Buffalo Chapter
of the Society for Neuroscience
and
University at Buffalo,
Neuroscience Program
present

Third Annual Neuroscience Research Day

September 26, 2009
University at Buffalo, North Campus
103 Center for the Arts, Buffalo, NY
SCHEDULE

8:00 am – 9:00 am  Continental Breakfast/Poster Set-up

9:00 am – 9:30 am  Opening remarks
Dr. Derek Daniels, president, Buffalo Chapter of the SFN

9:30 am – 10:30 am  

Distinguished Speaker
Dr. Richard J. Salvi
University at Buffalo

Phantom Sound of Tinnitus: Human Brain Imaging, Animal Models and Neural Correlates

10:30 am – 11:00 am  Coffee Break

11:00 – 12:30  Short talks
11:00 – 11:15  Prasad Purohit, PhD (advisor, Anthony Auerbach)
11:15 – 11:30  Cassandra Kussius (advisor, Gabriela K Popescu)
11:30 – 11:45  Islam Mohamed (advisor, Paresh Dandona)
11:45 – 12:00  Peter Vento (advisor, Derek Daniels)
12:00 – 12:15  Kelly Picchione (advisor, Bhattacharjee)

12:15 pm – 1:30 pm  Lunch

1:30 pm – 2:30 pm  

Keynote Lecture
Dr. Harvey J. Grill
University of Pennsylvania

Leptin and the systems neuroscience of meal size control

2:30 pm – 4:30 pm  POSTER SESSION

4:30 pm – 5:00 pm  Presentation of the Beverly P. Bishop and Harold Brody Awards
Closing Remarks
The following sponsors are gratefully acknowledged for:

**SUPPORT**

**OFFICE OF THE DEAN,**

Dean, Dr. Michael Cain

Steve Baker, steve.baker@olympus.com

Distributor of the Finest Clinical, Research, and Industrial Microscopes and custom Manufacturer of Components for Microscopy
Michael Grace, MichaelG@mvi-inc.com

Lori Stucchio, lori.stucchio@pearson.com

UB Commons, Suite 105 (off the Courtyard)
716-636-8440

**University at Buffalo Interdisciplinary Program in Neuroscience**
Malcolm Slaughter, Director

**ORGANIZING COMMITTEE**

**Society for Neuroscience, Buffalo Chapter Council**
President, Dr. Derek Daniels
President Elect, Dr. Gabriela K Popescu
Past President, Dr. Matthew Xu-Friedman
Dr. Arin Bhattacharjee
Dr. Stan Halvorsen
Dr. Malcolm Slaughter
Distinguished Speaker

The Ringing in Your Ear (Tinnitus) is Really in Your Brain

Hearing loss often gives rise to a loud, persistent and inescapable phantom sound (ringing, rushing or buzzing) that can be severe and disabling. The neural generator responsible for tinnitus was originally thought to reside in the inner ear where the phantom sound was perceived. However, modern brain imaging studies in humans as well as electrophysiological studies in animals indicate that the neural generator for tinnitus resides in the brain. The neural generators involved with tinnitus include several regions within classical auditory pathway and may recruit other regions within the limbic system associated with memory and emotion. The development of animal models that can “tell us” if they are experiencing tinnitus and what it sounds like has allowed researchers to investigate the neural and biological mechanisms of tinnitus and to screen drugs that might be used to suppress tinnitus in humans.

Dr. Richard Salvi
Professor, Dept. of Communicative Disorders & Sciences
Director, Center for Hearing and Deafness
UB Adjunct Professor in Neurology, Psychology, Biology and Otolaryngology

Dr. Salvi’s research spans a broad range of topics in auditory neuroscience and perception that include: (1) biological mechanisms of noise and drug induced hearing loss, (2) hair cell regeneration, (3) neural coding of sound with normal and abnormal hearing, (4) auditory brain imaging, (5) animal psychophysics and perception, (6) genomics and proteomic in normal and damaged ear and (7) human and animal studies of tinnitus.

Dr. Salvi has authored or co-authored more than 300 journal articles, book chapters and edited books dealing with auditory neuroscience, hearing loss, hair cell regeneration, auditory plasticity, noise-induced hearing loss, aging, ototoxicity and auditory perception. He has organized or co-organized more than a dozen international or national scientific conferences dealing hearing loss, auditory plasticity, hair cell regeneration, and tinnitus. Dr. Salvi has served as a regular or ad hoc member of numerous NIH grant review panels as well as grant review panels for the Office of Naval Research, Royal National Institute for the Deaf, National Organization for Hearing Research, Raine Medical Research Foundation of Australia, Pennsylvania Lion’s Club, Canadian Institutes of Health Research and other public and private review panels. He serves on the editorial board of a dozen journals, is the Chair of the Scientific Committee of the Tinnitus Research Initiative, was past Chair of the Scientific Committee and Member of the Board of Directors of the American Tinnitus Association, and is a member of the International Advisory Board of the Centre for Auditory Research at the University College of London. He is the recipient of the Chancellor’s Award of SUNY and is a Fellow of the Acoustical Society of America. Dr. Salvi’s research has been continuously funded by public and private research grants and industry contracts for more than 30 years. His research is currently funded by multiple grants from the NIH, the Tinnitus Research Initiative and subcontracts from The Jackson Labs.
Keynote Lecture

Leptin and the systems neuroscience of meal size control

The development of effective pharmacotherapies for obesity will benefit from a more complete understanding of the neural pathways, the neurochemical and intracellular signals whose actions result in the reduction of the size of meals. This talk will examine the neural control of meal size and the integration of two principal sources of that control - satiation signals arising from the gastrointestinal tract and CNS leptin signaling. Four types of integrations that are central to the control of meal size will be described and each involves neurons of the nucleus tractus solitarius (NTS) in the hindbrain. Data discussed show that NTS neurons integrate information arising from: [1] ascending GI-derived vagal afferent projections, [2] descending neuropeptidergic projections from leptin-activated arcuate nucleus neurons, [3] leptin signaling in NTS neurons themselves and [4] melanocortinergic input to NTS neurons and vagal afferent terminals that arise from NTS POMC neurons.

Dr. Harvey J. Grill

Professor of Behavioral Neuroscience
Director of Integrative Research, Institute of Diabetes, Obesity and Metabolism
Department of Psychology and Mahoney Institute of Neurological Sciences
University of Pennsylvania, Philadelphia PA

Harvey Grill is a regulatory physiologist and Professor of Behavioral Neuroscience at the University of Pennsylvania. His work focuses on identifying the neural circuits, neurochemicals, and intracellular signals that control energy balance. Progress on these questions is needed to develop more effective treatments for obesity and anorexia. Grill's work emphasizes the role of gastrointestinal signals and caudal brainstem processing in the control of meal size. He has advanced the hypothesis that leptin has its intake suppressive effect by amplifying the neural processing of gastrointestinal signals in neurons of the NTS. Grill has advanced the view that the neural control of energy balance is anatomically distributed in contrast to the generally held view that control is centered in the neurons of the arcuate hypothalamus. Grill's lab has generated a wide range of data that support a significant contribution to energy balance control arising from neurons in the caudal brainstem. Professor Grill and colleagues are also investigating the oral motor and gastrointestinal actions of anorexic agents. Professor Grill has been an invited speaker at international and national and conferences. He has authored over 120 research papers, served on NIH study sections, as president of the Society for the Study of Ingestive Behavior, in developing the scientific program for the Obesity Society and the Society for the Study of Ingestive Behavior, as a member of the editorial board for the journal Obesity and currently as director of integrative research, Institute of Diabetes, Obesity and Metabolism at the University of Pennsylvania. Grill has trained a number of prominent scientists including Kent Berridge, Gary Schwartz, Randy Seeley, Alan Spector, Diana Williams and Matt Hayes.
SPECIAL FOCUS:

University at Buffalo Brain Awareness Week: A tradition in the making

K. Picchione, J. Dolan, S. Amico-Ruvio

Every year, neuroscience education events are held around the world during Brain Awareness Week (BAW) to increase and advance public awareness about the progress and promise of brain research, and to inspire the next generation of neuroscientists. Starting in 2008, the Neuroscience Graduate Student Association from the University at Buffalo created and implemented an educational event during BAW for local elementary school students.

This event consisted of UB graduate students engaging 4th grade students and teachers from Highgate Heights Elementary School in an interactive neuroscience session. Participants visited four stations in which they either performed a fun yet educational task or learned about the sophisticated anatomy of the brain.

Through these stations the students were able to learn about intriguing neurological mechanisms and the complex abilities of the human brain. The Neuroscience Graduate Student Association would like to continue this tradition in future years and encourages other biomedical science graduate students and interested faculty to join us this coming March for our 3rd Annual Brain Awareness Week event!
Annual Awards

The Beverly P. Bishop award for the best talk by a student or postdoctoral fellow

Beginning this year, we honor the life and career of Dr. Bishop by renaming one of our annual awards in her honor. This award is presented to the student or postdoctoral fellow who delivers a short talk that is selected by the audience as the best in the session. We have reprinted a portion of her obituary below, but feel that it is important to also mention her specific contribution to this group. In fact, she was a driving force behind neuroscience at UB and her support and dedication were undoubtedly critical for the first two meetings of the revitalized Buffalo Chapter.

From the American Physiological Society:

Beverly Petterson Bishop was a SUNY Distinguished Teaching Professor of Physiology and Biophysics at the University at Buffalo, having had a career of teaching and research that spanned more than fifty years. She was the author of more than 150 scholarly articles, the editor of four books, and had taught and mentored thousands of students. Her research interests included the identification and analysis of the ways the nervous system controls muscle activity in both humans and animals. Her experimental work focused on the neural regulation of the respiratory muscles. She taught neurophysiology to nearly 40 classes of physical therapy students and produced monographs and book chapters that became seminal in that area.

Beverly kept close contact with many of her students over the years both personally and professionally. She viewed her students as individuals, first and foremost, and her extraordinary example continues to guide their professional lives.

The Harold Brody award for the best poster presentation by a student or postdoctoral fellow

The award for the best poster presentation has also been renamed this year. This award will honor Dr. Harold Brody, who started at UB in 1954 when he was hired to direct the neuroanatomy program. While directing the neuroanatomy program, he attended medical school at UB and earned his MD in 1961. His service to UB included time spent as a department chair, a distinguished teaching professor, an associate dean, and director of the Multidisciplinary Center for the Study of Aging. His numerous awards include the UB Medical School Dean’s Award, the UB Distinguished Medical Alumni Award, a Fullbright scholarship, and a research award from the Gerontological Society of America. Dr. Brody also served as an advisor to the 1981 White House Conference on Aging and was instrumental in the creation of the National Institute on Aging. In spite of these numerous achievements, those who had the pleasure of knowing Dr. Brody would likely say that his favorite was founding and serving as curator of his beloved UB Neuroanatomy Museum.
‘Feeling’ the transmitter-binding-site in spontaneously-gated nicotinic acetylcholine receptors

Prasad Purohit and Anthony Auerbach
Department of Physiology and Biophysics, SUNY at Buffalo, Buffalo 14214, USA

Nicotinic acetylcholine receptors switch between low transmitter-affinity/non-conducting and high transmitter-affinity/conducting conformations (C<->O) during channel-gating process. Each binding-site contains 5 aromatic residues that are important to both ligand binding- and channel-gating (αW149, αY93, αY190, αY198 and εW55/δW57). It has been difficult to probe in detail the role of these aromatic residues because their mutation reduces the affinity for agonists to an extent where measuring diliganded C<->O gating events becomes impossible. However, we have engineered multiple mutations in this protein that increase the diliganded gating equilibrium constant by an approximately parallel change in the unliganded gating equilibrium constant, because none of these mutations has a measurable effect on the agonist affinity to the closed AChRs. Now it is possible to quantify the gating energy changes experienced by these residues in mutant AChRs that spontaneously undergo the C<->O isomerization in the absence of exogenous ligands. Gating energy changes were largest for αW149, which was also the focus of energy coupling between residues. Mutating the aromatic residues reduces the affinity of the O conformation for the transmitter. The data also suggests that short- and long-lived openings appear to arise from alternative conformations of αW149, as influenced by both the tyrosine residues and αG147. We propose that at the onset of channel-opening, loop B (αW149 and flanking region) movements perturb the two Trp residues, to slow the dissociation of the transmitter and trigger the channel-opening conformational cascade.

