release in the striatum and the consequent dysregulation of striatal output. Most current therapies (e.g., L-DOPA) focus on restoring activation of DA receptors or correcting the abnormal striatal output at some more distant site (e.g., pallidotomy). Recently, however, several approaches have been suggested for the protection and/or rescue of DA neurons from degeneration or for their replacement. In this session we will consider four such approaches, focusing on the potential for bringing the treatment into the clinical and the critical issues that remain before that can be accomplished. First, Martha Bohn will discuss gene therapy, focusing on the use of viral vectors to increase the expression of trophic factors such as GDNF. Second, Valina Dawson will present data on the efficacy of immunophilins, small molecules that can be administered systemically and have trophic factor properties. Third, Paul Carvey will discuss evidence that DA receptor agonists can promote DA neuron growth and serve a neuroprotective function. Finally, Ron McKay will present his recent data on the capacity of stem cells to be differentiated into DA neurons and the impact of mesencephalic precursor cells in models of PD. Michael Zigmond will moderate the discussion and ensure that time is available for audience participation.

Panel · Thursday, January 31 · 7:30-9:30 AM ·
Erickson

The Importance of the Anterior Cingulate in Mood Regulation and Psychosis

W. Bunney, H. Mayberg, N. McFarland, C. Tamminga, S. Potkin

The important role of the anterior cingulate in regulation of attention, mood, psychosis and some motor behaviors is being increasingly appreciated. This

panel will review the supporting neuroanatomical, imaging and post mortem data as well as presenting original findings.

McFarland will review the connections between the anterior cingulate and several thalamic nuclei and present new neuroanatomical data. These important midline, anterior, and ventral thalamic nuclei project to limbic, premotor and motor areas, respectively. Mayberg will present O-15 PET data on the role of the rostral and subgenual anterior cingulate in mediating acute and chronic shifts in negative mood state. Using path analysis she will define the neural circuits involved and their relevance to understanding mechanisms of depression vulnerability, treatment and relapse. Tamminga will present O-15 PET data in schizophrenic patients at rest, during task performance and drug challenge, demonstrating that the anterior cingulate functions abnormally, and that the degree of abnormality is correlated with the degree of psychosis. She will compliment the imaging data with new data on GAD67 and glutamate receptor subunit expression in the anterior cingulate. Potkin will further define the role of the anterior cingulate in negative symptom schizophrenia by a series of contrasts with schizophrenic patients with positive symptoms during an attention task using FDG PET. He will present data on nicotine's modification of the anterior cingulate's function during attentional and emotional tasks.

Panel · Thursday, January 31 · 7:30-9:30 AM · Carroll

Black Diamonds and Black Label: Effects of Acute Stress on Responses to Drugs

H. de Wit, P. Piazza, Y. Shaham, R. Sinha

Clinical reports and studies with laboratory animals indicate that acute stressors can increase drug self-administration, and drug craving and relapse. However, the mechanisms underlying this effect are to a large degree not known. We will describe recent findings from human and non-human studies on the mechanisms by which acute stressors affect neuronal function and drug-seeking behavior. Piazza (INSERM) will present data on the effects of acute and chronic stress, and drugs of abuse on glucocorticoid receptor (GR) translocation, using a novel in vivo method that measures translocation and DNA binding of the GR. The implications of these data for the understanding of the role of the HPA axis in drug-taking behavior will be discussed. Shaham (NIDA) will present data from studies with rats and mice on the role of corticotropin-releasing factor and noradrenaline within the extended amygdala, and of leptin, in stress-induced relapse to heroin and cocaine. He also will demonstrate similarities between the effect of stress and reversible inactivation of the septum, a brain area known to be involved in response inhibition, on relapse to heroin. Sinha (Yale) will discuss recent findings on neurobiological correlates of stress and drug cue-induced cocaine craving in humans. She also will present data suggesting that stress increases the risk of cocaine relapse by interfering with processes

underlying response inhibition. De Wit (U Chicago) will present data on the effect of exposure to cortisol or stressors (physical or psychological) on the subjective and behavioral responses to stimulant drugs, in healthy human volunteers. Her data suggest that elevations in plasma cortisol have little effect on responses to a stimulant drug, but that exposure to a social stressor (giving a speech) alters selected responses to methamphetamine. Based on the data presented, the panel will discuss the concordance between the preclinical and the clinical data on the mechanisms underlying the effect of stress on drug-taking behavior.

Panel · Thursday, January 31 · 7:30-9:30 AM ·
Snobble

**GABAA Receptors and Disease: The Delicate Balance Between
Alpha 1 and Alpha 4 Subunits**

S. Russek, A. Brooks-Kayal, A.L. Morrow, J. Luebke

Alterations in the expression of GABAA Receptors has been postulated to play an important role in the etiology of certain neurological disorders such as temporal lobe epilepsy, generalized anxiety, and alcoholism. Several laboratories have accumulated data to suggest that a down-regulation in the expression of receptors containing alpha 1 subunits and upregulation in the expression of receptors with alpha 4 subunits is responsible for multiple disease phenotypes. Alteration in the expression of different alpha subunits is a natural occurrence with the development of the central nervous system and it has been suggested that a dysregulation during development may lay the foundation for future disease. Jennifer Luebke will present findings on the changes in GABAA receptor function that accompany the developing hippocampal formation, as studied in hippocampal slices, and will discuss the unique phenotype of receptor populations based on single cell gene analysis. Amy Brooks-Kayal will expand the discussion by presenting her findings that suggest a role for the alpha 4 subunit in the etiology of temporal lobe epilepsy and will discuss her results in the context of clinical studies that highlight the difficulty of interventional approaches that use current strategies. Furthering this discussion, Shelley Russek will present her results on the study of the promoters that drive alpha 1 and 4 gene transcription in cultured hippocampal neurons. She will also discuss the use of these DNA regulatory sequences, both in viruses and in decoy oligonucleotides, to test the hypothesis of alpha subunit involvement in disease and to develop novel pharmacological tools. Finally, Leslie Morrow will provide data to suggest that non-genomic effects can also disturb GABAA receptor function by showing that alcohol exposure alters the cell surface expression and endocytosis of alpha 1 and alpha 4 subunit containing GABAA receptors via PKC association with receptors in vivo.

