McGill University
Integrated Program in Neuroscience
Inaugural Retreat

Abstract Booklet

September 17-18, 2009
At the:
Centre Mont-Royal, Montreal

Poster	Name of PI	Abstract Title	Abstract Authors
3 1 A	Kathleen Cullen	How Actions Alter Sensory Processing: Reafference in the Vestibular System	Cullen KE, Brooks JX*, Medrea I*, Carriot J, Chang A, Massot C, Mitchell DE, Sader E
3 1 B	BAW	Brain Awareness Week	Erin Dickie*, Denise Cook* and Anne-Julie Chabot-Dore*
3 2 A	Keith Murai	Fragile X Related Protein 1 localizes to large dendritic spines in the hippocampus	Denise Cook*, Claude Lachance, Danuta Radzioch, Keith K. Murai
3 2 B	Ridha Joober	Catechol-O-Methyltransferase (COMT) gene and executive function in children with ADHD.	Zia Choudhry*, Natalie Grizenko, Sarojini Sengupta, Ridha Joober.
3 3 A	Lisa Koski	Neurorehabilitation Research Center	Dr. Lisa Koski Dr. Johanne Higgins Aisha Bassett Haiqun Xie Benjamin Whatley* Sue Konsztowicz*
3 3 B	Ridha Joober & Alain Brunet	The 5-HTTLPR polymorphism of the serotonin transporter gene and short term behavioral response to methylphenidate in children with ADHD	Geeta A. Thakur*, Natalie Grizenko, Sarojini M. Sengupta, Norbert Schmitz and Ridha Joober
3 4 A	Marilyn Jones-Gotman	The role of the amygdala in perception of graded pleasantness	Julie A. Boyle*, Jelena Djordjevic and Marilyn Jones-Gotman
3 4 B	Salvatore Carbonetto	Dystroglycan Function: New Insights from Genetic Studies in Drosophila	Nicola Haines*, Waris Shah*, Bryan Stewart and Salvatore Carbonetto
3 5 A	Laura Stone	A new pre-clinical model of low back pain due to degenerative disc disease	Maral Tajerian*, Magali Millecamps, Laura S Stone
3 5 B	Sam David	Prostaglandin D2 Mediates Inflammation and Secondary Damage after Spinal Cord Injury.	Adriana Redensek, (*Khizr I. Rathore*), Ruben Lopez-Vales and Samuel David
3 6 A	Laura Stone	Alpha-2 Adrenergic and Opioid Receptors: Analgesic Actions and Interactions	Anne-Julie Chabot-Dore*, Magali Millecamps, Laura S Stone.
3 6 B	Sam David	The Role of ALCAM in Spinal Cord Injury	Delphine Bouhy*, Adriana Redensek, Joshua Wiener, and Samuel David
3 7 A	Michael Petrides	The key role of the intraparietal sulcus region in the rearrangement of nonverbal information in working memory	Anne Sophie Champod* Michael Petrides
3 7 B	Sam David	CONTROL OF IRON EFFLUX FROM OLIGODENDROCYTES	K. Schulz, C. D. Vulpe, and S. David

3	8	A	Guillermina Almazan	Role of the p38 mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) signaling cascade in oligodendrocyte differentiation	Jeffery D. Haines*, Jun Fang, Walter E. Mushynski, Guillermina Almazan
3	8	B	Nicolas Cermakian	The deubiquitinating enzyme USP2 is involved in the regulation of circadian rhythms	David Duguay, Yaoming Yang, Gerry Baquiran, Lydia Oueller, Kai-Florian Storch, Simon S. Wing, Nicolas Cermakian
3	9	A	Guillermina Almazan	The counter-receptor Fas Ligand regulates the expression of nerve growth factor in Schwann cells in vitro	Manuelle Rongy*, Julie Desbarats, John White and Guillermina Almazan
3	9	B	Nicolas Cermakian	The regulation of orexin receptors by dynein light chains	Erika Belanger-Nelson, David Duguay, Valerie Mongrain, Anna Beben, Armen Khatchadourian, Nicolas Cermakian
3	10	A	Guillermina Almazan	Mitogen-Activated Protein Kinase p38 alpha Controls Schwann Cell Differentiation by Regulating Transcription Factors Krox-20 Expression and CREB Activation	Shireen Hossain, Miguel-Angel de la Cruz, David Parkinson, Walter E. Mushynski and Guillermina Almazan*
3	10	B	Nicolas Cermakian	The circadian clock controls immune response	*Erin E. Fortier, Julie Rooney, Hugues Dardente, Marie-Pierre Hardy, Aude Villemain, Nathalie Labrecque & Nicolas Cermakian
3	11	A	Michael Sinnreich	Characterization of lipid binding specificities of dysferlin C2 domains reveals novel interactions with phosphoinositides	Sabrina Di Fulvio*, Christian Therrien and Michael Sinnreich
3	11	B	Nicolas Cermakian	Circadian clock gene expression in extra-SCN human brain regions	Nicolas Cermakian, Elaine Waddington Lamont, Philippe Boudreau, Diane B. Boivin
3	12	A	Nahum Sonenberg	Postnatal deamidation of 4E-BP2 in brain enhances its association with raptor and alters kinetics of excitatory synaptic transmission	Michael Bidinosti*, Israeli Ran, Maria R. Sanchez-Carbente, Yvan Martineau, Anne-Claude Gingras, Christos Gkogkas, Brian Raught, Clive Bramham, Wayne S. Sossin, Mauro Costa-Mattioli, Luc DesGroseillers, Jean-Claude Lacaille, and Nahum Sonenberg
3	12	B	Shari Baum & Vincent Gracco	Neuroscience research from the CRLMB	Isabelle Deschamps, Vincent Gracco, Shari Baum
3	13	A	Yong Rao	Functional Analysis of Turtle/IGSF9 immunoglobulin superfamily members in axon tiling	Scott Cameron*, Wen-Tzu Chang and Yong Rao

3	13	B	Sylvain Williams	Theta rhythm as the "default state" of the hippocampus: an investigation using the isolated hippocampus in vitro	Romain Goutagny, Jesse Jackson*, Sylvain Williams
3	14	A	Naguib Mechawar	Expression of neurogenic markers in limbic brain regions of suicide subjects	Marissa Maheu*, Maria Antonietta Davoli, Gustavo Turecki, Naguib Mechawar
3	14	B	Jack Antel & Guillermina Almazan	Response of human oligodendrocyte progenitors to growth factors and axon signals	Qiao Ling Cui*, Gabriela Fragoso, Veronique Miron, Peter J. Darlington, Walter E. Mushynski, Jack Antel and Guillermina Almazan.
3	15	A	Naguib Mechawar	Neuregulin-1 increases cell proliferation in the mature dentate gyrus	Ian Mahar*, Maria Antonietta Davoli and Naguib Mechawar
3	15	B	Jack Antel	Fingolimod (FTY720) Enhances Remyelination Following Demyelination of Organotypic Cerebellar Slices	Veronique E. Miron*, Samuel K. Ludwin, Peter J. Darlington, Andrew A. Jarjour, Betty Soliven, Timothy E. Kennedy, Jack P. Antel
3	16	A	Nathalie Lamarche-Vane	TYROSINE PHOSPHORYLATION OF THE GUANINE NUCLEOTIDE EXCHANGE FACTOR TRIO IN NETRIN-1/DCC-STIMULATED SIGNALING PATHWAYS DURING NEURITE OUTGROWTH	Jonathan DeGeer*, Jerome Boudeau Susanne Schmidt, Anne Briancon-Marjolle, Anne Debant, and Nathalie Lamarche-Vane
3	16	B	Jack Antel	The Effect of FTY720P on expression of S1P receptors and associated signaling in human myeloid cells	T.A Johnson, C. Lambert, B.A Durafourt, V.E Miron, A. Bar-Or, J.P Antel
3	17	A	Nathalie Lamarche-Vane	Role of ERM proteins in netrin-1/DCC-mediated axon outgrowth and guidance	Judith Antoine-Bertrand*, Monique Arpin, Nathalie Lamarche-Vane
3	17	B	Jack Antel	The role of PTEN in astrocyte response to oxidative injury	Samuel Helman*, Trina Johnson & Jack Antel
3	18	A	Paul Clarke	Forebrain dopamine, tobacco addiction, reinforcement and affective neuroscience	Tina Scardochio*, Jennifer Wright*, Rob Sorge*, Annie Constantin and Paul Clarke
3	18	B	Jack Antel & Tim Kennedy	The role of netrins in regulating blood brain barrier function and immune cell passage into the brain	Cornelia Podjaski*, Peter Darlington, Nathalie Lebeurrier, Jack P. Antel, Timothy E. Kennedy and Alexandre Prat
3	19	A	Phil Barker	LGI1 is a Novel Nogo Receptor 1 Ligand that Blocks Myelin-based Growth Inhibition	Rhalena Thomas*, Kristy Favell, Jose Manuel Morante-Redolat, Christopher Kent, Melissa Wright, Madeleine Poole, Kathleen Daignault, Alyson Fournier, Philip A. Barker and Jordi Perez-Tur.

3	19	B	Michael Meaney	Epigenetic modifications by maternal behavior	Tie-Yuan Zhang*, Dara K. Shahrokh, Sabine K. Dhir, Josie Diorio, Michael J. Meaney
3	20	A	Reut Gruber	A Correlation Between Sleep Spindles and IQ in Children	Edmund Lam*, Xi Tong, Julie Carrier, corresponding author Reut Gruber
3	20	B	Tak Pan Wong	Role of glutamate in enhanced prefrontal cortical excitability in rats with neonatal ventral hippocampal lesions, a heuristic neurodevelopmental model of schizophrenia	Richard Ryan*
3	21	A	Pejmun Haghighi	The Drosophila miR-310 cluster negatively regulates synaptic strength at the neuromuscular junction	Karen Tsang, Kazuya Tsurudome, Edward H. Liao*, Jr-Shiuan Yang, Arthar Chishti, Eric C. Lai and A. Pejmun Haghighi
3	21	B	Tak Pan Wong & Michael Meaney	Regulation of hippocampal plasticity by maternal care and corticosterone: potential mechanisms	Rosemary C. Bagot*, Michael J. Meaney, & Tak Pan Wong
3	22	A	Pejmun Haghighi	Retrograde BMP signaling controls synaptic growth at the Drosophila neuromuscular junction by regulating Trio expression	Robin Ball*, Maude Warren-Paquin, Kazuya Tsurudome, Pejmun Haghighi
3	22	B	Terence Coderre	CHRONIC POST-ISCHEMIA PAIN: A NOVEL ANIMAL MODEL SUGGESTS THAT ISCHEMIA-REPERFUSION (I-R) INJURY, NO-REFLOW AND CHRONIC TISSUE ISCHEMIA CONTRIBUTE TO COMPLEX REGIONAL PAIN SYNDROME TYPE-I.	A. Laferriere, M. Millecamps, D.N. Xanthos, W. Xiao, G.J. Bennett, T.J. Coderre*
3	23	A	Peter McPherson	How to get in, out and around - the McPherson tour guide through the cell	Patrick D. Allaire, Jonathon L. Burman, Hatem Dokainish, Maryam Fotouhi, Martine Girard, Marilene Halin, Jason Hamlin, Yohei Katoh, Andrea L. Marat, Jacynthe Philie, Viviane Poupon, Brigitte Ritter, Sebastien Thomas, Jie Xu, and Peter S. McPherson
3	23	B	Weiya Ma	Injured nerve derived COX2/PGE2 is involved in the up-regulation of pro-inflammatory cytokine IL-6 in dorsal root ganglion neurons following nerve injury	Bruno St-Jaques, Remi Quirion and Weiya Ma*
3	24	A	Pierre Lachapelle	ANIMAL MODELS OF OXYDATIVE RETINOPATHIES: CLINICAL FINDINGS AND POSSIBLE THERAPEUTIC AVENUES.	P.Lachapelle*, A.L. Dorfman, A.Polosa, S.Joly, E.Zimak, J. Racine, O. Dembinska, M. Djavari, W. Liu, J. GarfinkleA, S.Chemtob

3	24	B	Weiya Ma	CONTRIBUTION OF INJURED NERVE DERIVED COX2/PGE2 IN THE UP-REGULATION OF BRAIN DERIVED NEUROTROPHIC FACTOR IN DORSAL ROOT GANGLION NEURONS	Pedro Cruz Duarte*, Bruno St-Jacques, Remi Quirion and Weiya Ma
3	25	A	Robert Zatorre	Intense Pleasure to Music is Mediated by Mesolimbic Dopamine Release: Converging Neurochemical, Hemodynamic, and Psychophysiological Evidence	Valorie N. Salimpoor*, Mitchel Benovoy, Kevin Larcher, Alain Dagher, Robert J. Zatorre
3	25	B	Yong Rao	Largescale genetic screen in Drosophila to identify novel regulators of Parkinson's disease genes	Caroline Fernandes*, Yong Rao
4	1	A	Alexander Thiel	Investigating Neuroplasticity following Stroke	S. Grant*, B. Radlinska*, C. Paquette, M. Sidel, & A. Thiel
4	1	B	Karsten Steinhauer	The effect of phrase length on implicit prosody and the processing of a syntactic "garden path" ambiguity in Korean: An ERP study	*Hyekyung Hwang & Karsten Steinhauer
4	2	A	Ji Zhang	Transforming growth factor-Î²1 impairs neuropathic pain through pleiotropic effects	Stefania Echeverry*, Xiang Qun Shi, Alexandra Haw, Hong Liu, Zhong-wei Zhang and Ji Zhang
4	2	B	Karsten Steinhauer	Neurocognition of Language (NCL) Laboratory (Ongoing Research Projects 2009/2010)	Karsten Steinhauer*, John E. Drury, Hyekyung Hwang, Shani H. Abada, Nicolas Bourguignon, Kristina Kasparian, Jen Mah, Monika Molnar, Efrat Pauker, Erin J. White, Masha Westerlund
4	3	A	Andrea Bernasconi	MAPPING THALAMIC NUCLEAR PATHOLOGY IN TEMPORAL LOBE EPILEPSY	Bernhardt, B. C.*; Kim, H.; Natsume, J.; Bernasconi, A.
4	3	B	Amit Bar-Or	Influence of glial factors on B-cell biology: implication in Multiple Sclerosis pathogenesis.	Antonia Kobert*, Nathalie Lebeurrier, Ichiro Nakashima, Aja Rieger, Philippe Saikali, Jack Antel, Yasuto Itoyama, Amit Bar-Or
4	4	A	Anne McKinney	Astrocytes modulate activity-dependent dendritic spine remodeling in mature hippocampal slice cultures	David Verbich*, George A Prenosil, Pico Caroni, Keith K Murai & R Anne McKinney
4	4	B	Amit Bar-Or	CD4 T cells cause GFAP fragmentation in primary human astrocytes in a Granzyme B dependent manner	Peter J. Darlington*, Jack P. Antel, Amit Bar-Or

