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

Fourth Annual Neuroscience Research Day

October 2, 2010
University at Buffalo, North Campus
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
Gabriela Popescu, Malcolm Slaughter, Susan Udin

9:30 am – 10:30 am **Distinguished Speaker**

Anthony Auerbach, PhD

Professor of Physiology and Biophysics, University at Buffalo

transmitter, receptor, synapse

10:30 am – 11:15 am Coffee Break and POSTERS

11:15 – 12:15 Short talks, moderated by incoming president **Dr. Fraser Sim**

11:15 – 11:30 **Dan Stolzberg**, Neuroscience PhD Student
11:30 – 11:45 **Mary Alice Garlipp**, Neuroscience PhD Student
11:45 – 12:00 **Thomas Covey**, Neuroscience PhD Student
12:00–12:15 **Michelle Rebello,** Biological Sciences PhD Student

12:15 pm – 1:15 pm Lunch

1:15 pm – 2:30 pm **POSTER SESSION**

2:30 pm – 3:30 pm **Keynote Lecture**

Todd Sacktor, MD

Professor of Physiology and Pharmacology, SUNY Downstate

Maintenance Mechanisms for Long Term Memories

3:30 pm – 3:45pm Awards presentation

Beverly Bishop Award for Best Short Talk
presented by Charles Bishop, Emeritus Professor of Medicine

Harold Brody Award for Best Poster
presented by Chris Cohan, Professor of Pathology and Anatomical Sciences

4:00 Closing Remarks
Fraser Sim, Incoming Chapter President

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Distinguished Speaker
Anthony Auerbach, PhD

Professor, Department of Physiology and Biophysics
University at Buffalo, SUNY

Dr. Auerbach is a Professor of Physiology and Biophysics in the School of Medicine and Biomedical Sciences at University at Buffalo, SUNY. He leads a successful team of scientists and investigates synaptic receptors and ion channels.

Dr. Auerbach is particularly interested in the molecular events that constitute agonist binding, receptor activation and ion permeation. His research program combines the approaches of pharmacology, enzymology, structural and molecular biology, electrophysiology, and mathematical modeling.

“transmitter, receptor, synapse”

Knowledge of synapses dates back to 1786, when Luigi Galvani discovered that electricity is how nerves make muscles twitch. Now, we understand synaptic transmission as a complex, interconnected series of molecular events. Transmitter molecules - synthesized, stored and released from presynaptic terminals - bind to receptors to promote conformational change and trigger a signaling cascade in the postsynaptic cell. The central focus of the talk will be on the initial “synaptic” event at the nerve-muscle synapse: By what mechanism do agonists promote the activation of nicotinic acetylcholine receptors? The answer will come from understanding the relationship between energy and structure.

Keynote Lecture

"Maintenance Mechanisms for Long Term Memories"

How long-term memories are stored as physical traces in the brain is a fundamental question in neuroscience. Persistent changes in synaptic strength are thought to underlie memory storage. One approach to understanding these changes is to characterize the mechanisms of synaptic plasticity, particularly the persistent synaptic enhancement, long-term potentiation (LTP). The talk will focus on what are the newly synthesized proteins that maintain LTP, how do they sustain synaptic potentiation, and do they store long-term memory?

Recent studies have identified a unique brain-specific, autonomously active PKC isozyme, PKMζ that is central to LTP maintenance. PKMζ is the independent PKCζ catalytic domain, produced from a PKMζ mRNA that persistently phosphorylate without second messenger stimulation. Once synthesized in LTP induction, PKMζ is both necessary and sufficient for maintaining late-LTP through persistent enhancement of NSF/GluR2-mediated AMPA receptor trafficking to the synapse.

Todd C. Sacktor, MD

Professor of Physiology and Pharmacology
Professor of Neurology
SUNY Downstate Medical Center, Brooklyn NY

"When Todd Sacktor was 9 years old, he conducted his first memory experiment, telling his younger brother every day to remember being told to remember. It was a bust: the young researcher himself forgot to keep the experiment going. But the fascination stuck." (US News, July 2 2009).

Currently, Dr Sacktor is investigating the mechanisms of long-term memory storage with molecular biology, enzymology, electrophysiology and behavioral studies.

SPECIAL FOCUS

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

Last March, the Neuroscience Graduate Student Association held their third annual Brain Awareness Week (BAW) event and what a huge success it was! Graduate students from Neuroscience, Biochemistry, IGPBS, Behavioral Neuroscience and even a few undergraduate classmen came together to teach young elementary students about the exciting field of Neuroscience through hands-on experiments. This year, they expanded the event and went to two local elementary schools: Universal School of Buffalo and Highgate Heights Elementary. In one day, they were able to share their knowledge of Neuroscience with over 100 elementary school students. This was possible due to the participation of 21 student volunteers!

This was a great interdepartmental activity, a truly fun and educational event, as well as a great way to strengthen the Neuroscience GSA. Students are encouraged to continue this tradition in the future.

ANNUAL AWARDS

The Beverly Bishop award for the best short talk

Beverly P. Bishop
(1922 – 2008)

This is the second 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

Harold Brody
(1923– 2008)

The award for the best poster presentation honors 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.

Short Talk Abstracts

(listed by order of appearance)

Identifying Cortical Mechanisms of Tinnitus in Rats

Daniel Stolzberg and Richard Salvi
Center for Hearing & Deafness, SUNY University at Buffalo

Tinnitus is characterized by the persistent perception of an inescapable phantom sound (e.g. ringing, buzzing) in the absence of any source in the environment. One leading theory of tinnitus implicates aberrant spontaneous activity permitted by cortical disinhibition. In support of this hypothesis, magentoencephalographic recordings from humans with tinnitus reveal decreased energy over the auditory cortex (AC) in the alpha band (8-12 Hz) – a frequency band which positively correlates with inhibitory processes – compared with normal subjects. Similarly, field recordings from the surface of the AC in chronically implanted awake rats showed a significant decrease in alpha energy following a high dose of salicylate: a drug known to reliably induce temporary tinnitus in humans and other animals. In order to investigate how salicylate-induced tinnitus affects inhibitory regulation of cortical activity, extracellular neural activity was recorded simultaneously across the lamina of the AC in anesthetized rats before and following a single systemic salicylate injection (300 mg/kg IP). Following salicylate administration, a decrease in alpha energy was observed near the brain surface and deeper electrodes; however, middle layers of the AC responded with an increase in alpha-band energy. Interestingly, salicylate strongly affected sound-driven responses across the AC lamina in a manner indicative of a cortical disinhibition. In addition, frequency receptive fields of AC neurons expanded and the best frequency of the receptive fields of most neurons shifted towards the behaviorally assessed tinnitus pitch (10-20 kHz). These physiological changes support the hypothesis that cortical disinhibition plays a significant role in the generation of salicylate-induced tinnitus and that tinnitus may emerge from an overrepresentation of cortical neurons tuned to the tinnitus pitch.