Panel · Thursday, January 31 · 7:30-9:30 AM · Janss

Adaptation to Altitude: Brain Hypoxia and Gene Response

S. Harik, J. LaManna, J. Dunn, G. Haddad, P. Dore-Duffy

The mammalian brain is exquisitely dependent on timely availability of both oxygen and glucose. Only minimal stores of either are present in the adult brain. Yet, mammals can exist and even flourish continuously at altitudes of up to 14,000 feet or more, and for brief periods at even higher elevations. The adaptive mechanisms that allow the brain to function over this wide range of environmental oxygen content reveal a complex metabolic and vascular control system, and an inherent structural plasticity that appears to be driven by the balance between delivery of oxygen and utilization of oxygen. These mechanisms come into play during normal physiological adaptation, as well as pathological responses to oxidative challenges. It has become apparent that there are differences in the strategies for acute hypoxic exposure and more long lasting hypoxic exposure. The short term strategy includes increased brain blood flow and hyperventilation. The longer term strategy involves a complex series of metabolic and vascular adaptations, including angiogenesis to decrease intercapillary diffusion distances and hypometabolism. These adaptations are reversible upon return to normoxia.

J. Dunn will describe the measurements of tissue oxygen tension and how they change with hypoxic exposure. G. Haddad will discuss the role of ion channels in the mechanisms of hypoxic adaptation and tolerance and how neuronal channels are altered to change cellular metabolic demand. P. Dore-Duffy will talk about pericyte regulation of the microvascular response to low oxygen, in particular the role of early signalling molecules, in the induction of VEGF and GLUT-1. J. LaManna will discuss the mechanism involved in accumulation of hypoxia-inducible factor (HIF-1) and the subsequent activation of genes with hypoxic response elements.

This session will focus on changes in brain oxygenation and the associated genetic alterations that occur in channel function, cytokine expression and vascularization with hypoxic exposure.

Panel · Thursday, January 31 · 4:30-6:30 PM ·

Hoaglund

Springtime for Glia

B. A. Sieber, Y. Sun, E. Anton, D. Bergles, E. Ullian

Although glial cells have long been considered an integral part of the development and maintenance of neural circuitry in the CNS, the dynamic and facile nature of glial involvement has neither been fully appreciated nor understood. Studies highlighting the versatility of glial function have recently blossomed within the scientific community, leading neuroscientists to re-

evaluate the previously scripted role of each subclass of glial cell and to consider novel ways in which these cells and their precursors contribute to neuronal-glial communication. This session is designed to highlight new findings in the field of glial biology and to consider how these discoveries impact upon our understanding of CNS function relevant to both health and disease, including development, cognitive function, neurodegeneration and neuropsychiatric disorders. The participants will discuss new findings on neural-glial interactions from the earliest stages of development through the maintenance of neural circuits in adulthood. Yi Sun (UCLA) will discuss new findings on the role of bHLH protein neurogenin (Ngn1), which directs neuronal vs. glial cell fate specification via two distinct mechanisms (Cell 104:365-376, 2001). Eva Anton (UNC) will present new data on the role of neuregulin-erbB signaling pathway in radial glial development, and will also highlight the role of integrins in cell-cell interactions between radial glia and migrating neurons that result in laminar organization and functional connectivity in the developing neocortex (Neuron 22:277-89, 1999; Neuron 27:33-44, 2000). Dwight Bergles (Johns Hopkins) will discuss progress on his intriguing discovery that a class of glial precursors, oligodendrocyte precursor cells (OPCs), form glutamatergic synapses with pyramidal neurons in the hippocampus in both developing and mature brain. These neuro-glial synapses provide a rapid signaling pathway that may be involved in regulating oligodendrocyte development and function as well as serving a neuromodulatory role throughout life (Nature 405:187-191, 2000). Erik Ullian (Stanford) will highlight recent studies investigating the role of astrocytes in the formation and dissolution of synaptic contacts both in vitro and in vivo, and discuss mechanisms by which astrocytes regulate synaptic plasticity by regulating the formation, function, and maintenance of neural circuits (Science 291:657-661, 2001). Together, these presentations will provide an entrée into discussion of the roles of glial cells in development and plasticity in addition to those already considered in regeneration and repair.

Panel · Thursday, January 31 · 4:30-6:30 PM ·
Sindair

alpha-Synuclein and Parkinson's Disease: Two Entities in Search of a Connection

R. Perez, V. Lee, Y. Schmitz, M. Lee

The recent discovery that mutations in alpha-synuclein can lead to Parkinson's disease (PD) has drawn considerable attention to this protein. However, although implicated in synapse stabilization and neuronal plasticity, the function of alpha-synuclein remains unknown. New studies suggest a role for alpha-synuclein as a chaperone molecule that regulates dopamine biosynthesis, dopaminergic neurotransmission, and ubiquitin-dependent degradation of proteins. This panel discussion will examine al-

pha-synuclein-related modulation of neuronal function and dopaminergic neurotransmission. The presentations will shed important insights regarding alpha-synuclein's normal function as well as its role in the pathogenesis of Parkinson's disease. Our session will begin with presentations by the speakers. Ruth Perez will present data indicating that alpha-synuclein regulates the activity of tyrosine hydroxylase. Yvonne Schmitz will present data suggesting a role for alpha-synuclein in regulating synaptic vesicle pools. Michael Lee will show that in vivo expression of A53T mutant, but not wild type, nor A30P mutant, alpha-synuclein in transgenic mice leads to neurodegeneration associated with neuronal ubiquitin and alpha-synuclein accumulation. Virginia Lee will discuss the pathogenesis of alpha-synuclein lesions with particular emphasis on the role of oxidative/nitrative stress in the development of these neurodegenerative synucleinopathies. Following these presentations, the speakers and members of the audience will join in a spirited discussion of the functions and pathophysiological significance of this likely-to-be-important molecule.