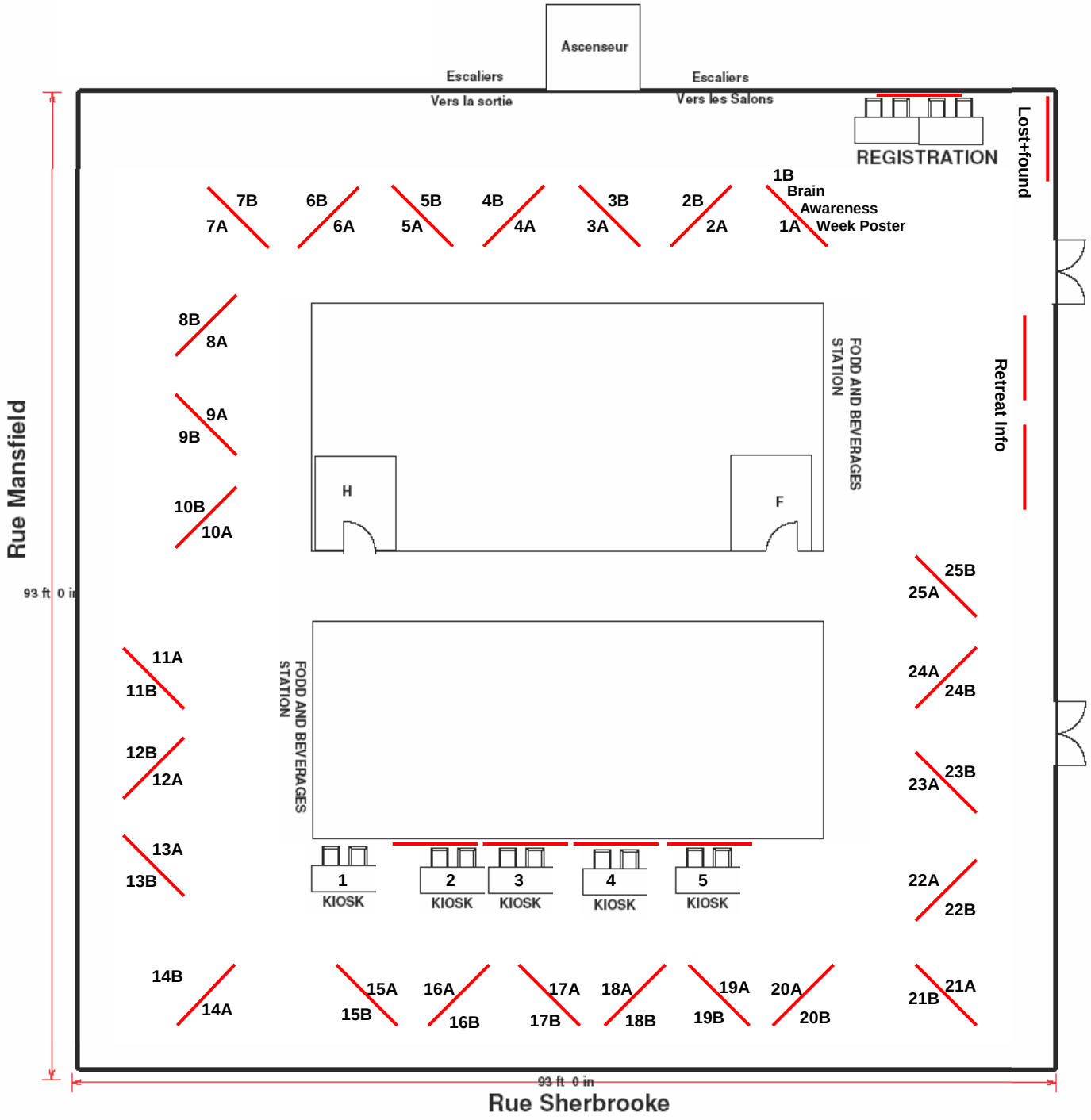
4	5	A	Catherine Bushnell	Chronic pain changes the brain	Bushnell Lab, Presented by Marta Ceko
4	5	B	Cecilia Flores	Post-pubertal expression of the protective phenotype of netrin-1 receptor deficient mice	Alanna Grant*, Zoe Speed, Cassandre Labelle-Dumais, Cecilia Flores
4	6	A	Catherine Bushnell	Late histological changes in frontal cortical morphology during neuropathic pain	P.S. KOCSIS*, D. SEMINOWICZ, A. C. L. LAFERRIERE, M. C. BUSHNELL
4	6	B	Chirstopher Barrett	The Development of a Novel Method of Reversibly Directing Neurite Outgrowth with Light	Miloslav Sailer*, Karen Lai Wing Sun, Jessica Robin, Christopher Barrett, Tim Kennedy.
4	7	A	Catherine Bushnell	The impact of long-term yoga practice on the brain and experimental pain perception	Valerie Cotton*, Dr. Chantal Villeneuve & Dr. M.C. Bushnell
4	7	B	Chris Pack & Daniel Guitton	Perisaccadic compression may be related to neural population interactions on a logarithmic map of visual space	*A. RICHARD, J. CHURAN, C. PACK, D. GUITTON
4	8	A I	Claire-Dominique Walker	Artificial rearing of rat pups reveals the beneficial effect of mother care on neonatal inflammation and adult sensitivity to pain	Cynthia B. de Medeiros*, Alison S. Fleming, Celeste Johnston, & C.-Dominique Walker
4	8	A II	Claire-Dominique Walker	Blame it on your mom! Early nutritional environment and adult dopamine function	Lindsay Naef*, Luc Moquin, Alain Gratton, Claire-Dominique Walker
4	8	B	Chris Pack & Wayne Sossin	Mathematical modeling of intracellular signal transduction involved in neural plasticity	Faisal Naqib*, Christopher C. Pack, Wayne S. Sossin.
4	9	A	David Juncker	Low cost nanopatterning of protein arrays and digital gradients of one-hundred-nanometer spots for studying neuronal navigation	RICOULT S.G.*, PLA-ROCA M., SAFAVIEH R.,CORREIA J.P., KENNEDY T.E. AND JUNCKER D.
4	9	B	Claire Brown	McGill University Life Sciences Complex Imaging Facility	Aleksandrs Sprumanis and Claire M. Brown*
4	10	A	David Stellwagen	The role of TNF-alpha in homeostatic plasticity, developmental plasticity, and behaviour	G. Lewitus*, M. Kaneko, M. Stryker, R. Malenka, and D. Stellwagen

4	10	B	Claudio Cuello	A NOVEL TRANSGENIC RAT MODEL WITH A FULL ALZHEIMER'S-LIKE AMYLOID PATHOLOGY DISPLAYING INTRACELLULAR AB ASSOCIATED COGNITIVE IMPAIRMENT	F. Canneva*, W. Leon, V. Partridge, S. Allard, F. Vercauteren, M. Szyf, A. Ducatenzeiler, L. Alhonen, C. Cuello
4	11	A	Derek Bowie	Novel Experience-dependent Changes in the Developing Retina	Patricia Brown, Ingrid Osswald, Mabel Chong, Beibei Zhao, Fiona Bedford & Derek Bowie
4	11	B	Diane Boivin	Circadian and homeostatic regulation of heart rate	Philippe Boudreau*, Guy Dumont, Diane B. Boivin
4	12	A	Eric Racine	WILL UNIVERSITY STUDENTS FEEL FREE TO USE PRESCRIPTION DRUGS AS "COGNITIVE ENHANCERS"? PERSPECTIVES FROM A QUALITATIVE STUDY	Cynthia Forlini* and Dr. Eric Racine
4	12	B	Diane Boivin	THE CIRCADIAN AND MENSTRUAL VARIATION OF SLEEP INERTIA: CORRELATION WITH SLEEP STAGE AND CORE BODY TEMPERATURE	Ari Shechter, B.Sc.* and Diane B. Boivin, M.D., Ph.D.
4	13	A	Eva Andermann	PHENOTYPIC VARIABILITY IN THE COURSE OF EPM1-UNVERRICHT-LUNDBORG DISEASE (ULD) IN TWO SIBLINGS	Dina Amrom, Mohsen Talani, Frederick Andermann, Anna-Elina Lehesjoki & Eva Andermann
4	13	B	Don van Meyel	Functional Diversification of Glial Cell Subtypes Through Neuron-Glia Interactions via Notch Signalling	Stephanie Stacey, Graham B. Thomas, Nara Muraro, Richard Baines, and Donald J. van Meyel*
4	14	A	Frederick Andermann	DEVELOPMENTAL DELAY AND LATE ONSET MYOCLONUS IN A PATIENT WITH INTERSTITIAL DELETION OF CHR 6Q21Q22.3.	Andermann, E.*, Lavoie, J., Andermann, F.
4	14	B	Douglas Arnold	The Effects of Simulated and Actual Z-Shifts on FreeSurfer-Segmented Whole-Brain, Lateral-Ventricle, and Hippocampal Volumes	Z. Caramanos*, V. Fonov, M. Derakhshan, D.L. Collins, S. Narayanan, and D.L. Arnold
4	15	A	Frederick Andermann	MUSICOGENIC EPILEPSY WITH INDEPENDENT BILATERAL TEMPORAL SEIZURES	Dina Amrom* Eva Andermann, Benjamin Zifkin, Francois Dubeau & Frederick Andermann
4	15	B	Edith Hamel	GABA, GLUTAMATE AND ASTROGLIAL MEDIATORS IN THE CORTICAL NEUROVASCULAR COUPLING RESPONSE TO BASAL FOREBRAIN CHOLINERGIC INPUT	Clotilde Lecrux, Ara Kocharyan, Claire Sandoe, Edith Hamel

4	16	A	Dusica Maysinger	The role of neural sirtuins in acute ischemia	Angela O Choi and Dusica Maysinger
4	16	B	Eric Shoubridge	Characterization of c3orf60 (NDUFAF3), a novel Complex I (NADH ubiquinone oxidoreductase) assembly factor.	Olga B. Zurita Rendon*, Eric A. Shoubridge.
4	17	A	Dusica Maysinger	NANOTHERAPEUTICS IN ALZHEIMER'S DISEASE: Nanogels Bind AÎ²1-42 and Prevent Cytotoxicity	Sebastien Boridy*,Haruko Takahashi, Kazunari Akiyoshi, & Dusica Maysinger
4	17	B	Heather Durham	HSP90 INHIBITORS AS POTENTIAL THERAPEUTIC AGENTS IN ALS	Jieun RC Cha*, Zahara M Jaffer, Ruihong Chen, Allan Rubenstein, and Heather D Durham
4	18	A	Veronique Bohbot	CROSS - CULTURAL DIFFERENCES IN VIRTUAL NAVIGATION	**Bhairavi Balram* and Veronique Bohbot**
4	18	B	Gustavo Turecki	Evidence of Altered Polyamine Concentrations in Brains of Suicide Completers	Gary Gang Chen*, Laura M. Fiori, Luc Moquin, Alain Gratton, Orval Mamer, Naguib Mechawar, Gustavo Turecki
4	19	A	Tim Kennedy	Investigating the functional significance of DCC trafficking during axon guidance.	Horn KE*, Girgis J, Bouchard JF, & Kennedy TE.
4	19	B	Hemant Paudel	Regulation of Protein Phosphatase 1 subcellular localization through interaction with 14-3-3 and its Implication for Alzheimer's Disease.	Myrka Jerome*; Yifan Lu, and Hemant K. Paudel
4	20	A	Tim Kennedy	Developing a Method to Transplant Allogenic Oligodendrocytes into Shiverer Organotypic Slices to Study Myelination	Jenea M. Bin*, Sarah-Jane Bull & Timothy E. Kennedy
4	20	B	Jones-Gotman Marilyn	Awareness of deficits during the etomidate speech and memory procedure	Sarah Jane Banks, Rose Debra Golinski, Jelena Djordjevic, Viviane Sziklas, Marilyn Jones-Gotman
4	21	A	Tim Kennedy	Mechanisms Regulating DCC Trafficking in Neurons	Jacklyn Girgis*, Katherine E. Horn & Timothy E. Kennedy
4	21	B	Jorge Armony	A LONGITUDINAL FMRI INVESTIGATION OF EMOTIONAL MEMORY ENCODING DURING RECOVERY FROM PTSD	Erin W. Dickie*, Alain Brunet, Vivian Akerib, and Jorge L. Armony

4	22	A	Giamal Luheshi	Dissecting the contribution of prenatal hypoferremia induced by turpentine in the development of schizophrenia-like behaviours	Argel Aguilar-Valles* , Cecilia Flores, Giamal & Luheshi
4	22	B	Jean-Francois Cloutier	Differential expression of Slitrk family members in the mouse nervous system	Francois Beaubien* Jean-Francois Cloutier
4	23	A	Jeffrey Mogil	"Not tonight, dear": Sex differences in decreased sexual behavior during genital and non-genital pain	Melissa A. Farmer*, Lindsay J. Chan, Emily Foxen-Craft, Julian Becher, Yitzchak M. Binik, James G. Pfaus & Jeffrey S. Mogil
4	23	B	Josephine Nalbantoglu	Role of Coxsackie and Adenovirus receptor in the Central Nervous System	Luyu Zheng*, Kuo-Cheng Huang, Josephine Nalbantoglu
4	24	A	Jeffrey Mogil	Oxytocin-induced analgesia is not mediated by the oxytocin receptor, but rather by the vasopressin-1A receptor: evidence from oxytocin- and vasopressin-receptor knockout mice	Ara Schorscher-Petcu*, Susana Sotocinal, Jacqueline N. Crawley, Larry J. Young, Remi Quirion & Jeffrey S. Mogil
4	24	B	Julio Cesar Morales	Neuropeptide Y Y1 and Y2 receptors reverse behavioral despairs by increasing neurogenesis in dentate gyrus in a rat model of depression	Julio Cesar Morales-Medina*, Yvan Dumont, Wenfeng Yu and Remi Quirion
4	25	A	Gloria Tannenbaum	Comparison of Effects of Continuous Central Infusion of Obestatin versus Ghrelin on Spontaneous Food Intake and Pulsatile GH Secretion	Zehra J. Khoja*, Juan P. Maianti, Cyril Y. Bowers and Gloria S. Tannenbaum
4	25	B	Alyson Fournier	Molecular approaches to identify novel therapeutic strategies for nerve repair	Ferraro, G.* Kent, C.* Ong Tone, S.* Pool, M.* Pribiag, H.* Shimada, T.* Fournier, A.E.
4	26	A	Jens Pruessner and Sonia Lupien	Cortisol levels in response to stressful versus non-stressful testing environments	Shireen Sindi*, Catherine Lord, Bruce Pike, Jens Pruessner and Sonia Lupien