Novel Association of Interphotoreceptor Binding Protein (IRBP) with Cone Outer Segments

Mary Alice Garlipp and Federico Gonzalez-Fernandez
Ross Eye Institute, Department of Ophthalmology, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Our long-term interest is to understand how IRBP targets the delivery and uptake of 11-cis retinal, all-trans and 11-cis retinol between the cells bordering the interphotoreceptor matrix (IPM). For example, IRBP has significant activity in promoting the outer segment delivery, and release of 11-cis retinal and all-trans retinol respectively. Although much attention has been given to the ease with which IRBP can be removed from the IPM by aqueous extraction, there are hints in the literature that not all of the IRBP is available for such extraction. Here, we ask whether IRBP demonstrates a physiologically relevant interaction with structures in the retina.

Xenopus laevis were selected for these studies due to the large size of their photoreceptors, and ability to detach the retina in light and dark. Full-length Xenopus IRBP (XIRBP) was expressed in a soluble form in E. coli and purified by a combination of anion exchange, Ni2+ affinity, and size exclusion chromatography. XIRBP was labeled with Alexa-647 at a 1:1 molar ratio. Anti-Xenopus IRBP serum raised in rabbits was used to localize native IRBP. Our experiments detected "wash-resistant" IRBP, and sites of exogenous IRBP binding. Neural retinas from light- or dark-adapted adult animals were detached under HBSS (pH 7.4) and washed 3x in 5 ml. Retinas from dark-adapted animals were detached and handled under infrared light. Wash-resistant IRBP was detected by indirect immunofluorescence using a secondary antibody conjugated to Alexa-647. In controls, the retina was detached under 4% paraformaldehyde and not washed. In other experiments, retinas were incubated with XIRBP-647, ovalbumin-647, or unconjugated Alexa-647. Sections were examined in cross-section or whole mounts.

Wash resistant IRBP mainly labeled photoreceptor outer segments (OS), predominantly cones, whereas in unwashed retinas matrix staining was diffuse and intense. Similar results were observed in exogenous IRBP experiments. XIRBP-647 staining was observed in cone OS. Ovalbumin-647 and unconjugated Alexa-647 dye showed minimal fluorescence. Dark-adapted retinas in both paradigms showed reduced staining. IRBP interacts with the cone OS in a light dependent manner. On-going experiments are aimed at defining whether the interaction is to the out segment or its matrix sheath.

Processing Speed, Neural Efficiency and Working Memory: Their Relationship with MRI Measures in Multiple Sclerosis

Thomas J Covey, Janet L Shucard, Robert Zivadinov and David W Shucard

Cognitive and Behavioral Neurosciences, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

In the present study, working memory (WM) performance, processing speed, and neural efficiency/neural noise were assessed in Multiple Sclerosis (MS) patients while undergoing a visual n-back task, and these behavioral measures were related to quantitative MRI measures of structural brain deficits. The results extend our previous findings (e.g., Parmenter et al., 2007) and provide new information about the most sensitive behavioral indices of n-back WM deficits in MS, and about the contribution of neural inefficiency to the slowed processing speed seen in MS patients during WM performance. Even when MS patients performed as well as controls as seen for the lowest WM load condition, they responded more slowly and were less efficient in their speed of responding. The performance accuracy findings indicated that, as hypothesized, the correct match trials, associated with top down processing and executive control, provide a sensitive marker of working memory impairment in MS patients. Further, disruption of executive control during manipulation of information in a high WM load task was associated with global damage that included gray matter; while slowing and inefficient information processing during a demanding WM task was associated primarily with global white matter disruption in MS. Importantly, relationships between processing speed, efficiency, performance and structural MRI measures were seen only during the highest WM load condition, the condition that required the most executive control. These findings and those of others suggest that the MRI/behavioral relationships present exclusively during the highest WM load condition reflect connectivity that involves frontal cortical systems, the site for executive control. Future work will examine variability of EEG Event Related Brain activity during the n-back task as a functional marker of neural efficiency and resource allocation in patients and controls.

Ryanodine Receptors Selectively Contribute to Taste-Evoked Calcium Signals in Mouse Taste Cells

Michelle R Rebello and Kathryn F Medler

Biology Department, College of Arts and Sciences, SUNY 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 activate G-protein coupled receptors (GPCRs) to cause Ca^{2+} release from intracellular stores, which is known to occur in Type II cells via a PLCβ2/IP_3R3 signaling pathway. Sour stimuli depolarize taste cells to cause Ca^{2+} influx through voltage-gated calcium channels (VGCCs), presumably in taste cells with chemical synapses. The transduction pathways of salty stimuli are less well defined. There is also a sub-population of taste cells that express VGCCs and detect bitter taste stimuli but do not express the PLCβ2/IP_3R3 pathway. These cells are termed dual-responsive and appear to express PLCβ3 and IP_3R1.

Using immunocytochemistry and calcium imaging, we have shown that ryanodine receptors (RyRs), specifically isoform 1, are expressed in taste cells and have different physiological roles depending on which signaling pathway is being expressed. In taste cells with VGCCs, we find that RyR1 contributes to the depolarization-induced calcium signal, similar to the functional coupling between RyRs and L- type VGCCs seen in skeletal and cardiac muscle. Our findings reveal an important role for RyRs in the transduction of taste-evoked responses and suggest that calcium signaling in taste cells is more complex than has previously been appreciated.This work was supported by NIDCD DC00635801 and NSF 0917893 to KM.