Panel · Thursday, January 31 · 4:30-6:30 PM ·
Erickson

New Kidz on the Block: Novel Neurotransmission in Pain and Analgesia

C. Fairbanks, S. Carlton, J. Mogil, J. Zadina

Several novel neurotransmitters/neuromodulators have recently been identified that contribute to nociception, analgesia, and related plasticity. That these molecules and peptides exist increases the complexity of the nociceptive and analgesic systems as previously defined. This new knowledge requires integration with currently held theories of nociceptive transduction and transmission and endogenous analgesic mechanisms. This panel will discuss four such novel neurotransmitters/neuromodulators and address their contributions to nociceptive and analgesic processing. Susan Carlton will present anatomical, behavioral and physiological data documenting a tonic inhibitory control of peripheral nociceptors by endogenous somatostatin. This inhibitory somatostatinergic system is independent of peripheral opioid systems. Jeff Mogil will review the comprehensive evidence supporting a nociceptive neuromodulatory role for opioid-related orphan receptor (ORL1) and its respective endogenous peptide ligand OFQ/nociceptin (OFQ/N) and discuss contradictions within the literature that suggest an exquisite sensitivity of the OFQ/N-ORL1 system to contextual factors (e.g. genotype and age). James Zadina will describe developments with the recently identified mu opioid receptor-selective peptides, endomorphin 1 (YPWF-NH₂) and endomorphin 2 (YPPF-NH₂), including new evidence that endomorphin content in the spinal cord is altered in animal models of chronic pain.

Carolyn Fairbanks will introduce new information that implicates a neuromodulatory role for the recently discovered endogenous NMDA receptor antagonist/NOS inhibitor agmatine (decarboxylated arginine) in endomorphin-2-induced analgesic tolerance and potentially other plasticity-related phenomena. Collectively, the panel will integrate the following: examination of the relationships of previously established pain neuromodulators to these newly identified contributors, the potential therapeutic utility of these novel agents and mechanisms, and consideration of how these investigations might be uniquely informative to other areas of neuroscience.

Panel · Thursday, January 31 · 4:30-6:30 PM · Carroll

Subcortical Influence on Cortical Processing

G. Tononi, M. Salbaum, F. Ghilardi, A. Schwartz

Subtle, global changes in excitability can have a profound effect on cortical processing in adults. Both diffuse and specific projections from subcortical structures can alter protein phosphorylation, gene expression and plastic phenomena shifting the firing patterns of cortical neurons. Recent work has uncovered changes in cortical gene activity related to subcortical activation. Specific manipulations of subcortical nuclei with diffuse projections to cortex are now possible with genetic engineering. Diseases of these projection systems lead to a deterioration in the ability to learn new behaviors. Finally, the development of new analytical techniques are needed for detecting subtle changes in cortical firing patterns related to behavioral state change. Dr. Tononi has found that the diffuse subcortical noradrenergic and serotonergic systems can have profound effects on gene transcription in many cortical regions with implications for the control of plasticity in different behavioral states. Dr. Salbaum will present a novel transgenic mouse system that makes use of a Cre/lox recombination strategy with an Adenovirus trigger to activate the central noradrenergic system specifically. Such gain-of-function studies will allow insights into brainstem/cortex interactions during development and adult animal behavior. Dr. Ghilardi will review the contribution and changes of cortical-subcortical interaction in acquisition and automatization of sequenced actions in normal humans and in basal ganglia disorders, showing a compensatory cortical activation with moderate striatal dopamine loss. New methods for analyzing the correlation between simultaneously recorded units will be illustrated by Dr. Schwartz as a means of detecting subtle changes in activity patterns. These new methods will help us understand how subcortical systems can transmit salient events and communicate this saliency virtually to the entire brain.

Panel · Thursday, January 31 · 4:30-6:30 PM ·
Snobble

The Big Bad Wolf and the Three Little Pigs: Substance Abuse and the Three Monoamines

G. Ordway, D. Goldman, A. Markou, T. Svensson

Despite a long-standing focus of neuroscientists on the role of dopamine systems in drug dependence and withdrawal, formidable roles of other neurotransmitters, e.g. serotonin, norepinephrine, in addiction neurobiology are being elucidated. Many substances of abuse, including tobacco, have effects on multiple monoamine neurotransmitter systems. For example, two constituents of tobacco smoke have effects on brain monoamines. Nicotine stimulates dopamine and norepinephrine neurons, and has complex effects on serotonin neurons. Tobacco smoke also contains an inhibitor of monoamine oxidases A and B, enzymes that catabolize brain dopamine, serotonin and norepinephrine. Some substances of abuse, e.g. cocaine and amphetamine, interfere with the function of all three of the monoamine transporters. The multiple monoaminergic effects of these substances likely play major roles in the acquisition and maintenance of drug dependence, as well as contribute to neurochemical consequences of withdrawal. The myriad of monoaminergic effects of these substances may also contribute to the high incidence of drug abuse among individuals with major depression and schizophrenia, since these disorders are associated, at least theoretically, with neuropathology of monoamine neurotransmitter systems. This panel of speakers will examine the complex interplay between substances of abuse and the monoamine neurotransmitters in terms of the effects of these substances on brain biology and behavior. Dr. Svensson will discuss the impact of glutamate and dopamine in the ventral tegmental area on the biochemical and behavioral effects of nicotine withdrawal. Dr. Goldman will present data demonstrating the influence of the serotonin transporter gene in neuroticism and smoking behavior, as well as its role in cocaine reward. Dr. Markou will present findings indicating that decreased serotonergic function mediates the reward decrements characteristic of nicotine and amphetamine withdrawal, and that certain affective aspects of drug withdrawal may be neurobiologically similar to non-drug-induced depressions. Dr. Ordway will discuss the effects of tobacco on central noradrenergic neurons and present findings suggesting that smoking-induced changes in noradrenergic biochemistry may serve to strengthen the smoking habit amongst patients with major depression. Together, the presenters will elucidate the important roles of multiple monoamine neurotransmitters in the biology of drug dependence and raise the possibility of new approaches for treating or reducing substance abuse.

