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3-1-A

Brain Awareness Week

Anne-Julie Chabot-Dore* and Denise Cook*

Brain Awareness Week (BAW) is an international event organized by The Dana Alliance for Brain Initiatives in collaboration with the Society for Neuroscience. In Montreal, the event is organized by a group of graduate students from McGill University, Université de Montréal, Concordia University and UQAM. Together, we organize several scientific activities for the general public such as presentations in elementary and high schools, open houses in research institutes and a neuroscience trivia contest. Every year, our activities reach about 10 000 kids and the event is growing in popularity among the scientific happenings in Montreal. The success of this event relies on the organization and preparation of these activities all year long. We
are currently looking for graduate students interested in organizing the next BAW campaign that will occur during March 2011. Interested? Come to the Brain Awareness Week Poster (3-1-A) at the IPN Retreat to get details about our upcoming information session. Don't miss this opportunity to gain valuable experience and have fun!

3-1-B

Role of p38 mitogen-activated protein kinase signaling in oligodendrocyte differentiation and myelination

Jeffery D. Haines1, Stéphane Richard3, Walter E. Mushynski2, Guillermina Almazan1*

The precise molecular mechanisms regulating myelin formation in the CNS are only started to be elucidated. The objective of our work was to assess whether p38 regulates oligodendrocytes differentiation and myelination. In oligodendrocytes (OLG) cultures treatment with p38 inhibitors decreased mRNA and protein for myelin-specific genes (myelin basic protein (MBP), myelin associated glycoprotein (MAG), 2',3'-cyclic nucleotide 3'-phosphodiesterase, and UDP galactose:ceramide galactosyltransferase). p38 inhibitors also blocked myelination of dorsal root ganglion neurons by OLGs and prevented the axolemmal organization of the axo-glial adhesion molecule Caspr. In addition, inhibition of the p38 substrate, mitogen-activated protein kinase activated protein kinase 2 (MK2) using CMPD1 decreased accumulation of myelin proteins. We corroborated these findings using a small-interfering RNA to MK2, which decreased galactosylceramide and MAG. CMPD1 also decreased the mRNA encoding myelin transcription factor 1 (Myt1), MAG and MBP. In contrast, increases were observed in OLG transcriptional repressors, including transcription factor 4, Notch1, and inhibitor of differentiation 2. To better understand how the p38 MAPK signaling cascade regulates OLG differentiation, we performed an Illumina rat whole genome microarray analysis of OLPs treated with PD169316 for 24 and 48 hours. Changes in factors affecting actin cytoskeletal arrangement, molecular transport, cell cycle regulation, transcription, and chromatin modification were detected. Our results suggest roles for this kinase in key regulatory steps in OLG differentiation and initiation of myelination. Clues from this work could result in the development of strategies to reinitiate myelination of axons in demyelinating diseases including multiple sclerosis. Funded by the MSS of Canada.

3-2-A

Unraveling the Regulatory Code of Myelin Genes

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Oligodendrocytes and Schwann cells elaborate myelin sheaths around large caliber central nervous system (CNS) and peripheral nervous system (PNS) axons, respectively. Despite distinct embryological origins, their myelin sheaths share common structural features and components and several myelin genes exhibit coordinated expression patterns during myelinogenesis. However, cell-specific proteins responsible for stabilizing compact myelin in the CNS and PNS are well documented. Thus, the transcriptional network regulating myelin genes is capable of driving several context-specific regulatory programs, potentially controlled by a large repertoire of transcription factor (TF) interactions. While several TFs have been shown to have a regulatory role in oligodendrocyte myelination, the corresponding regulatory DNA landscape and TF protein network is largely unknown. We have defined cis-regulatory regions that confer transcriptional control of a set of myelin genes expressed in oligodendrocytes. These validated enhancer sequences were combined with oligodendrocyte coexpression data and a novel sequence analysis algorithm to predict combinatorial TF interactions in a transcriptional network model. Notably, this model identifies TFs known to operate in oligodendrocytes, thereby validating the approach, and most importantly, identifies novel TFs not previously associated with oligodendrocyte development. The myelin enhancer collection, oligodendrocyte co-expression datasets, and predicted myelin gene transcriptional network presented here offer new insights into the complex regulatory mechanisms directing myelination in the oligodendrocyte lineage. Finally, we present use case examples using the oligodendrocyte TF network predictions that distinguish and expand on previously demonstrated myelin gene transcriptional mechanisms. The novel resources described here appear capable of significantly enhancing our understanding of oligodendrocyte myelin gene regulation.

3-2-B

Uncovering Comorbidity Patterns in Suicides with Histories of Alcohol Disorders

Yang Ding*, Eduardo Chachamovich, Gustavo Turecki

Suicide has been particularly associated with a history of alcohol abuse and dependence. It has been previously demonstrated that suicide attempters with alcohol-related disorders have distinctive psychopathological characteristics. However, no studies have investigated the psychopathological profile of suicide completers with alcohol disorders. Our study aimed to identify patterns of comorbidity unique to suicide completers with histories of alcohol disorders. 158 pairs of cases and controls were recruited from the Coroner's office in Montreal, Canada. Subjects were assessed by proxy-based interviews and classified either as alcohol-disorder cases or controls based on the presences of alcohol abuse or dependence according to the Diagnostic and Statistical Manual of Mental Disorders Version IV (DSM-IV) criteria. We conducted psychological autopsies with relatives of suicide completers to collect comprehensive psychopathological information on suicide completers by means of the Structuraled Clinical Interviews for DSM-IV Axis I and II disorders, as well as socio-demographic data and impulsivity and aggressiveness level using the Barratt Impulsivity Scale and Brown Goodwin Aggression History questionnaires. Suicides with histories of alcohol disorders had a significantly different clinical profile in Axis II comorbidity: particularly increased frequencies of and conduct problem (?2=9.457, p<0.009, OR=9.768) and antisocial personality disorders (?2=29.063, p<0.001, OR=30.112) and decreased frequencies of avoidant (?2=7.109, p<0.001, OR=10.272) and obsessive compulsive disorder (?2=7.754, p<0.021, OR=10.195). We also observed significantly higher aggression history (p<0.001) and impulsivity measures (p<0.001) in our cases. Our preliminary findings are consistent with previous work suggesting that different comorbidity patterns associates with suicide completers with alcohol-related disorders and characterize vulnerability factors unique to the suicide completers with varying degree of alcohol disorders.

3-3-A

Nogo-66 Receptor1 shedding in the central nervous system

Gino B. Ferraro* Isabel Rambaldi Alyson E. Fournier

Nogo-66 receptor 1 (NgR1) is a GPI anchored receptor expressed by neurons throughout the mammalian central nervous system (CNS). NgR1 binds with high affinity to three major myelin-associated inhibitors and plays important roles in restricting both plasticity and axonal regrowth following injury in the adult CNS. Previous studies have demonstrated that NgR1 is physiologically cleaved from the neuronal cell surface releasing a dominant negative fragment of NgR1. NgR1 shedding can be blocked with tissue inhibitors of metalloproteinases (TIMPs); however, the metalloproteinase that regulates physiological NgR1 shedding has not been identified. Using both overexpression and loss of function approaches we find that several membrane type matrix metalloproteinases (MT-MMPs) can promote NgR1 shedding from neurons and that loss of function of a single MT-MMP can regulate NgR1 shedding. We are currently studying the effects of MT-MMP overexpression and loss of function on myelin-dependent growth cone collapse to define the role of MT-MMPs in regulating neuronal responses to myelin.

3-3-B

Synapsin II in bipolar disorder: effects of lithium treatment on gene expression

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Genetic studies in bipolar disorder (BD) have identified a wealth of candidate genes and loci with limited replication between studies, indicating high heterogeneity among samples. For this reason, we have focused on patients who are excellent responders to lithium (Li) prophylaxis to find pertinent candidate genes in a more homogeneous population. Through a linkage study in Li-responsive BD patients followed by a microarray expression study in post-mortem BD and control brains Synapsin II (Syn2) has previously been identified as an interesting candidate gene. We showed Syn2 to be up-regulated in BD brains compared to controls, and in order to investigate the connection to Li-response, we sought to determine if Li modulates Syn2 expression. To model the genetic background of Li-responder BD patients, long-term Li treatment assays were performed in B-lymphoblastoid cell lines from BD patients classified as excellent Li responders, non-responders, as well as non-psychiatric controls. Additionally, to model brain expression patterns, treatment assays were performed in brain-specific cell lines and gene expression changes were quantified using real-time PCR. In both models, we found Syn2 to be upregulated by in the presence of Li in cell culture - which replicated our previous findings in post-mortem BD brain samples. By focusing on Li-responsive BD we have identified a strong candidate gene for the etiology of the disorder, as well as a potential mechanism for positive response to treatment in BD patients.

3-4-A

CRMP4 regulates the neuronal cytoskeleton and neuronal responses to myelin inhibitors

Mohammad R. Khazaei*, Stephan Ong Tone, Alyson Fournier.

Factors in the CNS environment including myelin-associated inhibitors (MAIs) have negative effects in neurite outgrowth during regeneration. Neurons respond to MAIs by activating RhoA, a promising but ubiquitous target for therapeutic intervention to promote CNS repair. We previously identified CRMP4b as a protein that functionally interacts with RhoA to inhibit neurite outgrowth. Overexpression of the amino terminal domain of CRMP4b (C4RIP, CRMP4b-RhoA Interfering Peptide) interferes with the RhoA-CRMP4b interaction and promotes neurite outgrowth on myelin substrates. We have developed a cell permeable version of C4RIP (TAT-C4RIP) to examine the therapeutic efficiency of C4RIP in axonal regeneration in vitro and in vivo. Here we report that TAT-C4RIP promotes neurite outgrowth of dorsal root ganglion neurons on myelin substrates justifying further studies on its affect on regeneration in optic nerve injury and spinal cord injury models in rat. To gain further insights into how CRMP4b influences neurite outgrowth, we overexpressed CRMP4b and C4RIP in rat hippocampal neurons. We find that manipulating CRMP4b function affects growth cone filopodia and the formation of actin-rich protrusions from neurites indicating that CMRP4b affects the neuronal actin cytoskeleton.

3-4-B

Epigenetic Modifications in Astrocytic Genes: A Suicide Endophenotype

Corina Nagy* Carl Ernst Gustavo Turecki

Many systems have been implicated in the neurobiology of depression and suicide, including the stress system, lipid metabolism, cell signaling and neurotransmission. Recently our lab has implicated astrocytic dysfunction as a possible neurobiological factor mediating suicidal behavior. Initially, astrocytes were thought of as a metabolic and structural support mechanism in the brain. Their role has since evolved to include but is not limited to; transmitter reuptake and release, regulation of ion concentrations and nervous system repair. Our lab has identified a network of astrocytic genes (SOX-9, CX30, CX43, GLUL, FGFR3, SLC1A3) which are differentially expressed in the brains of suicide completers compared to controls. Moreover, these genes were found to be extremely under expressed in a distinct sub-population of suicide completers. To date, our lab has identified 21 extreme low expressing male suicide completers from a total sample size of 98 male suicide completers, which represents ~1/5th of the disease phenotype. As suicidal behavior frequently occurs in individuals with a history of childhood adversity and recent evidence has demonstrated that environmental stressors can modulate gene expression by marking DNA without altering its underlying sequence, a compelling explanation could be attributed to epigenetics. Epigenetic mechanisms include: histone acetylation, methylation, ubiquitylation, phosphorylation and sumoylation, however DNA methylation is by far, the most studied example of epigenetics in suicide and other psychiatric disorders. The addition of a methyl group to a cytosine at a CpG site resulting in the conversion of cytosine to 5-methylcytosine, is one of the factors found to play an important role in the regulation of gene expression. As the environment can exert important and long lasting influence on suicide risk, we hypothesize that these influences are mediated through epigenetic mechanisms, and particularly promoter methylation, controlling the expression of genes associated with the above mentioned astrocytic network. Given the growing evidence implicating astrocytes in suicide, this study hypothesizes that methylation in the regulatory regions of these genes may account for their differential expression in suicide.

3-5-A

14-3-3 proteins regulate axonal growth cone responses by regulating PKA activity.

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The growth cone is a critical structure regulating the speed and direction of neuronal outgrowth during development. How the growth cone spatially and temporally regulates signals from guidance cues is not fully known. Through a proteomic analysis of a mechanically purified growth cone preparation from E6 chick RGCs we identified several isoforms of the 14-3-3 family of adaptor proteins as major constituents of the growth cone. 14-3-3 proteins bind and regulate the activity of multiple proteins through interactions with phospho-serine and phospho-threonine containing motifs. Using the 14-3-3 antagonist R18 or miRNA-mediated knockdown of individual 14-3-3 isoforms we find that 14-3-3 proteins mediate NGF-dependent effects on filopodial length, the retrograde flow of F-actin and growth cone turning. Intriguingly 14-3-3 disruption switches nerve growth factor-dependent repulsion to attraction in E13 chick and P5 rat DRG neurons. This switching effect and NGF-dependent effects on filopodial length are blocked by inhibitors of PKA indicating that 14-3-3 proteins may directly regulate PKA. Consistent with this model, specific 14-3-3 isoforms interact with the PKA regulatory subunit. Further, R18 expression results in a dissociation of the regulatory and catalytic subunit of PKA and increased phosphorylation of the catalytic subunit, indicating increased PKA activity. Together our data indicates that 14-3-3 proteins play a critical role in modulating growth cone responses to extracellular cues in part through regulating PKA. We are currently investigating additional 14-3-3-substrate interactions that regulate growth cone dynamics.

3-5-B

Is cortisol a predictor of progression to Alzheimer's disease in individuals with Mild Cognitive Impairment?