Poster Titles and Authors

(listed alphabetically by first author)

1. Localization of MT1 Melatonin Receptor Promoter-Driven RFP Protein in the cerebellum of BAC C3H/HeN Transgenic Mice

Ekue B Adamah-Biassi and Margarita L Dubocovich

Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Melatonin responses are mediated through activation of the MT_1 and MT_2 melatonin receptors. The goal of this study was to determine the cellular distribution of RFP-tagged MT_1 promoter in cerebellar slices from C3H/HeN transgenic mouse expressing Red Fluorescence Protein (RFP) cDNA at the start codon of the MT_1 receptor gene. RFP-tagged MT_1 promoter-containing cells were visualized by direct fluorescence microscopy and by direct immunohistochemistry with RFP antibodies. Free floating cerebellar slices (35 um) from RFP positive and RFP-negative mice were incubated with RFP biotinylated antibody and processed for immunohistochemistry staining and visualization with 3, 3'-Diaminobenzidine (DAB). Expression of RFP tagged MT_1 promoter was found in the granular, the Purkinje and the molecular cell layers. The cell specific expression of RFP tagged MT_1 promoter to Purkinje cells was assessed by double immunohistochemistry using a Purkinje cell specific antibody, calbindin. Cells expressing RFP-tagged MT_1 promoter include Purkinje cells in the Purkinje cells layer, the basket-stellate cells of the molecular layer and the granules cells of the granular layer. We conclude the human and mice cerebellum express MT_1 receptors in the basket-stellate cells and granule cells, while this receptor was also localized in the Purkinje cells of the mouse cerebellum.

2. Spine density changes in Gonadotropin-Releasing Hormone (GnRH) neurons during the rat estrous cycle

Armando Arroyo, Beom Su Kim, Phillip Garza and Glenna C L Bett

Department of Gynecology-Obstetrics and Physiology and Biophysics, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus play a critical role in controlling ovulation. Spines are important anatomical structures of GnRH neuron soma and dendrites. Here we determine whether spine density in medial preoptic area (MPOA) GnRH neurons changes across the rat estrous cycle and the effect of estrogen on spines in MPOA GnRH neurons. We measured spine density (# spines/50µm) in MPOA GnRH neuron soma and dendrites during diestrus, proestrus AM, proestrus PM, and estrus in cycling rats (n=5 rats/stage; 5 neurons/rat) using immunohistochemistry and confocal microscopy. We also measured spine density in MPOA GnRH neuron soma and dendrites in OVX rats treated with 17-β estradiol benzonate (n=5 rats/group; 5 neurons/rat) and oil. We found that spine density significantly increased in both GnRH neuron soma and dendrites during proestrus PM. Spine density in both MPOA GnRH neuron soma and dendrites was significantly higher in estrogen compared to oil treated OVX rats. We also determine whether the shape of MPOA GnRH neurons changes across the rat estrous cycle. We found that 62% are unipolar and 30% are bipolar. This proportion did not change across the rat estrous cycle. In conclusion we found that spine density in MPOA GnRH neurons increases during the evening of proestrus during the rat estrous cycle and that estrogen stimulates spine formation in MPOA GnRH neurons. This suggests that spines in GnRH neurons regulate the surge in GnRH secretion that occurs during the evening of proestrus in the rat.

3. Kinetic Effects of Cross-Linking the LBD Heterodimer Interface in NMDA Receptors

William F Borschel and Gabriela K Popescu

Department of Biochemistry, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Upon binding the neurotransmitter glutamate and the obligatory co-agonist glycine, NMDA receptors activate by opening a membrane-permeable pore or desensitize by switching into a high-affinity non-conducting conformation. Both activation and desensitization require that the agonist-binding clamshell within each subunit close to engulf the agonists. It has been hypothesized that this movement strains the contacts between agonist-binding domains of GluN1 and GluN2, and rupture of this interface causes receptor desensitization by disengaging agonist-binding from pore-opening. To test the hypothesis of the role of inter-subunit contacts in NMDA receptor gating, we cross-linked the heterodimer interface by introducing cysteine residues at positions predicted to interact across subunits: N521 and L777 of GluN1 and E516 and L780 of GluN2A, respectively. Steady-state single-channel recordings indicated that cross-linked receptors had drastically reduced open probabilities (~150-fold, P_O = 0.0032) due to ~4-fold shorter openings and ~115-fold longer closures (means, SEM): MOT = 1.8 ± 0.2 ms, MCT = 792 ± 213 ms (n = 6; 80,028 events). Surprisingly, the mean duration of closed intervals associated with desensitization remained unaltered (Wt, TauD = 2.7 s; Mut, TauD = 3.0 s). Reduction of the engineered disulfide bonds (10 mM DTT) significantly potentiated single channel currents (means, SEM: P_O = 0.14 ± 0.02) by restoring the mean duration of openings (10.5 ± 0.6 ms) and significantly shortening mean closed durations (80 ± 12 ms), but had no discernible effects on microscopic desensitization (n = 7; 262,396 events). Based on these data, we propose that rearrangements at the heterodimer interface between agonist-binding domains are integral to receptor opening, but not to the desensitizing reaction pathway.

4. Asymmetric Gating of the Neuromuscular Acetylcholine Receptor Subunits at the Pre-M1 Linker

Iva Bruhova and Anthony Auerbach
Department of Physiology and Biophysics, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Neuromuscular acetylcholine receptors (AChRs) mediate fast chemical synaptic transmission. Binding of two neurotransmitters at the extracellular domain (ECD) triggers a conformational change causing channel opening at the transmembrane domain (TMD). The ECD/TMD interface is a complex region that links 'binding' and 'gating'. The covalent connection between the ECD and TMD is the pre-M1 linker, a stretch of five residues following β10. In each subunit, this linker has a central Arg ('R3'), which only in the non-α subunits is flanked by positively-charged residues. Previous studies showed that mutations of R3 in the α subunit alter the gating equilibrium constant and reduce channel expression. We recorded single-channel currents and estimated the gating rate and equilibrium constants of adult mouse AChRs having mutations at the pre-M1 linker and the nearby residue E45 in non-α subunits. In all subunits, mutations of R3 had similar effects as in α. In ε, mutations of the flanking residues and E45 had only small effects, and there was no energy coupling between εE45 and εR3. The non-α R3 residues had Φ values that were similar to that for α. The results suggest that there is a general symmetry between the AChR subunits during gating isomerization in this linker and that the central Arg is involved in expression more so than gating. The energy transfer through the AChR during gating appears to mainly involve position E45, but only in the α subunits.