Panel · Thursday, January 31 · 4:30-6:30 PM · Janss

Scientific Meetings at High Altitude: a.k.a. Ischemic Preconditioning in the Brain

E. Aizenman, V. Dawson, M. Gonzalez-Zulueta, J. Hallenbeck

Totally out of breath as you jump off a cornice onto a mogul-studded double diamond on your first day at WCBR? Not getting enough oxygen into your brain may be actually doing more good than harm. Well, at least if you are going to have a stroke later on that day when you find out from a colleague that your grant application has been... triaged. Indeed, a short, sub-lethal ischemic event in the brain can lead to subsequent resistance of neurons to a more severe, normally lethal ischemic insult. This phenomenon is commonly referred to as ischemic tolerance or ischemic preconditioning. The precise cellular and molecular events that lead to this form of neuroprotection are not well understood, but subject to intense study. The presentations in this panel will describe recent work aimed at elucidating the mechanisms responsible for this unique form of brain self-preservation. Valina Dawson will describe how NMDA, ischemia and membrane depolarization all induce preconditioning to lethal ischemia through different initial cytosolic signaling events. She will invite the audience to discuss whether these divergent pathways converge upon a common transcriptional event, or whether there are multiple ways to protect the brain. Mirella Gonzalez-Zulueta will follow by presenting an integrated approach for the rapid identification and characterization of genes involved in ischemic preconditioning, a process that can also be applied to the study of neurological disorders. She will give examples for de novo gene identification by differential cloning techniques based on animal models of ischemic preconditioning and CNS disease, for massive gene expression profiling using cDNA arrays, for selection of potential targets by comprehensive pathway analysis, and for functional validation strategies. Elias Aizenman will present evidence that the activation of cell signals that are normally associated with cell death pathways are actually critically important for the expression of neuroprotection in an ischemic preconditioning model. He will show how blocking these normally damaging molecules can halt the protective process and discuss potential mechanisms to account for the induction of tolerance by the neurodestructive molecules. John Hallenbeck will continue on this topic by describing a vital role for the apoptogenic substrate ceramide in activating the preconditioning cascade. He will also introduce in vivo studies that validate this model and will describe signaling mechanisms that are involved in ceramide neuroprotection. The panel will conclude by inviting the audience to hold their breath while their latest pink sheets are distributed.

Panel · Thursday, January 31 · 8:30-1000 PM ·
Hooglund

Stem Cells and CNS Repair

S. Whittemore, E. Snyder, T. Hagg, M. Young

Stem cells have now been isolated from many tissues and show a remarkable plasticity to integrate and even transdifferentiate after engraftment into the adult CNS, where they can markedly influence endogenous repair mechanisms. However, it is also now recognized that stem cells require induction towards a given phenotype if they are expected to differentiate into desired cell types and become functional at specific locations. Lastly, enhancing and harnessing the potential of endogenous stem cells without transplantation, also may provide a viable strategy for cell replacement and CNS repair. In this panel, we will discuss these issues with an emphasis on their potential as well as limitations for therapeutic brain, retina and spinal cord repair. Dr. Hagg will discuss his recent work on endogenous stem cells that demonstrates that intrinsic neurogenesis in the adult rodent forebrain is regulated by endogenous CNTF and specific dopamine receptors and the migration of the newly formed neuroblasts by endogenous integrins. Dr. Snyder will discuss situations in which the fundamental biology of neural stem cells may play a therapeutic role in spinal dysfunction. These approaches may include both the differentiation of stem cells into lost or damaged neural cell types as well as provide therapeutic factors that promote the regrowth of some host fibers, the blunting of secondary injury, the inhibition of scar formation, and the preservation of damaged tissue. Dr. Whittemore will highlight how different CNS environments direct or restrict the lineage-specific differentiation of engrafted stem cells and present novel strategies to facilitate appropriate differentiation in vivo. Dr. Young will present his recent work on stem cells from the mammalian retina, both rodent and human, and the ability of stem cells to integrate into an adult host after retinal transplantation.

Panel · Thursday, January 31 · 8:30-1000 PM ·
Sindair

Basal Ganglia - Superior Colliculus Relationships: Novel Perspectives, New Directions

B. Stein, J. McHaffie, T. Stanford, P. Redgrave, E. Meloni

In attempting to understand the neural bases for behaviors, it is often the case that individual structures in an interconnected circuit are dealt with as separate entities. However, the present panel will present data showing how

multiple sites along the cortical-basal ganglia-superior colliculus network interact to produce coordinated sensorimotor behaviors. Peter Redgrave will present evidence for a novel anatomical projection from the superior colliculus directly to dopaminergic neurons in substantia nigra which may explain their exquisite sensitivity to unexpected biologically salient stimuli in a variety of contexts. Terrence Stanford will discuss how regions of the thalamus receiving inputs from the basal ganglia and superior colliculus contribute to context dependent control of saccadic eye movements. Edward Meloni will discuss how basal ganglia outputs to the deep layers of the superior colliculus mediate dopamine's effects on the acoustic startle response. John McHaffie will describe a model of basal ganglia-superior colliculus interactions that mediate interhemispheric control of visuomotor tasks and the role of this circuit in the induction and amelioration of the hemineglect produced by lesions of visual cortex. Together these presentations will show how activity within this sensorimotor network leads to coordinated responses to sensory stimuli and how disruptions at various points within this circuitry produce sensorimotor anomalies.

Panel · Thursday, January 31 · 8:30-1000 PM ·
Erickson

Synaptic and Non-Synaptic Regulation of Dopamine Neurons

C.A. Paladini, J. Tepper, I. Mintz, A. Bonci

Dysregulation of the control of extracellular dopamine (DA) concentration is a hallmark of many affective disorders such as schizophrenia. The highly addictive psychostimulants, cocaine and amphetamine, also affect the control of extracellular DA concentrations in certain brain regions. In particular, transient, impulse-dependent release of DA is known to be critical in the natural processing of the mesolimbic system. Afferent-dependent, transient increases in extracellular DA are driven by various inputs such as ionotropic and metabotropic glutamatergic synaptic afferents, GABAergic synaptic afferents, and non-synaptic auto-inhibition via dopaminergic receptors.