FOYER 3RD FLOOR



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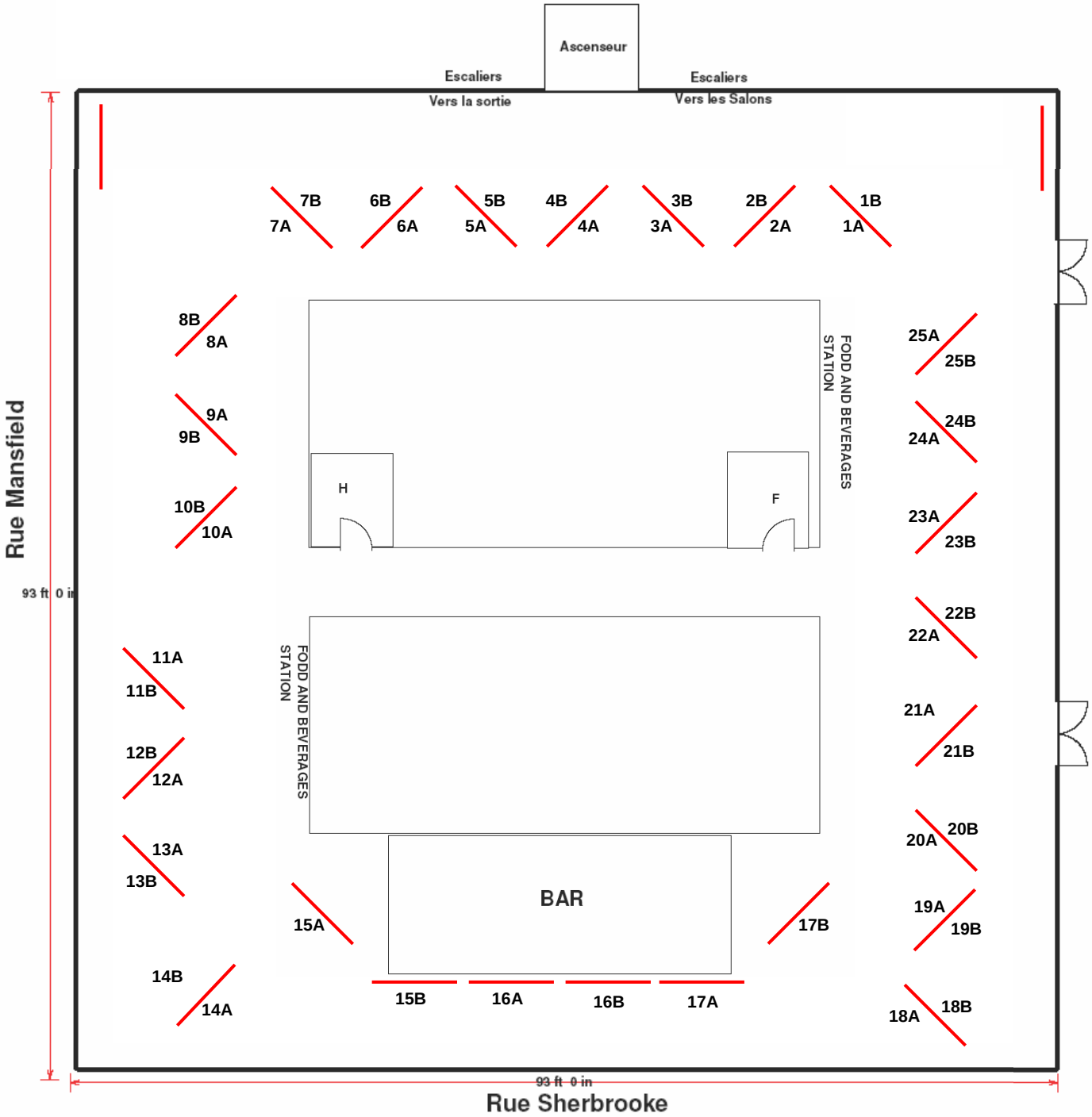

3-1-A

How Actions Alter Sensory Processing: Reafference in the Vestibular System

Cullen KE, Brooks JX*, Medrea I*, Carriot J, Chang A, Massot C, Mitchell DE, Sader E

Our vestibular organs are simultaneously activated by our own actions as well as by stimulation from the external world. The ability to distinguish sensory inputs that are a consequence of our own actions (reafference) from those that result from changes in the external world (exafference) is essential for perceptual stability and accurate motor control. Recent work in our laboratory has focused on understanding how the brain distinguishes between vestibular reafference and exafference during self motion. Single-unit recordings were made in both alert rhesus monkeys and mice during passive and voluntary (i.e., active) head movements. We found that while vestibular sensory afferent similarly encode reafference and exafference, neurons in earliest stages of central sensory processing (i.e., vestibular nuclei and cerebellum) distinguish between active and passive motion. This was the case regardless of whether self-motion was generated by rotations/translations of the i) head on body or ii) head and body together through space. To understand how neurons differentiate active from passive head motion, we systematically tested neuronal responses to different combinations of passive and active motion varying the level of certainly of the passively motion. Our findings show that that during active movements, a cancellation signal is generated to supress 'reafference', if the activation of proprioceptors matches the motor-generated expectation. These results are considered in relation to the sensory-motor transformations needed to guide accutate behavior.

3-1-B

Brain Awareness Week

Erin Dickie*, Denise Cook* and Anne-Julie Chabot-Dore*

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 from March 15th to 21th 2010. Interested? Come to our information session on Tuesday, September 22nd 2009 at 6:30 pm at Thompson House (room 404, 3650 McTavish Street, metro Peel,). You will have the opportunity to join one of the following committees: elementary and high school presentations, Brain Bees contest, funding, budget and purchasing, advertising and public relations. Don’t miss this opportunity to gain valuable experience and have fun!

3-2-A

Fragile X Related Protein 1 localizes to large dendritic spines in the hippocampus

Denise Cook*, Claude Lachance, Danuta Radzioch, Keith K. Murai

In response to synaptic activity, several new proteins are synthesized in dendrites. These proteins are required for long-lasting changes in synaptic strength and spine size and likely allow for synaptic modifications that are important for learning and memory. Fragile X Related Protein 1 (FXR1P) controls mRNA translation in the cytoplasm of non-neuronal cells. In hippocampal neurons, FXR1P is found at a subset of spines. However, it is not yet known whether FXR1P regulates mRNA translation in neurons and whether this regulation can occur locally in dendrites and at dendritic spines. We hypothesized that if FXR1P controls protein synthesis at spines, then overexpressing FXR1P might lead to a change in spine size. To test this hypothesis, we used biolistic transfection to introduce FXR1P tagged with green fluorescent protein and membrane-targeted red fluorescent protein (RFPf) into CA1 pyramidal cells in mouse hippocampal slices. We imaged RFPf signals from dendrites expressing FXR1P and control dendrites to compare spine density, shape and size. We found that neurons expressing FXR1P were similar in spine density, shape and size to control dendrites. Further analysis on spines from FXR1P over-expressing dendrites showed that FXR1P localized to spines that were on average larger than spines lacking FXR1P. These spines may be those that require ongoing protein synthesis to maintain their size and synaptic strength. Taken together our findings suggest that FXR1P controls mRNA translation at these large spines. Future experiments will test whether loss of FXR1P causes a decrease in spine size.

3-2-B

Catechol-O-Methyltransferase (COMT) gene and executive function in children with ADHD.

Zia Choudhry*, Natalie Grizenko, Sarojini Sengupta, Ridha Joober.

Objective: Exploring the relationship between SNPs rs6269, rs4633, rs4818, and rs4680 (Val108/158 Met) of the Catechol-O-Methyltransferase (COMT) gene and executive functions in children with Attention Deficit/Hyperactivity Disorder (ADHD). Methods: Four COMT SNPs; rs6269, rs4633, rs4818, and rs4680 were genotyped in 259 ADHD children, aged 6-12 years, recruited through Disruptive Behaviour Disorders Program at Douglas Hospital. The Wisconsin Card Sorting Test (WCST), Tower of London (TOL), and Self-Ordered Pointing Task (SOPT) were employed to evaluate executive functions. Neuropsychological task performance was compared across genotype groups using analysis of variance. Results: ADHD children were similar with regard to all demographic and clinical characteristics. Genotype effects of all COMT SNPs were observed on WCST perseverative responses and perseverative errors [Recessive model: rs6269 A/A vs. G+; F2,262 = 6.29, p=0.01; F2, 262 = 4.32, p=0.03, rs4633 T/T vs. C+; F2,258 = 4.07, p=0.04; F2,258 = 6.54, p=0.01, rs4818 C/C vs. G+; F2,254 = 6.88, p=0.009; F2,254 = 5.87, p=0.01, rs4680 Met/Met vs. Val+; F2,229 = 3.59, p=0.05; F2,229 = 6.19, p=0.01 respectively; age co-varied]. Similarly, genotype effects of rs4633, rs4818, and rs4680 were observed on WCST total errors [Recessive model: F2,258 = 3.64, p=0.05; F2,254 = 3.65, p=0.05; F2,229 = 4.08, p=0.04; respectively; age co-varied]. Finally, genotype effects of rs6269, rs4818 for TOL total correct in 1st trial score [F2,289= 3.08, p=0.04; F2,285= 3.67, p=0.02], and of rs6269 for SOPT error scores [F2,285 = 3.66, p=0.02] were observed. Conclusion: These results suggest that rs6269, rs4633, rs4818, and Val108/158 Met of the COMT gene modulate some aspects executive functions in ADHD children.

3-3-A

Neurorehabilitation Research Center

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The overall research program of our laboratory focuses on predicting and enhancing motor and cognitive function in the context of neurological disorders, predominantly in the geriatric population. This work involves a number of different projects, including studies on the neural bases of human behavior in normal volunteers, studies aimed at elucidating mechanisms of neuroplasticity in clinical populations, clinical trials of promising therapeutic interventions, and others. Current projects underway in our laboratory target people who have multiple sclerosis, mild cognitive impairment, or those who have suffered a stroke. Methods used in our lab include transcranial magnetic stimulation (TMS), structural and functional neuroimaging (fMRI), neuropsychological assessment, behavioral performance evaluation, and rehabilitative therapies. As will be described in further detail below, some of the interventions employed in our laboratory involve repetitive TMS (rTMS), physical rehabilitation, and cognitive rehabilitation. Our research represents a true multidisciplinary effort involving teams of scientists and clinicians from different backgrounds, including psychology, neurology, physical and occupational therapy, biostatistics, geriatric medicine, and anesthesiology. Research Projects: •The ENHANCE Study: Enhancing the response to rehabilitation after stroke with transcranial magnetic stimulation. •The Mirror study: A pilot study of the effects of a mirror on modulation of the neural motor pathways after stroke. •Neurophysiological abnormalities in MS: Disease process or functional compensation? •Measuring and predicting cognitive impairment in a geriatric clinic •Effects of cognitive intervention for older adults with memory decline: A pilot study •Duration of the effects of rTMS for treatment of chronic neuropathic pain

3-3-B

The 5-HTTLPR polymorphism of the serotonin transporter gene and short term behavioral response to methylphenidate in children with ADHD

Geeta A. Thakur*, Natalie Grizenko, Sarojini M. Sengupta, Norbert Schmitz and Ridha Joober

Introduction: In this study, we investigated the relationship between the 5-HTTLPR polymorphism in the serotonin transporter gene (SLC6A4) and the response to methylphenidate (MPH) treatment on ADHD relevant behaviors. Methods: 157 children (6-12 years old) were assessed with respect to their behavioral response to MPH (0.5 mg/kg/day) using a 2-week prospective within-subject, placebo-controlled (crossover) trial. Genotyping was conducted for the triallelic 5-HTTLPR polymorphism. Conners' Global Index for parents (CGI-P) and teachers (CGI-T) at baseline and at the end of each week of treatment with placebo and MPH were the main outcome measures. A mixed model analysis of variance was used to determine gene, treatment and gene X treatment interaction effects. Results: Mixed model analysis of variance revealed a gene X treatment interaction for CGI-P but not for CGI-T. Children homozygous for the lower expressing alleles (s+lG=s') responded well to placebo and did not derive additional improvement from MPH treatment compared to children carrying a higher expressing allele (lA). No main effects of genotype on either CGI-P or CGI-T were observed. Conclusions: A double blind placebo-controlled design was used to assess the behavioral effects of MPH in relation to the 5-HTTLPR triallelic polymorphism in children with ADHD. This polymorphism appears to modulate the behavioral response to MPH in children with ADHD as assessed in the home environment by parents. Further investigation is needed to assess the clinical implications of this finding. Funding: CIHR Institute of Human Development, Child and Youth Health (IHDCYH)

3-4-A

The role of the amygdala in perception of graded pleasantness

Julie A. Boyle*, Jelena Djordjevic and Marilyn Jones-Gotman

The role of the amygdala in the chemical senses still remains a source of debate. While some researchers have claimed that the amygdala is preferentially tuned to intensity rather than to valence, others have reported that it is preferentially activated to high intensity pleasant and unpleasant stimuli but not to neutral or low intensity stimuli. We used a set of binary odor mixtures to establish whether the amygdala responds to odor valence regardless of odor intensity. Twelve subjects underwent PET, and were scanned under eight conditions: pyridine (unpleasant), citral (pleasant), five mixtures of citral and pyridine in varying physical proportions (from 10/90 to 90/10), and an odorless baseline. All stimuli were perceived as being isointense and moderately strong, and a linear increase in perceived pleasantness was observed as one progressed from pyridine (most unpleasant) to the 50/50 mixture (neutral) and to citral (most pleasant). Using VOI analyses we extracted mean rCBF in left and right amygdala for all eight conditions. We also extracted mean rCBF values in the left and right piriform cortex as a control region. For both VOIs in the amygdala we found a U-shaped function: maximum rCBF in response to the pleasant and unpleasant mixtures and the smallest rCBF response for the neutral midpoint (50/50). In contrast, rCBF in the left and right piriform cortex showed no variation as a function of stimulus pleasantness. In conclusion our results are consistent with previous findings which suggest that the amygdala responds to odor valence in both directions, i.e. to pleasant and unpleasant stimuli but not to neutral stimuli. Interestingly, as our stimuli were not high in intensity these results suggest that the amygdala also responds to pleasant and unpleasant stimuli of medium intensity.