5.Differential Expression of Adhesion- and Extracellular Matrix-related Genes among Different Cochlear Partitions and the Inferior Colliculus

Center for Hearing and Deafness, College of Arts and Sciences, SUNY University at Buffalo

The cochlea is a sensory organ consisting of three distinct partitions: the sensory epithelium, the lateral wall, and the modiolus, each playing a distinct role in auditory perception and each responding differently to pathological insults. Investigation into the difference in the gene expression patterns among these structures can provide new insights into molecular mechanisms responsible for normal cochlear function and for cochlear pathogenesis. The current study was designed to profile the expression patterns of adhesion- and extracellular matrix-related genes in the three cochlear partitions and in the inferior colliculus of young Sprague Dawley rats (2-3 months) using a RT-qPCR array technique. The results showed that for all the tissue types, there was a large variation in expression levels among individual genes with the range of the difference being greater than 131,072 folds. In the cochlear sensory epithelia, the highly expressed genes include 12 adhesion-related genes (Ctnnb1, Catna1, Thbs1, Lamb2, Cdh1, Itgb4, Itgav, Sgce, Spp1, Itga3, Cntn1 and Postn) and 8 extracellular matrix-related genes (Sparc, Timp3, Ctgf, Tgfbi, Spock1, Lama2, Mmp11 and Col2a1). A third of examined genes in the lateral wall, the modiolus, and the inferior colliculus expressed differently as compared with those expressed in the cochlear sensory epithelia. As expected, the number of genes that differed in the expression level among the three cochlear partitions is less than that showed between the inferior colliculus and the cochlear tissues, suggesting that gene expression patterns are less diverse between cochlear tissues than between cochlear and non-cochlear tissues. Importantly, the study indentified 3 genes (Integrin α3, Periostin, HCAM) in the cochlear sensory epithelium that exhibited higher expression levels than those in other examined tissue types, suggesting that these genes may be involved in sensory cell function. (Supported by NIH R01 DC010154-01A2)

6. Group I mGluR Activation at the Endbulb of Held

Soham Chanda and Matthew A Xu-Friedman

Department of Biological Sciences, College of Arts and Sciences, SUNY University at Buffalo

Group I metabotropic glutamate receptors (mGluRs) have been shown to play a role in several aspects of neuronal plasticity. We studied the mechanisms and effects of mGluR activation in the mammalian cochlear nucleus. We found that mGluRs are expressed on the postsynaptic bushy cells (BCs) but not in the presynaptic terminals made by auditory nerve (AN) fibers. Activation of mGluRs with dihydroxyphenylglycine (DHPG) caused calcium influx through L-type calcium channels in the BCs. This calcium influx further activated TRP channels causing membrane depolarization. The membrane depolarization was sufficient to enhance the firing probability of BCs in response to AN stimulation and improved the spike timing by reducing the latency and jitter.

7. Histone Deacetylase Activity is Important for Human Glial Progenitor Cell Differentiation

Gregory D Conway, Melanie A O'Bara and Fraser J Sim

Department of Pharmacology and Toxicology, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Chronic demyelinating diseases, such as Multiple Sclerosis, are characterized by a failure of remyelination, the regenerative process that restores lost oligodendrocytes and myelin. Drug-based approaches to stimulate remyelination have not succeeded in part due to a lack of understanding of the molecular mechanisms of human glial development. In rodents, histone deacetylase (HDAC) activity is required for oligodendrocyte (OLG) differentiation from glial progenitor cells (GPCs), but the role of HDAC activity in human cells has not been examined. In this study, we asked whether HDAC inhibitors (HDACi) might prevent or delay OLG differentiation from human GPCs. Human CD140a$^+$ GPCs were isolated from 18-22 week fetal brain using immunomagnetic sorting. Matched GPC cultures were pulsed daily with HDACi; trichostatin A (TSA) (dose range: 0-33.3nM, IC_{50}=5nM) or sodium butyrate (SB) (0–5.0mM, IC_{50}=140mM) for 2 or 4 days (n=4, fetal samples). To assess GPC differentiation, we performed immunocytochemistry using O4 antibody, which labels oligodendrocytes, and Olig2, which labels the entire oligodendroglial lineage. Both HDACi drugs produced a dose dependent reduction in proportion of O4$^+$ OLGs at 2 and 4 days (1-way ANOVA, $p<0.05$), but did not alter either Olig2% or overall cell number. At 4 days, TSA substantially retarded O4$^+$ OLG formation from 25.0 ± 3.1% in vehicle to 9.3 ± 5.8% in 33.3nM TSA (Tukey's post-hoc test, $p<0.05$). Furthermore, ≥33.3 nM TSA and ≥5mM SB significantly inhibited the formation of complex O4$^+$ cell morphology ($p<0.05$). Since HDACi did not alter the proportion of glial lineage cells, the dose-dependent inhibition of OLG differentiation and morphological maturation indicate that HDAC activity is necessary for human GPC differentiation *in vitro,* and suggest that the role of HDACs is conserved in both human and rodent GPCs. As such, stimulation of HDAC activity in GPCs represents an important target for strategies aimed at inducing remyelination.

8. Comparison of the Effect of Long and Short Access Exposure to Cocaine on Affect Regulation and Motivation in Rats

Devika Dhamija, Michael Lisieski and Alexis Thompson

Research Institute on Addictions, College of Arts and Sciences, SUNY University at Buffalo; Neuroscience, School of Medicine and Biomedical Sciences, SUNY University at Buffalo

Repeated psychostimulant use leads to changes in affect regulation ("anxiety") and motivation ("craving'); most theories of drug addiction suggest that these changes underlie behavioral adaptations that drive compulsive drug seeking and taking (i.e., drug dependence). Animal models that distinguish between *drug use without dependence* and *drug use with dependence* are not available. George Koob's research group developed a set of rodent self-administration procedures that model, they argue, the behavioral differences between drug use and drug dependence. The research presented here attempts to replicate this model and test the hypothesis that both affect regulation and motivation are different between groups that model drug use (ShA) and drug dependence (LgA). Male Long-Evans (hooded) rats were trained to self administer cocaine (0.5mg/kg per infusion) and allowed either 1h daily access (ShA) or 6h daily access to cocaine (LgA) for 21 days. Measures of “anxiety-like behaviors” and motivation to work for drug or drug cues were then made over a 7-week period of drug abstinence. Group differences in “anxiety-like behaviors” were tested at 72 h and 2 weeks after the last daily access to cocaine, using the elevated plus maze and defensive burying paradigms, respectively. Group differences in motivation to self-administer cocaine were assessed at 1 and 6.5 weeks after the last daily access to cocaine by using reinstatement tests. As expected, differences in access led to significant differences in the total amount of drug intake over the 3-week access period (ShA = 199 mg and LgA = 1165 mg mean intake for 21 days). However, few group differences in the measures of anxiety and motivation during the prolonged period of drug abstinence were found. Our data does not support the ability of this procedure to induce unique behavioral adaptations that distinguish drug use and drug dependence. A number of alternative explanations for our results will be presented.