Kinetic effects of perturbations in the ligand-binding domain of NMDA receptors

Cassandra Kussius, Jason Myers, Kevin Barnum, and Gabriela Popescu
Biochemistry Department, School of Medicine and Biomedical Sciences

NMDA receptors become active only after both glycine and glutamate bind to their cognate ligand-binding domain (LBD) on NR1 and NR2 subunits, respectively. It has been proposed that the conformational changes that lead to channel opening are initiated by agonist-induced closure of the LBDs and that the stability of the closed structure correlates with the agonist’s efficacy. To probe this hypothesis we characterized kinetic changes in receptor gating arising from complementary perturbations at the NR2-LBD: a) NR2-specific partial agonists, L-homocysteate or SYM2081, each reported to have ~ 80% efficacy; and b) NR2-LBD mutations (N687C, K487C) which lock the LBD in a closed-cleft conformation. We recorded steady-state single-channel currents from cell-attached patches containing only one receptor at saturating agonist concentrations. Kinetic analyses of these data indicated that neither perturbation affected the core gating mechanism of the channel which consisted of five closed and two open states, including desensitization. Open durations were only minimally affected with most of the kinetic effects observed resulting from changes in the duration of closures. Two closed time components were significantly changed compared to Control (τa2 = 1.7 ± 0.1 ms, τa3 = 4.6 ± 0.2 ms, n = 5). These were increased by partial agonists to 3.5 ± 0.3 ms and 9.1 ± 0.8 ms, respectively (n = 10, p<0.05) and decreased for the locked-LBD mutant to 0.9 ± 0.1 ms and to 3.2 ± 0.2 ms (n = 4, p<0.05). These results are consistent with the hypothesis that the stability of the closed NR2-LBD conformation correlates with channel gating efficacy. Further, the data show that distinct local perturbations at the NR2-LBD affect gating through the same mechanism observed as changes in the duration of two specific closed time components.
Increased Expression of Alzheimer Disease Related Genes in Obesity

Islam Mohamed, Husam Ghanim and Paresh Dandona
University of Buffalo and Kaleida Health

Obesity has been shown to be strongly associated with inflammation. Recently, the relationship between Alzheimer’s disease (AD) & inflammation has been established. Obesity is also associated with higher risk of developing AD. We, therefore, hypothesized that obesity associated inflammation might play a role in the development of AD and that caloric restriction and weight loss may reduce both inflammation and AD risk. We investigated basal levels of genes involved in Amyloid β-42 (Aβ-42) peptide generation in the adipose tissue of obese and lean subjects and the effect of a hypo-caloric diet (1000 Calories/day) for 6 weeks on those genes in the obese group. Obese subjects have higher mRNA expression of genes involved in Aβ-42 production including an increase by 12.3% in amyloid precursor protein (APP) (P = 0.031), 16.9% in BACE (P = 0.022), 52.8% in ADAM9 (P = <0.001), 26% in ADAM17 (P = 0.004), 19.3% in IDE (P = 0.015), and 41.5% in Tau (P = 0.002) mRNA expression compared to age and gender matched lean subjects. This was also associated with a higher expression (by 179%) of the pro-inflammatory chemokine, MCP-1 (P<0.001). After 6 weeks of Hypo-caloric diet, there was a 58% reduction in MCP-1 mRNA expression (P<0.001) while there was no change in the expression of Aβ-42 processing genes. These results show the up-regulation of the two key proteins involved in the pathogenesis of AD: APP and Tau. In addition, the expression of several enzymes involved in the formation (BACE) and the clearance (ADAM-9, ADAM-17 and IDE) of Aβ-42 is also increased. These increases are associated with an increase in the expression of mediators of inflammation (MCP-1) in the adipose tissue of obese patients. Whether this increase in APP and Tau contributes to the cerebral overload of these proteins or is merely a parallel to the inflammatory processes in the brain in obesity will need further elucidation.

Angiotensin II-induced desensitization and the neurohormonal regulation of water and saline intakes.

Peter J. Vento and Derek Daniels
Department of Psychology, University at Buffalo

Angiotensin II (AngII) plays an important role in body fluid homeostasis. The physiological effects of AngII include increased vascular tone and elevated blood pressure and a complementary behavioral increase in water and salt intakes. The AngII type 1 (AT1) receptor rapidly desensitizes and this is thought to play an important role in cardiovascular health. In laboratory rats, this desensitization also leads to decreased water intake. A more complete understanding of the behavioral component may provide information about the coordinated response to AngII while offering a simple model to study the underlying mechanisms. Accordingly, we tested the effects of repeated AngII treatment on water and saline intakes and found that a regimen comprising 3 injections of AngII, each separated by 20 min, resulted in less water intake after a subsequent challenge injection of AngII. The AT1-selective antagonist losartan markedly attenuated this effect, suggesting AT1 mediation. Moreover, when given access to both water and saline, rats given multiple injections of AngII drank less water than rats in the control group, but we observed no differences in saline intake. These findings are consistent with the suggestion that G protein-mediated signaling pathways play a role in water, but not saline intake, and in vitro studies suggesting a prominent role for G protein uncoupling in receptor desensitization. Ongoing experiments are attempting to elucidate the specific intracellular signaling pathways involved in this phenomenon.
Reversal of exogenous DNA-induced hyperexcitability by the VZV IE63 protein in dorsal root ganglion neurons

Kelly E. Piccione, Linda A. Christen, William T. Ruyechan, and Arin Bhattacharjee

Pharmacology and Neuroscience, University at Buffalo

Dorsal Root Ganglion (DRG) neurons convey sensory information from the skin, muscles, and internal organs into the spinal cord. DRG neurons also play host to opportunistic DNA viruses, such as the Varicella-zoster virus (VZV). After initial infection, VZV can remain latent in DRG neurons for decades; reactivation of the virus causes shingles and painful postherpetic neuralgia. Emerging evidence suggests that chromatinization of viral genomes determines lytic and latent states of DNA viruses. Current-clamp recordings were performed on cultured embryonic DRG neurons either transfected or adenovirally-transduced with exogenous DNA. In both cases, neuronal hyperexcitability was observed after 48 hours. Changes in excitability resemble those seen in nerve injury, such as depolarized resting membrane potential (RMP) increased action potential half-width (HW) and multiple AP’s fired upon prolonged suprathreshold stimulation. These changes were reversed by introduction of the IE63 gene by adenovirus transduction, returning the RMP and HW to their untransfected levels, and decreasing the percentage of cells exhibiting multiple AP’s. IE63 is a viral protein that localizes to the nucleus, binds to histone chaperone proteins, and is important for VZV latency. Additionally we found that expression of IE63 led to a significant decrease in adenoviral genome-associated GFP expression. The effects of IE63 on excitability may lead to better understanding of the role IE63 plays during VZV latency. Specifically, DNA induced hyperexcitability and reversal by IE63 strongly suggests that epigenetic mechanisms are involved.
Poster Titles and Authors
(listed alphabetically by first author)

1. The Effect of Thimerosal on Intracellular Calcium Dynamics in Neurons
   Catherine C. Alsford, Elizabeth A. Hogan
   Biology Department, Canisius College

2. Diversity of NR1/NR2B Receptor Gating Kinetics
   Stacy Amico-Ruvio, Navjot Kaur and Gabriela K Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

3. Characterization of a mutant NMDA receptor less sensitive to voltage-dependent magnesium block
   Stacy Amico-Ruvio, Thomas P. Smith, and Gabriela Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

   Farda Barandeh and Shermali Gunawardena
   Department of Biological Sciences, The State University of New York at Buffalo, Buffalo, NY 14260.

5. Processing Speed, Neural Efficiency, and Task Accuracy during Working Memory and Their Relationship with Specific Structural MRI Measures in Patients with MS
   Thomas J. Covey, David W. Shucard, Robert Zivadinov, Wing Lee, Michael G. Dwyer, Janet L. Shucard
   Dept Neurology, Division of Cognitive and Behavioral Neurosciences, and Buffalo Neuroimaging Analysis Center, University at Buffalo, School of Medicine and Biomedical Sciences

6. Role of Pore Residues in NMDA Receptor Gating NMDA receptors
   Kevin J. Barnum and Gabriela Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

7. Effects of Cross-Linking the NR1-NR2A Ligand Binding Domain Dimer Interface
   William Borschel and Gabriela Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

8. A Low-affinity Antagonist Reveals Saturation and Desensitization in Mature Synapses in the Auditory Brainstem
   Soham Chanda and Matthew A. Xu-Friedman
   Department of Biological Science, School of Arts and Sciences, University at Buffalo

   Christopher Czaplicki, Bart Simon, and Elizabeth Hogan.
   Department of Biology, Canisius College

10. Effects of 2,5-dimethoxy-4-methylamphetamine and lysergic acid diethylamide on head twitch response and glutamate levels in medial prefrontal and somatosensory cortices of the rat.
    Casey L. Feeney¹, Ewelina Kotowska¹, David J. Lee², Alexis C. Thompson³, Richard A. Rabin² & Jerrold C. Winter²
    ¹Psychology, ²Pharmacology and Toxicology, & ³Research Institute on Addictions, University at Buffalo

11. Does methamphetamine enhance the value of sensory reinforcers?
Amy M. Gancarz, Jerry B. Richards  
Research Institute on Addictions, University at Buffalo, University at Buffalo

12. DISC1 Regulation of NMDA Receptors in Prefrontal Cortex  
Nick Graziane*, Jing Wei, Zhenglin Gu, and Zhen Yan  
Department of Physiology and Biophysics, State University of New York at Buffalo, School of Medicine and Biomedical Sciences, Buffalo, NY 14214.

13. Gating dynamics of the delta M2 cap in nicotinic acetylcholine receptors  
Shaweta Gupta, Anthony Auerbach  
Biophysics and Physiology, School of Medicine and Biomedical Sciences

14. Prenatal Ethanol Exposure Abolishes Endocannabinoids-Mediated Synaptic Plasticity at Glutamate Synapses of Rat Ventral tegmental area Dopamine Neurons  
Samir Haj-Dahmane; Jue Wang; Roh.-Yu Shen.  
University at Buffalo, Research Institute on Addictions

15. Effect of Amniotic-Fluid Ingestion on Vaginal-Cervical-Stimulation-Induced Fos Expression in Female Rats During Estrus.  
Robert F. Hoey, Seth W. Hurley, Mark B. Kristal, and Derek Daniels.  
Psychology, University at Buffalo

16. A Specific Visual Signaling Mode in Rat Retina  
Caiping Hu, Malcolm Slaughter  
Center for Neuroscience and Department of Physiology & Biophysics; University at Buffalo

17. Energy and structure of the M2 helix in acetylcholine receptor-channel gating  
Snehal Jadey, Archana Jha, Prasad Purohit and Anthony Auerbach  
Department of Physiology & Biophysics, SUNY at Buffalo

18. Dynamics of mono-liganded Acetylcholine receptor channels  
Archana Jha and Anthony Auerbach  
Department of Physiology and Biophysics, University at Buffalo

19. Knockout mutants of annotated GPCRs affect responses to chemoattractants and divalent ions in Tetrahymena.  
Thomas J. Lampert, Casey A. Diederich, Kevin D. Coleman, and Todd M. Hennessey  
Biological Sciences, University at Buffalo

Beth J. Lassman¹, Jennifer Griswold², Federico Gonzalez-Fernandez³, Debasish Ghosh²³  
¹Ross Eye Institute, Ophthalmology, SUNY & V.A. Medical Center, ²Hauptman-Woodward & ³Roswell Park Cancer Institutes

21. Inhibition of Stretch Activated Channels on Endothelial Cells Disrupts Nitric Oxide Mediated Arterial Outward Remodeling  
Nicholas Liaw, Omar Tanweer, Eleni Metaxa, Daniel S. Sternberg, Adnan H. Siddiqui, John Kolega and Hui Meng  
University at Buffalo