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Patients with Alzheimer's disease (AD) secrete more cortisol (a stress hormone) than healthy elderly individuals. People with Mild Cognitive Impairment (MCI), who also secrete more cortisol than healthy elderly individuals, are at an increased risk for developing AD. However, since not all MCI individuals progress to AD, determining which persons will develop AD becomes an important objective. The specific goal of this study was to evaluate whether cortisol levels measured in MCI contribute to a predictive model of AD. Salivary samples were collected one day at cohort entry in 59 MCI recruited at the memory clinic of the Jewish General Hospital. All participants were followed-up annually until December 2006 to distinguish MCI progressors (MCIp) from non-progressors (MCInp). The final model comprised age, APOe4 status, hippocampal volume and cortisol [AUC (95% CI) = 0.86 (0.76-0.96)]. Hippocampal volume measurement was the only independent variable that predicted progression to AD ($p<0.05$). Lower cortisol, though not an independent factor ($p=0.08$), contributed significantly to the model [AUC without cortisol (95% CI) = 0.77 (0.62-0.91)]. It is therefore possible that cortisol is an indirect measure of an explicative variable not measured in this study.

3-6-A

Developmental Cognitive Neuroscience and the Blameworthiness of Youth: Results from a Survey of Multiple Experts

Irina Demacheva, B.A.(*), Amir Raz, Ph.D.

Statistics indicate that 60% of delinquents in the juvenile justice system have behavioral, mental, or emotional disorders and are in need for treatment. Placing effort on the rehabilitation, rather than on punishment, of offenders may be an effective way to prevent both, crime and poor mental health of young delinquents. Developmental science may provide an insight on how young delinquents should be treated. While developmental and cognitive science, and especially neuroscience, have been percolating through legal theory and practice, the implications of research findings for the judicial system remain largely theoretical. We report data from an online survey assessing the opinions and beliefs of scientists, legal, and medical specialists regarding the impact of developmental factors on youth blameworthiness and ability to stand trial. Our findings reveal that medical and research communities are at odds with legal specialists. We outline how a closer dialogue between law and science is essential to insure a reasonable approach to young delinquents in the United States of America and worldwide.

3-6-B

Exploring the effects of computerized-targeted attention training in children

Amir Raz Elena Perez-Hernandez Sheida Rabipour* Victoria Ng

Objective: The present study sought to identify the optimal period for an attention training program aimed at children with Attention Deficit Hyperactivity Disorder (ADHD). We compared outcomes between preschool and primary school children. Participants and Methods: Thirteen ADHD children (six 4-6 years; seven 7-10 years) participated in a variation of a published attention training program: 10 sessions lasting 30 minutes each, occurring over a period of 3-4 weeks. Pre- and post-assessment: verbal and non verbal (RIST and sections of RIAS); parent report of hyperactivity and problems associated with attention based on the Behaviour Assessment Scales for Children (BASC2). Post assessment: two weeks after finishing the training program. Results: Within-subject ANOVAs assessed the effect of group (preschool/primary school) and assessment session (pre/post). Analysis revealed a significant interaction between assessment session and group [$F(1,6)=7.76$, $p<0.012$]. We applied Bonferroni-correction for all binary and multiple comparisons. Improvements were evident after two weeks of training for both groups on verbal as well as non-verbal tasks. Analysis of parent reports revealed a statistically significant reduction of negative symptoms in primary school children ($p<0.008$) while improvements in preschool children were not significant. Conclusions: Our findings suggest that the attention training used reduced ADHD symptomatology. Based on parent reports, primary school children – but not preschool children – experienced a significant reduction in undesirable symptoms. It may be beneficial to implement attention training in primary schools for children with ADHD.

3-7-A

Retinotopically organized resting-state functional connectivity within and between areas of the human visual cortex

Kuwook Cha*, Lindsay B. Lewis, Felix Carbonell, Janine D. Mendola & Amir Shmuel

Recent fMRI studies demonstrated resting-state functional connectivity (RS-FC) which has been used to group cortical areas to functional networks. It has been hypothesized that RS-FC is mediated by thalamo-cortical and cortico-cortical connections. However, the functional specificity of intra- and inter-areal RS-FC remains unknown. Here we aimed at testing whether RS-FC within and between areas of the human visual cortex are retinotopically organized. Eight subjects were scanned at 3 Tesla. Visual areas V1, V2, V3, V3A, V3B, hV4, LO1, LO2 and V5/MT+ were defined according to retinotopy and divided into sub-regions according to the eccentricity. The resting-state time series were band-pass filtered (0.01-0.1 Hz cut-off). The first principal component, which accounted for most of the variance in the global average, was removed. RS-FC measures between the pairs of ROIs were obtained by computing the correlation coefficients between the corresponding time-courses. When we correlated resting-state spontaneous activities between areas in each hemisphere, adjacent areas, e.g., V1-V2, V2-V3, V3-hV4, showed relatively strong RS-FCs. After dividing each area into sub-regions according to eccentricity, we observed retinotopic layout of intra- and inter-areal RS-FCs within hemispheres: the closer in the eccentricity representations the sub-regions were, the more correlated their spontaneous activity were both within-areas and between-areas. The observed pattern of RS-FCs within hemispheres were preserved in intra- and inter-areal RS-FCs between-hemispheres. These findings demonstrate within-area and inter-areal, inter-hemispheric, retinotopically-specific patterns of RS-FC. We expect that, to a first approximation, these RS-FC measures reflect network specificity and functional organization of the anatomical connections between visual areas.

3-7-B

Functional Analysis of the Cytoplasmic Domain of Coxsackie and Adenovirus Receptor (CAR) in Regulation of Cancer Cell Migration and Invasion

Hui Chen*, Zakaria Orfi and Josephine Nalbantoglu

The Coxsackie and Adenovirus Receptor (CAR), the primary binding receptor of both Coxsackievirus and many serotypes of Adenovirus is a cell adhesion molecule of the immunoglobulin superfamily. Low or absent CAR expression has been seen in many primary tumors in comparison to adjacent normal tissue. CAR is also downregulated in many cancer cell lines and its re-expression strongly inhibits growth of these cell lines. We have previously shown that CAR inhibits glioma cell migration, a priming step for cancer development and metastasis, through its direct interaction with microtubules and actin, and that the cytoplasmic domain of CAR is required for decreased invasion and intracerebral growth of human glioma xenografts. We have continued using glioma cells as a model to study the mechamism by which the cytoplasmic domain of CAR inhibits cell migration. To determine the minimum cytoplasmic region of CAR required for inhibition of cell migration, we have cloned truncated versions of CAR that lack different domains of the C-terminal portion, followed by stable expression in glioma cells and evaluation of cell migration ability using a ring cell migration assay that we developed, as well as characterizing the mutants in cell invasion assays. In parallel, we also examined the contribution of the four conserved tyrosines in the cytoplasmic tail of CAR by mutating each individually to alanine residues. In both cell migration and invasion assays, deletion of the last 26 amino acids (aa) results in loss of the inhibitory effect of CAR on glioma cell migration and invasion, suggesting that this 26aa part is essential for CAR's role in cancer cell migration. Further analysis suggested that deletion of the PDZ-binding motif "SIV" at the distal end of cytoplasmic domain also abolished CAR inhibition of glioma cell migration and invasion, pointing to the "SIV" motif as a determinant in this function of CAR. As well,, the single mutation of tyrosine 294 (Y294A) in the C-terminus of CAR abrogated CAR mediated inhibition of migration while the single mutation of the other three tyrosines 269, 313, 318 had a slight or no effect, demonstrating similar migration and invasion rates as those of cells expressing wild-type CAR. These findings suggest a novel CAR-mediated signaling pathway in inhibition of cancer cell migration and invasion. Further studies will shed new light on the mechanism by which CAR inhibits cancer cell migration and invasion, and eventually, tumor growth and metastasis.

3-8-A

DTI tractography and structure-function relationship in the human visual cortex

Debbie Dawson, Lindsay Lewis, Kuwook Cha, Janine Mendola, Amir Shmuel

Diffusion Tensor Imaging (DTI) is a magnetic resonance based technique used for estimating axonal connections based on local anisotropy of water diffusion in the brain. Although in the greater sense, the diffusion is isotropic, locally the diffusion is faster parallel to axonal bundles than orthogonal to them. Therefore, DTI allows us to quantify the orientation of maximal diffusion in individual voxels and then compute the likely presence of tracts based on continuity between adjacent voxels. Functional Magnetic Resonance Imaging (fMRI) recognizes the diamagnetism of oxyhemoglobin flowing to active areas in the brain and thus allows for the localisation of areas responding to a stimulus. Upon presentation of a stimulus, neuronal response in early visual areas corresponds spatially to the visual field, a concept called retinotopy. In order to map retinotopy, subjects view eccentric and radial stimuli that span the visual space. The combination of the eccentric and radial progressions in responsiveness allow for a delineation of visual areas. Using these delineations, Cha et al. (SFN 2010) demonstrated recently that resting state functional connectivity is retinotopically organized within and between visual areas. Those areas highly correlated at rest, in the absence of any visual stimulus, are expected to have direct neural tracts connecting them. My study investigates this hypothesis, namely, whether retinotopically organized functional connectivity is associated with a similar retinotopically organized DTI-based pattern of connections between visual areas. Combining this knowledge of functional connectivity and DTI data, we hope to outline a more complete map of the connections within the human visual cortex.

3-8-B

The novel cell adhesion molecule Coxsackievirus and Adenovirus Receptor undergoes ectodomain shedding by the ADAM family of metalloproteases and Presenilin/gamma-secretase-mediated intramembrane cleavage

Nadia Houri*, Kuo-Cheng Huang, Luyu Zheng and Josephine Nalbantoglu

The Coxsackievirus and Adenovirus Receptor (CAR) is a single-pass transmembrane protein originally identified as an attachment site for Coxsackie B viruses and a number of adenoviruses relevant for gene therapy. CAR, a cell adhesion molecule highly expressed in the developing brain, mediates neurite outgrowth. An increasing list of cell surface proteins, including cell adhesion molecules, are shed from cells by members of the ADAM family of metalloproteases. Often, such proteins also undergo an intramembrane cleavage mediated by the presenilin/gamma-secretase complex, releasing the intracellular domain into the cell (with consequences on expression of downstream genes in the case of Notch and others). Objective: To investigate the processing of CAR in neurons and glioma cells. Methods: We used pharmacological inhibitors, shRNA knockdown and mass spectrometry analysis to investigate cleavage of CAR. Results: CAR ectodomain was detected in conditioned media of embryonic hippocampal neurons and two human glioma cell lines. Pharmacological inhibitors and shRNA knockdown revealed ADAM10 as a candidate protease for CAR ectodomain shedding. The site of ectodomain cleavage, as predicted by in vitro studies, was confirmed in glioma cells expressing CAR mutants. Experiments with pharmacological inhibitors of gamma-secretase and presenilin1/2 knockout cells indicated CAR processing by the gamma-secretase complex. Preliminary data suggest that ectodomain shedding is required for CAR-mediated outgrowth of developing neurons. Conclusion: CAR undergoes ectodomain shedding and intramembrane proteolysis by ADAM10 and presenilin/gamma-secretase, respectively. It is likely that this proteolytic processing plays a role in CAR-mediated neurite outgrowth during development.

3-9-A

Caspase-6 expression and activation in human fetal and adult tissues: abundant active Caspase-6 in epithelial cells of the gastrointestinal system

Nelly Godefroy, Olivier C Maes, Jasmine Ramcharitar*, Steffen Albrecht, Cynthia G. Goodyer, Julio Faria, Catherine Bergeron and Andrea C LeBlanc

Objectives: The objective of this study is to investigate the physiological impact of Caspase-6 (Casp6) in humans. Casp6 is an effector caspase that is strongly activated in Alzheimer disease (AD) brains and could be responsible for axonal pruning and neurodegeneration. Despite this, Casp6 has not been thoroughly investigated. In order to understand the full physiological role of Casp6 in humans, Casp6 gene expression was investigated in fetal and adult human tissues. Results: Casp6 was ubiquitously expressed in various human fetal tissues but was highest in the gastrointestinal tissues. Active p10 and p20 Casp6 subunits and the p20 subunit of Casp1 were detected in fetal stomachs. Casp6 was detected in adult colon, stomach, spleen, kidney, and lung but low in other tissues including brain. The active p20 subunit of Casp6 was detected in the epithelial cells of normal adult colon tissue, but was absent in the disorganized regions of the cancerous colon. Casp6 activity did not induce cell death in colon carcinoma HCT-116 cells although it was highly activated in these cells. Conclusions: In conclusion, Casp6 is highly expressed in early development indicating a physiological role at this stage. Casp6 is likely important in the gastrointestinal system since it is most abundant and highly activated in this system from fetal to adult. However, Casp6 does not seem to be responsible for cell death in these tissues.

3-9-B

Patients diagnosed with non-epileptic seizures: their perspective and experience

Philip Dickinson* Karl Looper Danielle Groleau

Patients that suffer from psychogenic non-epileptic seizures are confronted with many obstacles in seeking effective treatment for their illness. Underlying many of these obstacles is the divergence between the medical model and the patient's perception of their illness. The objective of this qualitative study is to elucidate, through semi-structured interviews, the subjective illness and treatment experience of these patients, in order to answer the research question: How do non-epileptic seizure patients make sense of their illness experience? This may allow a better understanding of the impediments to proper care that the patients encounter. The results showed that the participants that implicitly incorporated epilepsy as an illness prototype demonstrated less effective treatment expectations and imposed greater life constraints on themselves, than the participant that utilized anxiety attacks as an illness prototype. The participants that defined an explanatory model with a psychosocial basis for illness onset were receptive and demanding of psychotherapeutic intervention. The importance of early diagnosis and improved diagnostic strategies is emphasized. Two overarching interconnected themes that emerged, loss of control and an inability to communicate appeared to characterize the underlying internal struggle that permeated the illness and treatment experience of the study participants.

3-10-A

ALTERNATIVELY SPLICED CASPASE-6B ISOFORM INHIBITS THE ACTIVATION OF CASPASE-6A.