Dr. Antonello Bonci will give a talk on the ionotropic glutamate receptor control of DA neurons and the effects of cocaine on LTD in DA neurons. Dr. Carlos Paladini will talk about the metabotropic glutamate receptor control of dopamine cells and the effects of amphetamine and cocaine. Dr. James Tepper will give a talk on the GABAergic control of DA cell firing. Dr. Isabelle Mintz will talk about the auto-inhibitory control of DA cell activity and the role of DA transporters.

Panel · Thursday, January 31 · 8:30-10:00 PM ·
Carroll

Cholinergic Mechanisms in Reward and Arousal

J. Yeomans, P. Clarke, S. Ikemoto, P. Rada

Mesopontine cholinergic neurons strongly excite dopamine neurons and thalamic nuclei via fast nicotinic and slow muscarinic receptors. These pathways are important for nicotine self-administration, brain-stimulation reward and cortical arousal, suggesting a more general function in mobilizing the brain during approach behaviors. This panel will review the neurons and receptors mediating these effects, and discuss the importance of other cholinergic neurons and receptors in the striatum and basal forebrain. Paul Clarke (McGill University) will review nicotinic receptor mechanisms related to reinforcement, locomotor stimulation and thalamocortical transmission. Satoshi Ikemoto (National Institute on Drug Abuse) will describe new methods for intracranial self-administration of cholinergic drugs, which are reinforcing in the ventral tegmental area and nucleus accumbens. Pedro Rada (Los Andes University) will describe acetylcholine and dopamine release during reward-related behaviors, such as feeding, drinking and brain-stimulation reward. John Yeomans (University of Toronto) will review muscarinic receptor mechanisms important for dopaminergic activation and brain-stimulation reward, and methods for studying receptors subtypes, including antisense DNA and mutant mice.

Workshop · Thursday, January 31 · 8:30-10:00 PM ·
Snobble

Branch, Elongate, or Retract, How are Arbors Defined?

R. Lane, L. Chalupa, M. Jacquin, R. Rhoades, F. White

The intricate and specific nature of mature sensory neuron cytoarchitecture is determined by the controlled outgrowth, branching, and pruning of axons and dendrites during development. Numerous factors including adhesion molecules, neurotrophins, neuropeptides and activity have been shown to influence arbor development. This workshop will bring together researchers from several disciplines to compare and contrast the elements that influence neuronal development in different regions of sensory systems. In the somatosensory system, Mark Jacquin will discuss the role of neurotrophins in defining the arbors of trigeminal neurons. The developmental impact of chemorepulsive axon guidance signals on the spinal somatosensory system will be discussed by Fletcher White. Bob Rhoades will examine the role of the neuropeptide serotonin in the formation of the barrel pattern by thalamocortical efferents from the ventral posterior nucleus

of the thalamus. In the visual system, Leo Chalupa will discuss the role of binocular interactions in defining the retinogeniculate arbors in fetal monkeys. The discussion will center on possible explanations for the variety of elements controlling arbor formation by discrete neuron populations in different regions.

Panel · Thursday, January 31 · 8:30-1000 PM · Janss

Inhibitory Processes in Brain Development and Repair

H. Geller, J. Fawcett, J. Raper, H. Keirstead, M.L. Mercado

Growth cones in the developing nervous system guide axons to their targets by responding to a combination of inhibitory and permissive signals. Regeneration of severed axons after injury to the central nervous system fails, in large part due to the re-expression of many of these same signals. This panel will present recent data that extend our knowledge of the inhibitory signals as well as applying novel strategies to overcome them. Hans Kierstead will talk about myelin and myelin-derived molecules as inhibitory factors to regrowth, and about the use of experimental methods of demyelinating the CNS to permit axonal regeneration through the demyelinated (and thus growth-permissive) CNS environment. James Fawcett will talk about the inhibitory proteoglycans that are upregulated in the glial scar, and about strategies for promoting regeneration of CNS axons by modification of the proteoglycan response. He will also talk about glial boundaries, where axon growth is blocked at the interface between different types of glial cells. Mary Lynn Mercado will talk about signaling molecules in the growth cone that direct growth cones to turn at inhibitory boundaries. In addition she will describe gene-therapy based approaches to block signaling within the growth cone that can overcome these inhibitory influences. Jonathan Raper will talk about the role of semaphorins and their receptors in transmitting inhibitory influences to growth cones, and how blocking these receptors can promote growth in an inhibitory environment. Together, these presentations are designed to provide the roadmap for future clinical studies in neural regeneration.

Panel · Friday, February 1 · 7:30-9:30 AM · Hooglund

Cell Biology of Huntington's Disease

E. Schweitzer, E. Cattaneo, J. Olson, C. Ross

Huntingtin protein (Htt) containing expanded polyglutamine repeats causes destruction of neurons by mechanisms still not well understood. Studies of Huntington's disease (HD) patient autopsy material and mouse models of HD have contributed substantially to our understanding of the phenomenology of the disease progress, but we still lack a detailed understanding

of the cellular and molecular causes of the disease. The recent establishment and analysis of cell culture models for HD has led to substantial new insights into the mechanisms of Htt-induced neuropathology. Cell culture models have reproduced key features of the human disease, including polyglutamine length dependent toxicity, protein aggregation, and selective neuronal cell death. Cell culture systems for HD therefore offer the potential for studying neuronal degeneration in a way not currently feasible for Alzheimer's disease or Parkinson's disease.