22. Cellular and Molecular Changes During Hemodynamic Initiation of Intracranial Aneurysms in a Rabbit Model  
Max Mandelbaum, Ling Gao, J Mocco, Adnan H. Siddiqui, Hui Meng, John Kolega
23. Quantification of cisplatin associated apoptosis genes in rat Hippocampus
Senthivelan Manohar1 and Richard Salvi
1Center for Hearing and Deafness, State University of New York at Buffalo, 137 Cary Hall, 3435 Main Street, Buffalo, NY 14214, USA

24. The anti-dipsogenic effect of ghrelin does not require the neuropeptide Y Y5 receptor
Elizabeth G. Mietlicki and Derek Daniels
Department of Psychology, University at Buffalo

25. Kinetic Mechanism of NMDAR Resistance to Proton Inhibition Conferred by Exon 5
Swetha Murthy and Gabriela Popescu
Biochemistry Department, School of Medicine and Biomedical Sciences

26. The Behavioral and Physiological Response of a Rat to a Predator Scent as a Function of Familiarity
Vincenzo Piraino, Mauricio Suarez, Alexis C. Thompson, and Jean M. DiPirro
1Psychology, 1Buffalo State College; 2Psychology, Univ. at Buffalo; 3Res. Inst. Addictions, Univ. at Buffalo, Buffalo, NY

27. Administration of urocortin I stimulates Fos expression in the paraventricular hypothalamic nucleus and the nucleus of the solitary tract
Kimberly S. Plyler, Naomi J. McKay, and Derek Daniels.
Department of Psychology, University at Buffalo

28. Effects of Chronic Cocaine on Hypothalamic Oxytocin-Like Immunoreactivity and Social Behavior
Adam J. Privitera, Mauricio Suarez, Derek Daniels, and Alexis C. Thompson
1Psychology, 2Res. Inst. Addictions, University at Buffalo

29. Contribution of ryanodine receptors to taste transduction in mouse taste cells.
Michelle Rebello, Kathryn Medler
Biological Sciences, University at Buffalo

30. Decreased TRPV Channel Function Restores Bitter Taste Response to C. elegans grk-2 Mutant Animals
Meredith Scheider, Elizabeth Hong, Angela Chaparro-Garcia and Denise M. Ferkey
Department of Biological Sciences, SUNY at Buffalo, Buffalo, NY

31. Soluble Receptor for Advanced Glycation End Products in Multiple Sclerosis: A Potential Biomarker of Disease Severity
Zohara Sternberg, Bianca Weinstock-Guttman, David Hohnacki, Kailash Chadha, Alicia Lieberman, Latif Kazim, Allison Drake, and Frederick Munschauer
1Department of Neurology, Baird MS center, Jacobs Neurological Institute, Buffalo, NY
2Department of Molecular & Cellular Biology & Department of Polymer Sciences, Roswell Park Cancer Institute, Buffalo, NY

32. Salicylate-Induced Tinnitus: Changes in Inferior Colliculus Tonotopic Map and Correlated Neural Activity
Daniel Stolzberg, Joseph Walton, Adam Dziorny, Richard Salvi
University at Buffalo and University at Rochester
33. The Serine:Glycine Response Ratio Identifies the α1 Glycine Receptor  
John Trimper, Ping Li, Jason Myers, and Malcolm M. Slaughter  
Center for Neuroscience and Department of Physiology & Biophysics, University at Buffalo

34. Ethanol Conditioned Place Preference and Operant Progressive Ratio Performance in Adult Rats after Prenatal and Adolescent Exposure to the Drug.  
Eric M. Truxell, Amy M. Gancarz, and Jerry B. Richards  
Research Institute on Addictions, SUNY Buffalo.

35. Glycogen Synthase Kinase 3 Regulates AMPA Receptor Endocytosis via the GDI-Rab5 Complex in Cortical Neurons  
Jing Wei, Wenhua Liu, Zhen Yan  
Physiology and Biophysics, University at Buffalo, School of Medicine and Biomedical Sciences

36. Effects of estradiol on food intake and meal patterns for diets that differ in flavor and fat content  
Danielle M. Wojcik, Shannon J. Clough, and Peter C. Butera  
Department of Psychology, Niagara University

37. Computational Fluid Dynamics to Assess Intracranial Aneurysm Rupture Status: Do Hemodynamics Separate Ruptured from Unruptured Aneurysm Better than Morphology?  
Jianping Xiang, Sabareesh K. Natarajan, Markus Tremmel, Elad I. Levy, J Mocco, and Hui Meng  
University at Buffalo

38. Target-cell-specific synaptic plasticity occurs cell by cell in the cochlear nucleus  
Hua Yang and Matthew A. Xu-Friedman,  
Biological Sciences, University at Buffalo, SUNY, Buffalo, NY 14260

39. Expression of MT1 Melatonin Receptor Promoter-Driven RFP Protein in BAC Transgenic C3H Mice  
Yahong Zhang1, Hosung Jung2, Jeanie Ramos2, Dongjun Ren2, Richard J. Miller2, Margarita L. Dubocovich1, 2  
1Department of Pharmacology and Toxicology, School of Medicine and Biomedical Science, University at Buffalo, Buffalo, NY; and 2Department Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine, Northwestern University, Chicago, IL

40. Biphasic Action on Internal Calcium by Metabotropic Receptors  
Jaeyoung Yang, Jason Myers, and Malcolm Slaughter  
Center for Neuroscience, Department of Physiology & Biophysics
Poster Abstracts
(listed alphabetically by first author)

1. The Effect of Thimerosal on Intracellular Calcium Dynamics in Neurons
   Catherine C. Alsford, Elizabeth A. Hogan
   Biology Department, Canisius College

   Thimerosal, an ethylmercury based compound, has been used as a preservative in vaccines. Previous research showed thimerosal inhibited neurite growth by inducing microtubule loss from advancing growth cones. We investigated the role of intracellular calcium in mediating thimerosal induced inhibition of neurite growth. To detect changes in intracellular calcium levels, we measured the percent change in fluorescence intensity of Calcium Green in Helisoma neuronal cell bodies exposed to thimerosal. Thimerosal caused a concentration dependent increase in fluorescence intensity, with 10µM showing the highest average percent change in fluorescence and 1µM thimerosal showing the least amount of change. Over the ten minute experimental period, at all concentrations, thimerosal triggered an initial increase in fluorescence within 30sec, followed by a decrease in fluorescence. These results suggest that thimerosal causes a transient increase in intracellular calcium in snail neurons.

2. Diversity of NR1/NR2B Receptor Gating Kinetics
   Stacy Amico-Ruvio, Navjot Kaur and Gabriela K Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

   NMDA receptors are heteromeric glutamate-activated ion channels composed of NR1- and NR2- subunits. Controlled expression of four NR2- isoforms (A – D) results in receptors with distinct gating properties, which contributes to the diversity of excitatory post-synaptic currents. Additionally, the NR1/NR2A isoform can itself respond with distinct kinetics due to modal gating. To investigate whether the NR1/NR2B isoform also gates with modal kinetics, we recorded steady-state single-channel activity in the continuous presence of saturating agonists, from cell-attached patches of HEK293 cells expressing NR1 and NR2B-subunits. Single-channel records (n = 31) revealed a variety of gating patterns illustrated by a 25-fold range in measured equilibrium open probability (P_o): 0.02 – 0.49 (range), 0.20 ± 0.03 (mean ± s.e.m.). This diversity reflected mainly differences in the duration of closures (MCT): 8 – 118 ms (range), 37 ± 6 ms (mean ± s.e.m.); with less spread for mean open durations (MOT): 1.8 – 11.3 ms (range), 5.1 ± 0.4 ms (mean ± s.e.m.). Kinetic analyses revealed that each record had 2 – 4 open and at least 5 closed components in the respective duration distributions. As with NR1/NR2A receptors, in most NR1/NR2B records we observed sporadic changes in gating modality due to sudden changes in MOT, indicative of modal behavior. We identified three gating regimes, each having at least two open time components: a ubiquitous brief component (τ_i = 0.34 ± 0.03 ms) and at least one of three longer components (τ_i = 2.7 ± 0.1 ms; τ_m = 5.8 ± 0.2 ms; τ_f = 13.2 ± 1.4 ms). When analyzed separately, and in contrast to NR1/NR2A channels, NR1/NR2B receptors displayed significant differences in MCTs between modes. Simulations with the deduced reaction mechanisms, including modal behavior, account for the previously observed diversity of macroscopic responses of NR1/NR2B receptors.

3. Characterization of a mutant NMDA receptor less sensitive to voltage-dependent magnesium block
   Stacy Amico-Ruvio, Thomas P. Smith, and Gabriela Popescu
   Biochemistry Department, School of Medicine and Biomedical Sciences

   NMDA receptors are heteromeric glutamate-activated ion channels with postsynaptic locations in the brain. Each receptor is composed of two NR1- and two NR2-subunits, with each subunit containing a large extracellular
amino-terminal domain, an extracellular ligand-binding domain, a pore region and an intracellular carboxy-terminus. NMDA receptors exhibit a voltage-dependent magnesium block (IC50, μM) in the pore. The mutation of a conserved asparagine residue in the NR2A subunit pore to a glycine residue alleviates this magnesium-block at the macroscopic level. To better understand the effects of this pore mutation on channel gating, we further characterized this NR1/NR2A(N+1G) receptor. Single-channel current traces were recorded from cell-attached patches of HEK-cells following transient transfection with NR1, NR2A or NR2A(N596G) and GFP. Kinetic analyses and modeling revealed that the NR1/NR2A(N+1G) receptor had reduced magnesium block at the single-channel level. When compared to the wild-type NR1/NR2A receptor with EDTA, the NR1/NR2A(N+1G) receptor both with and without EDTA demonstrated decreases in open probability, mean open time and durations of open time components, and increases in mean closed time and durations of closed time components. The calculated gating rate constants suggest that the NR1/NR2A(N+1G) receptor transitions slower toward open-pore conformations. Our results suggest that this NR2A(N+1G) perturbation in the receptor pore reduces extracellular magnesium block at the microscopic level and also affects the gating of NR1/NR2A receptors.

Farda Barande and Shermai Gunawardena
Department of Biological Sciences, The State University of New York at Buffalo, Buffalo, NY 14260.

ORMOSIL has emerged as a particularly attractive platform for creating the next generation of nanoparticles for biomedical uses. As a first step in determining if ORMOSIL could be used as a therapeutic delivery system for neurodegenerative diseases such as Alzheimer’s disease, we tested ORMOSIL in a living organism. We asked if ORMOSIL could penetrate into neuronal tissues perhaps via endocytosis and evaluated the affect of ORMOSIL on live neuronal tissues within Drosophila larvae. In this regard we tested three specific issues: 1) The effect of ORMOSIL on axonal transport, 2) the affect of ORMOSIL on inducing neuronal death, and 3) the affect of ORMOSIL on synapses and muscles. We used living Drosophila larvae as our model system. We find that ORMOSIL does penetrate into neuronal cell bodies and into axons. Within cell bodies, ORMOSIL appears to be present within the cytoplasm particularly within the ER. Within the axons ORMOSIL appears as single puncta. Further, ORMOSIL application does not cause aberrant axonal transport problems or neuronal cell death within living larval brains. These results are consistent with our feeding analysis, where feeding of ORMOSIL had no affect on organismal lethality. Taken together our results in living larvae indicate that ORMOSIL has great potential in the development of a potential drug delivery system in living neurons.