* Andrea W. Lee, Nathalie Champagne, Xiaojun Wang, Xiaodong Su, Cynthia Goodyer, Andrea C. LeBlanc

Caspase-6 (Casp6) is activated early in Alzheimer disease and involved in axonal degeneration but the regulation of Casp6 activity has not been explored. Several alternatively spliced forms of caspases act as inhibitors of caspase activation. The CASP6 gene generates an alternatively spliced transcript known as CASP6? in addition to the CASP6? that encodes proCasp6a. Here, we show that the CASP6? transcript and the proCasp6b protein are present in many cell lines, in primary neurons and human brains. Unlike most other alternatively spliced caspase transcripts, proCasp6b contains a catalytic site. However, purified proCasp6b did not have caspase activity nor did it inhibit already activated Casp6a. ProCasp6b prevented the proteolytic activation of proCasp6a in vitro and in cells. ProCasp6b interacts directly with proCasp6a. This work shows that proCasp6b is an inhibitor of proCasp6a activation. These results imply that proCasp6b could negatively regulate proCasp6a activation in neurons and prevent Casp6a-mediated axonal degeneration.

3-10-B

GABAA Transmission Plays Different Roles in Regulating Dendritic Spines in the Developing and Mature Hippocampus

Christopher K. Salmon, Emma V. Jones, Keith K. Murai

Synaptic transmission through GABAA receptors is excitatory in the neonatal brain. At this time, excitatory glutamatergic synapses form and mature. In particular, dendritic spines are established and stabilized. In mature neural networks, when inhibitory GABAA transmission is blocked, overexcitation results and spine density decreases drastically (30 - 40%). We expressed farnesylated enhanced green fluorescent protein (EGFPf) in area CA1 of the mouse organotypic hippocampal slice using viral gene delivery. We were then able to resolve fine morphology of dendrites, including spines, using spinning disk confocal imaging. We found that treatment with the GABAA antagonist, bicuculline, for 48 hours starting at 5 days in vitro (DIV) did indeed cause spine loss (33%). However, when we treated slices with bicuculline for 48 hours at 3 DIV, spine density increased by the same proportion. We also found that driving GABAA transmission with muscimol for 48 hours at 3 DIV decreased spine density. Thus, at 3DIV, when GABA is likely excitatory, blocking GABAergic transmission increases spine density. This suggests that excitatory GABA regulates synapse formation in the young organotypic hippocampal slice. These findings further implicate GABA in CNS developmental and hippocampal wiring. Furthermore, our data indicate that aberrant GABAergic signaling in the neonatal brain may be involved in disorders such as epilepsy and mental retardation where abnormal regulation of spines is thought to play a role.

3-11-A

Synapses on thin -shaped dendritic spines are the first to be lost after deafferentation in area CA1 of the mature hippocampus

Reist, N*., Chang, P. K-Y. & McKinney, R.A.

Dendritic spines, small protrusions from the dendritic tree, are the major postsynaptic components of the majority of excitatory synapses in the CNS. In plastic regions of the brain, such as the cortex and the hippocampus these structures are heterogeneous in shape and have been shown to undergo actin-dependent motility. The functional relevance of dendritic spine shape has been a source of much speculation. A strong correlation between size of spine head and the strength of the synapse is most probably related to the higher level of AMPA receptors in larger spines. There is also evidence that the smaller or weaker spines preferentially undergo long-term potentiation (LTP) whereas the larger spines are more stable and show less plasticity. These observations led to the idea that thin spines might be the “plastic” spines and large mushroom spines the “memory” spines. One function of spines is to compartmentalize chemical changes within individual synapses. Previous work from the laboratory showed that the AMPA receptors require continued activation and that treatment with the AMPA receptor antagonist NBQX results in a loss of dendritic spines, synapses and formation of more asymmetric shaft synapses. We have now investigated if a particular shape of spine is more likely to result in a loss of synapses or become an asymmetric shaft synapse after deafferentation. We performed live 4D imaging on tertiary portions of CA1 pyramidal cells expressing membrane GFP in mature hippocampal slice cultures (>3 weeks in vitro) over a course of 9 days in control conditions and in sister cultures undergoing chemical deafferentaion using NBQX. We found that larger mushroom shaped spines are the most stable, exhibiting minimal change in number during the 9 days of imaging. We also found there was no interchange of long thin spines to mushroom spines in NBQX treated cultures. In contrast long thin spines exhibited a significant decrease in their number in response to NBQX. We conclude that the thin spines are the most susceptible to lost during chemical deafferentation.

3-11-B

Fragile X Related Protein 1 clusters with ribosomes and messenger RNAs at a subset of dendritic spines in the mouse hippocampus

Denise Cook*, Maria del Rayo Sanchez-Carbente, Claude Lachance, Danuta Radzioch, Edward Khandjian, Luc DesGroseillers, Keith Murai

New protein synthesis is required for long-lasting changes to synapse strength and size. To make sure that new proteins are added specifically to the synapses undergoing these changes, new proteins can be synthesized locally from messenger RNAs and polyribosomes known to be present in dendrites and at spines. This local protein synthesis is controlled by RNA binding proteins. Although many RNA-binding proteins have been identified so far, few have been shown to control local messenger RNA translation in neuronal cells. Fragile X Related Protein 1 (FXR1) is an RNA-binding protein that controls how messenger RNAs are translated in non-neuronal cells. We therefore wondered whether FXR1 controls protein synthesis locally in dendrites and at spines. We hypothesized that if FXR1 controls local messenger RNA translation in neuronal cells, then it should be found with ribosomes and messenger RNAs in dendrites and at dendritic spines. To test this, we performed immunofluorescence and fluorescence in situ hybridization on mouse hippocampal neurons and quantified the degree of colocalization of FXR1 with ribosomes and messenger RNAs. We then co-expressed FXR1 tagged with green fluorescent protein and membrane-targeted red fluorescent protein in mouse organotypic slices and quantified the localization of FXR1 with respect to the dendrite and at spines. We found that FXR1 clustered with ribosomes and messenger RNAs in the dendrite and at a subset of spines in mouse hippocampal neurons. This suggests that FXR1 controls local protein synthesis in the dendrite and at spines.

3-12-A

Foxp1 and Lhx1 coordinate motor neuron migration with axon trajectory choice by gating Reelin signalling.

Elena Palmesino*, David L. Rousso, Tzu-Jen Kao, Avihu Klar, Ed Laufer, Osamu Uemura, Hitoshi Okamoto, Bennett G. Novitch and Artur Kania

Topographic neuronal maps arise as a consequence of axon trajectory choice correlated with the localisation of neuronal soma, but the identity of the pathways coordinating these processes is unknown. We addressed this question in the context of the myotopic map formed by limb muscles innervated by spinal lateral motor column (LMC) motor axons where the Eph receptor signals specifying growth cone trajectory are restricted by Foxp1 and Lhx1 transcription factors. We show that the localisation of LMC neuron cell bodies can be dissociated from axon trajectory choice by either the loss or gain of function of the Reelin signalling pathway. The response of LMC motor neurons to Reelin is gated by Foxp1- and Lhx1-mediated regulation of expression of the critical Reelin signalling intermediate Dab1. Together, these observations implicate specific transcription factors controlling the expression of axon guidance and soma migration effectors, revealing the molecular hierarchy of topographic map specification.

3-12-B

A dual role for spinal alpha-2A adrenergic receptors in opioid-adrenergic interactions

Anne-Julie Chabot-Doré* Magali Millecamps Tharsika Sinnathamby Laura Stone

Combinations of opioid and adrenergic ligands have been shown to be clinically beneficial for the treatment of pain. For example, co-administration can increase analgesia, decrease side-effects and protect against tolerance. The mechanisms underlying these interactions are complex. While combining opioids (i.e. morphine) with ?2-adrenergic receptor (?2-AR) agonists (i.e. clonidine) is typically synergistic, low doses of ?2-AR antagonists increase morphine analgesic efficacy. The ?2-AR family comprises three subtypes: ?2A-AR, ?2B-AR and ?2C-AR, and activation of both the ?2A-AR and ?2C-AR subtypes have been shown to result in analgesia. In mice expressing a functionally null ?2A-AR, morphine-clonidine synergy was abolished, suggesting that this subtype is necessary for this interaction. The ?2-AR subtype responsible for the potentiation of morphine in presence of a low dose of ?2-AR antagonist remains to be established. The objective of the current study was to further investigate the role of the ?2A-AR in opioid-adrenergic interactions in vivo. We therefore examined the time course and analgesic efficacy of morphine and its interaction with clonidine in the warm water (49°C) tail immersion assay using mice in which the ?2A-AR gene was deleted (?2A-AR-KO). Baseline tail flick latencies were lower in ?2A-AR-KO mice compared to wild type (WT) mice, suggesting a role in endogenous pain modulation. The time-course of morphine action was similar in WT and ?2A-AR-KO mice. In ?2A-AR-KO mice, the ED50 values of both systemically and spinally administered morphine was more potent than in WT mice. However, the increase in potency was more pronounced at the spinal level. Together, these results indicate that the efficacy of spinal morphine is enhanced in the absence of ?2A-AR. To explore the role of ?-opioid receptors (MOR) in the increased morphine potency observed in the ?2A-AR-KO mice, we tested the effect of a spinally administered MOR-specific agonist, DAMGO, which produced a similar analgesic profile in both mouse strains. Finally, isobolographic analysis of co-administration of morphine and clonidine resulted in synergistic analgesia in WT animals, but not in ?2A-AR-KO mice, confirming the role of ?2A-AR in opioid-adrenergic synergistic interactions. In conclusion, these results reveal a dual role for ?2A-AR where its activation or its deletion can lead to the enhancement of morphine analgesia. Understanding how ?2A-AR mediates these effects will enable the development of therapeutic strategies exploiting the analgesic potential of this receptor in combination with opioids.

3-13-A

The refinement of spinal motor axon guidance by ephrin-mediated cis-attenuation of ephrin:Eph forward signalling

Tzu-Jen Kao* and Artur Kania

Objectives: Eph kinase receptors and ephrin ligands are co-expressed on neuronal growth cones raising questions about their contribution to axon guidance. Two models of ephrin function have been proposed: (1) ephrins function as receptors and interact with Ephs on target cells leading to Eph:ephrin reverse signalling in trans or 2) ephrins bind to co-expressed Eph receptors and attenuate ephrin:Eph forward signalling in cis. The selection of a motor axon trajectory in the limb is a simple axon guidance system where lateral and medial lateral motor column (LMC) motor axons invariantly choose between a dorsal and a ventral limb trajectory. Functional in vivo experiments argue that EphA and EphB receptors enriched in lateral and medial LMC neurons, respectively, guide LMC axons by being repulsed from their corresponding ephrin-A and ephrin-B ligands expressed, respectively, in ventral and dorsal limb. Studies have demonstrated that ephrins are also expressed by LMC neurons prompting us to address the contribution of ephrin:Eph cis-attenuation to axon guidance. Results: Ephrin-A5 and ephrin-B2 are enriched in medial and lateral LMC, respectively, and several Ephs are expressed by most LMC neurons. Over-expression of ephrin-A5 and -B2 in LMC neurons and LMC-specific knock-down of ephrin-A5 and -B2 by siRNA lead to LMC axon misrouting. The over-expression of an ephrin-A5 mutant unable to bind to EphAs in trans or an ephrin-B2 mutant lacking the intracellular domain results in same LMC axonal re-direction phenotypes as over-expression of wild-type ephrins. In vitro challenge of LMC explants with ephrin stripes provides further evidence in support of axonal ephrin attenuation of ephrin:Eph signalling in cis. We thus propose that cis-attenuation of ephrin:Eph signalling increases the fidelity of motor axon trajectory selection.

3-13-B

Neurophysiological abnormalities in MS: Disease process or functional compensation?

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Previous studies using transcranial magnetic stimulation (TMS) indicate that multiple sclerosis (MS) may be associated cortical hyperexcitability. This anomaly could be the result of damage to the brain's inhibitory systems. However, hyperexcitability may also reflect a form of functional compensation. In our lab, we are attempting to differentiate between these competing hypotheses. If hyperexcitability reflects damage, then high excitability should be associated with greatest functional impairment. If hyperexcitability reflects compensation, then high excitability should be associated with lowest functional impairment. Working with a sample of patients from an MS clinic at the Montreal Neurological Institute, we are collecting functional data using the MS Functional Composite (MSFC), which evaluates cognitive, upper and lower extremity impairment, as well as the symbol-digit modalities test (SDMT). We are also using TMS to assess intracortical inhibition (ICI) and cortical silent period (cSP), two measures that reflect cortical excitability. Preliminary results indicate that there is a modest positive correlation between cortical excitability and MSFC scores (r=0.389). Associations are strongest between ICI and measures of cognition (PASAT: r=0.543; SDMT: r=0.469). None of the measures indicate a negative correlation between functional scores and cortical excitability. This initial work therefore supports the hypothesis that changes in cortical excitability reflect functional compensation. Future research will add an imaging protocol designed to measure cortical damage. Results from this proposed course of study will further refine our understanding of the relationship between damage, compensation, and functional impairment in patients with MS.