Recent work examining the effects of expanded repeat Htt on cultured cells has suggested several very different, but not mutually exclusive, hypotheses for how mutation of the normal htt gene causes disease. We will present evidence that supports the important roles played by loss of the normal function of Htt, alterations in gene transcription, including transcriptional dysregulation, caused by the expanded polyglutamine tract, and derangement of protein turnover through polyglutamine-mediated poisoning of proteasomes. We will discuss the implications of each of these models, the areas of overlap and conflict, the possibilities that each describes a different but similarly important aspect of the disease process, and ways in which these different cellular aberrations may interact ultimately to cause disease. We will use the information we have gathered from cell culture systems to formulate critical predictions that could serve to define more clearly our understanding of the overall processes responsible for cellular pathogenesis in Huntington's disease.

Panel · Friday, February 1 · 7:30-9:30 AM · Sinclair

Cellular and Genetic Coupling in the Circadian System

C. Colwell, D. McMahon, K. Obrietan, G. Block

In mammals, the part of the nervous system responsible for most circadian behavior can be localized to a pair of structures in the hypothalamus known as the suprachiasmatic nucleus (SCN). Importantly, when SCN neurons are removed from the organism and maintained in a brain slice preparation, they continue to generate 24-hour rhythms in electrical activity, secretion, and gene expression. Previous studies suggest that the basic mechanism responsible for the generation of these rhythms is intrinsic to individual cells in the SCN. If we assume that individual cells in the SCN are competent circadian oscillators, it is obviously important to understand how these cells communicate and remain synchronized with each other. The first purpose of this session is to describe recent progress in understanding coupling/cellular communication within the circadian system based in the SCN. In addition, the last few years have seen a stunning increase in our understanding of the molecular feedback loops that underlie the generation of the circadian oscillation. Thus the second purpose will be to discuss how to link our progress at a cellular level with the explosion of information about the mechanisms that underlie circadian oscillations at the molecular level."

Panel · Friday, February 1 · 7:30-9:30 AM · Erickson

Cocaine Craving: Cues and Clues

Y. Shaham, J. Grimm, T. de Vries, C. Bradberry, C. O'Brien

Environmental cues associated with cocaine intake induce drug craving in abstinent users and relapse to drug seeking in laboratory animals. The neuronal circuits underlying these effects of the cocaine-associated cues, however, are to a large degree not known. Our panel will present recent data, obtained from studies using rats, rhesus monkeys and humans, on the role of specific neurotransmitters and brain sites in cue-induced cocaine craving and relapse. Grimm (NIDA/IRP) will present data from rat studies on the important role of the basolateral amygdala, but not the nucleus accumbens, in cue-induced cocaine seeking. He also will present new data on time-dependent enhancement of cue-induced cocaine seeking over the first two months of cocaine withdrawal. De Vries (Free University, Amsterdam) will present data from rat studies suggesting that activation of the endocannabinoid system in the brain is involved in cue-induced reinstatement of cocaine seeking. De Vries and Grimm also will present data on the role D1, D2 and D3 receptors in cue-induced reinstatement of cocaine seeking. Bradberry (Yale) will present data from monkey studies in which the levels of dopamine, serotonin and glutamate were measured in the striatum and cortex after exposure to contextual and discrete cocaine cues. These studies demonstrate a dissociable neurochemical response to cocaine cues versus self-administered cocaine. O'Brien (U Penn) will present data from imaging studies on limbic activation (measured by regional cerebral blood flow) during exposure to cocaine cues in humans formerly dependent on cocaine. Preliminary data on endogenous dopamine release in humans responding to drug-related cues will also be presented. Based on the data presented, the panel will discuss two unresolved issues in current cocaine addiction research: (1) whether the neuronal responses to cocaine-associated cues are dissociable from the responses to cocaine itself, and (2) whether the neuronal and behavioral responses to cocaine cues generalize across species.

Panel · Friday, February 1 · 7:30-9:30 AM · Carroll

Extrasynaptic Neurotransmission and Tonic Inhibition: GABA-A Receptors

W. Wisden, W. Sieghart, H. Lüddens, Z. Nusser, E. Korpi

In this panel we aim to emphasize a previously undervalued mode of inhibitory neurotransmission. GABA is the most important inhibitory neurotransmitter in the brain, acting mainly through GABA-A receptors. Many of the GABA-A receptors are synaptically located: their activation leads to rapid inhibitory post-synaptic currents (IPSCs), termed phasic inhibition.

However, recent findings have highlighted that many neurons, for example cerebellar granule cells, have extrasynaptic GABA-A receptors that could be activated by GABA diffusing from the synapse. These receptors are persistently active, producing a so-called tonic inhibition. This type of inhibition may play a role in controlling the integrative properties of nerve cells, by altering the input resistance and the membrane time constant of the cells. Of the many GABA-A receptor subtypes found in the brain, two may be specialized for extrasynaptic transmission. These are receptors made, in part, from either the alpha 6 and delta subunits in cerebellar granule cells or alpha 4 and delta subunits in forebrain regions. In fact, the delta subunit is exclusively located extrasynaptically. This panel will focus on the properties of extrasynaptic GABA-A receptors. Sieghart will describe the biochemical evidence for their existence; based on recombinant work, Lueddens will discuss how these subunits selectively assemble together, and how they make high-affinity, non-desensitizing receptors; Nusser will describe electronmicroscopic evidence for the subcellular localization of these receptors, and review the electrophysiological properties of tonic/background inhibition; Korpi will describe mouse mutants lacking the background inhibition.