3-4-B

Dystroglycan Function: New Insights from Genetic Studies in Drosophila

Nicola Haines*, Waris Shah*, Bryan Stewart and Salvatore Carbonetto

Dystroglycan is widely expressed transmembrane glycoprotein that is implicated in numerous human diseases. In vertebrates, loss of Dystroglycan results in early embryonic lethality, whilst mutations that alter Dystroglycan function, through, for example, altering its glycosylation, result in animals with severe defects in brain and eye morphology; they also suffer from muscular dystrophy. Dystroglycan is also implicated in epithelial cell function and is deregulated in several types of cancer. The molecular pathways through which loss of Dystroglycan leads to cellular dysfunction are unclear. Studies in model invertebrate systems have a strong record of providing information on the fundamental function of proteins and we are using the Drosophila model system to study Dystroglycan. Our initial studies indicate that Dystroglycan is important in neural differentiation and we have identified phenotypes in muscle and epithelial cells that are associated with loss of Drosophila Dystroglycan. Work from other labs indicates that Dystroglycan mutants prefer lower ambient temperature and recent work has indicated that calcium deregulation may underlie changes in cellular metabolism and behavior observed. We are extending these findings to dissect the molecular pathways though which Dystroglycan functions. To this end we are exploiting the Dystroglycan associated phenotypes to assay candidate genes such as calcium leak channels and genes involved in energy metabolism. In an additional approach we have found that Dystroglycan null flies fail to develop at high temperature but thrive at low temperatures. We plan to use this simple assay in an unbiased, broad-based screen to identify novel genes that mediate this behavior.

3-5-A

A new pre-clinical model of low back pain due to degenerative disc disease

Maral Tajerian*, Magali Millecamps, Laura S Stone

Low back pain effects between 10-15% of the adult population and relief for sufferers is often elusive. Surprisingly little is known about the neurological and anatomical causes and consequences of low back pain. We use both human and animal models to understand this common yet poorly understood condition.

3-5-B

Prostaglandin D2 Mediates Inflammation and Secondary Damage after Spinal Cord Injury.

Adriana Redensek, (*Khizr I. Rathore*), Ruben Lopez-Vales and Samuel David

Prostaglandin D2 (PGD2) plays an important role as an inflammatory mediator. Its effects are mediated via two receptors (DP1 and DP2); activation of either receptor often results in divergent effects. Therefore, whether PGD2 is a pro- or anti-inflammatory mediator remains controversial. Spinal cord injury (SCI) triggers an inflammatory response that contributes to secondary damage. We studied the expression and role of PGD2 in the inflammatory response and secondary damage after SCI in adult mice. The expression of the two PGD2 synthases, hematopoietic prostaglandin D synthase (HPGDS) and lipocalin-type prostaglandin D synthase (L-PGDS) as well as the DP1 and DP2 receptors were assessed at different times after SCI. Upregulation of HPGDS mRNA and protein was seen soon after SCI and the levels remained high for 4 weeks. HPGDS was expressed in macrophages and oligodendrocytes after SCI. The cell type localization of L-PGDS did not change after injury and remained in the oligodendrocytes. This data suggests that HPGDS may be the main producer of PGD2 after SCI. DP1 and DP2, which are minimally expressed in the uninjured spinal cord are upregulated primarily in reactive astrocytes after SCI. The role of PGD2 produced via HPGDS in spinal cord contusion was assessed using HPGDS null mice (HPGDS-/-) and wildtype mice. HPGDS-/- mice showed significant improvement in locomotor recovery using the Basso Mouse Scale analysis as compared to wildtype mice. Furthermore, treatment with a selective inhibitor of HPGDS (HQL-79) confirmed these results. The locomotor improvement after SCI in HPGDS-/- mice was accompanied by a reduction in myelin loss, increase in serotonergic innervation and increase in motor neuron survival in the lesioned spinal cord as compared to wildtype mice. There was also a significant increase in IL-6 and a decrease in IP-10 levels in the injured spinal cord of HPGDS-/- mice. In addition, DP1-/- mice showed a similar pattern of recovery after SCI, suggesting that the detrimental effects of PGD2 is likely to be mediated via DP1 signalling.

3-6-A

Alpha-2 Adrenergic and Opioid Receptors: Analgesic Actions and Interactions

Anne-Julie Chabot-Dore*, Magali Millecamps, Laura S Stone.

Co-administration of analgesic agonists activating the opioid and alpha-2 adrenergic receptors results in a powerful synergistic interaction. We are using in vitro and in vivo approaches to understand the molecular mechanisms underlying these interactions.

3-6-B

The Role of ALCAM in Spinal Cord Injury

Delphine Bouhy*, Adriana Redensek, Joshua Wiener, and Samuel David

There is increasing evidence that inflammatory and immune mechanisms in the central nervous system (CNS) play an important role in neuropathic pain. Infiltration of inflammatory cells like neutrophils, T-cells and macrophages, as well as activation of resident microglial cells in response to CNS damage, leads to subsequent production and secretion of various inflammatory mediators. These mediators may contribute to pain hypersensitivity. Recently, it has been shown that activated leukocyte cell adhesion molecule (ALCAM), a 105kDa transmembrane glycoprotein of the Ig-superfamily, mediates leukocyte migration into the CNS in experimental autoimmune encephalitis (EAE), a widely used animal model of multiple sclerosis (MS) and that blocking ALCAM reduces the migration of lymphocytes and monocytes across the BBB-endothelium in vitro. The aim of this work was to assess the role of ALCAM in inflammatory cell infiltration, macrophage activation, and allodynia (perception of innocuous stimuli as painful) after spinal cord injury using ALCAM null and wildtype mice. A computer-controlled contusion device was used to make well-defined moderate contusion lesions in the lower thoracic spinal cord of adult ALCAM null and wildtype female C57BL/6 mice. Mice were sacrificed at various times post-injury. We assessed ALCAM expression by Western blot, and immunofluorescence. At-level allodynia following spinal cord injury was assessed using the von Frey hair test between 1 and 28 days following injury. ALCAM expression is increased after spinal cord injury and histological analyses showed that macrophages are the main cell type expressing ALCAM at the lesion site. Furthermore, the number of activated macrophages at the lesion site is significantly reduced in ALCAM null mice. Behavioural analyses also showed that ALCAM null mice have decreased allodynia compared to wildtype animals. Together, these results suggest that ALCAM mediated macrophage migration into the spinal cord after injury contributes to neuropathic pain.

3-7-A

The key role of the intraparietal sulcus region in the rearrangement of nonverbal information in working memory

Anne Sophie Champod* Michael Petrides

Concomitant increase in activity within the mid-dorsolateral prefrontal cortex (MDLFC) and the posterior parietal cortex (PPC) is observed in most functional neuroimaging studies of working memory. Despite broad consensus on the importance of these two brain regions in working memory, their unique contribution, especially that of the PPC, remains a matter of heated debate. The main objective of the present event-related functional magnetic resonance imaging (fMRI) study was to examine the hypothesis that the cortex in the intraparietal sulcus (IPS) region in the PPC is involved in the manipulation (i.e. rearrangement) of nonverbal information in working memory and to dissociate the involvement of this brain region from that of the MDLFC in working memory processes. The results show that the IPS region is centrally involved in manipulation processes, whereas activation of the MDLFC is related to the monitoring of the information that is being manipulated. This study provides evidence of a dissociation of activation in these two regions and, thus, succeeds in further specifying their relative contribution to working memory.

3-7-B

CONTROL OF IRON EFFLUX FROM OLIGODENDROCYTES

K. Schulz, C. D. Vulpe, and S. David

Iron is essential for many biological processes. However, because of its redox activity, its levels must be tightly regulated. Ferroxidases, which convert toxic ferrous iron into its non-toxic ferric form, are involved in maintaining iron homeostasis. One of these ferroxidases is Hephaestin (Heph), a transmembrane copper-dependent enzyme that is required for the export of iron from intestinal enterocytes. Heph is thought to facilitate iron efflux from enterocytes by oxidizing the ferrous iron transported across the cell membrane via the iron exporter ferroportin (Fpn). Here we show by double immunofluorescence that Heph and Fpn are expressed in oligodendrocytes in purified primary cell cultures from rat cortex and in spinal cord sections of C57BL/6 mice. Furthermore, Heph expression in oligodendrocytes is restricted to mature cells, while Fpn is expressed in mature as well as immature oligodendrocytes. We also show that Heph is required for iron efflux from oligodendrocytes in primary cell culture. In addition, immunofluorescence and Perl's histochemistry of spinal cord and brain sections of 'sex-linked anaemia' (sla) mice show iron accumulation in grey matter oligodendrocytes. These mice carry a mutation in the heph gene resulting in the expression of a truncated form of Heph with only partial ferroxidase activity. Furthermore, the increased iron accumulation was also accompanied by decreased motor coordination on a rotorod. These data show that Heph is expressed by oligodendrocytes and that it might be involved in exporting iron from these glial cells.

3-8-A

Role of the p38 mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) signaling cascade in oligodendrocyte differentiation

Jeffery D. Haines*, Jun Fang, Walter E. Mushynski, Guillermina Almazan

Oligodendrocytes (OLGs), the myelinating cells in the central nervous system, are the primary target of destruction in multiple sclerosis. The molecular mechanisms that underlie myelin formation remain poorly understood. p38 mitogen-activated protein kinases (MAPKs) are a serine/threonine kinase family that regulates multiple cellular functions including proliferation, survival and differentiation. Previous work in our laboratory demonstrated that p38 is necessary for both central and peripheral myelination. In order to better understand the role of p38 and the signaling mechanisms that regulate OLG differentiation and myelination, we have identified downstream kinases that may be involved in this process. Treatment of OLGs with MAPK-activated protein kinases 2 (MAPKAPK2 or MK2) inhibitor resulted in reductions in galactosylceramide (GalC) and sulfatide levels, as well as levels of myelin basic protein, and myelin-associated glycoprotein (MAG). Knockdown of MK2 with small interfering RNA caused decreases in GalC and MAG, corroborating our findings with the MK2 inhibitor. Furthermore, co-immunoprecitation studies demonstrated that p38alpha and MK2 can form a protein complex in differentiating OLGs. Therefore, MK2 is a downstream target of the p38 signaling cascade that regulates OLG differentiation. Studies are underway to identify the mechanisms by which p38, MK2 and other downstream targets regulate OLG differentiation and central nervous system myelination.

3-8-B

The deubiquitinating enzyme USP2 is involved in the regulation of circadian rhythms

David Duguay, Yaoming Yang, Gerry Baquiran, Lydia Oueller, Kai-Florian Storch, Simon S. Wing, Nicolas Cermakian

Post-translational modifications of clock proteins are involved in the mechanisms governing circadian physiology. Ubiquitylation by enzymes SCFFbxl3 and SCFbeta-TRCP1/2 is required for the proper functioning of the clock, raising possibilities about the involvement of deubiquitinases. The deubiquitinase Usp2 is rhythmically expressed in many peripheral organs and in the SCN. We have generated Usp2 KO mice to assess the involvement of USP2 in the molecular clockwork and clock output. The locomotor activity of Usp2 KO mice (n=6) and their wild-type littermates (n=9) was studied in running-wheel cages. The endogenous period was increased by 16±6.0 minutes in Usp2 KO. Phase resetting after an advance of 6 hours of the light/dark cycle was slower while phase resetting after a delay of 6 hours was faster in Usp2 KO. The phase-response curve (phase shift induced by light pulses at different circadian times) was altered in Usp2 KO: a pulse at CT14 induced a larger delay while advances after pulses at CT20 and CT22 were blunted in KO. In MEF, PER1 and PER2 protein levels were increased in cells prepared from Usp2 KO embryo. The first circadian peak of Per2 and Rev-erb ? mRNA expression after synchronization was increased in Usp2 KO MEF. Biochemical studies showed that USP2 interacts with PER1, PER2 and BMAL1. Furthermore, highly ubiquitinated PER1 was found to be a target of USP2. Our results suggest that USP2 is involved in the regulation of core clock proteins, with influences at the level of circadian timekeeping and response to photic cues.

3-9-A

The counter-receptor Fas Ligand regulates the expression of nerve growth factor in Schwann cells in vitro

Manuelle Rongy*, Julie Desbarats, John White and Guillermina Almazan

Fas Ligand (FasL), mostly known as a ligand for Fas, can act as a counter-receptor and signal in the FasL-bearing cell, a mechanism called reverse signalling. FasL is a member of the tumour necrosis factor (TNF) superfamily and is expressed as homotrimers at cell surface and in secreted isoforms in cells of the immune, nervous, and reproductive systems. Fas engagement in primary sensory neurons has been shown to induce neurite outgrowth and we decided to study the effect of FasL signalling in Schwann cells, the cells ensheathing neurons in the peripheral nervous system. Primary mouse Schwann cells and a mouse Schwann cell line were treated with a Fas-Fc protein chimera to engage FasL signalling. We have found that nerve growth factor (NGF) secretion and NGF mRNA levels were increased in Schwann cells when treated with Fas-Fc. Following FasL engagement, phosphorylation levels of signalling kinases, Erk1/2, Akt, p38 and Src, were rapidly increased. Recruitment of growth / survival pathways downstream of FasL and secretion of NGF by Schwann cells may contribute to regeneration after injury in the peripheral nervous system.