5. Processing Speed, Neural Efficiency, and Task Accuracy during Working Memory and Their Relationship with Specific MRI Measures in Patients with MS
Thomas J. Covey, David W. Shucard, Robert Zivadinov, Wing Lee, Michael G. Dwyer, Janet L. Shucard
Dept Neurology, Division of Cognitive and Behavioral Neurosciences, and Buffalo Neuroimaging Analysis Center, University at Buffalo, School of Medicine and Biomedical Sciences

Multiple Sclerosis (MS) has been associated with cognitive dysfunctions that include deficits in working memory (WM) and simple and complex information processing speed (PS). Simple PS refers to the amount of time required to perform undemanding attentional tasks, such as target detection. Complex PS is the amount of time needed to perform more demanding tasks that require mental manipulation, an important component of WM. In the present study, we examined how simple and complex PS relate to quantitative structural brain imaging (MRI). Twenty-seven MS patients and 19 matched controls were studied. A subset of 15 MS patients (12 relapsing-remitting and 3 relapsing-progressive) received MRIs. All participants performed a visual n-back task under three WM load conditions (0-1-and 2-back). As previously reported from our laboratory (Parmenter et al., 2006, 2007), simple PS was defined as reaction time (RT) to the 0-back condition and complex PS as RT to the 1-back and 2-back tasks. The standard deviation of RT for each subject (SDRT), a purported measure of neural noise or neural efficiency, was also assessed. To our knowledge, this behavioral measure has not been used previously to study neural efficiency in MS. Results showed that MS patients had longer RTs for correct matches
(CM, a measure of performance accuracy) in all n-back conditions; however, accuracy and SDRT differed between MS and controls only during the 1-and 2-back conditions. The only significant relationships between n-back accuracy, RT, SDRT and quantitative structural brain imaging occurred for the 2-back condition, the condition with the greatest WM load. These findings indicate that MS patients have deficits in both simple PS and complex PS/WM. Importantly, speed and neural noise measures were associated with MRI white matter deficits; whereas measures of response accuracy were associated with gray matter and more global MRI indices of brain involvement. Although a number of previous studies have shown relationships between cognitive performance and structural MRI, to our knowledge, this is the first study to be able to link specific measures of WM performance with specific quantitative MRI measures in MS.

6. Role of Pore Residues in NMDA Receptor Gating NMDA receptors
Kevin J. Barnum and Gabriela Popescu
Biochemistry Department, School of Medicine and Biomedical Sciences

NMDARs are glutamate-gated ion channels that are critical to brain function. The channel pore constitutes a central element of gating, conferring ionic permeability and specificity, and coupling ligand-binding with ion flow. Because the crystal structure of the NMDAR channel pore is not available, we used its strong sequence homology with the bacterial KcsA channel to formulate hypotheses about the roles of particular residues in gating and permeation. We used single-channel current recordings and kinetic analysis to investigate the role of pore residues W608 and G612 in channel gating. We will use these data to develop hypotheses about the influence of pore residues on gating and permeation.

7. Effects of Cross-Linking the NR1-NR2A Ligand Binding Domain Dimer Interface
William Borschel and Gabriela Popescu
Biochemistry Department, School of Medicine and Biomedical Sciences

NMDA receptors are composed of a dimer of heterodimers of a glycine binding NR1 subunit and a glutamate binding NR2 subunit. The NR1-NR2A ligand binding domains (LBDs) are arranged in a back-to-back fashion with a pseudo two-fold axis between the corresponding subunits. Hydrogen bonds and salt bridges form three distinct interaction sites between both the top and bottom lobes of the LBDs of each subunit. Previous work with other GluRs has suggested that LBD dimer interface contacts play a critical role in receptor desensitization. Cysteine mutations at N521 and L777 of NR1 and E516 and L780 of NR2A produce disulfide bonds that cross-link the LBDs. Single channel recordings from LBD cross-linked mutants displayed significantly shorter open and longer close durations (means, s.d.): Po = 0.0032 ± 0.0006, MOT = 1.8 ± 0.2 ms, MCT = 792 ± 213 ms (n = 6; 80,028 events). Kinetic analyses reveal significant alterations in the receptor gating mechanism but no difference in desensitization rates. Reduction of the disulfide bond by the addition of 10 mM DTT to the recording solution significantly potentiated single channel properties (means, s.d.): Po = 0.14 ± 0.02, MOT = 11.7 ± 1.6 ms, MCT = 90 ± 19 ms (n = 7; 262,396 events). Macroscopic recordings from LBD cross-linked mutants with and without 10 mM DTT demonstrated similar trends in receptor gating as predicted by the single channel kinetics. These results suggest a novel role for the LBD dimer interface in NMDA receptor gating.

8. A Low-affinity Antagonist Reveals Saturation and Desensitization in Mature Synapses in the Auditory Brainstem
Soham Chanda and Matthew A. Xu-Friedman
Department of Biological Science, School of Arts and Sciences, University at Buffalo

Postsynaptic receptor desensitization has been observed to contribute to depression in immature synapses. However, it is not clear whether desensitization persists and causes depression in mature synapses. We investigate this issue at the endbulb of Held, where depression influences the processing of sound information. Experiments using cyclothiazide (CTZ) have implicated desensitization in endbulbs from P16–21 mice, but application of d-glutamylglycine (DGG) did not reveal desensitization in endbulbs >P22. To reconcile these
findings, we have studied the effects of both CTZ and DGG on endbulbs from P16–40 CBA/CaJ mice. In paired-pulse protocols, both CTZ and DGG reduced depression in all ages at intervals <10 ms, consistent with their effects preventing desensitization. However, DGG increased depression at intervals >20 ms, consistent with DGG’s use to prevent saturation. DGG application revealed receptor saturation even under conditions of very low release probability. Preventing desensitization by CTZ occludes the effects of DGG on desensitization and reveals the effects of saturation at short intervals. We developed an approach to separate DGG’s effect on saturation from its effect on desensitization, which reveals that desensitization has an impact during bursts of auditory nerve activity, and is likely to affect sound processing in the mature auditory system.


Christopher Czaplicki, Bart Simon, and Elizabeth Hogan.
Department of Biology, Canisius College

We have previously shown that resveratrol, a polyphenol phytoalexin, promotes neurite outgrowth by increasing the rate of growth cone advancement. Since resveratrol enhances SIRT2 mediated tubulin deacetylation, we hypothesized that resveratrol stimulates neurite outgrowth by its effect on microtubule assembly in growth cones. Using immunofluorescent microscopy, we examined the effect of resveratrol on growth cone microtubules by comparing the relative area of the growth cone occupied by microtubules (area of microtubule in growth cone/area of growth cone) in neurons treated with 100 µM resveratrol to untreated neurons. Resveratrol treatment resulted in a two fold increase in the area of the growth cone occupied by microtubules. Since dynamic microtubules in growth cones extend into the peripheral domain, we compared the relative distribution of microtubule ends in the peripheral domain of resveratrol treated growth cones to untreated growth cones. Resveratrol treatment decreased the relative distance of microtubules from the edge of the growth cone. These results suggest that reserveratrol treatment enhances microtubule assembly and dynamics in growth cones.

10. Effects of 2,5-dimethoxy-4-methylamphetamine and lysergic acid diethylamide on head twitch response and glutamate levels in medial prefrontal and somatosensory cortices of the rat.

Casey L. Feeney1, Ewelina Kotowska1, David J. Lee2, Alexis C. Thompson3, Richard A. Rabin2 & Jerrold C. Winter2

Psychology, 2Pharmacology and Toxicology, & 3Research Institute on Addictions, University at Buffalo

Hallucinogenic compounds such as lysergic acid diethylamide (LSD) and 2,5-dimethoxy-4-methylamphetamine (DOM) induce a head twitch response in rats through a 5-HT2A receptor-mediated mechanism that includes the induction of cortical glutamate release to induce the final behavioral response. The cortical area(s) at which the neurochemical interaction between 5HT2A receptors and glutamate may occur during hallucinogen - induced head twitch is unknown. The present study was designed to measure the effect of DOM and LSD on head twitch and, at the same time, glutamate release in the medial prefrontal cortex (mPFC) and somatosensory cortex (SSc). Microdialysis probes were implanted into the mPFC (n=9) and SSc (n=9) of male rats and glutamate levels (30-min samples) from the extracellular space were obtained for 1 h before and 2 h after a systemic injection of DOM (0.6 mg/kg, IP), or vehicle, and then 1 h before and 1.5 h after a systemic injection of LSD (0.1 mg/kg, IP), or vehicle. The frequency of head twitch response was measured during the last 5 min of each 30-min sample collection period. Significant increases in head twitch were observed within 30 min of DOM administration. LSD, in rats that had previously received vehicle, also induced an increase in the frequency of head twitch response. LSD in rats that had previously received DOM, however, did not show an increase head twitch response. Results correlating changes in glutamate in mPFC and SSc with head twitch response after DOM and LSD treatment will be presented at the meeting.
11. Does methamphetamine enhance the value of sensory reinforcers?
Amy M. Gancarz, Jerry B. Richards
Research Institute on Addictions, University at Buffalo, University at Buffalo

Previous research suggests the stimulants have the ability to enhance operant responding for sensory reinforcers. In our laboratory, we have found that methamphetamine (METH) enhances preference for novel sensory reinforcers (visual stimuli, VS) more than for familiar VS. Here, we tested the hypothesis that co-occurrence of the novel VS with the hedonic effects of METH resulted in a conditioned association of the VS with METH via classical conditioning. Formation of this association is more likely when the VS is novel than when it is familiar, thus rats receiving METH injections in association with a novel VS may have an enhanced preference when compared to controls. Groups of rats that had the VS paired with Meth (Paired) were compared to groups of rats that experienced the VS in the absence of Meth (Unpaired). The results indicated that the rats did not learn to associate the VS with the hedonic effects of METH. However, both Paired and Unpaired groups exhibited an enhanced total responding compared to SAL on the test day. The increase in total responding in the absence of an increase in preference for the Active alternative on the test day indicates that an association was made between the response activating effects of METH and the VS. Taken together, these results indicate that there is a dissociation between the hedonic and activating effects of methamphetamine on responding for a visual reinforcer.

12. DISC1 Regulation of NMDA Receptors in Prefrontal Cortex
Nick Graziane*, Jing Wei, Zhenglin Gu, and Zhen Yan
Department of Physiology and Biophysics, State University of New York at Buffalo, School of Medicine and Biomedical Sciences, Buffalo, NY 14214.

Recent genetic studies have identified DISC1 (Disrupted-in-Schizophrenia-1) as one of most prominent risk factors for schizophrenia (SZ), however it remains unclear how the aberrant DISC1 function leads to the pathogenesis of neuropsychiatric disorders. Despite some progress on understanding the significance of DISC1 at cortical development, little is known about how DISC1 regulates synaptic function in cortical neurons. Since NMDA receptor hypofunction has been strongly linked to the pathophysiology of schizophrenia, one potential target of DISC1 that is critically involved in the regulation of cognition and emotion is the NMDA receptor. We found that cellular knockdown of DISC1 significantly increased NMDAR-mediated ionic currents, while overexpression of the C-terminal-truncated DISC1, a SZ-related mutant, significantly decreased NMDAR currents in pyramidal neurons of prefrontal cortex. These effects were accompanied by DISC1-induced changes in surface and total NMDAR subunit expression. Our results suggest that DISC1 exerts an important impact on NMDAR-mediated synaptic transmission and plasticity in the cortex. Knowledge gained from this study would shed light on how DISC1 and the NMDA system are mechanistically linked and how their interactions are critical for maintaining a normal mental state.

13. Gating dynamics of the delta M2 cap in nicotinic acetylcholine receptors
Shaweta Gupta, Anthony Auerbach
Biophysics and Physiology, School of Medicine and Biomedical Sciences

Nicotinic acetylcholine receptors mediate fast synaptic transmission at the vertebrate neuromuscular junction. These receptors alternate between (C)losed -nonconducting and (O)pen- conducting conformations. Many different residues in this large, heteropentameric membrane protein have been shown to contribute to the free energy difference between C and O structures. Using phi value analysis, we have measured the relative timing of the 'gating' movements for residues in the pore-lining M2 helix of the delta subunit. We used cell attached, single-channel analysis to quantify the effects of mutations (mouse oβ2HEK 293 cells, +70mV pipette, 22°C, activated by 20mM choline or 500uM ACh). The side chain substitutions I274 (F), S275 (D, F), K276 (Y), R277 (Y, A) and P279 (K) changed the diliganded gating equilibrium constant (E2) by >10 fold whereas other mutations had little or no effect. The substantial changes in E2 arose from changes both in channel
opening and closing rate constants. Analyses show that the δM2 C-terminal ‘cap’ moves with a phi of 0.30, suggesting that this domain moves relatively late during the gating pathway. This result suggests that the main sequence of motions for the cap region in different subunits is $\alpha >\phi >\delta$, with residues that are approximately at the same latitude having different phi values and perhaps moving at different times in the gating reaction.