Panel · Friday, February 1 · 7:30-9:30 AM · Snobble

Common Processing Themes in Rat Prefrontal Cortex and Related Structures

G. Schoenbaum, S. Ramus, K. Anstrom, G. Quirk

Primate prefrontal cortex is divided into broad subdivisions based on projections from mediodorsal thalamus and other structures. These subdivisions and related posterior cortical areas are proposed to form systems that conduct similar operations on different types of information. Do similar systems exist in rat prefrontal cortex and are there common processing characteristics in different areas? In this panel, we will consider neurophysiological data to address this question. These discussions will take a systems approach, bringing to bear data from within prefrontal cortex and related structures. Geoffrey Schoenbaum will begin the panel by presenting data from orbital areas and ventral agranular insular cortex during odor-guided discrimination training. Seth Ramus will discuss data from the same prefrontal region during odor-guided delayed-non-match performance. Together these studies - using similar cues in different behavioral paradigms - will serve to start our discussion. Although notable differences are evident in prefrontal processing between the two paradigms, similarities suggest that this prefrontal region uses associative information flexibly to guide choice performance. Data will be related to findings in entorhinal cortex and amygdala. Kristin Anstrom will then discuss neural firing in posterior agranular insular cortex. This region is thought to be mainly gustatory, yet cells there are more active to tones that are used to guide responses than to

the same tones presented unexpectedly without a response contingency, again suggesting that prefrontal areas are specialized to use cues to guide performance. Finally Gregory Quirk will discuss findings in medial prefrontal cortex during acquisition and extinction of fear conditioning. Lesions in this area impair extinction but not acquisition of conditioned fear, and recording data show that neurons there develop selective responses to conditioned tones not during conditioning but during extinction training, when the rat must modify or manipulate cue representations to guide flexible behavior. These findings will be contrasted with data from amygdala and auditory cortex. Individual presentations will be followed by short question periods, and the panel will conclude with a group discussion to explore commonalities and notable differences in these diverse data sets.

Panel · Friday, February 1 · 7:30-9:30 AM · Janss

Mechanisms of Chronic Central Pain: From Molecules to Man

C. Hulsebosch, P. Dougherty, K. Sluka, T. Morrow, C. Sang

Chronic central pain (CCP) is difficult to manage in the clinic due in large part to the lack of knowledge regarding the mechanisms involved in the pathophysiology of persistent pain states. Only in recent years, have reliable animal models been developed for CCP studies. The panelists have been selected because of the breadth of approaches used to study CCP, which span the gamut from molecular approaches to clinical trials. P. Dougherty will present data collected from in vivo whole cell patch clamp recording methods that have led to the identification of "silent" dorsal horn neurons that have latent low-threshold or nociceptive specific receptive field properties revealed by changes induced in passive cell membrane properties that appear to be regulated by changes in function of membrane potassium currents. K. Sluka will discuss an animal model of CCP, initiated by hyperalgesia induced by intramuscular acid injections which is maintained by changes in the central nervous system. Pharmacological approaches to alter receptor activation and intracellular pathways will be presented in this model. C. Hulsebosch will present data that supports the use of molecular and pharmacological approaches to attenuate dorsal horn hyperexcitability evident in an animal model of CCP after spinal cord injury. T. Morrow will present data that demonstrates the effects of spinal cord injury on increased fore-brain regional cerebral blood flow in the rat and its relationship to CCP. C. Sang will conclude the session by presenting completed and ongoing clinical Phase I trials for treatment of CCP in patients with spinal cord injury, in which a variety of pharmacological agents are tested that were developed in animal models of SCI. Thus, the panelists will present data that will suggest mechanisms that provide the substrate for CCP based on techniques that range from molecular approaches, include cell and systems approaches, and translate to therapeutic approaches in clinical trials.

Panel · Friday, February 1 · 4:30-6:30 PM · Hooglund

Dopamine Behavior in the CNS: Regulation of Release and Efficacy

M. Rice, S. Cragg, D. Sulzer, M. Wightman

Indirect evidence for exocytotic release of neurotransmitters originally came from studies of the neuromuscular junction, with release inferred from postsynaptic events. The use of carbon-fiber microelectrodes for direct detection of transmitter release has permitted significant advances beyond those early, indirect observations. This panel will focus on recent studies to characterize factors that regulate dopamine release and behavior in the CNS. Dopamine (DA) is of particular interest because of its pivotal role in motor control, emotive processes, light-dark adaptation, as well as pathologies from Parkinson's disease to addiction. Mark Wightman, who pioneered the use of amperometry to detect exocytotic catecholamine release from adrenal chromaffin cells, will describe DA release from retinal DA neurons isolated from mice that express placental alkaline phosphatase (PLAP) in tyrosine-hydroxylase expressing cells. David Sulzer will describe regulation of DA release from striatal terminals based on evidence from novel mouse models, including VMAT2 and alpha-synuclein knockouts. Stephanie Cragg will discuss DA release probability and its plasticity in different striatal projection regions, based on voltammetric and EM data; she will also present a model of the sphere of influence and efficacy of released DA. Margaret Rice will describe the novel calcium dependence of somatodendritic DA release in the substantia nigra and will highlight points of contrast between the efficacy and influence of somatodendritic vs. striatal DA behavior. Together, these presentations will provide a comprehensive, new picture of DA release and regulation in the CNS.

Panel · Friday, February 1 · 4:30-6:30 PM · Sinclair

BDNF: Of Mice and Men

B. Lipska, A. Morozov, L. Mamounas, C. Weickert

Brain-derived neurotrophic factor (BDNF) promotes a variety of neuromodulatory processes in the brain including neuronal survival, neurite outgrowth and synapse formation. BDNF mRNA is abundantly expressed throughout life in highly plastic regions of the rat and human brain, the neocortex and the hippocampus. In this panel, we will discuss reciprocal regulation of BDNF expression and serotonergic (5-HT) and dopaminergic (DA) activity in the cortex, and important implications of these interactions for neuropsychiatric diseases. Dr. Morozov will present data from studies on conditional BDNF knockout mice. Mice lacking BDNF in the cortex exhibit abnormal patterns of behavior suggesting deficient 5-HT and DA neurotransmission. Dr. Mamounas will show that BDNF is an important enhancer of 5-HT functioning and plasticity. Chronic BDNF infu-

sion into the neocortex or hippocampus stimulates the regenerative sprouting of neurotoxin-lesioned 5-HT axons back into their normal target fields. BDNF +/- null mice exhibit behavioral changes in conjunction with altered 5-HT neurotransmission. Dr. Lipska will demonstrate that blockade of DA receptors by haloperidol and clozapine markedly suppresses BDNF mRNA expression in the hippocampus and tends to reduce it in prefrontal cortex. Rats with neonatal lesions of the hippocampus show even more pronounced suppression of BDNF mRNA in these regions in response to neuroleptics. Dr. Shannon Weickert will present the results of postmortem studies showing that BDNF mRNA is reduced in the hippocampus and prefrontal cortex of patients with schizophrenia. These data suggest that BDNF may be an important determinant of 5-HT and DA neuronal functioning, plasticity and nerve terminal integrity in the adult brain, and as such may have a role in emotional and mental health in humans.