3-9-B

The regulation of orexin receptors by dynein light chains

Erika Belanger-Nelson, David Duguay, Valerie Mongrain, Anna Beben, Armen Khatchadourian, Nicolas Cermakian

Orexins are neuropeptides involved in the regulation of sleep, feeding and reward. The function of these peptides is governed by Orexin Receptors 1 and 2 (OX1R, OX2R). The loss of orexins or mutations of the receptors have been shown to cause the sleep disorder, narcolepsy. In aim to understand the intracellular mechanisms involved upon activation of these receptors, we have identified the dynein light chain Dynlt1 as a partner of OX1R. Our hypothesis is that Dynlt1 is important for OX1R intracellular regulation. Yeast two-hybrid assays were used to measure the interaction of OX1R and Dynlt1 and identified the last 10aa of OX1R and the C-terminus of Dynlt1 as being crucial for the interaction, which was confirmed in mammalian cells by coIP. Western blots for phosphorylated and total ERK proteins were done on extracts of HEK293 cells expressing OX1R with or without Dynlt1, and then stimulated with OX-A. The ERK response to OX-A is less sustained upon overexpression of Dynlt1, while its downregulation has the opposite effect (i.e. more sustained). Confocal microscopy was used to visualize the intracellular localization of OX1R-GFP in HEK293 cells following OX-A stimulation and upon over-expression or down-regulation of Dynlt1. At resting conditions, OX1R is localized to the plasma membrane and is internalized and localizes to early endosomes following stimulation with OX-A. Our work suggests a role for Dynlt1 in ligand-mediated OX1R internalization. This research may have important implications on our knowledge of sleep, feeding and reward disorders and in developing treatment for orexin-related diseases.

3-10-A

Mitogen-Activated Protein Kinase p38 alpha Controls Schwann Cell Differentiation by Regulating Transcription Factors Krox-20 Expression and CREB Activation

Shireen Hossain, Miguel-Angel de la Cruz, David Parkinson, Walter E. Mushynski and Guillermina Almazan*

Schwann cells (SC) originate in the Neural Crest and in close contact with axons, develop and undergo differentiation to myelinate nerves of the peripheral nervous system (PNS). Deficiencies in SC development and myelin result in neuropathies such as Charcot-Marie Tooth disease. The molecular mechanisms by which PNS myelination occur have yet to be fully elucidated. We previously demonstrated a pivotal role for p38 Mitogen Activated Protein Kinases (MAPK) in laminin or ascorbate-induced SC myelination. The expression of several key myelin genes including myelin basic protein (MBP), myelin associated glycoprotein (MAG) and protein zero (P0) are regulated by p38, however, the mechanism by which this takes place, remains obscure. Our objective was to identify transcription factors regulated by p38 MAPK to modulate expression of these myelin genes. Using a specific p38 alpha/beta inhibitor (PD169316) and an siRNA directed against p38 alpha, the predominant isoform expressed in SCs, we demonstrate a marked reduction in protein levels of the zinc-finger transcription factor krox-20 (Egr2) in myelinating SC-Dorsal root ganglion (DRGN) cocultures. Krox-20, a master regulator of several myelin genes including MAG, P0 and MBP, is critical for PNS myelin formation. PD169316 also reduced protein levels of the cyclin-dependent kinase inhibitor p27kip1 (expressed by non-proliferating cells) and MAG (an early marker of myelination), but failed to stimulate proliferation and the expression of Sox-2, an HMG transcription factor and a negative regulator of SC differentiation. Overexpression of krox-20 using an adenovirus was insufficient to promote the formation of MBP positive internodes in the presence of PD169316, despite the expression of MAG. Pharmacologically inhibiting MK2 (MAPKAPK-2), a downstream target of p38 alpha, dose-dependently reduced the protein levels of several myelin genes and of krox-20. Thus, MAPK p38 appears to regulate SC differentiation is at the level of the transcription factor krox-20 expression in SCs, possibly via MK2. We find that cAMP-regulated transcription factor CREB is potently activated following initiation of myelination with ECM. CREB phosphorylation was effectively blocked by PD169316, suggesting another mechanism by which p38 MAPK may be regulating SC differentiation and thus myelination. Henceforth, we present a molecular mechanism by which p38 MAPK modulates SC differentiation and myelination of DRGNs involving Krox-20 expression and CREB activation but not Sox-2 expression.

3-10-B

The circadian clock controls immune response

*Erin E. Fortier, Julie Rooney, Hugues Dardente, Marie-Pierre Hardy, Aude Villemain, Nathalie Labrecque & Nicolas Cermakian

Circadian variations have been found in the immune system, including daily rhythms in circulating numbers of leukocytes and serum concentration of cytokines. Although the circadian clock is known to control various physiological systems, very little is known about the timing of events in the immune system. We hypothesized that a clock in lymph nodes controls T cell function. The aims of this study were to identify clock gene expression in mouse lymph nodes (LNs), to investigate Tcell proliferation rhythms, and to examine LN rhythms in mice with a dysfunctional clock. Adult WT and Clock mutant mice were entrained to a light-dark cycle and sacrificed at regular intervals over 24 hours. LNs were sampled and used to: i) Extract RNA and quantify clock gene expression by real-time PCR; ii) Measure T-cell proliferation following anti-CD3 stimulation iii) Examine expression of T cell signaling proteins. Our results show that LNs exhibit rhythmic clock gene expression. T cells show a robust circadian variation in proliferation after stimulation via the T cell receptor (TCR) that are lost in Clock gene mutant mice. In addition, the tyrosine kinase ZAP70, which is immediately downstream of the TCR in the T cell activation pathway, exhibits rhythmic expression. This is the first evidence for control of the immune response by the molecular clockwork. Our results have uncovered a novel mode of regulation of T-cell proliferation. This study linking circadian rhythms and immune response may also provide cues for more efficient vaccination strategies.

3-11-A

Characterization of lipid binding specificities of dysferlin C2 domains reveals novel interactions with phosphoinositides

Sabrina Di Fulvio*, Christian Therrien and Michael Sinnreich

Limb-girdle muscular dystrophy type 2B (LGMD2B) is caused by mutations in the dysferlin gene, which codes for a large type II transmembrane protein containing seven C2 domains and two dysferlin (DysF) domains. Dysferlin is found at the plasma membrane and on intracellular vesicles. It is believed that dysferlin's C2 domains mediate lipid and protein interactions. This study sought to characterize the lipid binding specificities of dysferlin's seven C2 domains, which are poorly characterized. Recombinant cloning techniques were used to create GST-C2 domain fusion proteins. The phosphoinositide interactions were studied using lipid strips, protein-lipid overlay assays, and liposome centrifugation assays. These assays showed that each dysferlin C2 domain can bind to phosphatidylserine (PS). Dysferlin's C2A domain bound PS very strongly and in a calcium-dependent manner, whereas the other domains evidenced weaker, calcium-independent PS binding. Dysferlin's C2A domain also binds phosphoinositide 4-phosphate (PtdIns(4)P) and phosphoinositide 4,5-bisphosphate (PtdIns(4,5)P2) in a calcium-dependent fashion. The other C2 domains did not show significant binding to these phosphoinositides. Dysferlin is involved in calcium-dependent sarcolemmal membrane repair: in the event of muscle fiber injury, an influx of calcium triggers dysferlin to fuse subsarcolemmal vesicles to the plasma membrane wound site. This study suggests that the calcium influx would activate dysferlin's C2A domain. Dysferlin at the injury site could bind to PS and PtdIns(4)P on nearby subsarcolemmal vesicles. Activated dysferlin found on intracellular vesicles could bind PS and PtdIns(4)P on other nearby vesicles, and to PS and PtdIns(4,5)P2 on the plasma membrane, thus assiting in the generation of a membrane patch.

3-11-B

Circadian clock gene expression in extra-SCN human brain regions

Nicolas Cermakian, Elaine Waddington Lamont, Philippe Boudreau, Diane B. Boivin

Circadian oscillators have been observed throughout the rodent brain. In humans, rhythmic gene expression has been reported only in the pineal gland and little is known about the expression of circadian clock genes in other brain regions. We sought to determine whether clock gene expression could be detected and whether their expression varies as a function of time of day in the bed nucleus of the stria terminalis (BNST) and cingulate cortex, areas known to be involved in decision-making and motivated behaviors, as well as in the pineal gland of Alzheimer's disease patients and aged controls. Relative expression levels of PERIOD1 (PER1), PERIOD2 (PER2), and BRAIN AND MUSCLE ARNT-LIKE PROTEIN-1 (BMAL1) were measured using quantitative PCR. PER1, PER2, and BMAL1 RNAs were detected in all three brain regions. A dual-harmonic regression model revealed significant circadian rhythms of PER1 in the cingulate cortex of control subjects and in the BNST of AD subjects. PER2 RNA rhythm was significant in the cingulate cortex and BNST of control subjects, but in all three regions of AD patients. BMAL1 RNA showed a significant rhythm in all groups, except in the cingulate cortex of controls. Fitted maxima of clock gene expression occurred at different times of day in control vs. AD samples, and were variable across brain regions in AD samples. These results have implications for the understanding of circadian rhythm disturbances in AD patients, as they indicate that non-SCN brain oscillators might be functional but desynchronized in the brains of these individuals. Funding: CIHR, FRSQ.

3-12-A

Postnatal deamidation of 4E-BP2 in brain enhances its association with raptor and alters kinetics of excitatory synaptic transmission

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The eIF4E-binding proteins (4E-BPs) disrupt eIF4F complex formation, and thereby repress translation by precluding ribosome association with mRNAs. There are three 4E-BPs in mammals, of which 4E-BP2 is enriched in the brain and plays an important role in long-lasting synaptic plasticity and learning and memory formation. Here we describe asparagine deamidation as a novel posttranslational modification of 4E-BP2 in the brain. Deamidation is the spontaneous conversion of asparagines to aspartates. Two major sites of deamidation in 4E-BP2 were mapped to an asparagine-rich sequence unique to 4E-BP2. Deamidated 4E-BP2 exhibits increased binding to the mammalian Target of Rapamycin (mTOR)-binding protein, raptor, which leads to reduced association with eIF4E. 4E-BP2 deamidation occurs during postnatal development, concomitant with the attenuation of the activity of the PI3K-Akt-mTOR signalling pathway. Expression of deamidated 4E-BP2 in 4E-BP2-/- neurons yielded mEPSCs exhibiting increased charge transfer with slower rise and decay kinetics, relative to wild type 4E-BP2. We propose a function for 4E-BP2 deamidation as a compensatory mechanism for the reduced activity of the PI3K-Akt-mTOR module to facilitate translation and impact synaptic activity.

3-12-B

Neuroscience research from the CRLMB

Isabelle Deschamps, Vincent Gracco, Shari Baum

The CRLMB functions to promote an interactive and multidisciplinary environment for the study of the neurobiology of language with an emphasis on the application of fundamental principles of language use and comprehension to promote innovation in areas such as language learning and instruction, reading, literacy and the treatment of human communication disorders. Language use and comprehension rely on the dynamic integration and interaction of multiple cortical and subcortical brain areas. Neural circuits are used to process linguistic and metalinguistic information from multiple sensory modalities (auditory, visual, somatosensory) to inform perceptions, make decisions and ultimately to execute movements associated with communication and interpersonal interaction (by speech and gesture). A thorough understanding of the brain areas involved and the manner in which neural networks interact for speech, language and communication is a major challenge in systems neuroscience. Beyond the complexity of language processes in the brain, theories about how language works attempt to understand the complexity of language structure, how we associate meaning with the sounds or signs of language, how context influences meaning, how syntax is used to produce and understand sentences and the interaction of cognition and language. Here we study basic neural processes of language use with a wide array of neuroscientific techniques including functional and structural neuroimaging, transcranial magnetic stimulation, electroencephalography, auditory and somatosensory perturbation, electromyography and kinematics.

3-13-A

Functional Analysis of Turtle/IGSF9 immunoglobulin superfamily memebers in axon tiling

Scott Cameron*, Wen-Tzu Chang and Yong Rao

Restriction of adjacent same-type axons/dendrites to separate single columns for specific neuronal connections is commonly observed in vertebrates and invertebrates, and is necessary for proper processing of sensory information. Columnar restriction is conceptually similar to tiling, a phenomenon referring to the avoidance of neurites from adjacent same-type neurons. We have previously identified Turtle, a member of the conserved Tutl/Dasm1/IgSF9 subfamily of the immunoglobulin superfamily as a key mediator of this process. here we show that Turtle interacts both genetically and biochemically with CG16857, a highly related, previously undescribed molecule of the same subfamily as Turtle.

3-13-B

Theta rhythm as the 'default state' of the hippocampus: an investigation using the isolated hippocampus in vitro

Romain Goutagny, Jesse Jackson*, Sylvain Williams

During exploratory locomotion and rapid eye movement sleep in rodents, the hippocampus exhibits rhythmic oscillatory field potentials at frequencies ranging from 3 to 12 Hz (theta frequency). Theta oscillations are thought to represent the on-line state of the hippocampus, with the synchronization of hippocampal neurons during theta activity serving as a reference for information encoding by hippocampal place cells. In the actual model, it is postulated that the hippocampal theta rhythm is generated by both the medial septum and the enthorinal cortex. However, it has also been proposed that the hippocampus itself might act as a rhythm generator. To test this hypothesis, we used complete hippocampal preparations in vitro from rat (postnatal day 15-28). By placing these intact hippocampus in a recoding chamber perfused with normal aCSF, we examined if hippocampal oscillations were spontaneously elicited using field recordings of the CA1 area. In this experimental paradigm, we were able to record continuous spontaneous oscillations in 53 isolated hippocampus with a mean frequency of 5.9±0.3Hz. The depth profile of these oscillations showed a graduate phase reversal between the stratum oriens and the stratum radiatum and the largest amplitude in the stratum radiatum, consistent with the coordinated activity of at least two current generators (dipole). We then tested pharmacologically the receptors involved in these theta oscillations. We showed that this rhythm was blocked by hippocampal application of the GABAA receptor antagonist bicuculline (10µM; n=6) or the selective AMPA receptor antagonist NBQX (10µM; n=5). However, the application of the NMDA receptor antagonist AP-V (10µM; n=8) or the selective kainate receptor antagonist SYM2081 (10µM; n=7) did not induce any modifications of the hippocampal theta oscillations. Finally, these oscillations were not affected by the application of either the muscarinic receptor antagonist atropine (10µM; n=9) or the nicotinic receptor antagonist tubocurarine (10µM; n=8). Taken together, these results show for the first time that 1) theta oscillations can be generated continuously within the hippocampus in-vitro without pharmacologically activating the circuitry; and 2) theta oscillations does not require cholinergic activation of the intrahippocampal theta generator as previously postulated.