14. Prenatal Ethanol Exposure Abolishes Endocannabinoids-Mediated Synaptic Plasticity at Glutamate Synapses of Rat Ventral tegmental area Dopamine Neurons

Samir Haj-Dahmane; Jue Wang; Roh.-Yu Shen.
University at Buffalo, Research Institute on Addictions

Prenatal ethanol exposure has been shown to induce long-lasting behavioral changes. One of the behavioral changes is increased risk of addiction. It is known that dopamine (DA) neurons in the ventral tegmental area (VTA) play an important role in mediating reward signals and addiction. Specifically, increased glutamatergic synaptic strength in VTA DA neurons is associated with increased sensitivity to the rewarding properties of drugs and risk of addiction. In the present study, we examined the possibility that glutamatergic synaptic strength in VTA DA neurons was indeed increased after prenatal ethanol exposure.

Using the brain slice preparation obtained from 3-6-week-old rats, we observed that prenatal ethanol exposure (6 g/kg ethanol per day via intragastric intubation; GD8-20) profoundly increased the rectification of AMPA receptor-mediated synaptic currents (AMPA EPSCs), indicating an increase in synaptic AMPA receptors lacking the GluR2 subunit. In addition to this change, we found that prenatal ethanol exposure abolished the long-term depression (LTD) of glutamate-mediated EPSC induced by pairing low frequency presynaptic stimulation with postsynaptic depolarization (-30 mV). Further examination revealed that the LTD was mediated by a decrease in glutamate release caused by reduced retrograde endocannabinoid messengers. These findings indicate that prenatal ethanol exposure inhibits endocannabinoid signaling in VTA DA neurons, which represents a novel mechanism by which prenatal ethanol exposure can alter synaptic plasticity in the VTA.

Taken together, prenatal ethanol exposure leads to a persistent increase in the glutamatergic synaptic strength in VTA DA neurons by both pre- and postsynaptic mechanisms. Increased synaptic strength in VTA DA neurons has been associated with increased sensitivity to the rewarding properties of drugs of abuse and therefore could contribute to increased risk of addiction in individuals with fetal alcohol spectrum disorders.

15. Effect of Amniotic-Fluid Ingestion on Vaginal-Cervical-Stimulation-Induced Fos Expression in Female Rats During Estrus.

Robert F. Hoey, Seth W. Hurley, Mark B. Kristal, and Derek Daniels.
Psychology, University at Buffalo

Placental Opioid Enhancing Factor (POEF) is a substance found in amniotic fluid (AF) that, when ingested, potentiates opioid mediated, but not non-opioid mediated, hypoalgesia. Vaginal-cervical stimulation (VCS) produces a stimulus-bound, opioid-mediated hypoalgesia that previous research has shown to be potentiated by AF ingestion. This vaginal-cervical stimulation induces hypoalgesia during late pregnancy and parturition and ingestion of POEF in afterbirth enhances the effect. To further understand the mechanism of opioid enhancement by POEF ingestion we investigated the pattern of neural activation that is produced by a bout of VCS known to produce hypoalgesia, with or without co-administration of AF. Specifically, virgin Long-Evans rats in estrus were briefly handled (control) or received VCS (75g pressure for 1 min) using a spring-loaded glass syringe with a glass-rod probe. Rats were also given an orogastric infusion of either 0.25ml AF or 0.9% saline to produce four treatment groups (VCS or handling; AF infusion or saline). Rats were subsequently perfused transcardially and brain sections were processed by immunohistochemistry for Fos. The number of Fos-immunoreactive cells was counted in structures previously shown to express Fos in response to VCS (MPOA, PAG, NTS, Medial Amygdala, VMH). Data collection is ongoing but initial results indicate that our VCS procedure is subthreshold for stimulation of Fos expression in the MPOA, unless it is paired with AF ingestion. This result indicates that AF ingestion potentiates VCS effects in the CNS, as measured by Fos expression.
16. A Specific Visual Signaling Mode in Rat Retina  
Caiping Hu, Malcolm Slaughter  
Center for Neuroscience and Department of Physiology & Biophysics; University at Buffalo

The retina senses the external environment and encodes the specific attributes of scenes through parallel pathways that are transmitted to higher brain centers. Much of the coding in retina occurs at the synapse between bipolar cells and ganglion cells. We identified a specific signaling mode used by select subsets of these synapses. This mode uses low-voltage-gated Ca²⁺ (T-type) channels in bipolar cells and ganglion cells. These pathways were revealed physiologically and morphologically using patch clamp and confocal imaging techniques. Two subtypes of T-type channels (α1G, α1H) dominate in different bipolar cells and ganglion cells. The bipolar cells’ terminals and ganglions’ dendrites that use the α1G channels mediate ON responses while other bipolar and ganglion cells possess the α1H channels and carry OFF signals. In addition, one type of intrinsically light sensitive ganglion cell (Ip RGC), the bistratified Ip RGC, belongs to this signaling mode. Our findings show discrete but complementary parallel signaling pathways from bipolar to ganglion cells in rat retina. For visual function, the T-type calcium channel seems to be involved in high sensitivity signaling. This includes the rod pathway, involved in the detection of dim light stimuli, and a subset of the cone pathway.

17. Energy and structure of the M2 helix in acetylcholine receptor-channel gating  
Snehal Jaday, Archana Jha, Prasad Purohit and Anthony Auerbach  
Department of Physiology & Biophysics, SUNY at Buffalo

One M2 helix from each of the five acetylcholine receptor (AChR) subunit forms the narrow region of the ion conduction pathway. As part of an overall project of trying to understand the mechanism of the C(llosed)↔O(pen) conformational change (‘gating’) in this protein, we studied single-channel currents from AChRs having a point mutation in the β or e subunit (mouse, α2bde). Two parameters were quantified: 1) the diliganded gating equilibrium constant (E₂), which reflects the energy difference between C and O conformations and 2) the correlation between the forward, opening rate constant (f₂) and E₂ on a log-log scale (Φ), which illuminates the energy character of the residue (C- vs. O-like) at the transition state of the C↔O isomerization. Residues 2’ to 26’ in eM2 were scanned (140 mutants), and the largest E₂ changes were observed in the cytoplasmic half of the helix (5’, 9’, 12’, 13’ and 16’). Four residues in bM2 were scanned (20 mutants). 9’, 12’, 13, and 16’, all in the cytoplasmic half, showed substantial E₂ changes. Φ was ~0.54 for most eM2 residues and for 16’ of bM2, and was ~0.31 at positions (9’, 12’, and 13’ of both e and b) that had the largest E₂ changes. The measurements suggest that the 9’, 12’ and 13’ residues experience large and late free energy changes in the channel-opening process. We speculate that in the gating isomerization, the pore-facing residues >6’ and <16’ experience multiple energy perturbations associated with changes in protein structure and hydration.

18. Dynamics of mono-ligated Acetylcholine receptor channels  
Archana Jha and Anthony Auerbach  
Department of Physiology and Biophysics, University at Buffalo

The acetylcholine receptor-channel (AChR) has five subunits and two transmitter binding sites. In neuromuscular AChRs, large ligands such as curare and conotoxins, have distinct closed-channel affinities (Kₒ) for the αδ and αε sites. However, single-channel measurements of Kₒ for small ligands such as ACh are unclear as to whether the sites have equal or different values. We measured Kₒ in AChRs that have only one site able to be occupied by an agonist molecule, by using the following approach. The transmitter binding site residue W149 in the α-subunit was mutated to M in one subunit, to block agonist binding. Rate constants for ACh binding (to the native site) and channel gating were estimated by using single-channel kinetic analyses. Application of 500μM ACh to a double-mutant construct failed to activate, indicating a complete loss of binding at both binding sites. However, un-ligated gating kinetics for this mutant remains wildtype. With one native binding site (AChRs with W149+M149) elicits only one population of mono-ligated currents. The mono-ligated gating equilibrium constant (4.3x10⁻³) was, energetically, approximately half way between the equilibrium constants for un-
liganded and di-liganded gating. The results indicate that the two transmitter binding sites have approximately the same affinity for ACh (~140 μM), and that the Monod-Wyman-Changeux (MWC) formalism for allosteric proteins is a good model for AChRs.

19. Knockout mutants of annotated GPCRs affect responses to chemoattractants and divalent ions in *Tetrahymena*.

*Thomas J. Lamport, Casey A. Diederich, Kevin D. Coleman, and Todd M. Hennessey*

*Biological Sciences, University at Buffalo*

*Tetrahymena* are free-swimming eukaryotic unicells that change their swimming behavior in response to many types of stimuli to direct them away from dangerous areas and towards preferred areas, such as food sources. Some of the cellular receptors and pathways involved may be sufficiently conserved to allow the use of *Tetrahymena* as a simple and humane model system for chemosensory transduction studies in these “free swimming sensory cells”. In general, chemoattractants cause somatic hyperpolarization, faster forward swimming and more linear swim paths while chemorepellents cause depolarizations, slower forward swim speeds and action potentials at threshold concentrations to cause bouts of backward swimming. We have found 2 putative GPCR (G-protein coupled receptor) sequences in the *Tetrahymena* Genome Database and used them to generate knockout mutants by homologous recombination. One mutant, G6, shows a constitutive decrease in Ni++ sensitivity, as assayed by Ni+++ immobilization. The other mutant, G6, shows a constitutive decrease in Ba++ sensitivity but normal responses to Ni++, suggesting different constitutive effects on divergent ion permeabilities. The resting membrane potentials (Vm) are not altered in either mutant, suggesting that these permeabilities do not contribute significantly to Vm. The G6 mutant is also unable to respond to chemoattractants such as lysophosphatidic acid (LPA), suggesting that this GPCR may be a chemosensory receptor. The G6 mutant can be phenocopied by either pertussis toxin or calphostin C, suggesting a G-protein and protein kinase C involvement in this chemoresponse. This same G-protein may modulate basal divergent ion conductances, producing the constitutive defects in Ba++ permeability.


*Beth J. Lassman*, *Jennifer Griswold*, *Federico Gonzalez-Fernandez*, *Debashis Ghosh*  

1Ross Eye Institute, Ophthalmology, SUNY & V.A. Medical Center, 2Hauptman-Woodward & 3Roswell Park Cancer Institutes

Interphotoreceptor retinoid-binding protein (IRBP) shuttles retinoids in the visual cycle and is implicated in preserving the oxidative state of retinol. The mechanism of IRBP’s protective oxidative function is unknown. Molar excesses of dithiothreitol (DTT), a thiol-based reducing agent are required to purify bovine IRBP (bIRBP) in a soluble, stable and active form. Free thiols in IRBP could serve to protect all-trans retinol from oxidation. We test the hypothesis that bIRBP has free thiol-based antioxidative property. Antioxidant activity is assayed using the absorbance of the free radical ABTS++ (2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)). ABTS++ absorbance at 750nm decreases with increasing radical-scavenging activity of bIRBP. bIRBP’s ability to scavenge free radicals is compared to thioredoxin, a thiol-based antioxidant, in the presence and absence of N-ethylmaleimide (NEM). NEM covalently modifies free, accessible thiols. Mass spectroscopy is used to identify covalent modification of thiols. bIRBP demonstrates a concentration-dependent antioxidant activity. The activity is greater than that of thioredoxin. When incubated with the thiol-alkylating agent NEM, bIRBP is 10% less active in reducing ABTS++ compared to the unmodified bIRBP(p <0.007). Covalent modification by NEM is confirmed by mass This study reveals that the antioxidant activity of bIRBP is partially thiol-dependent. The activity is impaired by the thiol-alkylating agent NEM that modifies 3 Cys residues possibly involved in the reduction process. Elucidation of relative locations of these residues with respect to the retinol-binding site will be crucial in ascertaining the biochemical and physiological relevance of the antioxidative roles of IRBPs.
21. Inhibition of Stretch Activated Channels on Endothelial Cells Disrupts Nitric Oxide Mediated Arterial Outward Remodeling

Nicholas Liaw, Omar Tanweer, Eleni Metaxa, Daniel S. Sternberg, Adnan H. Siddiqui, John Kolega and Hui Meng
University at Buffalo

Arteries undergo outward remodeling to accommodate chronically elevated flow in a process that depends on endothelial cells (ECs) and endothelial nitric oxide synthase (eNOS). The mechanism by which ECs sense elevated flow is unknown, but it has been proposed that stretch-activated channels (SACs) act as mechanosensors for blood flow. Experiments were performed to evaluate the role of SACs in regulating flow-induced arterial expansion and flow-induced NO production by ECs.