9. The Role of GSK3β and Presenilin (PS) in Amyloid Precursor Protein (APP) Vesicle Transport

Kunsang Dolma and Shermali Gunawardena
Department of Biological Sciences, SUNY University at Buffalo

Intracellular transport of essential components, including signaling proteins, neuroprotective molecules, vesicular components, are required for neuronal viability. Recent studies shows defects in axonal transport pathways may contribute to the initiation of chronic neurodegenerative diseases. Presenilins are integral membrane proteins with eight transmembrane domains. It has been reported that PS1 not only has a role in regulating intramembrane proteolysis of proteins such as APP, but it may also have a role in the regulation of kinesin-1 during axonal transport. Previously our lab suggested that APP could function as a kinesin-1 receptor during transport. Since PS is also transported within the axon we investigated if PS and GSK3β influences APP vesicle transport. We used genetic interaction analysis between PS and GSK3β loss of function mutants. We also over expressed both PS and GSK3β to evaluate gain of function combinations. Although we do not see a genetic interaction between PS and GSK3β loss of function mutants, we do see an interaction in transgenic larvae over expressing both PS and GSK3β.Ongoing work will concentrate on elucidating the role PS and GSK3β play in APP vesicle transport.

10. Defects in Axonal Transport Causes Synaptic Problems by Downregulating BMP Signaling

Shermali Gunawardena, Min Jung Kang, Monique Michiewicz, Samantha Fye and Tadeusz Kaczynski
Department of Biological Sciences, College of Arts and Sciences, SUNY University at Buffalo

Formation of new synapses or maintenance of existing synapses requires the delivery of synaptic components from the soma to axodendritic sites via axonal transport. Here we examine how perturbations in axonal transport influence synaptic morphology and function. Using pre and post synaptic markers we found that both kinesin and dynein motor protein mutants in Drosophila show defects in the total number of boutons, in the ratio of the pre and post synaptic size of boutons and in the synapse length. Similar defects were observed in larval synapses expressing a cytoplasmic polyQ repeat protein or the human amyloid precursor protein with an FAD mutation. Previous work showed that both these disease mutants had axonal blockages similar to motor protein mutants. In contrast, analysis of loss and gain of function mutants of synaptotagmin showed synaptic defects but no axonal blockages were seen. Taken together we suggest that while axonal transport defects can induce synaptic defects, synaptic defects have no direct effect on axonal transport. Synaptic defects could arise due to transport dependent down regulation of BMP signaling components, since BMP growth factors regulate the development, growth and function of synapses in *Drosophila*. Reductions in the level of pMAD and WIT were observed in motor protein mutants and both mad and wit mutants showed genetic interactions with kinesin and dynein mutants. Thus, disruption of axonal transport may cause synaptic defects by downregulation of BMP signaling. Perhaps problems in long distance transport could trigger events that ultimately contribute to neurodegenerative disease pathology observed in Alzheimer's disease and Huntington's and other polyQ diseases.

11. Mapping Enthalpy Changes within the Acetylcholine Receptor-channel Gating Isomerization

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We studied the temperature dependence of gating in wild-type and mutant neuromuscular acetylcholine receptor-channels (AChRs; 5-35^{o}C). The mutations were in the α-subunit [W149, G153, A96, Y127, E45, P272, P265 and C418] or the δ-subunit [V269 and L265]. Gating rate and equilibrium constants were estimated from both ligand-activated and spontaneous single-channel currents. The wild type gating equilibrium constant was approximately temperature-independent, but the forward and reverse isomerization rate constants were temperature-dependent (activation enthalpy ~22 kcal/mol; Q_{10}~3.8). For three different agonists (acetylcholine, choline and carbachol), αG153S and αW149A/T the free energy change (ddG^o, at 25^{o}C) and the enthalpy change (ddH^o) were approximately equal but differed by >2 kcal/mol for αY127C/E, αP272G, αW149F/N/R and δV269C/A. The slope of the rate-equilibrium free energy relationship (ϕ) residues αW149 and δV269 was constant with temperature, and the slope for the enthalpy component of this relationship was equal to ϕ. These results suggest that the map of gating enthalpy changes consequent to mutation may be different than that for free energy changes.

12. Stress Hormone Levels and Hippocampal Neurogenesis Following Acoustic Trauma

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High intensity noise exposure has long been known to damage the inner ear; however, our recent study demonstrated that a single unilateral noise exposure (2h, 126dB, 12kHz) resulted in decreased hippocampal neurogenesis measured 10 weeks post noise exposure. Given the known ability of stress hormones to reduce hippocampal neurogenesis, we hypothesized that the reduction in hippocampal neurogenesis following unilateral noise exposure might be mediated by a sustained elevation in stress hormone levels. To test this hypothesis we monitored blood plasma levels of the stress hormone corticosterone in rats following acoustic trauma. Rats were divided into 4 groups: (1) unilateral or (2) bilateral noise exposure (2h, 126dB, 12kHz) under isoflurane anesthesia, (3) bilateral noise exposure (2h, 110 dB, 12kHz) unanaesthetized, or (4) 2h isoflurane anesthesia control. Blood samples were collected before, 45 minutes after and 1-6 weeks post exposure and plasma corticosterone levels were measured using an enzyme immunoassay kit. DPOAEs, a measure of OHC function, were suppressed 24 hours post noise exposure. Noise exposure caused a short-term increase in corticosterone levels; however, corticosterone levels did not remain elevated in the weeks following noise exposure. Thus the reduced neurogenesis, as previously observed, is not likely to be mediated by a sustained elevation in corticosterone levels following noise trauma. Further investigation into the effects of manipulating corticosterone levels during and following noise exposure will help clarify this point. Unexpectedly, we observed that 2 hours of isoflurane anesthesia dramatically (>10 fold) increased corticosterone levels measured 45 minutes post exposure. This increase in corticosterone was much greater than the effects of noise exposure alone; this may underlie the protective effects of isoflurane against noise trauma previously reported. Supported in part by NIH grants R01DC0090910 & R01DC009219-01.

13. Specific Bipolar Cell Types and More in Salamander Retina

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The salamander retina is often used as a model for vertebrate retinal function. I combined electrophysiology and cell staining to identify unusual cell types in this retina. Although retinal bipolar cells are thought to be short relay neurons, I found a subset that expressed large voltage-gated sodium currents and had a unique morphology. I also identified another set of bipolar cells that express large currents generated by T-type calcium channels. Finally, I also characterized atypical "ON"/"OFF" bipolar cells, identified both physiologically and morphologically. Two groups of interplexiform cells were confirmed with patch clamp methods. But in addition I identified neurons that had properties that were intermediate between bipolar cells and interplexiform cells. The results indicate a diversity and complexity of second order neurons in salamander retina. Thus, these relay neurons are divided into subclasses that allows for the efficient decomposition of visual information. The complicated outside world enforces this variety on the second order neurons in the visual system.