3-14-A

Expression of neurogenic markers in limbic brain regions of suicide subjects

Marissa Maheu*, Maria Antonietta Davoli, Gustavo Turecki, Naguib Mechawar

Accumulating evidence suggests that adult brain neurogenesis may be disturbed in psychiatric conditions such as schizophrenia and mood disorders. Most studies have focused on the dentate gyrus of the hippocampus, and little is currently known about the state of other neurogenic regions within the limbic system. In the present study, we examine endogenous markers of proliferation and neurogenesis in human post-mortem limbic tissues (amygdala, olfactory bulb) from well-characterized subjects having died by suicide and matched sudden-death controls. Markers of cell proliferation as well as of neuronal migration and differentiation are quantified using immunoblotting and visualized in situ by immunocytochemistry.

3-14-B

Response of human oligodendrocyte progenitors to growth factors and axon signals

Qiao Ling Cui*, Gabriela Fragoso, Veronique Miron, Peter J. Darlington, Walter E. Mushynski, Jack Antel and Guillermina Almazan.

Our objective was to define the capacity of growth factors (GFs) and neurons to enhance growth and differentiation of human fetal and adult oligodendrocyte (OGC) progenitor cells (OPCs). OPCs were isolated from 15-18 week fetal and adult human CNS based on A2B5 expression, and grown in dissociated cultures in defined media (DFM) ± GFs alone or in co-culture with rat dorsal root ganglia neurons (DRGNs). A small number of dissociated fetal cells in DFM expressed myelin lineage markers (10% Olig2+; 4% O4+. PDGF-AA/bFGF enhanced meiosis of Olig2+ (38%) and O4+ (62%) cells (versus 25% and 30%, respectively for DFM alone). BDNF/IGF-1 had little effect on meiosis but promoted differentiation of O4+ cells (96% co-expressed galactocerebroside (GC) relative to PDGF-AA/bFGF (46 ± 4%) or DFM (20%) and had more complex morphology. In culture with DRGNs, BDNF/IGF-1 increased the numbers of MBP+ cells 10-fold. This treatment also enhanced attachment to and ensheathment of axons. Most adult cells expressed O4 and Olig2 in DFM. BDNF/IGF-1 and PDGF-AA/bFGF promoted their survival, differentiation, and significantly increasing MBP expression, process extension and membrane sheath formation. In culture with DRGN, all adult OPCs acquired MBP; the presence of PDGF-AA/bFGF and BDNF/IGF-1 enhanced their attachment to axons. However, adult OPCs were less capable of ensheathing axons as compared to fetal cells. Our study demonstrates that human OPCs show distinctive age dependent survival and differentiation responses to selected GFs and axonally delivered signals.

3-15-A

Neuregulin-1 increases cell proliferation in the mature dentate gyrus

Ian Mahar*, Maria Antonietta Davoli and Naguib Mechawar

Objectives Abnormal signaling of neuregulin-1 (NRG1), a growth factor well known for its involvement in neuronal migration and differentiation in the developing brain, has recently been implicated in the etiologies of schizophrenia and depression. The current study examined whether short-term peripheral NRG1 administration increases cell proliferation in the dentate gyrus (DG) of the adult hippocampus, a developmental phenomenon also thought to play a role in the emergence of these psychiatric disorders. Methods Adult male C57Bl6 mice were implanted subcutaneously with osmotic mini-pumps chronically delivering either saline (controls; n=6) or NRG1 (n=6) at a constant rate of 10 µg/d for 24 hours. Bromodeoxyuridine (BrdU; 50 mg/kg, i.p.) was injected once at implantation, and once two hours prior to sacrifice. Following administration, animals were perfused intracardially with formaldehyde, and brains processed for BrdU immunocytochemistry. Statistical significance was determined using Mann-Whitney U-tests. Results Cell proliferation in the DG was increased in NRG1 exposed animals (53.98±6.09, mean ± SEM) compared to controls (39.56±2.32; p=.01). This increase was significant in the caudal DG within the ventral hippocampus (-2.54 to -3.80mm from bregma; p=.001), but not the rostral DG within the dorsal hippocampus (-1.46 to -2.54mm from bregma; p=.3). Conclusion We found that peripherally administered NRG1 increases the proliferation of new cells in the DG, specifically in a region associated with affective regulation. These data, with particular relevance to schizophrenia and affective disorders, are the first to suggest that NRG1 modulates adult hippocampal neurogenesis. Acknowledgments: This research was funded by an NSERC Discovery Grant to N.M.

3-15-B

Fingolimod (FTY720) Enhances Remyelination Following Demyelination of Organotypic Cerebellar Slices

Veronique E. Miron*, Samuel K. Ludwin, Peter J. Darlington, Andrew A. Jarjour, Betty Soliven, Timothy E. Kennedy, Jack P. Antel

Multiple sclerosis (MS) is characterized by oligodendrocyte loss and demyelination. Experimental animal systems demonstrate that remyelination occurs subsequent to demyelination, contributes to functional recovery, and is mediated by oligodendrocyte progenitor cells (OPCs) that have differentiated into myelinating phenotypes. The impact of MS therapeutics on myelin maintenance and remyelination may be critical in determining long-term functional outcome. Fingolimod is in clinical trials for MS due to its systemic anti-inflammatory properties, yet may directly impact cells within the CNS via its ability to cross the blood-brain barrier and signal via S1P receptors. Mouse organotypic slices were used to assess the effects of fingolimod on myelin-related processes in system containing only resident CNS elements. Physiological doses of the active phosphorylated form of fingolimod were applied for 3 weeks to determine the impact on myelin maintenance, or for 2 weeks following lysolecithin-induced demyelination to evaluate effects on remyelination. We found that fingolimod treatment under had no impact on myelin under basal culture conditions. Functional remyelination and reformation of nodes of Ranvier following lysolecithin-induced demyelination was documented by electron microscopy by the presence of thin myelin sheaths associated with paranodal loops. Fingolimod treatment following demyelination enhanced the recovery of myelin and process extension in OPCs (PDGF?R+) and mature oligodendrocytes (NogoA+) relative to control. Fingolimod increased microglia cell numbers (IBA-1+) and immunoreactivity for an astrocytic marker (GFAP+) compared to remyelinating controls; however, phagocytosis of bacteria was decreased by fingolimod at this time. We conclude that fingolimod directly impacts myelin-related processes and neural cells in an in vitro system that closely models in situ conditions. Fingolimod enhanced remyelination in demyelinated slices which was associated with increased glial reactivity. The ability of fingolimod to enhance remyelination may result from direct signaling through cells of the oligodendroglial lineage or through effects on surrounding microglia and astrocytes.

3-16-A

TYROSINE PHOSPHORYLATION OF THE GUANINE NUCLEOTIDE EXCHANGE FACTOR TRIO IN NETRIN-1/DCC-STIMULATED SIGNALING PATHWAYS DURING NEURITE OUTGROWTH

Jonathan DeGeer*, Jerome Boudeau Susanne Schmidt, Anne Briancon-Marjolle, Anne Debant, and Nathalie Lamarche-Vane

During nervous system development, neurons extend axons towards their associated targets in a process that is mediated by extracellular cues. The chemotropic guidance cue netrin-1 promotes neurite outgrowth through its receptor DCC (Deleted in Colorectal Cancer) and Rac1 activation. Recently we have identified that the guanine nucleotide exchange factor (GEF) Trio mediates Rac1 activation during netrin-1/DCC signaling—the deficiency of which leads to defects in netrin-1-induced axon outgrowth and guidance. We have demonstrated that Trio appears in a signaling complex with Nck-1, PAK1, and DCC, however the molecular mechanisms leading to Trio activation remain unknown. Since the Src-kinase-family member Fyn has been shown to phosphorylate DCC and thereby play an essential role in netrin-1 signaling, we have investigated whether Fyn regulates Trio function by phosphorylation. Indeed, Trio and Fyn co-expression in COS-7 and N1E-115 neuroblastoma cells lead to tyrosine phosphorylation of Trio, an effect that is increased in the presence of DCC. The in vivo phosphorylation of Trio by endogenous kinases in N1E-115 cells is increased in the presence of DCC, and this feature is diminished by the Src kinase inhibitor PP2. Furthermore, DCC-enhanced Fyn-mediated phosphorylation of Trio appears to require the last 20 amino acids of DCC and is absent when N1E-115 cells are cultured in the presence of netrin-1 function-blocking antibodies. Altogether these preliminary findings engage Fyn kinase activity in the regulation of Trio by phosphorylation. We are currently mapping the tyrosine residue(s) of Trio that are targeted by Fyn and we seek to determine how their phosphorylation modulates Trio activity.

3-16-B

The Effect of FTY720P on expression of S1P receptors and associated signaling in human myeloid cells

T.A Johnson, C. Lambert, B.A Durafourt, V.E Miron, A. Bar-Or, J.P Antel

Background: Fingolimod (FTY720) retains a subset of lymphocytes in lymph nodes. This redistribution creates an expected reduction in peripheral blood. Yet, fingolimod patients have normal numbers of circulating monocytes, as this cell type is not sequestered. FTY720P, the active phosphorylated form of the drug, signals through S1P receptors (S1PRs). Studies in glial cells have indicated that activation of the S1P1R isoform results in the phosphorylation of the MAPK pathway protein, ERK1/2, whereas activation of S1P3R and S1P4R is associated with the phosphorylation of myosin light chain II (MLCII). Objective: To characterize the S1PR mRNA expression profiles in monocytes, monocyte- derived macrophages and dendritic cells, and to determine which signaling pathways are induced by FTY720P. Methods: Peripheral blood mononuclear cells were isolated from healthy human donors; monocytes were isolated by immunomagnetic bead separation. Monocytes were stimulated with FTY720P or differentiated into macrophages or dendritic cells using either M-CSF or GM-CSF and IL-4 respectively. S1PR expression was assessed by quantitative RT-PCR and signaling was assessed by immunoblotting for phospho-ERK and phospho-MLCII. Results: Ex vivo, monocytes were found to express S1PRs in relative abundance of S1P3R/4R > S1P1R. Differentiation of monocytes into macrophages or dendritic cells led to an altered expression profile of S1P1R > S1P3R/4R. Treatment with FTY720P (1μM) did not alter the pattern of S1PR mRNA expression on macrophages derived from monocytes. Treatment of monocytes with FTY720P did not induce phosphorylation of ERK1/2 or MLCII. In contrast, macrophages stimulated with FTY720P demonstrated a rapid decrease in phospho-ERK levels and a corresponding increase in phospho-MLCII. Conclusions: Monocytes and macrophages or dendritic cells express distinctive profiles of S1PR. FTY720P transduces a differential signaling response in macrophages resulting in MLCII phosphorylation. The increase in phospho-MLCII levels suggests that FTY720P mediates its effects downstream of S1P3R and S1P4R and downregulates signaling events through S1P1R. The phosphorylation of MLCII is an important step in the regulation of the cytoskeleton. Given the finding that macrophages express lower levels of the S1P3R/4R transcripts compared to S1P1R, this signaling may be the result of preferential cell-type specific G-protein coupling or differential affinities of FTY720P for receptor subtypes.

3-17-A

Role of ERM proteins in netrin-1/DCC-mediated axon outgrowth and guidance

Judith Antoine-Bertrand*, Monique Arpin, Nathalie Lamarche-Vane

As the nervous system develops, newborn neurons extend their axon towards a defined target by responding to specific extracellular cues. Deleted in Colorectal Cancer (DCC) is a receptor involved in the attractive response to the conserved axon guidance cue, netrin-1. Upon netrin-1 stimulation, DCC becomes highly phosphorylated and mediates axon outgrowth and guidance through the activation of the rhoGEF Trio and the small GTPase Rac1. The molecular mechanisms that couple DCC/Rac1 activation to actin remodelling during axon guidance still remain elusive. Here we investigate the role of F-actin-binding ERM proteins (Ezrin-Radixin-Moesin) in the context of netrin-1/DCC-mediated axon outgrowth and guidance. GST pull-down assays and co-immunoprecipitation of DCC and ezrin in the N1E-115 neuroblastoma cells confirmed the interaction between DCC and ezrin. In N1E-115 cells, ERM proteins are relocalized to the cell membrane when DCC is overexpressed. Moreover, co-expression of DCC and inactive mutants of ezrin significantly decreases DCC-induced neurite outgrowth in these cells. Preliminary data also indicate that netrin-1/DCC signalling is involved in the activation of ERM proteins. Therefore, these results suggest that DCC and ezrin are found in the same protein complex and that ERM activity is required for DCC to mediate neurite outgrowth.

3-17-B

The role of PTEN in astrocyte response to oxidative injury

Samuel Helman*, Trina Johnson & Jack Antel

In this study, particular attention is being directed at the phosphatase PTEN (phosphatase and tensin homologue deleted on chromosome 10). PTEN is a tumor suppressor implicated in a wide variety of human cancers. PTEN is a dual lipid and protein phosphatase that dephosphorylates phosphatidylinositol 3,4,5-triphosphate (PIP3) and in this way is a primary negative regulator of the phosphoinositide 3-kinase (PI3K/AKT) signaling pathway. This relationship is extremely important as PI3K allows for downstream activation of growth and proliferation pathways, and AKT (also referred to as PKB) plays a critical role in controlling survival and apoptosis. Loss of PTEN results in increased signaling through the phosphatidylinositol 3' kinase/ AKT pathway. The PI3K/AKT pathway is responsible for the promotion of differentiation, proliferation, migration, and survival with cell-specific roles in different cell types. In our study we sought to delineate a role for the PTEN/PI3K and PTEN/p53 pathway in survival from sublethal oxidative damage, and to determine if phosphorylation of PTEN (phospho-PTEN) could be a marker of other sublethal insults similar to those acquired during neuroinflammation. We hypothesized that the pharmaceutical inhibition of PTEN will result in the promotion of proliferation of astrocytes; this is a fundamental part of the astrocyte response to sublethal hydrogen peroxide injury. Furthermore, P-PTEN, the inactive form of the PTEN protein, may be a marker of oxidative damage, but not apoptotic damage in astrocytes.