Flow in the right common carotid arteries (CCAs) of mice was elevated by ligating the contralateral CCA, and arterial expansion was assessed 7 days after surgery by measuring CCA dimensions on histological sections. 7 mice were treated with streptomycin to inhibit SACs, while 8 received placebo. Expansion of the CCA in streptomycin-treated mice was significantly less than in placebo-treated controls (p= 0.015). Cultured bovine aortic ECs were exposed to flow with wall shear stress (WSS) of 15-100dynes/cm² for 24 hours in the presence or absence of streptomycin. Endothelial nitric oxide synthase (eNOS) under different WSS was quantified by immunofluorescent staining. Streptomycin treatment had no effect on eNOS expression in ECs in static culture or under baseline WSS (15-25dynes/cm²), but significantly inhibited eNOS expression at WSS above 25dynes/cm² (p=0.001). **Conclusions:** Inhibition of SACs impairs flow-induced outward remodeling of CCAs in mice and flow-induced eNOS expression in cultured ECs. Activation of SACs in response to chronically elevated WSS may contribute to flow-induced vessel expansion in vivo by stimulating eNOS expression in ECs.

22. Cellular and Molecular Changes During Hemodynamic Initiation of Intracranial Aneurysms in a Rabbit Model

Max Mandelbaum, Ling Gao, J Mocco, Adnan H. Siddiqui, Hui Meng, John Kolega
University at Buffalo

Hemodynamics constitute a critical factor in the formation of intracranial aneurysms (IAs). However, little is known of the molecular response to aneurysm-initiating hemodynamic insult and how that response contributes to aneurysmal morphological changes. We studied early cellular and molecular responses at the rabbit basilar terminus (BT) to local hemodynamic alteration induced by bilateral carotid ligation. Within 2 days and 5 days of hemodynamic insult, internal elastic lamina (IEL) was degraded in the peri-apical region that experienced high wall shear stress (WSS) and high positive WSS gradient (WSSG), albeit with a continuous intact overlying endothelial layer indicated by PECAM-1 staining. The prominent IEL loss was associated with localized apoptosis and elevated expression of matrix metalloproteinase (MMP)-2 and -9. Although a small number of inflammatory cells were scattered through the bifurcation adventitia, no spatial correlation with IEL loss and MMP elevation existed. This suggests that the high WSS/high positive WSSG hemodynamic condition triggers degenerative changes manifested by apoptosis and increased expression of MMPs in non-inflammatory cells already present in the media and intima. This destructive response to a specific hemodynamic stimulus may explain how hemodynamic alterations contribute to aneurysm-initiating morphological changes, and potentially implicates a non-inflammatory mediated process.

23. Quantification of cisplatin associated apoptosis genes in rat Hippocampus

Senthivelan Manohar¹ and Richard Salvi

¹Center for Hearing and Deafness, State University of New York at Buffalo, 137 Cary Hall, 3435 Main Street, Buffalo, NY 14214, USA

Cisplatin is a well known anticancer drug that exerts antitumor effects by forming covalent adducts between the platinum and DNA bases of rapidly dividing tumor cells. As results of DNA adduct formation, DNA repair mechanisms and cell replications are blocked thereby inducing apoptosis in tumor cells as well as some normal
cells. The hippocampus contains a population of rapidly dividing stem cells that differentiate into neurons and glial cells making them particular susceptible to the toxic effects of cisplatin. To determine if cisplatin induced cell death in the hippocampus, we treated rats with 12 mg/kg of cisplatin and harvested the mRNA from the hippocampus and used qRTPCR to quantify the changes in gene expression in 84 apoptosis related genes. At 2 days post-treatment, expression changes were noted in 25 genes; 5 pro-apoptotic genes (Bik, Bid and Bok, Trp53bp2 and card6) were significantly up-regulated (p < 0.05) and 1 anti-apoptotic gene (Bcl2) was significantly down regulated (p<0.05). At 7 days post-treatment, only a few changes were detected. One pro-apoptotic genes (Bik) was significantly upregulated and three pro-apoptotic genes (Casp8, Tnfrsf10b and Tnfrsf5) were significantly (p<0.05) down regulated. These results show that cisplatin can induce a strong apoptotic response in the hippocampus.

24. The anti-dipsogenic effect of ghrelin does not require the neuropeptide Y Y5 receptor

Elizabeth G. Mietlicki and Derek Daniels
Department of Psychology, University at Buffalo

Ghrelin attenuates angiotensin II (AngII)-induced water intake, but almost nothing is known about how or where in the brain this effect is mediated. In contrast, much is known about the effect of ghrelin on food intake, including its mediation of hyperphagia through neuropeptide Y (NPY). Because the hyperphagic effects of ghrelin depend on the NPY Y5 and Y1 receptors, we tested if the attenuation of fluid intake by ghrelin also requires Y5. To this end, we pretreated rats with a Y5 receptor antagonist or vehicle before injection of ghrelin or vehicle and AngII. Subsequent food and water intakes were measured. Consistent with our previous findings, ghrelin-treated rats drank less in response to AngII than vehicle-treated controls. These studies, however, found no support for the hypothesis that Y5 is required for the anti-dipsogenic effect of ghrelin. A pilot study using a Y1 receptor antagonist also failed to find evidence for a role of the Y1 receptor in the anti-dipsogenic effect of ghrelin. Nevertheless, our studies provide the first documented suggestion that the Y1 and Y5 receptors play a role in AngII-induced drinking. Specifically, pretreatment with either the Y1 or Y5 receptor antagonist decreased water intake in response to AngII. Further studies are needed to clarify the potential role of other NPY receptors in the anti-dipsogenic effects of ghrelin, as well as to investigate the possible role for NPY receptors in the mediation of AngII-induced water intake.

25. Kinetic Mechanism of NMDAR Resistance to Proton Inhibition Conferred by Exon 5

Swetha Murthy and Gabriela Popescu

Biochemistry Department, School of Medicine and Biomedical Sciences

NMDA receptors are glutamate-activated ion-channels that mediate fast excitatory transmission, synaptic plasticity and excitotoxicity. They assemble as hetero-tetramers of two NR1 and two NR2 subunits. Multiple isoforms with distinct kinetic, pharmacologic and physiologic roles are selectively expressed during development and in various regions of the central nervous system. Differential splicing of the NR1 transcript results in NMDA receptor isoforms with distinct sensitivities to proton inhibition, which may contribute to region-specific vulnerabilities to glutamate toxicity.

To determine how differential splicing of exon 5 affects channel gating and inhibition by protons we recorded single-channel currents from cell-attached patches of HEK 293 cells transfected with NR1-1a (which lacks exon 5) or NR1-1b (which incorporate exon 5) and NR2A, in the presence of saturating concentrations of glutamate and glycine, and proton concentrations in the range pH 6.5 to 8.5.

Based on kinetic analyses of single-channel currents recorded from one-channel patches, we found that exon 5 had no effect on stationary gating, as both isoforms had similar open probabilities (Po), mean open durations (MOT) and mean closed durations (MCT) at pH 8.0. However, increasing proton concentration to pH 6.5 decreased the Po of NR1-1a/2A receptors from 0.47 ± 0.05 (n = 6) to 0.09 ± 0.04 (n = 6), whereas the Po of NR1-1b/2A receptors decreased from 0.46 ± 0.03 (n = 5) to 0.2 ± 0.05 (n = 9). We traced this 2-fold smaller reduction
in P₀ at pH 6.5 for receptors containing exon 5 to both a 2-fold smaller decrease in MOT and a 2-fold smaller increase in MCT. Therefore we show that exon 5 had no effect on NMDA receptor gating and did not abolish its sensitivity to protons but reduced this sensitivity by a mechanism affecting the durations of both open and closed intervals. A more detailed picture of how protons affect NMDA receptor functions will help better understand how changes in extracellular pH regulate synaptic transmission, plasticity and neuroprotection.

26. The Behavioral and Physiological Response of a Rat to a Predator Scent as a Function of Familiarity

Vincenzo Piraino¹, Mauricio Suarez², Alexis C. Thompson³, and Jean M. DiPirro⁴

¹Psychology, ²Buffalo State College; ³Psychology, Univ. at Buffalo; ⁴Res. Inst. Addictions, Univ. at Buffalo, Buffalo, NY

The purpose of this study was to investigate the relationship between the defensive response of a rat to a predator stimulus (cat scent) and the location of stimulus exposure. The goal was to determine if a predator stimulus is experienced as more threatening in a familiar, traditionally “safe” environment or in a less familiar environment. A previous study in our laboratory found that a rat’s defensive response to a predator stimulus was greater in magnitude when the stimulus was presented in the rat’s home cage versus a less familiar open field apparatus. However, in that study, the home cage differed in size from the open field apparatus, and therefore, it was unclear whether this finding could be attributed to the difference in the familiarity of the exposure location or to the size of the apparatus. The present study was designed to clarify this relationship. Rats were exposed to cat scent or its control either in their home cage or in an open field apparatus of the same size and shape as the home cage and their defensive response and blood glucose response to the stimuli were measured. Cat scent produced greater increases in defensive withdrawal behavior and blood glucose levels in the open field apparatus than the home cage. These results suggest that familiarity and physical features, such as cage size, are both important for determining the magnitude and type of defensive response to a predator stimulus.

27. Administration of urocortin I stimulates Fos expression in the paraventricular hypothalamic nucleus and the nucleus of the solitary tract

Kimberly S. Plyler, Naomi J. McKay, and Derek Daniels.

Department of Psychology, University at Buffalo

Central application of urocortin I (UcnI), a member of the corticotropin-releasing factor family, decreases food intake and increases plasma glucose. UcnI activates forebrain and hindbrain structures, including the paraventricular hypothalamic nucleus (PVN), amygdala, lateral septal nucleus, nucleus of the solitary tract (NTS), and parabrachial nucleus. Whether these areas are activated directly by UcnI or indirectly through mediating pathways remains an open question. Earlier studies found that a fourth ventricle (4V) injection of UcnI activated neurons in both forebrain and hindbrain structures. Even though the UcnI injection was made into the hindbrain, disrupting ascending pathways at the level of the midbrain blocked the response in both forebrain and hindbrain structures. In order to further explore the connectivity of areas activated by UcnI, we needed to first identify the threshold dose for UcnI-induced Fos after hindbrain or forebrain ventricle administration. Initial studies indicate that Fos expression was elevated in both the PVN and NTS regardless of whether UcnI was injected into the LV or 4V. The number of Fos-positive cells in the PVN, however, was significantly greater when UcnI was injected into the LV than when injected into the 4V. In contrast, there was more Fos expression in select levels of the NTS after 4V UcnI than after LV UcnI. These findings represent an important first step toward our goal of understanding the connectivity in the UcnI-responsive network.
28. Effects of Chronic Cocaine on Hypothalamic Oxytocin-Like Immunoreactivity and Social Behavior
Adam J. Privitera1, Mauricio Suarez2, Derek Daniels1, and Alexis C. Thompson2
1Psychology, 2Res. Inst. Addictions, University at Buffalo

Oxytocin (OXY), a neurohypophyseal neuropeptide with central and peripheral effects, has been implicated in behavioral processes from social behavior to drug addiction. The psychostimulant cocaine, a popular drug of abuse, has been shown to decrease hypothalamic OXY content after chronic exposure. Whether or not this observed decrease in OXY content is accompanied by a change in social behavior has yet to be evaluated. Male Long-Evans rats were injected with cocaine or saline once a day for 21 days (R group), or 3 times a day for 7 days (X group) and then evaluated in a modified social interaction (mSI) test in a drug dependent or withdrawal state. Brains were then harvested for OXY immunohistochemistry after transcardial perfusion. Chronic cocaine had no effect on social behavior as measured by social contact. Analysis of OXY-like immunoreactivity and additional behavioral measures are currently being conducted and will be presented at the meeting.