3-14-A

Fragile X Mental Retardation Protein and Synaptic Targeting in the Drosophila Central Nervous System

Vedrana Cvetkovska*, Alexa Hibbert* and Brian Chen

The most common heritable form of mental retardation in humans is Fragile X syndrome, caused by the silencing of the Fragile X Mental Retardation gene (fmr1). The fmr1 protein product, FMRP, is an RNA binding protein and regulator of protein synthesis, and is thought to participate in the suppression of translation of its target RNAs. Lack of FMRP results in increased protein synthesis and excessive structural features in neurons. However, it is not known how loss of FMRP and the morphological changes associated with it affects the fine targeting of developing neural circuits. To address these questions we used the highly stereotyped axonal branching pattern of an identifiable Drosophila mechanosensory neuron to examine how different levels of FMRP alter the wiring of innate circuits. We imaged the axonal arbors of single mechanosensory neurons labelled with a lipophilic fluorescent dye using fluorescent microscopy. Flies that lack one or both alleles of Drosophila FMR (dFMR) have an increased occurrence of branching errors compared to controls, in addition to exhibiting an overall excessive branching phenotype. Our results show dFMR's highly regulated role in controlling the expression of molecules that may be involved in axonal branch formation or synaptic targeting, or both. Our ongoing experiments will investigate how dFMR controls neuronal wiring through regulation of structural molecules (i.e., actin, MAP1B) versus targeting molecules (i.e., Dscam, plexin).

3-14-B

Sex differences in the emotional modulation of associative memory.

Jeanette Mostert* David Luck, Martin Lepage

Emotional events are remembered better than neutral ones. This effect is larger in women than in men and is reflected by enhanced neural activity in the amygdala, medial temporal lobe and prefrontal cortex. However, remembering events not only requires memory for items, but also the binding of various items of information into memory. This study investigated sex differences in the emotional modulation of associative memory. Healthy participants (17 men, 16 women) were presented with 90 pairs of pictures while in a MRI scanner. Each pair was composed of a central scene and a peripheral unrelated object. Trials were either positive, negative or neutral depending on the emotional valence of the scene. Subjects were tested on recognition and recall of the studied scene-object pairs. While no significant effects were found on the recognition task, women performed better than men on recall of positive compared to neutral and negative pairs. Negative content on the other hand impaired performance of women, but not of men. At the neural level, positive compared to neutral trials elicited greater activation in women compared to men in the right amygdala, as well as in an extensive network involving visual attention, memory and emotion processing areas. In contrast, encoding of negative compared to neutral associations elicited greater activation in visual attention areas in men, but greater activation in frontal emotion processing areas in women. This suggests a dissociation between how positive and negative emotions influence neural activity in men and women and how this influences associative memory formation.

3-15-A

Opposing Roles of Plexin A and Plexin B Receptors in Neural Wiring

Shay Neufeld* Brian Chen

Establishing correct synaptic connectivity during development is crucial for functionality of the nervous system. However, the molecular mechanisms underlying synapse specification and targeting are not well understood. The transmembrane receptor family Plexins are known to mediate axon guidance through their interactions with semaphorins during embryonic development. Here we investigate the role of Plexin A and Plexin B in axonal branching and synaptic targeting in adult Drosophila flies. Using carbocyanine dye-filling to fluorescently label and image single mechanosensory axons, we were able to analyze the axonal morphology and synaptic targeting in single neurons lacking Plexin A or Plexin B. We show that decreasing Plexin A or Plexin B expression in a small group of mechanosensory neurons results in distinct axonal branching and synaptic targeting phenotypes. Reducing Plexin A expression increased the morphological complexity and number of putative synaptic complexes along the axon. In contrast, reducing Plexin B expression decreased morphological complexity of the mechanosensory axon. Therefore our data suggest that Plexin A and Plexin B play opposing roles in the fine neural wiring that occurs following axon guidance, where Plexin A functions to repress excessive synaptic targeting and branching, and Plexin B functions to facilitate growth and axonal branching. These results demonstrate a novel opposing role for Plexin A and Plexin B in axonal branching and synapse specification, and also is the first study to characterize the role of Plexin B following axon guidance.

3-15-B

Peripheral neuregulin-1 administration increases the number of adult-born dentate gyrus cells and produces antidepressant effects

Ian Mahar*, Maria Antonietta Davoli, Stephanie Tan, Sergio Dominguez-Lopez, and Naguib Mechawar

Objectives Neuregulin-1 (NRG1) is a growth factor involved in neuronal migration and differentiation in the developing brain. Abnormal NRG1 signaling has been implicated in the etiologies of schizophrenia and depression. We investigated whether short-term peripheral neuregulin administration increases neurogenesis in the adult dentate gyrus (DG). Our hypothesis was that DG neurogenesis would increase, and be accompanied by antidepressant behavior. Methods Adult male C57Bl6 mice were implanted s.c. with osmotic mini-pumps delivering either saline (controls; n=6) or NRG1 (n=6) at a constant rate of 10 µg/d for 3d. During this period, BrdU (50 mg/kg, i.p.) was injected twice daily. Behavioral tests (locomotor and forced swim task (FST)) were conducted 28d after administration. Animals were sacrificed by cardiac perfusion with formaldehyde, and their brains processed for BrdU immunocytochemistry (ICC). Surface area and volume of DGs were determined using Cavalieri estimation. Statistical significance was assessed using t-tests. Results Overall new DG cell numbers increased 28d after NRG1 administration (31%; p=0.042). As observed previously for cell proliferation, this increase occurred only in the caudal DG (50%, p=0.013; rostral: p=0.20). Compared to controls, these animals showed decreased immobility (p=0.0062) and increased swimming (p=0.0062) in the FST, without locomotor differences (duration: p=0.32; distance: p=0.26). Conclusion Peripheral subchronic administration of NRG1 increases DG cell proliferation, specifically in a region involved in affective regulation. Four weeks post-treatment, the increase is maintained, presumably reflecting increased neurogenesis. Interestingly, this treatment also leads to antidepressant effects. These data suggest that levels of peripheral NRG1 can regulate both hippocampal plasticity and mood.

3-16-A

Investigations on the NGF metabolism in a new transgenic rat model of Alzheimer's disease-like amyloid pathology and in Down's syndrome cortical neurons

Iulita MF*, Leon WC, Melis T and Cuello AC

Alzheimer’s disease (AD) is characterized by progressive memory loss that can be attributed to the atrophy of cholinergic basal forebrain neurons. These cells depend throughout life on the endogenous support of Nerve Growth Factor (NGF). Our group has previously described the metabolic pathway by which NGF is released as a precursor (proNGF), matured and degraded. We also found alterations of this metabolic pathway in AD brains, even at the mild cognitive impairment stage. We are currently investigating whether our transgenic (tg) rat model of AD-like amyloid pathology reproduces alterations in the NGF metabolic pathway, as observed in the human brain. Specifically, we are looking at the levels of proNGF and of key proteins responsible for its maturation (tPA: tissue plasminogen activator; plasminogen; plasmin; neuroserpin) and degradation (MMP9: matrix metallo-protease 9; TIMP1: tissue inhibitor of metallo-proteases). 13-month old tg rats, corresponding to a stage when the amyloid pathology is well established, exhibited significantly increased proNGF levels in cortex. We also found significantly elevated plasminogen levels and lower tPA levels in the tg group. Currently we are investigating the levels of neuroserpin and MMP9 as well as its enzymatic activity. Interestingly, we recently observed increased proNGF levels at the pre-plaque stage of AD-like amyloid pathology, concurrent with cognitive impairments. In addition, given that Down’s syndrome (DS) cortical neurons accumulate intracellular A-beta we hypothesize that these alterations might also be present in these cells. Initial experiments indeed show abnormal NGF metabolism in DS cortical neurons, suggesting that A-beta mediated alterations in NGF processing may also contribute to AD progression in DS individuals.

3-16-B

Evidence of astrogliosis in the anterior cingulate white matter of depressed suicides

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Background: Increasing evidence suggests that cortical astrocytic function is disrupted in mood disorders and suicide. The fine neuroanatomy of cortical astrocytes, however, remains to be investigated in these psychiatric conditions. Here we performed detailed morphometric analyses of 3D-reconstructed grey and white matter astrocytes in Golgi-impregnated anterior cingulate cortex (ACC) samples from depressed suicides and matched controls. Methods: Postmortem ACC samples (BA24) from 10 well-characterized depressed suicides and 10 matched sudden-death controls were obtained from the Quebec Suicide Brain Bank (Douglas Institute). Golgi-impregnated astrocytic cell bodies and processes from layer VI and underlying white matter were reconstructed in three dimensions and quantified using the Neurolucida software. Ten randomly selected cells per subject were analyzed from coded slides so as to remain blind to diagnosis. For each cell, the soma size as well as number, length and branching of processes were determined. Results: Protoplasmic astrocytes in layer VI of the grey matter displayed no significant differences between groups for any of the quantified parameters. However, fibrous astrocytes in the white matter displayed significantly larger somas and longer processes in depressed suicides compared to controls. Sholl analysis revealed that this increased process length was most significant between 30-80 ìm from the cell body, with values in depressed suicides being more than twice as high as those measured in controls. Conclusions: These results provide the first evidence of altered astrocytic processes in mood disorders and suicide. The presence of hypertrophic astrocytes in ACC white matter is in agreement with recent reports suggesting cerebral inflammation in depression. Supported by CIHR, FRSQ, and CONACYT.<

3-17-A

Profiling regional cholinergic and glutamatergic changes with advancing pathology in the Thy-1-APP mouse model of Alzheimer's disease

Aaron Hackett*, Simon Allard, A. Claudio Cuello

There are several lines of evidence which suggest that the integrity of the cholinergic system is compromised in Alzheimer's disease (AD). The primary goal of the current study is to profile the progression of cholinergic changes with the evolution of AD pathology. Using the aggregate results of multiple mouse models of AD, Bell and Cuello (2006) have demonstrated an early increase in the presynaptic cholinergic bouton population followed by a subsequent and dramatic loss corresponding with the transition to the post-plaque phase. The current study has utilized immunohistochemistry to establish whether the cholinergic synaptic changes described by Bell and Cuello (2006) can be observed within a single mouse model of AD, the McGill-Thy1-APP model. Moreover, this study has extended the investigation to the glutamatergic system to see if the pattern of cholinergic synaptic changes is mirrored by other neurotransmitter systems. Collectively, the results of the current study provide novel evidence for regional differences in cholinergic susceptibility with advancing pathology. If restoration of cholinergic atrophy is to be a primary pharmacological target then this approach will enable identification of the appropriate therapeutic time window for drug delivery and allow focusing of treatment to regions most at risk to atrophy.

3-17-B

The effects of prenatal infection on hippocampal long-term depression (LTD) and spatial processing in the adolescent rat.

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Prenatal infection is an early environmental factor associated with increased risk for developing schizophrenia. To investigate if prenatal infection causes changes in CNS function, we used a rat model in which bacterial endotoxin, lipopolysaccaride (LPS) is administered during prenatal development. Prenatal LPS has been shown to produce structural alterations, including decreased neurogenesis and dendritic aborization, within the hippocampus of rat offspring. Previous studies examined plastic properties of hippocampal synapses, namely long-term potentiation (LTP), a cellular model for learning and memory, and found no effects. However, long-term depression (LTD), another form of hippocampal plasticity, remains to be investigated. Using Sprague-Dawley rats we examined the effects of 100 ?g/kg of LPS on gestational days 15 and 16 on adolescent offspring and looked at LTD in the hippocampus, as well as a behavioural correlate, spatial processing. We utilized an N-methyl-D-aspartate (NMDA)-dependent LTD protocol, paired-pulse (PP)-LTD, in hippocampal CA1 slices. We also examined spatial memory in the Morris water maze (MWM) using a short, 1 day training protocol followed by a 24 hour retention probe. We found that prenatal LPS treatment abolished NMDA-dependent PP-LTD in the CA1 slices. Also, rats treated prenatally with LPS showed a deficit in retention in the MWM, with no significant memory for the platform location in the probe trial. This is interesting because NMDA-dependent LTD has previously been implicated in consolidation of spatial memory in the MWM. Such results indicate the hippocampus, a structure of noteworthy vulnerability in schizophrenia, is susceptible to the deleterious effects of prenatal infection. Supported by the Canadian Institutes of Health Research.

3-18-A

Determining the Role of TRP Channels in Oxidative Hair Cell Death

Jerneja Stare*, Dr. Melissa A. Vollrath

The auditory and vestibular sensory hair cells in the inner ear are sensitive to aging, ototoxic drugs, and excessive noise. All of these factors have been shown to cause hair cell death, resulting in hearing and balance impairment, through reactive oxygen species (ROS) production. The link between the production of ROS and cell death is poorly understood in hair cells. We propose that the ion channel TRPM2 is a key participant in the ROS-mediated cell death pathway in these cells. Members of this family of ion channels have been shown to be involved in ROS-activated cell death in other tissues, and our lab has shown that TRPM2 is highly expressed in hair cells. However, the properties and functions of TRPM2 in hair cells have not been investigated. The aim of this research is to characterize the electrophysiological properties of TRPM2 in vestibular hair cells and investigate the channel's role in ROS-mediated cell death on a tissue level. This research has the potential to identify new therapeutic targets for preventing hair cell death, and auditory and vestibular dysfunction.