Panel · Friday, February 1 · 4:30-6:30 PM · Erickson

Does Prediction Help in Surviving the Moguls? Overcoming Performance Constraints Through Prediction and Adaptation

E. Keller, S. Heinen, A. Schwartz, J. Bloedel, L. Young

Motor performance in highly skilled tasks is limited in accuracy and response time by the resolution and delays present in the sensory systems that guide behavior. Attempts to ski in a whiteout make this abundantly clear. It would be a mistake, often made in the past, to consider such motor control as though it were merely a closed loop servomechanism, slavishly driven to reduce the difference between current and intended position. Alternative strategies used by the nervous system to partially circumvent the basic limitations imposed by the characteristics of sensorimotor integration include the use of predictive and adaptive modes of performance. This session will quantify how these strategies are implemented with specific examples gathered from human and monkey subjects. Steve Heinen will present evidence that neurons in the supplementary eye fields in monkey can predict whether the trajectory of a moving visual target will take that target through a pre-defined "strike zone" while the animals are attempting to play eye movement baseball. Andy Schwartz will show evidence of predictive strategies observed in monkeys during tracing of circles and ellipses. Jim Bloedel will discuss eye-finger coordination in normal humans and in cerebellar patients in a task in which prediction is not possible. Larry Young will discuss the question of feed-forward and feedback cues for context specific dual adaptation, using head movements in humans during artificial gravity as the unusual stimulus.

Panel · Friday, February 1 · 4:30-6:30 PM · Carroll

Manipulating CNS Myelination in Development and Repair

R. Franklin, C. ffrench-Constant, J. Goldman, I. Duncan

The process whereby an oligodendrocyte invests an axon with a myelin sheath is one of the most intriguing in neurobiology. It occurs during perinatal development and can also occur as a regenerative event, called remyelination, that may follow demyelination of the mature CNS. The molecules involved in the orchestration of this process have been widely studied in developmental myelination and are becoming an increasing focus of interest in remyelination. Indeed, the concept that remyelination involves a recapitulation of myelination, based on the shared objective of investing an axon with a myelin sheath, has been a useful basis for elucidating the mechanisms of remyelination. The ability to alter the processes of myelination and remyelination by altering signalling systems provides a powerful means of studying mechanism, and in the context of remyelination, indicates the feasibility of promoting repair in clinical demyelinating disease. In this session the interactions between different signalling mechanisms involved in orchestrating the behaviour of oligodendrocyte lineage cells will be considered and how these might be manipulated to change myelination and remyelination discussed. The first talk will be by Charles ffrench-Constant who will describe how the pattern of integrin expression on oligodendrocyte lineage cells affects the manner in which these cells respond to growth factors and the implications this has for growth factor-based manipulation of remyelination. James Goldman will talk about the properties of the various "progenitor" cells that have been described in the adult and remyelinating brain (both rodent and primate), and also the growth factor receptor profiles and responses to factors of the cycling, immature populations from adult rat white matter. Robin Franklin will talk about manipulating levels of expression of growth factors and other signalling molecules during CNS remyelination using viral vector and transgenic approaches, and highlight the problems inherent in 'single molecule' strategies. Ian Duncan will conclude the session with a talk on how cell transplantation can be used to manipulate myelination and remyelination and how this approach can benefit from increased knowledge of the mechanisms involved in the intrinsic processes of myelination and remyelination.

Panel · Friday, February 1 · 4:30-6:30 PM · Snobble

Electrical Synapses Among Inhibitory Cortical Neurons

S. Hestrin, M. Bennett, H. Monyer, B. Connors, M. Galarreta

Recent work showed that electrical synapses among GABAergic interneurons in the cerebral cortex, thalamus, striatum and cerebellum form extensively interconnected networks. These networks may define functionally diverse groups of GABAergic interneurons. We will discuss these results and

their possible functional significance trying to gain insights in circuit organization. Mike Bennett will discuss experiments showing up-regulation of Cx32 and Cx36 in CA1, which may aid in the survival of inhibitory interneurons. Hannah Monyer will talk about experiments using a mouse deficient in Cx36 which may be the main connexin in these synapses. Barry Connors will talk about two distinct, electrically coupled networks of inhibitory neurons in the neocortex, and the ability of one of them to generate synchronized inhibition across the local circuit. Mario Galarreta will talk about recent experiments suggesting that electrical networks of GABAergic neurons may play a role in the detection and promotion of synchronous activity within the neocortex.

Panel · Friday, February 1 · 4:30-6:30 PM · Janss

The Sweet Glow of Success: Applications of GFP Technology for the Study of Neural Development

K. Greif, G. Feng, M. Nonet, M. Westerfield

Green fluorescent protein (GFP) and derivatives with altered spectral properties have become powerful molecular probes to examine processes in neural development. This panel provides examples of the kinds of questions that can be answered using these unique markers as tools. Karen Greif and Michael Nonet examine the development of synapses and the regulation of localization of presynaptic components to the synapse. Greif focuses on the ability of early developing neurites in vitro to transport synaptic components to growth cones, using adenovirus-mediated transfer of GFP fusion proteins. Nonet combines imaging with forward genetic methods such as screening for mutants in *C. elegans*. Monte Westerfield will discuss the functions of developmental regulatory gene promoters by analyzing GFP fluorescence encoded by transgenes in living zebrafish embryos. Recently this technology has been extended to support screens for mutations in genetic pathways and to study gene function in loss and gain of function experiments. Finally, Guoping Feng generated a large set of transgenic mice in which red, green, yellow, or cyan fluorescent proteins were expressed in subsets of neurons. These transgenic mice provide a useful tool to study neuronal function and development in vivo.