3-18-A

Forebrain dopamine, tobacco addiction, reinforcement and affective neuroscience

Tina Scardochio*, Jennifer Wright*, Rob Sorge*, Annie Constantin and Paul Clarke

Our group is mainly interested in how drugs affect brain function, particularly in the context of drug addiction and motivation. Our research focuses on dopamine (DA), and we hypothesize that this neurotransmitter serves several different biopsychological roles, with major differences existing between caudate-putamen, nucleus accumbens and olfactory tubercle. We are exploring this theme using a combination of neuropharmacological manipulations and behavioural tests in rats. Current projects in our lab include: 1) Reinforcement mechanisms related to tobacco addiction. We have recently developed a new model of nicotine self-administration in rats, and are investigating brain mechanisms underlying this behavior. Nicotine is a surprisingly weak reinforcer, and therefore we are also broadening our scope to include some of the 4000 other chemical components of tobacco smoke. 2) Spatially segregating the rewarding and aversive effects of dopamine within the nucleus accumbens. Pursuing our recent findings, we are examining the effects of intracerebral drug infusions on conditioned place preference/aversion in rats. 3) Ultrasonic vocalizations. Rats make a rich variety of ultrasonic calls, some of which communicate affective state. For example, 22-kHz calls signal distress or danger, whereas certain 50-kHz calls are associated with the anticipation or receipt of rewarding stimuli such as drugs, food or sex. We are currently characterizing ultrasonic vocalizations produced by rewarding doses of amphetamine and electrical brain stimulation in adult rats. We feel that rat ultrasonic vocalizations represent a largely untapped source of information relevant to affective neuroscience. Funding: CIHR, NSERC, FRSQ.

3-18-B

The role of netrins in regulating blood brain barrier function and immune cell passage into the brain

Cornelia Podjaski*, Peter Darlington, Nathalie Lebeurrier, Jack P. Antel, Timothy E. Kennedy and Alexandre Prat

Netrins are a small family of secreted laminin-related proteins that are best known for their role as long-range chemotropic guidance cues. Gradients of extracellular netrin-1 protein direct cell and axon migration during development. Recent findings provide evidence that short-range actions of netrins contribute to regulating cell-cell and cell-matrix adhesion. Several studies demonstrate that netrins are expressed by vascular endothelial cells and contribute to the development of the vasculature. We hypothesize that netrins are expressed in the specialized brain microvasculature, regulating junctional complexes, controlling blood brain barrier permeability and transendothelial migration of immune cells into the brain. We have screened primary human brain-derived endothelial cells (HBECs) for the expression of netrins and netrin receptors, and compared their expression under barrier-promoting or inflammatory conditions. Additionally, we have assessed the influence of netrin function on BBB-permeability using an in vitro transwell model of the BBB. We are also investigating netrin and netrin receptor expression by lymphocytes, and assessing possible roles in mediating adhesion between lymphocytes and vascular endothelium. Our findings provide evidence for a novel role for netrins influencing the BBB by regulating cell-cell connectivity and immune-endothelial communication. Netrins may therefore play key roles in neurological diseases that are characterized by BBB leakiness and immune cell invasion into the CNS such as multiple sclerosis.

3-19-A

LGI1 is a Novel Nogo Receptor 1 Ligand that Blocks Myelin-based Growth Inhibition

Rhalena Thomas*, Kristy Favell, Jose Manuel Morante-Redolat, Christopher Kent, Melissa Wright, Madeleine Poole, Kathleen Daignault, Alyson Fournier, Philip A. Barker and Jordi Perez-Tur.

Leucine Rich Glioma Inactived gene 1 (LGI1) is a secreted protein recently identified as a causative locus in human autosomal dominant lateral temporal lobe epilepsy. There are 4 LGI family members in humans and their next closest homologs are members of the SLIT family, secreted proteins involved in axonal repulsion and growth cone collapse. We therefore considered the possibility that LGI1 may regulate neuronal process extension or growth cone collapse. LGI1 did not alter process extension from rat cerebellar granule neurons or from chick DRG sensory neurons but instead, LGI1 was a potent antagonist of myelin based growth inhibitors (MBGIs). LGI1 facilitated growth of rat cerebellar granule cells on myelin substrates and blocked myelin-induced growth cone collapse of chick DRG sensory neurons. NgR1, p7NTR, and Lingo1 function as core components of a MBGI receptor complex and we tested whether any of these also function as LGI1 receptors. Cell surface AP-LGI1 binding assays showed that NgR1, but not p75NTR or LINGO1, functions as a receptor for LGI1. Competition assays using Fc-NgR1 indicated that LGI1 and Nogo66 share overlapping binding epitopes. We conclude that LGI1 functions as a specific NgR1 ligand that antagonizes binding of MBGI to NgR1.

3-19-B

Epigenetic modifications by maternal behavior

Tie-Yuan Zhang*, Dara K. Shahrokh, Sabine K. Dhir, Josie Diorio, Michael J. Meaney

Early life experience including parenting and the quality of the familial environment influences the offspring's neurobehavioral development. A critical issue that emerges from epidemiological studies is whether there is a direct link between environmental factors and the neural systems that mediate relevant cognitive and emotional function. Our lab addresses these questions using an animal model that exploits naturally occurring variations in maternal care, focusing on pup licking/grooming (LG). We are currently studying several aspects of maternal care including: 1) studies of maternal care on epigenetic modifications including DNA methylation and histone remodeling which alters gene expression involved in the regulation of endocrine responses to stress; 2) the impact of maternal care (ie: nutritional factors and variations in behavior) on the phenotype of the offspring as leading to metabolic syndrome; 3) the impact of the early environment on the female reproductive system, development and function. We present some data here show that by comparison to High-LG male offspring, Low-LG male offspring have increased cytosine methylation levels in the GAD1 promoter in the hippocampus. Estrogen receptor alpha (ER alpha) mRNA and protein levels are significantly increased in the adult female offspring of High-LG dams compared to Low-LG dams in the medial preoptic area (mPOA). We also found that brain derived neurotrophic factor (BDNF) expression levels are higher in the hippocampus and ventral tegmental area (VTA) of High-LG mothers. In addition, association of BDNF exon IV promoter with acetylated histone H3 lysine 9 (H3K9) is higher in the hippocampus of High-LG dams compared to Low-LG dams. Taken together, these results suggest that epigenetic modifications through natural variations in maternal care lead to significant and lasting changes in gene expression, biochemical alterations and behavior.

3-20-A

A Correlation Between Sleep Spindles and IQ in Children

Edmund Lam*, Xi Tong, Julie Carrier, corresponding author Reut Gruber

Sleep spindles are a signature characteristic of NREM sleep and are considered to be generated by oscillations in the thalamocortical network. Sleep spindle activity remains relatively stable between nights in individuals, but there is a large amount of interindividual differences in spindle activity. Recently, sleep spindle activity has been correlated with performance IQ in adults. However, there has been little analysis of sleep spindles in children and its correlation with general intelligence. The aim of this study was to examine the relation between sleep spindle activity and IQ scores in children. We hypothesized that the children who have a higher activity (density, number, duration) of stage 2 spindles will perform better on the Wechsler Intelligence Scale for Children-IV. Sleep spindles were found to be correlated with WISC-IV Perceptual Reasoning Index scores and sub-scores in children. Despite age related differences in spindle frequency and topography, robust relationships were found in the central and parietal areas which are consistent with reports in adult subjects. A higher fast-spindle activity generated by the thalamocortical network may allow for a higher degree of performance in perceptual and analytical tasks.

3-20-B

Role of glutamate in enhanced prefrontal cortical excitability in rats with neonatal ventral hippocampal lesions, a heuristic neurodevelopmental model of schizophrenia

Richard Ryan*

Schizophrenia is a devastating psychiatric disorder which burdens not only on the individual and their family, but is also very taxing on society. Schizophrenia is believed to be due to both genetic and environmental factors that cause deficits in brain development during puberty. These deficits lead to abnormalities in prefrontal cortex (PFC) functions, including working memory, executive function and social interaction. The neonatal ventral hippocampus lesion (NVHL) model has been used extensively to model impairments of PFC functions, including increased sensitivity to stress and psychostimulants, deficits in prepulse inhibition, sensory motor gating, working memory and reward. While dopaminergic abnormality has been implicated in the deficit of PFC function in NVHL rats, increasing findings suggest that impairments could be found in glutamatergic and GABAergic inputs, which regulate the excitability of PFC neurons. We propose that apart from dopaminergic deficits, abnormality of glutamate synaptic functions could contribute to the abnormal excitability seen in PFC neurons in this animal model. Hypothesis: An increase in excitatory synaptic function is responsible for the enhancement of excitability of PFC neurons in NVHL rats. Methods: Sprague-Dawley (SD) pups, at postnatal day 7 (P7), received bilateral injections of ibotenic-acid inducing excitotoxic lesions of the ventral hippocampus (VH). At P40 to P60 we looked at spontaneous tetrodotoxin-insensitive miniature excitatory post synaptic currents (mEPSC) in pyramidal neurons of the medial PFC (mPFC) of both NVHL and sham operated rats. Using whole-cell patch clamp recording, we recorded mEPSCs from layer V pyramidal neurons in the presence of GABAA receptor blockers bicuculline and picrotoxin. Neurobiotin was added to intracellular solution for labelling recorded neurons for morphological identification. Results: We observed a significant increase in the amplitude of mEPSCs in the NVHL rats compared to the sham animals. The results suggest that an upregulation of excitatory synaptic function could be related to the increased excitability of PFC neurons and the expression of schizophrenia-like symptoms in NVHL rats. Future studies: Since neuronal excitability is mediated by a balance between excitatory and inhibitory inputs, we intend to look at the impact of NVHL on inhibitory synaptic function in the same manner.

3-21-A

The Drosophila miR-310 cluster negatively regulates synaptic strength at the neuromuscular junction

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Emerging data implicate microRNAs (miRNAs) in the regulation of synaptic structure and function, but we know little about their role in the regulation of neurotransmission in presynaptic neurons. Here, we demonstrate that loss of miR-310-313 cluster leads to significant enhancement of neurotransmitter release at the Drosophila larval neuromuscular junction. These defects are rescued by temporally restricted expression of a mir-310-313 transgene in larval presynaptic motor neurons. Interestingly, heterozygosity for the kinesin protein khc-73 restores normal synaptic release in mir-310-313 mutants. Furthermore, mir-310-313 cluster mutants show an increase in the active zone protein Bruchpilot (Brp) accompanied by an increase in electron dense T-bars. Consistently, we show that heterozygosity for the calcium channel Cacophony significantly rescues the electrophysiological defects. We propose that miR-310 cluster regulates neurotransmitter release at presynaptic terminals by attenuating the expression of Khc-73 and thereby restricting the accumulation of Brp to active zones.

3-21-B

Regulation of hippocampal plasticity by maternal care and corticosterone: potential mechanisms

Rosemary C. Bagot*, Michael J. Meaney, & Tak Pan Wong

Natural variations in maternal care produce differences in stress reactivity and hippocampal learning in the rat. Adult offspring of high licking/grooming (LG) dams show enhanced hippocampal-dependent spatial learning and object recognition memory. However, in a relatively more stressful hippocampal test, contextual fear conditioning, low-LG offspring show enhanced memory relative to high-LG offspring. Studies of hippocampal long-term potentiation (LTP) reveal similar regulation by maternal care such that basally, LTP is enhanced in high-LG offspring but following corticosterone incubation, LTP is enhanced in low- and suppressed in high-LG offspring. The present studies examined molecular mechanisms of hippocampal synaptic plasticity regulation by maternal care and corticosterone. LTP is triggered by activation of NMDA glutamate receptor subtype (NMDARs) and expressed by increased efficacy of AMPA glutamate receptor subtype (AMPAR)-mediated synaptic transmission. The first study examined if maternal care, which influences NMDAR and AMPAR protein and mRNA expression, affects their function in glutamate synapses. Using whole cell patch clamp, we examined AMPAR:NMDAR activation in evoked EPSCs in high- and low-LG dentate gyrus slices treated with vehicle or corticosterone. AMPAR:NMDAR was greater in high- than low-LG rats and corticosterone reversed this effect. To determine if the effect on AMPAR:NMDAR was due to AMPAR changes, we assessed basal synaptic transmission through field EPSPs input-output functions. The lack of differences, indicating equivalent AMPAR activity, suggest the maternal care effect on AMPAR:NMDAR is due to alterations in NMDAR. In addition to ionotropic glutamate receptors (iGluRs), AMPARs and NMDARs, metabotropic glutamate receptors (mGluRs) also contribute to hippocampal LTP. The second study examined regulation of mGluRs by maternal care. Western blot revealed increased mGluR1 expression, but not mGluR5, in high-LG rats. While maternal care may affect LTP through modulating mGluR1, surprisingly, we also noted that mGluR-mediated LTD is absent in low-LG rats. These findings suggest that maternal care likely modulates bidirectional hippocampal synaptic plasticity. Taken together, these results demonstrate the importance of mGluR as well as iGluR signaling and bidirectional plasticity in understanding the effects of maternal care on hippocampal learning and plasticity.

3-22-A

Retrograde BMP signaling controls synaptic growth at the Drosophila neuromuscular junction by regulating Trio expression

Robin Ball*, Maude Warren-Paquin, Kazuya Tsurudome, Pejmun Haghighi

A growing body of evidence indicates that retrograde signaling is essential for coordinating the growth of synaptic structures. However, it is not clear how retrograde signaling can lead to modulation of cytoskeletal dynamics and structural changes at presynaptic terminals. We show that loss of retrograde bone morphogenic protein (BMP) signaling at the Drosophila larval neuromuscular junction (NMJ) leads to a significant reduction of Rac GEF Trio levels and a diminution of transcription at the trio locus. We further find that Trio is required in motor neurons for normal structural growth. Finally, we show that transgenic expression of Trio in motor neurons can partially restore NMJ defects in larvae mutant for BMP signaling. Based on our findings, we propose a model in which a retrograde BMP signal from the muscle modulates GTPase activity through transcriptional regulation of Rac GEF trio, thereby regulating the homeostasis of synaptic structural growth at the NMJ.