29. Contribution of ryanodine receptors to taste transduction in mouse taste cells.
Michelle Rebello, Kathryn Medler
Biological Sciences, University at Buffalo

Taste buds are sensory end organs that detect chemical substances occurring in foodstuffs and relay the relative information to the brain. Taste stimuli activate distinct signaling pathways in taste receptor cells present in these taste buds. Bitter, umami and sweet taste stimuli (complex stimuli) are detected via G-protein coupled receptors (GPCRs) that cause calcium release from intracellular stores, while salty and sour stimuli depolarize taste cells to cause calcium influx through voltage-gated calcium channels. While it is well established that complex taste stimuli activate GPCRs to evoke inositol 1,4,5-trisphosphate (IP3)-mediated release of intracellular Ca2+, we investigated the contribution of the previously ignored ryanodine receptors to this process. RT-PCR analysis of mRNA isolated from taste buds revealed the expression of ryanodine receptors in the circumvallate and foliate taste buds. Immunocytochemical analysis revealed the co-localization of ryanodine receptors and IP3 receptors in taste cells, indicating that multiple signaling pathways may be contributing to the formation of stimulus evoked taste signals. Our initial physiological studies indicate that even though ryanodine receptors are extensively expressed in taste cells, these receptors contribute to the formation of bitter evoked taste responses but not to umami or sweet responses. This indicates that there is a selective contribution of ryanodine receptors to the transduction of taste stimuli.

30. Decreased TRPV Channel Function Restores Bitter Taste Response to C. elegans grk-2 Mutant Animals
Meredith Scheider, Elizabeth Hong, Angela Chaparro-Garcia and Denise M. Ferkey
Department of Biological Sciences, SUNY at Buffalo, Buffalo, NY

Since C. elegans use chemical cues to navigate their environment, signaling through chemosensory G protein-coupled receptors (GPCRs) must be tightly regulated. One mode of regulation is via G protein-coupled receptor kinases (GRKs), which phosphorylate activated GPCRs to terminate signaling. Despite the previously described role of GRKs in GPCR signal downregulation, C. elegans lacking GRK-2 function are not hypersensitive to odorants. Instead loss of GRK-2 broadly disrupts chemosensation and animals are unresponsive to a number of chemical stimuli detected by the ASH, AWA and AWC sensory neurons.

We find that loss-of-function mutations in the transient receptor potential vanilloid (TRPV) channels OSM-9 and OCR-2 selectively restore grk-2 behavioral avoidance of bitter tastants., revealing modality-specific mechanisms for TRPV channel function in the regulation of C. elegans chemosensation. We find that TRPV channel function in sensory neurons contributes specifically to the inability of grk-2 animals to respond appropriately to bitter stimuli. Additionally, a single amino acid point mutation in OCR-2 that disrupts TRPV channel-mediated gene expression, but does not decrease channel function in chemosensory primary signal transduction, also restores grk-2 bitter taste avoidance. Thus, loss of GRK-2 function may lead to changes in gene expression, via OSM-
31. Soluble Receptor for Advanced Glycation End Products in Multiple Sclerosis: A Potential Biomarker of Disease Severity

Zohara Sternberg¹, Bianca Weinstock-Guttman¹, David Hojnacki¹, Kailash Chadha², Alicia Lieberman², Latif Kazim³, Allison Drake³, and Frederick Munschauer³
¹Department of Neurology, Baird MS center, Jacobs Neurological Institute, Buffalo, NY
²Department of Molecular & Cellular Biology & Department of Polymer Sciences, Roswell Park Cancer Institute, Buffalo, NY

Objectives: To compare serum levels of sRAGE between multiple sclerosis (MS) patients and healthy control subjects and investigate whether serum sRAGE levels correlate with MS disease severity as indicated by the Expanded Disability Status Scale (EDSS).

Background: RAGE, the receptor for advanced glycation end products (AGEs) has been implicated in diabetes and in neurodegeneration. Inhibition of RAGE reduces the infiltration of inflammatory immune cells into the CNS and suppresses Experimental Autoimmune Encephalomyelitis (EAE). The soluble isoform of RAGE (sRAGE) is reduced in patients with Alzheimer’s Disease. We hypothesized that sRAGE may represent an effective biological marker of MS disease severity.

Method: Serum levels of sRAGE were measured in 37 MS patients, and 22 age- and gender-matched healthy control subjects by ELISA. MS patients were clinically stable and naïve to MS disease modifying drugs for the previous 6 months.

Results: Serum levels of sRAGE were significantly lower in MS patients (998 ± 52.6 pg/ml compared to levels in healthy controls (1292.2 ± 77.1 pg/ml) (p=0.005). Serum sRAGE levels tended to be lower in female patients compared to male patients (p=0.05). An inverse relation between sRAGE and EDSS, and between sRAGE and rate of clinical relapse in the previous two years (R²=0.166, P=0.012) were observed. No correlations between serum sRAGE levels and MS disease duration, and between serum sRAGE levels and age at disease onset, were observed.

Conclusion/Relevance: The reduction of sRAGE in MS patients relative to controls supports the potential role for RAGE axis in MS clinical pathology, as lower levels of sRAGE may be associated with enhanced inflammatory responses. Serum sRAGE could be a potential biomarker of MS disease severity/progression.

32. Salicylate-Induced Tinnitus: Changes in Inferior Colliculus Tonotopic Map and Correlated Neural Activity

Daniel Stolzberg, Joseph Walton, Adam Dziorny, Richard Salvi

University at Buffalo and University at Rochester

Tinnitus, the perception of a sound which has no corresponding source in the environment, affects ~14% of the population. The underlying neural mechanisms of the generation of this phantom sound are often studied using administering a single high dose of sodium salicylate (aspirin) which is known to induce transient tinnitus in humans and some animal species. The purpose of this study was to investigate changes in neuronal firing patterns across the tonotopic axis of the central nucleus of the inferior colliculus (ICC), a midbrain auditory region which receives inputs from many brain regions and is important in processing both spectral and temporal properties of sounds, in tranquilized but conscious mice (CBA/J) during salicylate-induced tinnitus. Recordings were made from the mouse ICC using multi-channel silicon microelectrodes; sampling multi-unit and single-unit activity from regions across the entire tonotopic axis of ICC simultaneously. Neural activity was recorded before and each hour up to 4 h following salicylate administration (250 mg/kg IP) during 4 conditions: 1) brief tone-bursts to characterize the excitatory response properties of neurons to sounds; 2) two-tone stimuli to assess the state of neural inhibition; 3) silent gaps in noise to assess temporal acuity; 4) spontaneous neural activity in
quiet. A preliminary analysis revealed a significant large increase in correlated spontaneous neural activity 1.5 h following injection in regions which responded best to high frequency tones (~44 kHz).

33. The Serine:Glycine Response Ratio Identifies the α1 Glycine Receptor
John Trimper, Ping Li, Jason Myers, and Malcolm M. Slaughter
Center for Neuroscience and Department of Physiology & Biophysics, University at Buffalo
The discovery of multiple glycine receptor (GlyR) subtypes has not been accompanied by pharmacological tools to differentiate the various receptors. One method of identification is the use of selective agonists. Consequently, we compared the action of a variety of glycine analogs on α1-4 GlyR subunits expressed in HEK293 cells. In an initial screen we compared the agonist potency on α1 vs α2 homomeric GlyRs. Most agonists were more potent at the α1 GlyR, but L-serine was notable in that it had over a five-fold lower EC₅₀ at the α1 GlyR. Because of the shift in the dose-response curve at the two receptors, 500 μM serine produced an average of 44% of the maximal current (produced by 2 mM glycine) in α1 GlyRs but less than 6% of maximum at the α2 GlyR. The α3 GlyR was even less sensitive to serine: 500 μM serine produced essentially no current. The α4 GlyR was almost as sensitive to serine at the α1 GlyR. Thus, the response ratio of 500 μM serine/2 mM glycine can identify the presence α1/α4 GlyRs vs. α2/α3 GlyRs. In many systems, where α4 GlyRs are absent, the serine/glycine ratio can be used to identify the presence of α1 GlyRs.

34. Ethanol Conditioned Place Preference and Operant Progressive Ratio Performance in Adult Rats after Prenatal and Adolescent Exposure to the Drug.
Eric M. Truxell, Amy M. Gancarz, and Jerry B. Richards
Research Institute on Addictions, SUNY Buffalo.
The effects of pre-exposure during important development stages were measured in adult rats using condition place preference (CPP) and operant progressive ratio (PR) procedures. The CPP procedure is thought to measure the hedonic impact ethanol and PR procedures is thought to measure the reinforcing efficacy of ethanol. Rats in three different pre- and postnatal drug treatment conditions display conditioned place preference. However, there was no difference between the pre exposed groups and the ethanol naïve group. The PR procedure that we used, has the virtue of measuring responding for ethanol prior to allowing access to ethanol so that responding is always measured in the absence of the drug. This has the effect of creating a clear differentiation between appetitive and consummatory measures of affinity for the drug. Using PR procedure we found that rats in pre-exposed groups responded more (had higher break points) for ethanol than the naïve group but that, consumption (the amount the rats drank after they completed the Ratio requirement) did not differ between groups. This illustrates the importance of having a clear distinction between measures of reinforcement and consumption. Taken together these data indicate that the CPP and PR procedures may measure different aspects of the reinforcing consequences of ethanol.

35. Glycogen Synthase Kinase 3 Regulates AMPA Receptor Endocytosis via the GDI-Rab5 Complex in Cortical Neurons
Jing Wei, Wenhua Liu, Zhen Yan
Physiology and Biophysics, University at Buffalo, School of Medicine and Biomedical Sciences
Accumulating evidence has suggested that glycogen synthase kinase 3 (GSK-3) is a multifunctional kinase implicated in neuronal development, mood stabilization, and neurodegeneration. However, the synaptic actions of GSK-3 are largely unknown. In this study, we examined the impact of GSK-3 on AMPA receptor (AMPAR) channels, the major mediator of excitatory transmission, in cortical pyramidal neurons. Application of GSK-3 inhibitors or knockdown of GSK-3 caused a significant reduction of the amplitude of miniature EPSC (mEPSC), a readout of the unitary strength of synaptic AMPARs. Treatment with GSK-3 inhibitors also decreased surface and synaptic GluR1 clusters on dendrites and increased internalized GluR1 in cortical cultures. The effect of GSK-3 inhibitors on mEPSC amplitude was abolished by knockdown of Rab5, the small GTPase controlling early
endocytic membrane traffic. Inhibiting the function of Guanyl nucleotide dissociation inhibitor (GDI), which regulates the cycle of Rab proteins between membrane and cytosol, prevented the effect of GSK-3 inhibitors on mEPSC amplitude. Moreover, treatment of cortical slices with GSK-3 inhibitors increased the formation of GDI:Rab5 complex and the activity of Rab5. The effect of GSK-3 inhibitors on GDI:Rab5 complex was lost in cells transfected with the non-phosphorylatable GDI mutant GDI[S45A]. These data suggest that GSK-3 regulates AMPAR endocytosis via changing the phosphorylation state of GDI and the formation of GDI:Rab5 complex. It provides a molecular mechanism underlying the role of GSK-3 in synaptic transmission and plasticity.