14. The MT1 and MT2 Melatonin Receptors Facilitate Methamphetamine-Induced Locomotor Sensitization

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The magnitude of drug-induced locomotor sensitization and reward-seeking behavior differs according to time of day (reviewed in Falcón & McClung, *Neuropharmacology* 2009;56:91-96). Although certain circadian regulatory systems are known to modulate the induction of sensitization, the precise physiological mechanisms governing diurnal variations in stimulant-induced behavioral responses have not yet been identified. We sought to determine how the pineal hormone melatonin, the synthesis of which is subject to a circadian rhythm, which peaks at night, interacts with the MT_1 and MT_2 melatonin receptors to influence the behavioral effects of the psychostimulant methamphetamine. Locomotor sensitization was induced in C3H-HeN mice by the daily administration of 6 injections of methamphetamine (1.2 mg/kg, i.p.), followed by 4 days of drug abstinence. The mice were tested for sensitization by measuring their distance traveled following a methamphetamine challenge injection. When tests were conducted during the daytime (5-7 h after the onset of the light phase of a 12h:12h light-dark cycle, when circulating levels of endogenous melatonin are low), wild-type mice pretreated with methamphetamine expressed significantly more locomotor activity when challenged with methamphetamine than did control animals subjected to repeated vehicle injections, indicating the strong expression of sensitization. Likewise, knockout mice lacking either the MT_1 or MT_2 receptors also exhibited robust sensitization, whereas double knockout mice lacking both receptors did not. Our results indicate that, under these experimental conditions, the expression of locomotor sensitization requires the intact expression of the MT_1 and MT_2 melatonin receptors. Future studies will confirm the role of endogenous melatonin in modulating locomotor sensitization and will explore the role of the MT_1 and MT_2 melatonin receptors in drug-seeking behavior using the MT_1 and MT_2 receptor knockout mice.

15. Energy Changes for Small Molecules at the Acetylcholine Receptor-Channel Transmitter Binding Site

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Acetylcholine receptors (AChRs) are ligand-gated ion channels involved in vertebrate neuromuscular transmission. Binding of acetylcholine (ACh, the endogenous neurotransmitter) increases the equilibrium constant of the 'gating' isomerization and the probability that ion channel domain adopts an ion-permeable conformation. The ratio of the isomerization equilibrium constants with two and zero bound agonist molecules (E_2/E_0) is equal to the ratio of agonist affinities in the inactive vs. active conformations of the protein, at two identical binding sites [$(K_d/J_d)^2$]. We define $R=K_d/J_d$ which is driving force of the gating reaction. Different agonists have different efficacies because they have different R values (E_0=6.5E-7). For ACh (=100 mV, 23 °C, mouse $a_2$bde), E_2=28.2 and R=6500. For choline, E_2=0.05 and R=270. For tetramethylammonium and carbachol, E_2=6.8 and R=3300. As part of a larger project to engineer the AChR transmitter-binding site to behave in predictable ways, we have measured E_2 and R values for a series of small molecular fragments. The goal is to generate an atomic map of the isomerization-induced energy changes at the ligand [kcal/mol=0.59ln(R)]. We first studied a series of four-, five- and six- membered N-containing rings (fragments of nicotine). In the nicotine-bound AChBP structure, the pyrrolidine ring of the ligand is at the center of an aromatic 'box'. Systematic substitutions of the atoms of this ring are being made and the corresponding R-values are being determined. Preliminary work suggests that the following small molecules activate wild-type AChRs: 1,1-Dimethyl Pyrrolidin-1-ium (E_2~0.37, R~757), 1,1-Dimethyl Piperidinium (E_2~0.05, R~280), 1,1-Dimethyl Thiazolidin-1-ium (E_2~0.53, R~903) and 4,4-Dimethyl Morpholinium (E_2~0.33, R~713), 4,4-Dimethyl Thiomorpholinium (E_2~0.75, R~1074).

16. Unipolar Brush Cells Express DCX in Dorsal Cochlea Nucleus, Paraflocculus and Flocculus of Adult Rat

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Adult neurogenesis is now a well-established phenomenon for granule cells of the dentate gyrus of the hippocampus and the subventricular zone (SVZ), the source of new cells that migrate to the olfactory bulb. However, some preliminary studies suggest that limited neurogenesis may also occur in the brainstem and cerebellum. To investigate this possibility, we used immunoreactivity for doublecortin (DCX) to identify immature neurons. We discovered many DCX-labeled cells in the granule cell layers of three circumscribed regions, the dorsal cochlear nucleus (DCN) and adjacent regions of the cerebellum in the flocculus (FL) and a small region of the ventral paraflocculus (PFL). DCX-labeled cells had the morphological appearance of unipolar brush cells (UBCs) with an oval cell body and a single dendrite ending in a "brush". Double-label immunofluorescence showed colocalization of DCX with calretinin (CR) or with epidermal growth factor substrate 8 (Eps8), two well-known markers for unipolar brush cells. There was no colocalization of DCX with GFAP ruling out the possibility that the DCX-labeled cells were glia. These data suggest the possibility of adult unipolar brush cells proliferation in the DCN, PFL and FL. These DCX-positive neurons may participate in neuroplastic processes in the auditory (e.g., localization, tinnitus) or vestibular system (e.g., vestibular compensation). Supported by NIH grants (R01DC0090910; R01DC009219-01)

17. Prospective Mechanistic Analysis of Fe-accumulation by the Brain

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Excessive accumulation of iron in brain has been linked to several neurological diseases including Alzheimer's, Parkinson's, and aceruloplasminemia. In the current literature, the evidence regarding physiologic mechanisms of iron influx into brain is unclear and controversial. To address this gap in knowledge, we focus on iron transport across the blood-brain barrier (BBB) and investigate the hypothesis that iron influx relies on the cooperation of two proteins: ferroportin, expressed in brain capillary endothelial cells (BCECs) and GPI-anchored ceruloplasmin, expressed on astrocytes. Ferroportin (Fpn) is the only known mammalian iron exporter and it requires ferroxidase activity for proper transport. To investigate whether the GPI-anchored ceruloplasmin expressed on astrocytes provides this necessary ferroxidase activity we will use an *in vitro* BBB model-system, consisting of monolayers of BCECs and astrocytes separated by a thin semi-permeable membrane. This model allows quantification of ^{55}Fe transport across the BCECs. Further, manipulations of the proteins of interest in either the BCECs (ferroportin) and/or the astrocytes (ceruloplasmin) will help delineate the transport mechanisms involved. Uncovering the physiological routes of iron transport into brain may provide novel protein targets to control and prevent pathological iron accumulation associated with a number of neurological diseases.