3-18-B

A comparison of linear and nonlinear methods for registration of PET images

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Objective: Anatomical differences between healthy and neurologically affected populations may constitute a significant confounding factor when PET images are analyzed using voxel based statistics.Non-linear registration of PET images based on MRI information can potentially minimize the impact of anatomical variability on group analysis of PET data. Here we compare the effect of MRI-based non-linear registration in voxel-based t-statistics maps contrasting [11C]ABP688 binding potential (BPND) between normal controls (Ctrls) and patients harboring unilateral temporal lobe epilepsy (TLE). MRI examination of TLE patients commonly reveals atrophy of the temporal structures, especially in the hippocampus. Methods: 10 TLE patients (5 right, 5 left; mean age 34 + -14 std) and 9 Ctrls (mean age 40 + 20 std) had a dynamic scan conducted in a ECAT HR + after injection of 370MBq of [11C]ABP688 IV followed by a 15 mins transmission scan. Images were reconstructed using filter back projection and subsequently analyzed using the Logan's reference tissue method with the cerebellum as a reference region. All participants had a T1 weighted 1mm isotropic MRI for coregistration purposes. Individual PET-MRI images were linearly registered using rigid body transformation. The MRIs were then linearly registered to the MNI157 space using 9 parameters. The PET images subsequently underwent a nonlinear registration using a deformation field to warp the image to the best possible fit. Patients with right TLE had their PET flipped in the x-direction prior to registration in order to keep the epilepsy hippocampus in the left side. T-statistics were calculated by comparing the left hemisphere of TLE patients versus Ctrls with linear and nonlinear registration. Results: Unilateral abnormalities in the epileptogenic hippocampus of TLE patients could be clearly identified with both linear and nonlinearlytreated images, with significant declines of [11C]- ABP688 BPND (t (linear) = 6.6 as compared to t(nonlinear) = 5.6). However, nonlinearly registered maps could identify the maximum peak within subiculum-CA1 regions, whereas linearly registered images showed a more homogeneous cluster involving the whole hippocampal head. Hippocampal cluster peaks were 5mm apart and maximum t-value was higher for linearly coregistered maps (6.6 as compared to 5.6). No difference in cluster extent was observed (voxels of t > 3.0 within the hippocampal clusters: 2906 versus 2896). Conclusions: In TLE, we were able to show that in a group of patients with structural abnormalities involving small and complex structures such as the hippocampal formation, linear registration might bias the anatomical location of PET information. In the particular case of TLE, receptor binding studies such as [11C]ABP688-PET can provide detailed information that can be later correlated with pathological findings of cell loss and gliosis within specific hippocampal subfields. References 1. Ashburner J, Friston KJ. Nonlinear Spatial Normalization Using Basis Functions. Human Brain Mapping 1999;7:254–66. 2. Myers R. The application of PET-MR image registration in the brain. The British Journal of Radiology 2002;75:S31–5.

4-1-A

Mechanisms of AMPA and GABAA receptor trafficking in response to TNF-alpha

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The pro-inflammatory cytokine tumor necrosis factor-? (TNF?) functions to regulate cell-surface expression of AMPA receptors (AMPAR) and GABAA receptors (GABAR) in cultured neurons. Physiologically, TNF? is released by glia in response to activity blockade, and is required to mediate one form of homeostatic synaptic plasticity, which concurrently increases synaptic AMPAR content while decreasing synaptic GABAR content. The molecular pathways activated in response to TNF? which lead to trafficking of these two types of receptors remain largely unexplored. We are using multiple experimental approaches to (1) identify the relevant signaling cascades downstream of TNF receptors, and (2) determine the receptor subunits required for this effect. For AMPAR trafficking pathways, we assayed for the phosphorylation state of the GluA1 subunit, which is implicated in regulation of AMPAR trafficking. We found that inducing homeostatic synaptic plasticity in neuron cultures through two days of activity blockade resulted in an increase in phospho-Ser845. To investigate subunit requirements for AMPARs we recorded mEPSCs from cultured neurons derived from mice deficient for the GluA1 subunit. We found that homeostatic synaptic plasticity induced by activity blockade does not require the GluA1 subunit. For GABARs we have used a heterologous expression system to assess the role of subunit content and found that all three beta subunits can mediate a rapid reduction in cell-surface expression in response to TNF? exposure. We are currently investigating the properties of GABAAR trafficking in cultured cortical and hippocampal neurons in response to acute TNF? exposure and activity manipulations.

4-1-B

The deubiquitinase USP2 regulates circadian timekeeping and response to light via its action on clock protein function.

David Duguay*, Yaoming Yang, Adeline Rachalski, Gerry Baquiran, Lydia Ouellet, Kai-Florian Storch, Simon S. Wing, Nicolas Cermakian

Post-translational modifications govern clock protein function and regulate circadian physiology. PER and CRY proteins are targeted by ubiquitin ligases, but involvement of deubiquitinases in clock mechanism remains to be defined. The gene encoding the deubiquitinase USP2 is among the few genes to be rhythmically expressed in multiple tissues. To test its role in the clockwork, we have generated Usp2 knock-out (KO) mice and studied locomotor activity rhythms in running wheels (KO, n=6; WT, n=9). The endogenous period was increased by 16 minutes in Usp2 KO mice compared to WT mice. Advancing the light/dark cycle by 6 hours led to a slower phase resetting in Usp2 KO mice while delaying it by 6 hours produced the reverse. The phase-response curve was altered in Usp2 KO mice: a light pulse at CT14 induced larger delays while advances after a pulse at CT20 were blunted compared to WT mice. In vitro, USP2 interacted with PER1/2, CRY1/2 and BMAL1 and was able to target ubiquitinated PER1. CLOCK/BMAL1-induced luciferase reporter activity driven by Per1 promoter was reduced by USP2, while transcriptional repression by PER/CRY heterodimer was increased by USP2. Consistent with this, PER1 and PER2 protein levels were increased in fibroblast prepared from Usp2 KO embryo. The first circadian peak of Per1, Per2 and Rev-erb? mRNA expression after fibroblast clock synchronization was increased, while that of Bmal1 was reduced in Usp2 KO cells. Taken together, our results indicate a key role for USP2 in the post-translational regulation of core clock proteins.

4-2-A

Maturation of glutamatergic synapses possessing only AMPA receptors

Ingrid K. Osswald*, Mabel Chong, Mark Aurousseau, Shannon Olinoski, Fiona K. Bedford and Derek Bowie

Recruitment of AMPA receptors into developing glutamatergic synapses is carefully timed by a switch in the molecular composition of NMDA receptors. Early in development, AMPAR insertion is restrained by signaling through NR2B-containing NMDARs. However, as development proceeds, NR2B's dominance dissipates as more and more synapses accumulate NR2A-containing NMDARs which promote AMPAR insertion. This interplay between the NMDAR and AMPAR is thought to govern assembly at all glutamatergic synapses. However, not all neurons express NMDARs suggesting, in some instances, an entirely different set of rules may regulate AMPAR recruitment. Here, we have studied glutamatergic synapse development in retinal AII amacrine cells which lack NMDARs. In the light-adapted retina, AMPARs are recruited into glutamatergic synapses soon after eye-opening (i.e. P14) suggesting that the maturation process relies on signaling events triggered by light entering the eye. In support of this, synapse maturation is delayed in the dark-reared retina. AII cells express calcium-permeable AMPARs (CP-AMPARs) in both light-adapted and dark-reared retina consequently the disruption in synapse maturation is unlikely to be due to differences in AMPAR divalent permeability. Instead, the effect of sensory experience on synapse development apparently reflects a switch in AMPAR composition. CP-AMPARs expressed in the dark-reared retina are sensitive to polyamine block suggesting they lack the GluA2 AMPAR subunit. In contrast, CP-AMPARs expressed by AII cells in the light-adapted retina are insensitive to polyamines suggesting, unexpectedly, that they contain GluA2. Ongoing experiments are examining whether sensory experience affects CP-AMPAR composition in AII amacrine cells by regulating GluA2 transcription, translation and/or trafficking.

4-2-B

The Influence of Fever and Inflammation on Circadian Clock Genes

Susan Westfall*, Argel Aguilar Valles, Valérie Mongrain, Giamal N. Luheshi, Nicolas Cermakian

Background: The circadian clock is a 24-hour biological timer maintaining synchrony between environmental cues (light dark cycle) and internal homeostasis. The clock consists of autonomously cycling, interlinked transcriptional regulators termed core clock components. The 'master' clock resides within the suprachiasmatic nucleus (SCN) and coordinates peripheral 'slave' oscillators found in most organs via humoral, neurological and/or autonomic mechanisms. Recently, the proinflammatory factors interleukin-6 (IL-6) and prostaglandin E2 (PGE2) were proposed to influence peripheral clock dynamics, demonstrating how molecularly, infection and inflammation affect clock function. Further, inflammatory disorders including rheumatoid arthritis, asthma, sepsis and even cancer have long been known to be influenced by the circadian cycle, from prognosis, to treatment to symptom generation. Thus, elucidating the circadian-immune crosstalk will provide essential insights into many pathologies and their treatment. Objectives: Our aim is to elucidate the effect of fever and inflammation on core clock components in peripheral tissues and delineate the mechanism accounting for these effects. Results: Using an intramuscular turpentine injection as a model of inflammation, we have determined that there are significant tissue- and gene-specific effects of inflammation on clock components, which depend on both injection and sacrifice time. To define the mechanism, we attenuated the fever response with ibuprofen treatment, a COX-2 inhibitor, finding that there was no effect on clock gene expression. Next, we plan to abolish circulating IL-6 levels to determine if IL-6 is the cross-talk mediator. Finally, we plan to conduct in vitro experiments in primary hepatocyte cultures to confirm the results obtained in vivo.

4-3-A

Molecular Characterization of the Binding Site of Nematode GABA-A Receptors

Michael V. Accardi* Sean G. Forrester

Haemonchus contortus is a parasitic nematode that is controlled in large part by nematocidal drugs that target receptors of the parasitic nervous system. Hco-UNC-49 is a nematode GABA receptor that has a relatively low overall sequence homology to mammalian GABA receptors but is very similar to the UNC-49 receptor found in the free living nematode Caenorhabditis elegans. However, the nematode receptors do exhibit different sensitivities to GABA which may be linked to differences in the putative GABA binding domains. Mutational analysis conducted in this study identified at least one amino acid, positioned near the GABA binding domain, which may partially account for differences in nematode GABA sensitivity. In addition, positions reported to be crucial for GABA sensitivity in mammalian receptors also affect GABA sensitivity in Hco-UNC-49 suggesting that the GABA binding domains of the mammalian and nematode GABA receptors share some pharmacological similarities. However, there were some differences observed. For example, unlike the mammalian GABA receptors where the GABA binding domain is located within two dissimilar subunits, it appears the nematode GABA receptor binding domain is located between to similar subunits.

4-3-B

Participation of the atypical MAP kinase ERK4 in brain functions

Adeline Rachalski*, Justine Rousseau, Erika Vigneault, Sonia Klinger, Benjamin Turgeon, Sylvain Meloche and Nicolas Cermakian

Although MAP kinases are among the most studied signaling molecules, very little is known about the physiological role of the atypical MAP kinase ERK4. Since the brain is the organ with the highest expression of Erk4, our aim was to study in detail Erk4 mRNA expression in the mouse brain, and the participation of ERK4 protein in upper brain functions. First, we analyzed Erk4 mRNA expression by in situ hybridization in mouse brain sagittal slices. We observed high Erk4 expression in forebrain structures such as the striatum and a specific pattern of expression in olfactory system, cortex, hippocampus and cerebellum. Moreover, no expression was detectable in white matter. We then analyzed the phenotype of Erk4 knockout (Erk4-/-) mice in several behavioral paradigms. Erk4-/- mice did not present alteration of locomotor activity or coordination compared to wild-type mice. While no difference was found in spatial learning between the two groups, a trend for a reduced anxiety-like phenotype was observed in Erk4-/- mice. Importantly, Erk4-/- showed increased depression-like behaviour compared to Erk4+/+ mice. In conclusion, the specific expression pattern of Erk4 gene in the mouse brain, and the alteration of behavior observed in Erk4-/- mice, together suggest a role for the atypical MAP kinase ERK4 in brain function. Further experiments will allow to dissect the role of ERK4 in specific brain areas.

4-4-A

Novel GABAA Receptor Mutants in Idiopathic Generalized Epilepsy

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Epilepsy is a heterogeneous neurological disease affecting around 50 million people worldwide. While in some cases the underlying cause of epilepsy is known, the disease is mostly idiopathic. In recent years, several genes have been associated with epilepsy phenotypes. Mutations in ion channels contribute significantly to the growing list of causes. In this study, we have identified novel mutations in the GABAA receptor subunits of patients diagnosed with familial IGE. Here, we characterize the functional consequences of the three novel ion channel mutations: K353int+19X and D219N in the a1 subunit, and P83S in the g2 subunit. To do this, wild-type and mutant a1 and g2 subunits were co-expressed in HEK 293 cells with wildtype b2 subunits. We used biochemistry and patch-clamp electrophysiology to investigate their functional and pharmacological properties. Our results identify and 2 new a1 subunit mutations found in patients with genetics form of epilepsy. Biochemical and electrophysiological analyses suggest that these mutants greatly diminish GABAA receptor function. Intriguingly, the g2 subunit mutant was indistinguishable from the wildtype subunit. Further experimentation is required to elucidate their roles in epilepsy.

4-4-B

The role of dopamine, norepinephrine, and serotonin in the production of adult rat 50-kHz vocalizations

Wright JM*, Dobosiewicz M, Clarke PBS

Rationale: Recently, we have shown that the 50-kHz ultrasonic vocalizations (USVs) emitted by adult rats can be classified into at least 14 distinct subtypes. Furthermore, both social context and systemic amphetamine (AMPH) administration differentially altered the rats' call profiles. These findings add to evidence that individual call subtypes may differ in their behavioural significance and neurochemical basis. Objective: The main objective of this study was to investigate the potential contribution of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) transmission to the production of the 14 subtypes of spontaneous and AMPH-induced 50-kHz USVs. Methods: Male adult Long-Evans rats were recorded following treatment with cocaine, the DA reuptake inhibitor GBR 12909, the NE reuptake inhibitor nisoxetine, or the serotonin reuptake inhibitor fluoxetine. In a separate series of experiments, rats were tested with AMPH or saline after various doses of the following pre-treatments: the D2 antagonists haloperidol or sulpiride, the D1 antagonist SCH 23390, the ?2-adrenergic agonist clonidine, and the ?1-adrenergic receptor inhibitor prazosin. Results: While cocaine significantly increased the emission rate of 50-kHz USVs and the proportion of trill calls, GRB 12909, nisoxetine, and fluoxetine failed to affect either the call rate or call profile. However, SCH 23390, haloperidol, clonidine, and prazosin markedly and dose-dependently decreased USVs emitted under AMPH, and increased or inhibited some call subtypes preferentially. In contrast, sulpiride affected neither the call rate nor the call profile under AMPH. Conclusions: The failure of nisoxetine, GBR 12909, and fluoxetine to elicit USVs suggests that increased noradrenergic, dopaminergic, or serotonergic transmission alone is not sufficient to elicit 50-kHz USVs. However, the reduction in AMPH-induced calls by SCH 23390, haloperidol, clonidine, and prazosin suggests that both dopamine and noradrenaline are necessary for the effect of AMPH on USVs. The inability of sulpiride to inhibit 50-kHz calls potentially reflects this drug's atypical antipsychotic profile. The role of serotonin in AMPH-induced calls requires further study.