36. Effects of estradiol on food intake and meal patterns for diets that differ in flavor and fat content

Danielle M. Wojcik, Shannon J. Clough, and Peter C. Butera
Department of Psychology, Niagara University

Apart from the well known inhibitory effects of estradiol on food intake and body weight that have been documented over the past thirty years, a more recent report by Boswell et al. (2006) presents the opposite finding; that a large dose of estradiol can increase food intake and weight gain in gonadally intact female rats presented with a palatable diet. The purpose of the present experiment was to further examine this hypothesis by evaluating the ability of estradiol to influence feeding behavior in ovariectomized rats presented with diets that differ in flavor and fat content. Female rats were given a cyclic regimen of estradiol benzoate treatment (5.0 or 20.0 µg) or the oil vehicle and were presented with the standard chow diet or a chocolate/fat diet. Food intake, meal size, and meal number were monitored three days after the first injection of estradiol or oil. Compared to the chow diet, food intake increased when animals had access to the chocolate/fat diet. Compared to oil treatment, both doses of estradiol significantly decreased food intake, meal size, and body weight gain when animals were presented with either the standard chow diet or the chocolate/fat diet. These findings indicate that estradiol does not stimulate the intake of a palatable diet in ovariectomized rats, and suggest that previous results showing that estradiol enhanced eating and weight gain stemmed from a disruption of the hypothalamic-pituitary-gonadal axis when intact females received a large dose of exogenous estradiol.

37. Computational Fluid Dynamics to Assess Intracranial Aneurysm Rupture Status: Do Hemodynamics Separate Ruptured from Unruptured Aneurysm Better than Morphology?

Jianping Xiang, Sabareesh K. Natarajan, Markus Tremmel, Elad I. Levy, J Mocco, and Hui Meng
University at Buffalo

To identify significant morphological and hemodynamic parameters that can predict intracranial aneurysm rupture status using 3D angiography and computational fluid dynamics (CFD) and compare their relative importance.

33 aneurysms (9 ruptured, 24 unruptured) were evaluated for a range of morphologic and hemodynamic parameters. Parameters were analyzed with Student's t-test or Wilcoxon rank-sum test for significance. Receiver-operating characteristic analysis identified optimal thresholds separating ruptured and unruptured aneurysms. Significant parameters were further examined by multivariate logistic regression analysis to determine independently significant parameters that correlated with each group. Three morphology-based parameters (Aspect Ratio [AR], Size Ratio [SR], and Nonsphericity Index [NSI]) and six hemodynamics-based parameters (Average Wall Shear Stress [WSS], Low WSS Area, Percentage of Low WSS Area, Average Oscillatory Shear Index [OSI], Number of Vortices, and Relative Resident Time) achieved statistical significance (p<0.01). Logistic regression analysis demonstrated SR to be the only independently significant morphological factor, whereas Average WSS and Average OSI were independently significant hemodynamic variables. In the combined model, SR lost significance and only Average WSS and Average OSI remained
Independent significant. **Conclusions:** Hemodynamic parameters *Average WSS* and *Average OSI* from CFD are better predictors of the rupture status of an aneurysm than even the best morphological parameter (*SR*).

**38. Target-cell-specific synaptic plasticity occurs cell by cell in the cochlear nucleus**

*Hua Yang and Matthew A. Xu-Friedman,*

*Biological Sciences, University at Buffalo, SUNY, Buffalo, NY 14260*

Individual neurons typically form synapses onto multiple target cell types. The characteristics of short-term synaptic plasticity onto different target cell types can differ, even when the synapses are formed by the same individual cell. This phenomenon is called “target-cell-specific synaptic plasticity”, and the mechanisms are unknown. We studied this phenomenon at auditory nerve fiber synapses in the anteroventral cochlear nucleus, and assessed plasticity using paired-pulse and train stimulation in voltage clamp. Auditory nerve fibers form synapses onto bushy cells and stellate cells. Synapses onto these cells show distinct plasticity, with bushy cells showing depression, and stellate cells showing facilitation. We studied this phenomenon on a more precise level by characterizing the plasticity of multiple converging auditory nerve fibers onto individual bushy cells. These “sibling” inputs had particularly similar plasticity, while inputs onto different cells were more different. This raises the idea of target-cell-specific synaptic plasticity to a much higher level, and has important implications for synaptic development.

**39. Expression of MT₁ Melatonin Receptor Promoter-Driven RFP Protein in BAC Transgenic C3H Mice**

*Yahong Zhang¹, Hosung Jung², Jeanie Ramos², Dongjun Ren², Richard J. Miller², Margarita L. Dubocovich¹,²*

¹Department of Pharmacology and Toxicology, School of Medicine and Biomedical Science, University at Buffalo, Buffalo, NY; and ²Department Molecular Pharmacology and Biological Chemistry, Northwestern University Feinberg School of Medicine, Northwestern University, Chicago, IL

The hormone melatonin is rhythmically synthesized in the pineal gland and plays an important role in regulating seasonal and circadian rhythms. Two types of melatonin receptors, MT₁ and MT₂, have been cloned in mammals which mediate distinct and complementary functions of melatonin. In recombinant cellular systems, melatonin differentially regulates MT₁ and MT₂ receptor functions in a time- and concentration-dependent manner, suggesting these two receptors interplay in mediating the temporal signaling of melatonin *in vivo*. In order to reconcile the discrepancies in the published results regarding the expression pattern of MT₁ and MT₂ receptors and to examine whether MT₁ and MT₂ melatonin receptors are differentially regulated *in vivo*, we embarked on generating BAC transgenic mice expressing fluorescent MT₁-RFP or MT₂-EGFP melatonin receptors. Here, we described the transgenic mice in which red fluorescence protein (RFP) is expressed under the control of MT₁ promoter, by inserting RFP cDNA at the start codon of *Mtnr1a* gene within a bacterial artificial chromosome (BAC) and expressing this construct as a transgene. These mice showed a normal circadian phenotype as their circadian rhythm of wheel running activity entrained to the L/D cycle, free run in constant dark, showed identical circadian period and amplitude as wild type and negative littermates. MT₁-RFP expression was examined either directly under fluorescent microscope or immunohistochemically using antibody against RFP protein. The overall expression of MT₁-RFP in the brain is in agreement with melatonin functions and is consistent with and more restricted than detected by immunohistochemistry, binding autoradiography and in situ hybridization. MT₁-RFP was observed in many brain regions including parts of the ependyma lining of the lateral and third ventricles. Ependyma lining of the aqueduct, subcommissural organ, sagittal strip along the top of aqueduct, hippocampus, Bergmann glia and scattered cells in the whiter matter of cerebellum and pars tuberalis. This MT₁-RFP transgenic model would provide a unique tool for studying MT₁ receptor function *in vivo*. **Supported by MH 42922.**
40. Biphasic Action on Internal Calcium by Metabotropic Receptors

Jaeyoung Yang, Jason Myers, and Malcolm Slaughter

Center for Neuroscience, Department of Physiology & Biophysics

Metabotropic receptors, such as glutamate and GABA receptors, are present in the retina and throughout the brain. Often they serve to regulate transmitter release by suppressing presynaptic, voltage-gated calcium currents. We used whole-cell voltage clamp recording and calcium imaging to evaluate the effects of several metabotropic receptors on internal free calcium in rat retinal neurons.

Acutely dissociated or cultured retinal cells from 10 - 16 day Sprague-Dawley rats were treated with various superfused drugs. Internal calcium was monitored using fluo3-based imaging while calcium currents were measured using whole cell patch clamp techniques.

We focused on the effects of metabotropic glutamate receptors activated by ACPD and on the newly discovered sweet taste receptors activated by aspartame. Both agonists raised internal calcium in a subset of isolated retinal neurons. However, if cells were depolarized by 50 mM KCl, then both receptor agonists reduced internal calcium. In the studies of sweet taste receptors, the aspartame EC50 for suppression of elevated calcium was 13 μM, but the EC50 for the enhancement of basal calcium was 1.7 mM. Aspartame suppressed high-voltage activated calcium currents. Other sweet receptor agonists (2mM D-tryptophan, 1mM D-phenylalanine, 1mM saccharine, and 50mM glucose) also enhanced intracellular calcium levels. The calcium elevation was inhibited by nimodipine or cadmium block of voltage-gated calcium channels or by caffeine depletion of internal calcium stores. The effects on sweet taste receptors could be duplicated by the action 100uM ACPD on metabotropic glutamate receptors. The effects of ACPD and aspartame did not necessarily occur on the same neurons, indicating they acted on different receptor pathways. In both systems, micromolar doses of agonist acted to suppress voltage-gated currents while millimolar concentrations elevated internal free calcium.

In conclusion, metabotropic receptor agonists produced a biphasic modulation of internal calcium: raising calcium in resting neurons and reducing calcium in stimulated neurons. Bimodal modulation implies that metabotropic receptors can activate opposing biological cascades with a single agonist.
Registered Participants

Adamah-Biassi, Ekue
Alsford, Catherine
Amico, Stacy
Auerbach, Anthony
Baker, Steve
Barnum, Kevin
Beedon, Kelly
Bhattacharjee, Arin
Borschel, Will
Bruhova, Iva
Bungo, Alexandria
Butera, Peter
Cadugan, Dave
Carr, Katelyn
Caven, Alex
Chakraborty, Srirupa
Chan, Angela
Chanda, Soham
Cohan, Chris
Covey, Tom
Czaplicki, Chris
Daniels, Derek
Dent, Micheal
Dhamija, Devika
DiNardo, Nicole
DiPirro, Jean
Dubocovich, Margarita
Evrard, Matthew
Feeney, Casey
Ferkey, Denise
Gancarz, Amy
Garaycochea, Jay
Garcia, Kristen
Garlipp, Mary Alice
Ghanim, Husam
Gonzalez-Fernandez, Federico
Grace, Michael
Graziane, Nick
Gunawardena, Shermali
Gupta, Shaweta
Halvorsen, Stan
Hare, Laura
Hayes, Sarah
Hennessey, Todd
Hoey, Rob
Hogan, Liz
Hu, Bohua
Hu, Caiping
Hudson, Randall
Hurley, Seth
Hutchinson, Antony
Jadey, Snehai
Jamesdaniel, Samson
Jha, Archana
Jimenez, Zarina
Jose, Jorge
Kline, Brian
Kosman, Don
Kotowska, Ewelina
Kraft, Justin
Kristal, Mark
Kumar, Ajay
Kussius, Cassandra
Lampert, Tom
Lassman, Beth
Lee, Janine
Leung, Yi Kan
Liaw, Nicholas
Lima, Raquel
Luo, Wei
Mandelbaum, Max
Manohar, Senthivelan
McKay, Naomi
Medler, Kathryn
Miao, Xin
Mietlicki, Elizabeth
Mohamed, Islam
Morrison-Nozik, Alex
Mu, Xiuqian
Murthy, Swetha
Myer, Jason
Neilans, Erikson
Neumann, Anne
Niec, Mark
Nuwer, Megan
Paganelli, Megan
Patel, Mulchand
Picchione, Kelly
Piraino, Vincenzo
Plyler, Kimberly
Popescu, Gabriela
Privitera, Adam
Purohit, Prasad
Radziwon, Kelly
Rajnarayanan, Rajendra
Rebello, Michelle
Richards, Jerry
Rumschik, Sean
Salvi, Richard
Samir, Haj-Dahmane
Scarbinsky, Kate
Schucard, David
Schucard, Janet
Seigel, Gail
Sethuramanujan, Santosh
Shen, Roh-Yu
Sim, Fraser
Simon, Bart
Slaughter, Malcolm
Smith, Thom
Song, Yunbo
Sternberg, Zohi
Stolzberg, Dan
Suarez, Mauricio
Sun, Wei
Swartz, Meghan
Tao, Ge
Thompson, Alexis
Trimmer, John
Truxell, Eric
Udin, Susan
Ulm, Valerie
Vento, Peter
Visapragada, Sarada
Wei, Jing
Welch, Tom
Wood, Jordan
Xiang, JainPing
Xu-Friedman, Matthew
Yan, Zhen
Yang, Jaeyoung
Yang, Hua
Zhang, Minyou
Zhou, Bo