18. Direct and Indirect Activation of the PVN and the NTS by Urocortin I

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Urocortin I (UcnI) reduces food intake, increases blood glucose, and stimulates Fos expression in brain structures such as the paraventricular nucleus of the hypothalamus (PVN) and the nucleus of the solitary tract (NTS). Previous studies indicate that these effects occur with a similar magnitude regardless of whether UcnI is injected into the lateral ventricle (LV) or fourth ventricle (4V); however, it remains unclear which brain areas mediate these responses and which are activated directly by ventricular application of UcnI. To address these open questions, we have begun comparing the effects of UcnI after application to the LV, 4V, NTS or PVN. We confirmed earlier findings related to feeding, glucose, and Fos expression after ventricular administration of UcnI, but found that Fos expression in the PVN was more sensitive to LV injections of UcnI than it was to 4V injections. We also replicated earlier studies by finding that UcnI administered directly to the PVN decreased food intake. Contrary to our prediction based on earlier work using decerebrate rats, injection of UcnI into the NTS did not increase blood glucose. Current studies are measuring Fos expression in the hindbrain and forebrain after application of UcnI to the PVN or NTS. Taken together, our preliminary studies suggest that the PVN is involved in the behavioral response to UcnI and can be activated both directly and indirectly, and that UcnI in the NTS fails to recruit pathways required for at least one of the physiological effects of UcnI.

19. Ghrelin Reduces Salt Intake Under Some Natriorexigenic Conditions

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Recent studies suggest that ghrelin plays a role in fluid balance in addition to its well-established effect on food intake. Previous work in our lab demonstrated that rats treated with ghrelin drank less water than controls after injection of hypertonic saline or angiotensin II (AngII) and another lab reported a similar effect of ghrelin after water deprivation or injection of polyethelene glycol (PEG). Although the effect of ghrelin on water intake has been evaluated under a variety of circumstances, its effect on salt intake has not been tested. Accordingly, we measured water and salt intakes after injection of ghrelin in rats receiving icv AngII or rats exposed to a water deprivation-partial rehydration (WD-PR) paradigm. Although our preliminary studies using AngII suggested the possibility of a more selective effect of ghrelin on saline intake than on water intake, a more complete set of studies using a two-bottle approach found that ghrelin treatment decreased AngII-induced water intake without affecting concomitant 1.8% NaCl intake. When we used the WD-PR paradigm to stimulate saline intake, ghrelin reliably decreased intake of 1.8% NaCl. Preliminary data from ongoing studies in the lab suggest that ghrelin reduces saline intake after PEG treatment without affecting water intake. Thus, it appears that ghrelin attenuates salt intake in some, but not all, natriorexigenic conditions. Understanding the physiological basis for these differences and determining the mechanism of action involved merit further investigation.

20. Cortisol Levels and Verbalization in High-Functioning Autism

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Children with autism spectrum disorders have been found to score higher on measures of anxiety and social worries. Research has also shown these individuals secrete a higher amount of cortisol during the day when compared to typical peers. It has been hypothesized that daytime school attendance and being subjected to a highly social environment may be contributing factors to the hyper-release of this stress-response hormone. There have also been numerous studies that have found a relationship between higher cortisol levels and decreased vocalizations in bulls, guinea pigs and a special population of human children with retardation. The current study examined the relationship between cortisol levels and total verbalizations in a sample of children with high-functioning autism spectrum disorders (n=14). Each child participated in two game sessions (each session involved 20 minutes of the game "Uno" followed by a salivary cortisol collection). One session was with a familiar peer and the other with an unfamiliar peer and the participants were randomly assigned to the order condition. Videotapes were then transcribed for five minutes in duration, twenty minutes prior to the collection of cortisol. Results indicated significantly fewer verbalizations when cortisol levels were high and more verbalizations when cortisol levels were low. This relationship, when considered in the context of other research involving high anxiety, social weariness and relatively high cortisol levels, may suggest a contributing factor to the social impairment of this at-risk population.

21. The NMDA Receptor Supports Ferrous Iron Accumulation

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Over-activation of N-methyl-D-aspartate receptors (NMDARs) and the resulting calcium flux into the post-synaptic neuron is linked to a variety of neuropathologies including epilepsy, cerebral ischemia and Alzheimer's disease (AD). Ferrous iron, Fe(II), an essential but cytotoxic metal ion endogenous to the mammalian central nervous system has been linked also to the pathophysiology underlying several neurodegenerative diseases such as Parkinson's and AD. Moreover, there is evidence that Fe(II) modulates the function of the NMDAR by mechanisms not yet characterized. Here we show that Fe(II) is transported by NMDAR regardless of the presence of the agonists glutamate and glycine; this uptake is quantitatively the same in absence and presence of Ca^{2+}. In contrast, Mg^{2+} inhibits NMDAR-dependent ^{55}Fe-uptake by ~90% ($p<0.001$); this inhibition of ^{55}Fe-uptake by Mg^{2+} is not observed for the N+1G GluN2A pore mutant that is resistant to magnesium block. Mg^{2+} has no effect on ^{55}Fe-uptake supported by the divalent metal ion transporter DMT1 used as a positive control. Additional experiments using truncations and site-directed mutants of NMDAR subunits are needed to map the Fe binding site on the subunits of NMDAR.

22. Role of Salt Bridges within the Ligand Binding Domains of NMDA Receptors during Receptor Activation

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Glutamatergic synaptic transmission mediated by the *N*-methyl-D-aspartate receptor (NMDAR) plays a fundamental role in numerous central nervous system processes, but how the receptor becomes active is insufficiently understood. Structural studies of isolated ligand binding domains (LBDs) revealed that agonists bind between two flexible lobes (D1 and D2) and cause the lobes to move closer together engulfing the ligand. In many cases, the degree of agonist-induced domain closure of isolated LBDs and the stability of the closed cleft LBD conformation have been positively correlated with the agonist's ability to activate the intact, tetrameric receptor. However, the role of native cross-lobe interactions in the activation of intact NMDARs is unknown. To evaluate the contribution of individual cross-cleft interactions implicated by previous studies in stabilizing agonist-induced LBD closure, we produced receptors that lacked these interactions by alanine substitution and quantified their activities by kinetic analyses of single channel traces. We were surprised to find that receptors containing GluN1 (K483A) and GluN2 (K487A) had activities that were ~10% higher than wild-type (WT) controls, suggesting that in the absence of a cross-cleft salt-bridge, lobes close further. Receptors containing GluN1 (K483M) subunit had WT-like activity, whereas those containing GluN2 (N687L) subunits had activities that were ~30% lower than WT controls. These results suggest that removal of cleft-spanning interactions allows for more flexibility and, thus, greater compression of the LBD lips during gating, and they serve to restrict the LBD from achieving maximal cleft-closure.