4-5-A

Effects of actual and simulated Z-shifts on T2-lesion volumes in patients with multiple sclerosis.

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Background: Precise magnetic-resonance-imaging (MRI) quantification of T2-hyperintense lesion volumes (T2LV) in patients with multiple sclerosis (MS) may be affected by gradient distortions (GD) – particularly along the magnet's Z-axis. Methods: Over 2 years, 12 MRI datasets were acquired in 6 patients on a 1.5T Siemens Sonata. A GD-correction field (GDCF) was generated using spherical harmonic expansion to map coordinates from an "ideal" system (Lego-DUPLO® phantom) to the scanner's imaging system. T2-LV masks were generated using a manually-corrected, Bayesian-tissue-classification approach. We estimated: (i) the effect of actual Z-shift-associated GD; and (ii) the effect of a greater range of simulated Z-shifts (-50-mm to +50-mm, in 5-mm steps), a range that is commonly-seen in clinical trials of MS patients. Results: The actual locations of the centers-of-mass of the patients' heads on T2-imaging had a 44.7-mm range (-15.1 to 29.6) along the Z-axis in the 12 scans; applying the GDCF decreased the observed T2-LVs in all of the scans [mean (range) = -1.9% (-0.7%, -2.6%)]. Simulated 50-mm Z-shifts into, and out of, the magnet had significant, but asymmetric, effects on mean T2-LVs [out: -2.0% (-5.3%, 0.6%), p=0.003; in: -7.1% (-10.1%, -3.7%), p<0.0001]; this effect was smaller and more symmetric in scans in which lesions were located closest to magnetic isocenter, reflecting a typical barrel-distortion effect. Conclusions: Z-shift-associated GD artifacts can have significant effects on T2LV quantifications, increasing as the distance-from-isocenter of the lesions increases. Accordingly, inadvertent Z-shifts should be avoided or corrected for in order to generate more-reliable T2LV estimates, and increased statistical power.

4-5-B

THE RELATIONSHIP BETWEEN EXPERIMENTAL PAIN AND REWARD PROCESSING.

Wiebke Tiede* Nathaniel Elfassy Petra Schweinhardt

Pain and reward are thought to occupy two extremes of a hedonic spectrum. Interactions between the two might exist and indeed, reward processing circuitry is postulated to be altered in chronic pain. We conducted a psychophysical study to investigate how the presence of short-term pain influences risk-taking in healthy volunteers. Healthy subjects (13 males, 12 females) performed a modified Balloon Analogue Risk Task (BART) either in the presence or absence of pain. The BART measures risk-taking as follows: subjects can earn increasing amounts of money when inflating a balloon; however with each pump, the probability of the balloon exploding increases. Pain was induced by cold water immersion and at the end of each condition subjects rated the pleasantness/unpleasantness of the cold water. The total number of pumps, a measure of how much risk the subject is willing to take, was compared across conditions and between genders. Pain influenced risk-taking behavior differently in males and females ($F_{1,25}=5.12$; $p=0.03$) with women showing a decreased number of pumps under pain ($t_{11}=-2.72$; $p=0.02$) and men not changing their risk-taking across conditions. Also, women with low hedonic ratings under pain showed less influence of pain on risk-taking behavior. This study suggests that women might decrease their risk-taking behavior under pain due to decreased motivation. In order to compensate for a low hedonic state though, females might be relatively more reward-seeking under pain depending on their unpleasantness rating. Our results highlight gender differences in risk-taking behavior under pain and hint to differ in psychological mechanisms.

4-6-A

Inflammatory Response of Microglia to Gold Nanoparticles Depends on Nano-geometry

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Gold nanoparticles (GNPs) are among the most investigated in biological systems. The OBJECTIVE of the present study was to define the interaction between GNPs and microglia. More specifically, we investigated the role of GNP morphology and surface in modulating the inflammatory response of microglia. Different GNP morphologies (spheres, rods, and urchins) coated with poly(ethylene glycol) (PEG) or cetyl trimethylammonium bromide (CTAB), were characterized and tested in vitro using a microglial cell line (N9). Two-photon luminescence was employed to assess GNP localization, while biochemical assays were used to assess cell metabolic activity, nitric oxide release, cytokine release, and toll-like receptor expression. Furthermore, in vivo bio-luminescent imaging of microglial activation was performed in real-time using a unique transgenic mouse expressing luciferase driven by the microglia-specific toll-like receptor-2 (TLR-2) promoter. Our results indicate that, (i) microglia internalize GNPs to differential extents based on their surface properties and shape, (ii) following intranasal administration of GNPs, bio-luminescent imaging in vivo, in real-time, revealed transient TLR-2 receptor up-regulation in the olfactory bulb and in parietal brain regions of mice, and (iii) in vitro administration of GNPs led to differential modulation of microglial TLR-2 expression, in addition to interleukin 1 alpha (IL-1a), granulocyte-macrophage colony-stimulating factor (GM-CSF) and nitric oxide (NO) release. Results from this study indicate that GNP morphology and surface can strongly influence the inflammatory response of microglia, suggesting that nanoparticle–microglia interactions can be differentially regulated by tuning nano-geometry. ACKNOWLEDGEMENTS: Dr. Paul De Koninck, Jacynthe Laliberte, CIHR

4-6-B

The Schweinhardt Lab: Investigation of Pain using Neuropsychopharmacological Tools.

Rebecca Price*, Audrey Laferriere*, Wiebke Tiede, Susanne Becker, Petra Schweinhardt.

Our lab focuses on advancing our understanding of cerebral mechanisms of pain perception and modulation combining psychophysical investigation, including quantitative sensory testing (QST), pharmacological tools, and brain imaging techniques. Current projects are investigating brain alterations accompanying the development of chronic nerve-injury pain following surgery using QST and brain imaging (Positron Emission Tomography, anatomical Magnetic Resonance Imaging, Diffusion Weighted imaging and Magnetic Resonance Spectroscopy); the relationship between reward processing and pain in a psychophysical study in healthy subjects with pharmacological manipulation of the dopaminergic system as well as functional imaging techniques ; alterations of pain sensitivity in obesity and potential underlying mechanisms with psychophysical and pharmacological tools (opioid antagonist naltrexone); and the contribution of central beta-adrenergic receptor activation to context-conditioned hyperalgesia in a psychophysical study with pharmacological manipulation using with the centrally-acting beta-blocker propranolol. Future studies will investigate the involvement of the amygdaloid complex in pain increase induced by aversive context conditioning.

4-7-A

SH3 DOMAINS FROM A SUBSET OF BAR-PROTEINS DEFINE A NOVEL UBL-BINDING MODULE AND IMPLICATE PARKIN IN SYNAPTIC UBIQUITINATION

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Mutations in the parkin gene are responsible for a common inherited form of Parkinson's disease (PD). The protein parkin is a RING-type E3 ubiquitin ligase with a N-terminal ubiquitin-like (Ubl) domain. By virtue of its similarity to ubiquitin, the parkin Ubl can interact with ubiquitin-binding domains (UBDs). However, almost nothing is known about the selectivity of parkin Ubl towards UBDs or its role in recruiting ubiquitination substrates. We report here that the SH3 domains of endophilin-A, syndapin and amphiphysin-II interact with parkin Ubl but not with ubiquitin or other Ubl's. These endocytotic SH3 proteins all have a BAR domain that can bind and induce curvature in lipid bilayers. The NMR structure of the Ubl-SH3 complex identifies the PaRK extension, a unique C-terminal motif in the parkin Ubl required for SH3 binding and for parkin-mediated ubiquitination of endophilin-A in vitro. The Ubl binds the same SH3 surface as proline-rich domains (PRDs), effectively competing with the dynamin and synaptojanin PRDs. In nerve terminals, conditions that promote phosphorylation enhance the interaction between parkin and endophilin-A and increase the levels of ubiquitinated proteins within PRD-associated synaptic protein complexes in wild type but not parkin knockout brain. The findings identify a pathway for the recruitment of synaptic substrates to parkin with the potential to explain the defects in synaptic transmission observed in recessive forms of PD.

4-7-B

NRAGE and NEDD9 function downstream of p75NTR to propel cancer cell migration

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The p75 neurotrophin receptor (p75NTR) plays an important role in regulating cellular survival and death decisions in the developing and mature nervous system. We previously identified a protein, termed NRAGE, that directly binds the p75NTR intracellular domain and functions to activate pro-apoptotic signaling in vitro and in vivo. The mechanism through which NRAGE accesses the cell death machinery is not known and to address this, we performed yeast-two hybrid assays to identify NRAGE-interacting proteins that may lie on this pathway. Several of the identified open reading frames encoded NEDD9, a member of the Cas family that has been implicated in Jun kinase signaling and in cell migration. These functions have been also associated with p75NTR activation, we have initiated a detailed characterization of the p75NTR-NEDD9 interaction. Pull-down assays established that GST-NEDD9 directly binds to NRAGE and showed that a helix-loop-helix domain within NEDD9 was responsible for NRAGE binding activity whereas the C-terminal domain of NRAGE bound to NEDD9. NRAGE and NEDD9 could be co-immunoprecipitated from cells in which p75NTR, NRAGE and NEDD9 are endogenously expressed and their association can be regulated by NGF, a ligand for p75NTR. This indicates that NRAGE and NEDD9 interact under physiological circumstances. Finally, functional assays have established that NRAGE depletion reduces migration of WM 266-4 melanoma cells. Taken together, these studies have identified a novel interaction between NRAGE and NEDD9 and suggest that a p75NTR-NRAGE-NEDD9 cascade may regulate cell migration.

4-8-A

Does feedback enhance transient signal detection? A computational study.

Daniel Zysman* John E. Lewis

This study investigates the role of neuronal feedback in the detection of small amplitude transient signals. We focus specifically on how the weakly electric fish Apteronotus leptorhynchus capture prey such as Daphnia in a noisy environment, by means of its electric sense. Using the electrosensory network as a blueprint, we build a computational model that allows us to test detection performance in two different scenarios: in the absence of neuronal feedback (open loop) and in the presence of feedback (closed loop). For each network scenario, spike count distributions across realizations are computed and ROC (Receiver Operating Characteristic) curves are calculated to assess differences among these distributions. The area under the ROC curve (AUC) and the equal error rate (EER) are used to quantify the performance of the different network configurations. For body-object distances < 20 mm, the closed loop model results in a more robust and reliable object detection than does open loop. For longer distances, there are no differences in between open and closed loop. These results depend on the exact choice of parameters for the model, in particular those controlling feedback inhibitory input strength and global feedback delay. This study shows in a simplified model how feedback can enhance the detection of weak transient signals. The results are generally applicable, as feedback is ubiquitous in many other sensory systems. Further implications and possible technological applications are discussed.

4-8-B

Grey matter density in auditory regions at age 10 predicts ability on auditory tasks 5 years later

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Previous research has shown that auditory abilities are linked to morphological features in auditory and related areas. However, it has not yet been shown whether there are structural differences before such practice that may contribute to the observed behavioral differences. We investigated whether grey matter density in the auditory cortex of 10-year old children could predict an individual's ability on a melodic transposition task in mid adolescence. We tested this hypothesis with a longitudinal study involving 39 healthy, right-handed participants who were scanned at the ages of 10 and 15 years; at age 15, they were also tested on auditory tasks involving phonemes and melodies. Using voxel-based morphometry, we found that the grey matter density in posterior regions of both the left and right auditory cortices at the age of 10 years were able to predict performance on the auditory tasks at the age of 15 years. Taken together, our results indicate that grey matter density in posterior auditory regions at the age of 10 years is able to predict performance on auditory tasks five years later. This finding suggests that the morphology of auditory regions is linked to musical abilities, perhaps reflecting inherent predispositions, and that this effect is stable through time.

4-9-A

Elevation of Reactive Oxygen Species cause inactivation of neuronal nAChRs through a highly conserved cysteine ring

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In diseases such as diabetes, elevations in mitochondrial reactive oxygen species (ROS) cause long lasting, use dependent inactivation of neuronal nicotinic acetylcholine receptors (nAChRs) and produce dysautonomias. The target for ROS appears to be a highly conserved ring of cysteine residues located at the intracellular mouth of the receptor channel. Consistently, muscle nAChRs, receptors highly homologous to nAChRs on neurons lack this ring of cysteines residues and are not affected by elevations in ROS. Here we ask whether we can confer ROS sensitivity to muscle nAChRs. To test this, we mutated muscle nAChR subunit (?1,?1,?,?) to include a cysteine residue in the M1-M2 linker domain, transfected them into HEK 293 cells and used whole cell voltage clamp techniques to record ACh-evoked inward currents. To elevate ROS, we added antimycin-A to our intracellular recording electrode to block complex III of the mitochondrial electron transport chain. We found that mutating muscle nAChRs functioned well although the inclusion of the cysteine ring may have alter their sensitivity to ACh, their desensitization or their kinetics for recovery from desensitization. On the other hand, antimycin-A did not appear to produce a use-dependent, long-lasting inactivation of the receptors. These results suggest that the cysteine ring is necessary but not sufficient to confer sensitivity to ROS and long-lasting inactivation to nAChRs. In addition to the cysteine ring at the cytoplasmic mouth of the pore, other structural determinants likely have a role in receptor inactivation. Supported by CIHR.

4-9-B

Musical Chills: Linking Emotion and Pleasure in the Brain

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Emotion and reward have long been associated, but how emotions become pleasurable is not entirely clear. Music provides an excellent medium to examine this relationship, since (1) music can be both pleasurable and emotionally arousing; (2) the pleasurable aspects of music are thought to result from emotional arousal; and (3) the temporal and dynamic nature of musical stimuli allow for an examination of build-up in emotional arousal and how this may contribute to pleasure. In contrast to previous fMRI experiments that have used experimenter-selected music, we used self-selected music, thereby allowing for a fuller range of emotional experience. The “musical chills” response, a marker of peak autonomic nervous system activity, was used to index intense emotional arousal. Functional MRI scans were collected as individuals listened to music while providing continuous subjective ratings of pleasure. A parametric analysis confirmed that voxels showing a correlation with increases in subjective pleasure were found in dorsal and ventral striatal regions implicated in reward and motivation, consistent with previous studies. However, this study offers the novel finding that peak periods of emotional arousal were also associated with activity in these regions, providing a direct link between emotional arousal and pleasure during music listening. Moreover, time-series analysis revealed distinct patterns of activity in different portions of striatal, limbic, and frontal regions during periods leading up to the peak of emotional arousal as opposed to during and after this moment, providing a glimpse of how a build-up in emotional arousal can lead to pleasurable feelings.

4-10-A

UNDERSTANDING AMBIVALENCE IN STAKEHODLER REACTIONS TO AND COMPREHENSION OF COGNITIVE ENHANCEMENT

Cynthia Forlini* and Eric Racine

Prescription medications are being used to improve cognition in the healthy, a practice often called “cognitive enhancement” (CE). One example is the use of methylphenidate (MPH) by university students to improve concentration. Bioethics has generated some optimistic accounts of the impact of CE on society despite an unclear understanding of the efficacy of so-called “cognitive enhancers” and the perspectives of stakeholders. This qualitative study aimed to gather and examine stakeholder perspectives with regard to CE, popular analogies, and media coverage. Sixty-five stakeholders (university students, parents of university students and healthcare professionals) discussed the non-medical use of MPH during focus groups (n=9). Stakeholders expressed ambivalence regarding CE (i.e., reactions, safety, risks, and benefits). Stakeholders offered varied definitions using the terms (or combinations of) “prescription abuse”, “cognitive enhancement” and “a lifestyle choice”. Stakeholders were reluctant to equate the non-medical use of MPH with the popular analogies of steroids and caffeine although some similarities were identified. Stakeholders appreciated the role of media coverage for public awareness but stated that the articles lacked some information in addition to inadvertently promoting the non-medical use of MPH. The ambivalence of stakeholders may reflect uneasiness with the social implications of CE in academic and work environments as well as the larger role that pharmaceuticals could play in helping individuals cope with increasing social demands for performance. Forms of public dialogue that would help voice the unease and ambivalence of public stakeholders should be pursued to avoid opting hastily for permissive or restrictive health policies for CE.

4-10-B

Evidence for Visual-Auditory Cross-Modal Plasticity after Auditory Deprivation

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Research in visual to auditory cross-modal plasticity suggests that auditory deprivation is related to increased visual processing in auditory areas and enhanced peripheral motion processing. The current research investigates this phenomenon by comparing peripheral visual abilities with visually-evoked neural responses measured using functional MRI in early deaf adults. Participants consisted of 13 early deaf and 13 hearing controls, matched for age, gender, and handedness. Both profoundly deaf and hard of hearing participants were included in the early deaf group. All participants performed four behavioural tasks, examining peripheral visual processing with regards to motion sensitivity, distribution of attention, and contrast sensitivity. Participants also underwent fMRI while viewing central and peripheral, moving and stationary, sinusoidal gratings. Consistent with previous research, behavioural results confirm that deaf and hearing people differ in the lateralization of motion processing: deaf participants demonstrated better motion sensitivity in the right visual field compared to the left visual field, while hearing participants demonstrated the opposite pattern. Behaviourally, deaf participants also showed a tendency for better peripheral motion processing than hearing participants. Preliminary analysis of fMRI data indicates increased activity in the right-hemisphere auditory cortex in deaf participants as compared with hearing, when viewing moving stimuli as compared to static. Group differences in neural activity will be discussed in light of behavioural differences for peripheral motion processing.

4-11-A

CHALLENGES OF THE SOCIAL NEUROSCIENCE REVOLUTION: PUBLIC DIALOGUE AND DUAL-USE

Emma Zimmerman, Eric Racine

Communication of science is particularly challenging when the knowledge generated by scientific endeavors strays outside the explanation of physical or biological phenomenon and into the realm of behavior, culture and personality; potentially challenging our assumptions about human-nature, free-will, social norms, and morality as well as influencing social practices and policy, or being harnessed for non-peaceful or manipulative ends. This project focuses on the challenges presented by social neuroscience, which is a sub-discipline in neuroscience at the intersection of brain and society—forging deterministic connections between the brain and behavior, thus contributing to the potentially disquieting implications of neuroscience. As communication of these findings to the public has the potential to be challenging, this project is an analysis of mainstream ethical guidance available on the topics of the communication of science, and its implications for science which has the potential to be misused or militarized. A list of major international and national research policies (Canada, USA, Australia, and UK) were reviewed alongside keyword searches for topics of public dialogue and dual-use. Of the guidelines reviewed, we identified several areas where research ethics guidelines were insufficient in dealing with issues of communication in the context of social neuroscience. In general, we found that guidance in these areas was limited and superficial at best, as the guidelines are limited to a biomedical context and do not capture the potential social outcomes of research. By identifying gaps in these policies, we hope to recommend more robust ethical guidelines on the communication of scientific findings.

4-11-B

Novel Protein Nanopatterning Process to Investigate Cellular Response to Protein Nanogradients

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Cells navigate by integrating signals derived from discrete binding of signaling proteins to individual receptors that are typically a few nanometers in diameter and interact with single proteins. There is thus a great interest in creating deterministic in vitro patterns to address how the density and distribution of proteins control intracellular signaling and cell navigation. Investigation of these issues in vitro has been limited by the lack of available and affordable methods. Here we present results obtained using a microcontact printing process that we developed. We introduce a double nanoreplication method that allows for the creation of multiple copies of a single e-beam patterned Si master into a photopolymer. These photopolymer masters were subsequently used as lift-off stamps for microcontact printing of proteins by contacting them with a flat stamp inked with the protein – the contacted proteins are then lifted-off by removing the stamp. The flat stamp is then printed onto the target substrate and the remaining proteins are transferred. We patterned 200-nm-wide spots of fibronectin and showed that they could be recognized by an anti-fibronectin antibody as well as by cells which formed focal adhesions on these spots. Next, we formed digital gradients of protein patterned as 200 nm spots over a distance of 400 micrometers with a variable spacing between 100 nm to 10 micrometers. This method will be useful for rapid and low cost formation of nanopatterns of proteins for a wide range of applications, such as for the study of axonal migration in response to gradients.

4-12-A

Ovariectomy-induced Inhibitory Changes in Spinal Cord Nociceptive Systems in the Mouse

Yen May Ong* and Fernando Cervero

Aim of the investigation: Chronic functional abdominal pain affects 1.7% of the general population, with women being the majority of sufferers. Estrogen has been implicated in many chronic pain states and may similarly contribute to this gender bias. We have previously shown that ovariectomy (OVX) induces a chronic hyperalgesic state in mice starting 5 weeks post-surgery, confined to the abdomen and lower extremities. With past evidence reporting a role of estrogen in inhibitory neurotransmission, we have investigated here the effects of OVX on GABAB receptor and estrogen receptor ? (ER?) expression in the spinal cord of mice. Methods: Female C57LB/6 mice (20-35g) were used in this study. Mechanical pain behaviours were tested using von Frey filaments (1-32 mN) at 1, 5 and 8 weeks after OVX. For the immunohistochemical experiments, animals were anesthetized with urethane (2 g/kg) before perfusion with 4% paraformaldehyde. Frozen sections (20 ?m) were made using a cryostat before staining. For the Western blots, animals were anesthetized with isoflurane and decapitated before spinal cord extraction. The spinal cords were then crushed in extraction buffer for extraction of proteins before Western blot analysis. Results: Using immunohistochemical methods and Western blots, we have found that the levels of GABAB receptors in the lumbarsacral spinal cord of OVX mice are decreased by 16.7 ± 7.9% ($p < 0.05$) 8 weeks post-surgery, in line with the time course for the development of the increased pain behaviours observed in these animals. In addition, immunohistochemical results indicate no change of ER? expression levels in the spinal cord at both weeks 5 and 8 post-OVX compared to control and sham-operated controls. The region within the spinal cord showing GABAB receptor decrease in OVX mice overlaps with regions that express ER?. Conclusions: It is conceivable that the cells showing a decrease in GABAB receptor expression are related to those expressing ER?. Furthermore, the decrease in GABAB receptors observed could be the result of a decline in ER? signalling. Acknowledgements: This study was support by the CIHR (DOP73908).

4-12-B

Glutamatergic neurons of the mouse medial septum and diagonal band of Broca synaptically drive hippocampal pyramidal cells: relevance for hippocampal theta rhythm

Carey You Lim Huh* Romain Goutagny Sylvain Williams

Neurons of the medial septum and diagonal band of Broca (MS-DBB) provide an important input to the hippocampus and are critically involved in learning and memory. Although cholinergic and GABAergic MS-DBB neurons are known to modulate hippocampal activity, the role of recently described glutamatergic MS-DBB neurons is unknown. Here, we examined their electrophysiological properties and tested whether they provide a functional synaptic input to the hippocampus. We used MS-DBB slices from transgenic mice in which GFP is expressed specifically by vesicular glutamate transporter 2-positive neurons. We also employed an in vitro septohippocampal preparation, stimulated the fornix or locally activated the MS-DBB using NMDA microinfusions. We found that glutamatergic MS-DBB neurons as a population display a highly heterogeneous set of firing patterns including fast-, cluster-, burst- and slow-firing. Remarkably, many exhibited fast-firing properties, prominent Ih and rhythmic spontaneous firing at theta frequencies. Activation of the MS-DBB led to glutamatergic responses in CA3 pyramidal cells. These results suggest that the glutamatergic septohippocampal pathway may play an important role in hippocampal oscillations and relevant functions.

4-13-A

GENETIC DEACTIVATION OF FATTY ACID AMIDE HYDROLASE PRODUCES ANXIOLYTIC-LIKE AND ANTIDEPRESSANT-LIKE BEHAVIOURS AND MODIFIES SEROTONERGIC TRANSMISSION IN THE DORSAL RAPHE, PREFRONTAL CORTEX AND HIPPOCAMPUS

Bambico FR*, Cassano T, Dominguez-Lopez S, Katz N, Walker CD, Piomelli D, Gobbi G

Pharmacological enhancement of the endocannabinoid system has been argued beneficial in the treatment of mood disorders. The inhibition of the enzyme fatty acid amide hydrolase (FAAH), which degrades the endocannabinoid anandamide, has been shown to produce CB1 receptor-mediated analgesic, anxiolytic-like and antidepressant-like effects in rodents. Genetic deletion of FAAH also increases anandamide-CB1 receptor signalling. Using a battery of behavioural tests for emotional reactivity (forced swim, tail suspension, novelty-suppressed feeding, elevated plus maze and open field tests), we have characterized the emotional phenotype of mice lacking the FAAH gene (FAAH-/-) in comparison to wildtype. Since serotonin (5-HT) is involved in the mode of action of antidepressants and anxiolytics, we performed electrophysiological recordings to characterize 5-HT activity in these mice. FAAH-/- mice exhibited antidepressant-like and anxiolytic-like behaviours. Single-neuron recordings in the dorsal raphe (DR) nucleus, the major source of 5-HT innervation of the brain, revealed a significant increase in the spontaneous firing activity of 5-HT neurons. Microiontophoresis and electrophysiological recordings of pyramidal neurons in the ventromedial prefrontal cortex showed desensitized 5-HT2A/2C receptors in FAAH-/- mice, indicated by a significant decrement in the response of these neurons to the 5-HT2A/2C agonist (±)-DOI. In the hippocampus of FAAH-/- mice, the increased disinhibition of pyramidal neurons in response to the 5-HT1A receptor antagonist WAY100635 indicated enhanced tonic activity of 5-HT1A receptors, an effect associated with antidepressant-like activity. Together, these findings suggest that genetic deletion of FAAH produces anxiolytic-like and antidepressant-like activity, paralleled by modifications in 5-HT neurotransmission and in postsynaptic 5-HT1A and 5-HT2A/2C receptor function.

4-13-B

Multiple intrinsic gamma rhythm generators govern the topography of hippocampal output

Jesse Jackson*, Romain Goutagny, Sylvain Williams

Hippocampal output is principally governed by the subiculum. The subiculum is anatomically arranged as independent modules that provide segregated reciprocally connected input and output with specific cortical and subcortical nuclei. However, it remains unclear how closely apposed functionally dissociable areas of the subiculum could independently process information flowing through hippocampal circuits. Here we show, using the isolated hippocampus in vitro, that the subiculum, in contrast to the CA3 and CA1 areas, has intrinsic network properties that spontaneously give rise to simultaneously occurring low (30-50Hz) and high gamma (80-180Hz) oscillations which undergo amplitude modulation by theta phase. The ongoing dynamics of gamma oscillations served to topographically modulate the spike rate and timing within both the gamma and theta cycles. Furthermore, spontaneous gamma oscillations of multiple frequencies were independently generated in local subicular modules via fast GABAergic inhibition. Therefore, different regions of the subiculum ensure highly localized control of precise spiking dynamics by autonomously generated gamma oscillations. We propose that these independently oscillating modules serve to compute and segregate dissociable components of episodic memory.