23. Engineering Transmitter Binding Sites in AChRs

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Nicotinic acetylcholine receptor channels (nAChRs) can undergo R(**C**losed)↔R^*(**O**pen) spontaneous gating transitions. However, the equilibrium constant of this switch is very low (~10^{-7}). In presence of physiological agonist acetylcholine, the probability of liganded gating transition is increased to ~10^2. The R-state acetylcholine affinity (K_d) is ~150µM. From the relationship $E_2/E_0=(K_d/J_d)^2$,the estimated R^*-state affinity (J_d) for acetylcholine is ~22nM. Thus, the equilibrium constant of the liganded AChR gating conformational change is coupled to an affinity change for agonists at the transmitter-binding-sites. Experimental measurement of E_2 and K_d are feasible, however, direct estimation of E_0 and J_d is challenging. Here we present a novel approach to measure E_0 directly. We performed E_0 estimations in 25 constructs having multiple gain-of-function mutations. The estimated E_0 was correlated with the product of the predicted fold-increase in the E_2 caused by each mutation alone. The calculated E_0^{wt} is ~6.5E-7. We then measured single-channel activation parameters for apo-AChRs having combinations of mutations of 10 transmitter-binding-site residues in the α(Y93, G147, W149, G153, Y190, C192, and Y198), ε(W55 and P121), or δ(W57) subunit. Gating energy changes were largest for the tryptophan residues. αG147 acts as an 'activation' hinge where backbone flexibility maintains high values for E_0, K_d and the net ligand binding energy. αG153 acts as a 'deactivation' hinge that maintains low values for these parameters. αW149 (between these two glycines) mainly serves to provide ligand binding energy for gating. Together, these results provide a basis for understanding energetics of receptor conformational switch.

24. GABAB Receptor Feedback Regulation of Bipolar Cell Transmitter Release

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GABAergic amacrine cell feedback to bipolar cells has been described, activating both $GABA_A$ and $GABA_C$ receptors. We explored whether metabotropic $GABA_B$ receptors also participate in this feedback pathway. CGP55845, a potent $GABA_B$ receptor antagonist was employed to determine the endogenous role of these receptors. Ganglion cell EPSCs and IPSCs were monitored to determine the output of bipolar and amacrine cells. Using the tiger salamander slice preparation, we found that $GABA_B$ receptors pathways regulate bipolar cell release directly and indirectly. In the direct pathway, the $GABA_B$ receptor antagonist reduces EPSC amplitude, indicating that $GABA_B$ receptors cause enhanced glutamate release from bipolar cells. In the indirect pathway, the $GABA_B$ receptor antagonist also reduces EPSC amplitude. This effect is only evident when $GABA_A$ receptors are inhibited, and is blocked by a glycine receptor antagonist. Thus, this second feedback pathway involves direct glycine feedback to the bipolar cell and this glycinergic amacrine cell is suppressed by a GABAergic amacrine cell through both $GABA_A$ and $GABA_B$, but not $GABA_C$, receptors. Overall, $GABA_B$ receptors contribute to feedback regulation of bipolar cell transmitter release; however, unlike the ionotropic GABA receptor pathways, the metabotropic GABA receptor pathway acts to enhance transmitter release. The results also implicate three discrete, non-overlapping bipolar to ganglion cell pathways, indicating there are unique channels of information flow to the output neurons of the retina.

25. Estrogen Protects Against the Detrimental Effects of Repeated Stress

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Converging evidence has suggested that females and males show different cognitive and emotional responses to stress, however little is known about the mechanism underlying the sexually dimorphic effects of stress. In this study, we found that juvenile female rats exposed to 1 week repeated restraint stress exhibited normal AMPAR- and NMDAR-mediated synaptic transmission in pyramidal neurons of prefrontal cortex (PFC), which is in sharp contrast to the significantly reduced glutamatergic transmission in PFC neurons from stressed male rats. Injection of the estrogen receptor (ER) antagonist ICI182,780 to female rats led to significantly diminished AMPAR and NMDAR surface expression and synaptic responses after repeated stress, while injection of the ER agonist estradiol to male rats led to normal glutamatergic signaling after repeated stress. In parallel, stressed female rats exhibited much better performance than stressed male rats on the novel object recognition (NOR) task, a cognitive function depending on synaptic excitation in PFC. Females rats with injection of ICI 182,780 showed significantly worse performance, while male rats with injection of estradiol showed significantly improved performance, in the NOR task after repeated stress. These results suggest that estrogen can protect against the detrimental effects of repeated stress on synaptic transmission and PFC-dependent memory, which may underlie the resilience of females to chronic stress.

26. Target-Cell-Specific Synaptic Plasticity Occurs Cell by Cell in the Cochlear Nucleus

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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.

27. Repeated Stress Causes Cognitive Impairment by Suppressing PFC Glutamate Receptors

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It is known that chronic stress could trigger maladaptive changes that lead to cognitive and emotional disturbances symptomatic of stress-related mental disorders, such as depression, anxiety and post-traumatic stress disorder (PTSD). However, the molecular and cellular mechanisms underlying the action of chronic stress remain elusive. In this study, we found that exposing juvenile male rats to repeated restraint stress led to significantly impaired performance in the novel object recognition task, a paradigm for working memory controlled by prefrontal cortex (PFC). Concomitant with this behavioral impairment, significantly reduced

AMPAR- and NMDAR-mediated synaptic transmission was found in PFC pyramidal neurons from repeatedly stressed animals. The expression of GluR1 and NR1 subunits in PFC was also selectively reduced by repeated stress. All these effects relied on activation of glucocorticoid receptors and the subsequent enhancement of ubiquitin/proteasome-mediated degradation of glutamate receptor subunits. Our results suggest that repeated stress dampens PFC glutamatergic transmission by facilitating the turnover of glutamate receptors, which may underlie the detrimental effect of long-term stress on PFC-dependent cognitive processes.

Registered Participants

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