4-14-A

Melatonin decreases serotonergic activity in the dorsal raphe neurons by direct action on MT1 receptors

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Melatonin (MLT) and serotonin (5-HT) are two biosynthetically related compounds both implicated in the etiology of mood disorders whose reciprocal interaction is not yet been completely understood. In this study, using single unit extracellular recordings in anesthetized rats, we assessed the effect of MLT (1mg/kg, i.v.) on pinealectomized (PX) rats in the dark phase (19-7Hrs), we explored the contribution of specific receptor subtypes using the MT1-MT2 receptor antagonist luzindole (LUZ, 1mg/kg, i.v.) and the MT2 receptor antagonist 4PP-DOT (1mg/kg, i.v.) and, we tested MLT (1 and 10 mg/kg, i.p.) effect on the forced swim test (FST). MLT reversed the nocturnal PX induced-increase of 5-HT firing rate ($F(2,64)=3.184$, $p<0.05$) and of 5-HT spontaneously active neurons ($F(2,20)=4.906$, $p<0.05$) to basal conditions values. 4P-PDOT did not prevent the acute 5-HT firing rate inhibition induced by MLT ($F(5,15)=4.886$, $p=0.015$), but LUZ potently blocked the effect of MLT on 5-HT firing rate ($F(5,15)=1.735$, $p=0.203$). In the FST, MLT (1mg/kg) induced a significant increase of immobility duration ($F(3,34)=9.18$, $p<0.001$) and a significant decrease of total swimming duration ($F(3,34)=8.15$, $p<0.001$. Our results suggest that MLT exerts a tonic inhibition over a sub-population of DR 5-HT neurons during the dark phase. MLT induced-inhibition of 5-HT neurotransmission seems to be mediated by MT1 receptors and paralleled by a depressive-like behavior in the FST. The decrease in 5-HT neurotransmission by MLT may represent a biological mechanism underlying affective disorders characterized by an increase in MLT secretion during the seasonal affective disorders.

4-14-B

Effect of anti-NGF antibody in a mouse chronic post-ischemia pain model of complex regional pain syndrome type-I

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Ischemia-reperfusion (IR) injury in rodents evokes microvascular dysfunction and pain symptoms resembling the clinical characteristics of patients with complex regional pain syndrome type-I (CRPS-I). Nerve growth factor has been shown to contribute to nociceptive sensitization underlying painful symptoms (allodynia/hyperalgesia) in a variety of neuropathic pain models. NGF is also shown to be chronically upregulated following an IR injury. We hypothesized that anti-NGF antibody might reduce mechanical allodynia/hyperalgesia and cold allodynia in a chronic post-ischemia pain (CPIP) model of CRPS-I. In our studies, we induced CPIP by creating ischemia in the mouse hind limb for 3 hours. The mice were injected with high, medium and low doses of anti-NGF antibody either systemically or into the plantar surface of the ipsilateral (injured) paw. The mice were tested for mechanical allodynia/hyperalgesia and cold allodynia at different time points following systemic or intraplantar injections. We found that systemic injection of the medium dose and the intraplantar injection of the high dose of the antibody significantly reduced mechanical and cold allodynia and, mechanical hyperalgesia for at least 3 days after systemic injection and at least 20 minutes following intraplantar injection. The effects of anti-NGF antibody were short lasting and did not permanently reverse the allodynia/hyperalgesia observed following the IR injury. Our results strongly suggest that NGF mediates, at least in part, some features of chronic post-ischemia pain.

4-15-A

Altered Synaptogenesis and Plasticity in Mice Lacking Receptor Protein Tyrosine Phosphatase Sigma

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The LAR subfamily of receptor protein tyrosine phosphatases in vertebrates is composed of LAR, RPTP?, and RPTP?. Of these three, RPTP? is particularly widely expressed by neurons in the developing and mature mammalian central nervous system. Previous studies indicate that LAR and RPTP? promote axon extension, that LAR promotes synaptogenesis, and that RPTP? promotes synaptic plasticity. In contrast, RPTP? is a receptor for chondroitin sulfate proteoglycans associated with glial scars, and functions to inhibit axon extension during development and axon regeneration in the injured mature central nervous system. Here we address RPTP function in the intact brain. We demonstrate that RPTP? is enriched in synaptosomes isolated from developing and adult central nervous system and assess its contribution to the development, maintenance, and plasticity of synaptic connections. Loss of RPTP? function in knockout mice results in increased synapse density, increased dendritic spine length and width, and increased mossy fiber axon sprouting resulting from aging or induced seizure activity. Examination of activity-dependent plasticity at hippocampal Schaffer collateral-CA1 synapses revealed that RPTP? null mice exhibit reduced long-term potentiation, while behavioral testing identified enhanced recognition memory. Our findings, and previous reports by others, indicate that RPTP? and NGR1, which are receptors for chondroitin sulfate proteoglycans and myelin associated inhibitors respectively, the two major identified classes of inhibitors of axonal regeneration, are both associated with synapses in the intact undamaged central nervous system and function to regulate structural and functional synaptic plasticity.

4-15-B

Role of leptin in fever and pyrogenic signalling to lipopolysaccharide in obese rats.

Pohl,J.,* Somay,G., Frate,C., Woodside,B., & Luheshi,G.N.

Introduction: Research suggests that leptin can modulate the fever response to lipopolysaccharide (LPS). Leptin may also affect brain pyrogenic mechanisms through microglia activation and IL-1ß release. We have previously reported that obese rats exhibit an enhanced fever response and increased circulating leptin levels. Here we investigated the role of leptin in the inflammatory response of obese rats, by fasting (Exp.1) or neutralizing leptin through leptin specific anti-serum (LAS) (Exp. 2). We then measured fever and pyrogenic signalling in the hypothalamus. Methods: Male Wistar rats (250-300g) were given access to a liquid diet supplement in addition to standard laboratory chow, until their body weight exceeded by 15% that of control rats. To reduce endogenous leptin levels, rats were either fasted for 24h prior to LPS injection (Exp.1) or were injected with LAS i.p (Exp. 2). Body temperature was measured using remote radio-biotelemetry (TA10TA-F40, Data Sciences). Gene expression of IL-1ß and CD11b, were quantified in the hypothalamus in rats of Exp.1. Results: Both fasting and LAS attenuated the fever response of obese rats ($p < 0.05$) but LAS treatment had a greater effect. Fasting did not change expression for either IL-1ß or CD11b ($p > 0.05$). Conclusion: Together these data suggest that leptin contributes to the enhanced fever response. Although IL-1ß and CD11b expression was not changed, their levels were only analyzed in Exp.1. Given that the attenuation in fever in this experiment was modest, it is possible that LAS administration may have a greater effect. Exp. 2 is presently being analyzed.

4-16-A

Inhibition of Food Intake, Body Weight Gain and GH Release via a Putative Ghrelin O-Acyltransferase (GOAT) Inhibitor

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New approaches are urgently needed for the treatment of metabolic diseases and disorders such as obesity. The recent discovery of ghrelin O-acyltransferase (GOAT) that catalyses the addition of octanoate to Ser-3 of the ghrelin peptide, and is essential for ghrelin's stimulatory actions on appetite, food intake and GH secretion, offers an opportunity for novel strategies; i.e. to inhibit the synthesis of active ghrelin by a GOAT inhibitor. To this end, in the present study we designed and synthesized, within a series of ghrelin analogs, a duodecapeptide designated FI-I-GOAT (GOAT-12) and examined its effects on food intake, body weight gain and GH release via the CNS. In the first set of experiments, food intake was monitored on an hourly basis for 5 hours during the light phase of the L-D cycle. Intracerebroventricular (icv) administration of 10 µg GOAT-12 to male rats significantly ($P<0.02$) inhibited cumulative food intake at 4 and 5 hours after injection compared with vehicle icv-injected controls; body weight gain over 24 h was also decreased during ad libitum food intake. In addition, the latency time to first meal was significantly ($P<0.05$) prolonged following icv GOAT-12 and the duration of that meal was decreased. Furthermore, the inhibition of 24-h body weight gain by GOAT-12 was reproduced in rats maintained on a reverse L-D cycle and icv-injected with GOAT-12 during the dark phase ($P<0.01$). In the second experiment, spontaneous 4-6 h plasma GH profiles were obtained from free-moving rats. Centrally administered GOAT-12 (10 µg) caused a 2-to 3-fold decrease in mean plasma GH levels compared with vehicle icv-injected controls (GH AUC: 29 ± 8 vs. 81 ± 26 ng.h/ml). Although activity of GOAT-12 has yet to be determined in a newly developed GOAT assay, the initial results reported here suggest that inhibiting and/or disrupting the endogenous GOAT-ghrelin system may provide novel strategies/useful drugs to regulate food intake and GH secretion in the treatment of metabolic disorders such as obesity and its complications.

4-16-B

Expression of the transcription factor Runx1 in spinal motor neurons relevant to ALS.

Nicolas Stifani*, Nicolas Guizard, Pierrick Coupe, D. Louis Collins and Stefano Stifani

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting both upper and lower motor neurons. Stem cell based motor neuron regeneration is a promising strategy to treat this disease. However, the success of this approach would likely be greatly improved if we were able to promote the regeneration of specific motor neuron subtypes that are more susceptible to ALS such as those innervating the diaphragm. Spinal motor neuron diversity is controlled by a combination of intrinsic factors that determine phenotype specificity, allow motor neurons to respond differently to extrinsic cues, and regulate axonal targeting. We have previously demonstrated that the transcription factor AML1/Runx1 (Runx1) is expressed in specific upper spinal cord motor neuron populations. We have shown further that Runx1 is both necessary and sufficient to suppress interneuron-specific developmental programs and promote maintenance of specific motor neuron characteristics (ref. 1, 2). Here we characterize the precise expression pattern of Runx1 in the developing mouse spinal cord. We demonstrate that Runx1 expression defines subsets of motor neuron populations in the cervical spinal cord. Some of the Runx1 expressing motor neurons display characteristics suggesting that they correspond to phrenic and lateral motor column (LMC) motor neurons. Moreover, we provide evidences that Runx1 expression is dependent upon signals from the limb. Taken together these results strongly suggest a role for Runx1 in late aspects of motor neuron specification.

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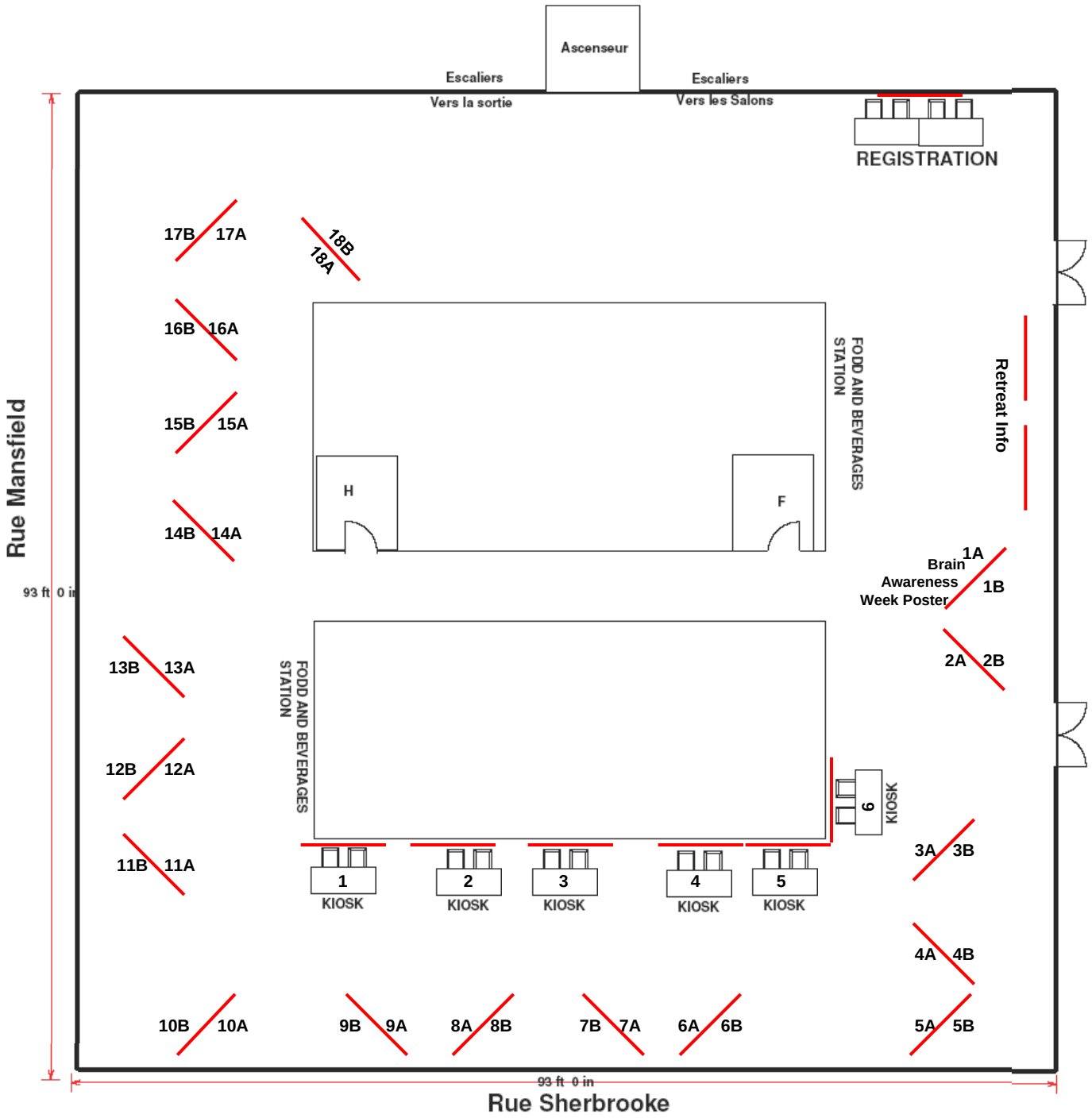

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