3-22-B

CHRONIC POST-ISCHEMIA PAIN: A NOVEL ANIMAL MODEL SUGGESTS THAT ISCHEMIA-REPERFUSION (I-R) INJURY, NO-REFLOW AND CHRONIC TISSUE ISCHEMIA CONTRIBUTE TO COMPLEX REGIONAL PAIN SYNDROME TYPE-I.

A. Laferriere, M. Millecamps, D.N. Xanthos, W. Xiao, G.J. Bennett, T.J. Coderre*

Chronic post-ischemia pain (CPIP) is an animal model of CRPS-I produced by prolonged (3 hrs) I-R injury of the rodent hindpaw. Using tight fitting O-rings as ankle tourniquets, rats initially exhibit hyperemia and edema of the ischemic hindpaw for several hrs after reperfusion. Subsequently, rats and mice develop mechanical and cold allodynia for at least 4 weeks post-reperfusion. Rats also develop prolonged mechanical allodynia following I-R injury produced by clamping all blood vessels supplying the hindpaw. Light and electron microscopic analysis of the tibial nerve close to the site of the tourniquet indicates that there is no nerve injury associated with tourniquet-induced compression. These findings, as well as electrophysiological studies demonstrating that there is normal conduction velocity in the tibial nerve, suggests that CPIP rats are similar to patients with CRPS-I (i.e., no clinical signs of nerve injury). However, co-incident with mechanical allodynia, CPIP rats exhibit a no-reflow phenomena, including abnormality of capillary endothelial cells in skeletal muscle and nerve (determined by electron microscopy), and a gross reduction in blood flow to the affected hindpaw (determined by light microscopy following perfusion of India ink). Chronic tissue ischemia results in mitochondrial dysfunction in skeletal myocytes as evidenced by reduced TTC staining in hindpaw muscle. Importantly, in association with observed no-reflow in endoneurial capillaries, there is also abnormal spontaneous activity in A-beta, A-delta, and C fiber primary afferent neurons in the sural nerve. Results suggest CPIP and CRSP-I may depend on I-R injury, no-reflow and chronic tissue ischemia in muscle and nerve.

3-23-A

How to get in, out and around - the McPherson tour guide through the cell

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Every mammalian cell exploits intracellular trafficking to communicate with its environment and to translate external signals into functional responses. In the McPherson laboratory, we study the mechanisms that control trafficking pathways involved in neuronal communication, cell differentiation, and survival. Importantly, a number of neurodegenerative and other diseases are caused by alterations of these intracellular transport pathways. Clathrin-mediated endocytosis is a crucial cellular entry pathway for nutrients that also regulates the cell surface levels of receptors and synaptic vesicle recycling. Endocytosed receptors are transported through the endosomal system, where sorting decisions at various check points control their fate. Receptors can either continue to signal, recycle back to the plasma membrane, or are degraded in the lysosome. The integration of these decisions determines if a cell proliferates, differentiates, or undergoes apoptosis. Our lab also studies trafficking pathways involved in the secretory routes that send newly synthesized proteins and lipids from the ER to the Golgi, from where they are either sent to the plasma membrane or sorted for delivery to the endosomal system. For example, efficient lysosomal degradation, and thus signaling control and nutrient release depends on the clathrin-mediated delivery of newly synthesized lysosomal hydrolases from the TGN to the lysosomes. We have used subcellular proteomics and biochemical approaches in different tissues and cell types to identify new proteins involved in endocytosis and intracellular trafficking. Our poster highlights some of the proteins we discovered and shows how we combine a wide variety of techniques to reveal their importance for efficient intracellular transport and study their cellular localization and function.

3-23-B

Injured nerve derived COX2/PGE2 is involved in the up-regulation of pro-inflammatory cytokine IL-6 in dorsal root ganglion neurons following nerve injury

Bruno St-Jaques, Remi Quirion and Weiya Ma*

Interleukin-6 (IL-6) is a pro-inflammatory cytokine involved in the pathogenesis of neuropathic pain. Nerve injury increases IL-6 in injured nerves, dorsal root ganglion (DRG) and spinal dorsal horn. We showed before that up-regulated COX2/PGE2 in injured nerves contributes to IL-6 induction in invading macrophages. Here we examined if injured nerve derived COX2/PGE2 also contributes to IL-6 induction in DRG. IL-6 immunoreactive (IR) neurons, mostly of small to medium size, constitute one-fourth DRG neurons in naïve adult rats. PGE2 EP4 receptors were predominantly expressed in IL-6-IR neurons. We tested the hypothesis if exogenous PGE2 is able to induce IL-6 in DRG neurons. A stabilized PGE2 analog, 16,16-dimethy PGE2 (dmPGE2), dose- and time-dependently increased mRNA and protein levels of IL-6 in DRG explants. This event was mediated by EP4 receptor, since its agonist induced IL-6 and its antagonist attenuated dmPGE2 induced IL-6 expression. dmPGE2 increased phosphorylation of PKC and ERK/MAPK in DRG neurons. The inhibitors of PKC and MEK suppressed dmPGE2 induced IL-6. In vivo, perineural injection of a selective EP4 receptor antagonist significantly attenuated neuropathic pain and suppressed IL-6 levels in DRG. Taken together, our data suggest that injured nerve derived COX2/PGE2 plays a role in inducing IL-6 in DRG neurons following nerve injury. EP4, PKC and ERK/MAPK are involved in PGE2 induced IL-6. Stimulating the synthesis of pain-related cytokines in nociceptors is a novel mechanism underlying the involvement of COX2/PGE2 in the pathogenesis of neuropathic pain. (Supported by grants from Canadian Institutes of Health Research to WM and RQ)

3-24-A

ANIMAL MODELS OF OXYDATIVE RETINOPATHIES: CLINICAL FINDINGS AND POSSIBLE THERAPEUTIC AVENUES.

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PURPOSE: Over the past decade we have developed two animal models of degenerative retinopathies, namely: Oxygen-Induced Retinopathy (OIR) with features reminiscent of the human Retinopathy of Prematurity (ROP) and Light-Induced Retinopathy (LIR) with features reminiscent of Retinitis Pigmentosa (RP) and Age-Related Macular Degeneration (AMD). With this presentation, I will summarize what we have learned of the pathophysiological processes involved and our successes in slowing them down. METHODS: Newborn Sprague Dawley (SD) and Long-Evans (LE) rats were exposed to hyperoxia (80% O2) or a bright luminous environment (10,000 lux) from birth to the end of the first month of life. OIR treatment included: Trolox-C and NOS inhibitors; LIR treatment included: Ad.BDNF, FGF-2 and CNTF. Severity of retinopathy and outcome of treatment were assessed with the electroretinogram (ERG: flash and multifocal), the visual Evoked Potential (VEP), retinal histology, retinal flatmounts, western blots and immunohistochemistry. RESULTS: OIR begins as a vasculopathy and rapidly progresses towards a severe and irreversible impairment of the retinal structure and function beyond the Outer Plexiform Layer (OPL). The latter does not appear to be the direct result of the initial vasculopathy, but a combination of several factors of which retinal maturation appears to be the most important contributor. The resulting retinopathy is significantly more severe in pigmented animals. Treatment with free radical scavengers partly attenuated the retinal and cortical sequels. In contrast, LIR has detrimental effects on the retinal structure and function above the OPL and beneficial effects on layers below (mostly INL). This retinopathy is significantly more severe in albino animals, pigmented rats demonstrating what appears to be a beneficial effect (thickening of retina and enhancement of ERG). Use of neurotrophic factors are effective in slowing down the pathophysiological process triggered, although one cannot rule out the possible contribution of free radicals, an avenue that will be explored shortly. CONCLUSION: Our animal models of OIR and LIR offers the unique experimental opportunity to further our understanding of initially inner and outer retinal disorders and explore new therapeutic avenues in retinal disorders that share several common features with their human analogue namely: ROP, AMD and Retinitis Pigmentosa respectively. Supported by CIHR and NSERC

3-24-B

CONTRIBUTION OF INJURED NERVE DERIVED COX2/PGE2 IN THE UP-REGULATION OF BRAIN DERIVED NEUROTROPHIC FACTOR IN DORSAL ROOT GANGLION NEURONS

Pedro Cruz Duarte*, Bruno St-Jacques, Remi Quirion and Weiya Ma

Neuropathic pain is a debilitating disease caused by diseases or physical damage to the nervous system. Inflammation in injured nerves is important to determine the outcome of this disease. Nerve injury up-regulates inflammatory and pain mediator PGE2 and its synthesizing enzyme cyclooxygenase 2 (COX2) in invading macrophages. Elevated PGE2 might chronically stimulate the synthesis of pain-related molecules in dorsal root ganglion (DRG) neurons. Brain-derived neurotrophic factor (BDNF) is one of these molecules up-regulated in DRG neurons and involved in the genesis of neuropathic pain after nerve injury. In the present study we tested the hypothesis that injured nerve derived PGE2 is involved in BDNF induction in DRG neurons. We found that partial sciatic nerve ligation (PSNL) increased BDNF levels in DRG neurons. Perineural injection of a selective COX2 inhibitor or a selective PGE2 EP4 antagonist significantly relieved neuropathic pain and suppressed increased BDNF, suggesting that injured nerve derived PGE2 and EP4 receptors are involved in BDNF induction in DRG neurons. In DRG explant cultures, we found that a long acting PGE2 analog 16,16 dimethyl PGE2 increased both mRNA and protein levels of BDNF, suggesting that PGE2 is an inducer of BDNF in DRG neurons. We postulate that PGE2 over-produced in invading macrophages may stimulate BDNF production in DRG neurons by acting on injured or spared axons in injured nerves. Our study will allow a better understanding of the possible interactions between two pain mediators and their role in the pathogenesis of neuropathic pain. (Supported by CIHR operating grant to W.Ma).

3-25-A

Intense Pleasure to Music is Mediated by Mesolimbic Dopamine Release: Converging Neurochemical, Hemodynamic, and Psychophysiological Evidence

Valorie N. Salimpoor*, Mitchel Benovoy, Kevin Larcher, Alain Dagher, Robert J. Zatorre

Music can arouse feelings of intense pleasure described as similar to that of dopamine-mediated rewarding stimuli such as drugs, food, and sex. Using the neurochemical specificity of [11C]raclopride as a radioligand with PET and the temporal specificity of fMRI, we provide the first direct evidence for endogenous dopamine release in the striatum and converging hemodynamic activity during intensely pleasurable music listening. We further demonstrate a temporally mediated neurofunctional distinction between the dorsal and ventral striatum: the caudate is more involved in the anticipation and the nucleus accumbens in the experience of peak emotional responses to music, as indexed by the musical “chills” response.

3-25-B

Largescale genetic screen in Drosophila to identify novel regulators of Parkinson's disease genes

Caroline Fernandes*, Yong Rao

Parkinson’s disease (PD) is the second most common neurodegenerative diseases. Although the pathology and pathophysiology of PD is well characterized, very little is understood regarding the mechanism of pathogenesis of this intensely researched condition. However, newly identified genes associated with PD represent potentially useful targets for elucidating the molecular mechanisms associated with this disease. To tease out the mechanism of PD pathogenesis, we are using a Drosophila model of PD mutant for either PINK1 (a putative serine/threonine kinase) or parkin (an E3 ubiquitin ligase) which have recently been implicated in PD pathogenesis. Since PINK1 and Parkin mutant flies exhibit robust and easily scorable phenotypes (than their corresponding mice mutants), it is an ideal background for performing a screen. We have developed a sensitized dominant PINK1 and parkin mutant background, which is being used to screen the entire fly genome for modifiers of the PD gene-induced phenotype. This sensitized approach will aid in the identification of novel regulators and bona fide PD substrates which have eluded past screens.

4-1-A

Investigating Neuroplasticity following Stroke

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In the Neuroplasticity Laboratory at the Lady Davis Institute and Jewish General Hospital, our research is aimed at understanding how the brain reorganizes its functional networks following damage due to stroke. We aim to identify the mechanisms that facilitate this neuronal reorganization and define predictors of successful post-stroke recovery. The use of functional Magnetic Resonance Imaging (fMRI) enables us to visualize activation in the motor cortices of stroke patients performing a motor task involving the paretic limb. fMRI is an important means of monitoring changes in cortical activation and lateralization of motor function. Diffusion Tensor Imaging (DTI) is a tool we use to study changes in the integrity of white matter tracts, specifically the pyramidal tract (PT), following subcortical stroke. DTI can be used to determine how a subcortical lesion affects the PT and to quantify white matter tract damage as early as 2 weeks post-stroke. We also use Positron Emission Tomography, a nuclear medicine technique for molecular imaging of post-stroke changes on a cellular level. This allows us to study inflammatory processes and their role for neuroplasticity in vivo and to measure nerunal density in the cortex. Finally, we employ Transcranial Magnetic Stimulation as a diagnostic instrument to assess PT integrity using motor evoked potentials, and as a treatment tool to modulate motor cortex excitability in patients. The use these multimodal techniques allows us to investigate morphological, molecular, and electrophysiological markers of stroke in an attempt to influence post-stroke neuroplasticity.

4-1-B

The effect of phrase length on implicit prosody and the processing of a syntactic 'garden path' ambiguity in Korean: An ERP study

*Hyekyung Hwang & Karsten Steinhauer

Effects of phrase length on parsing preferences have been discussed as a compelling evidence for implicit prosody during silent reading (e.g., Hwang & Schafer, to appear). However, most evidence is indirect. Our ERP experiment investigated specific brain responses reflecting the on-line processing of phrase length in Korean. An early ambiguous dative noun-phrase (NP) could associate with either the matrix or the relative clause, with very different interpretations. In presence of a second dative-NP further downstream, the usually preferred interpretation results in initial misunderstandings (‘garden-path’ effect). Manipulating the length of sentence initial subject-NPs was expected to change implicit prosody and, thereby, to weaken this garden-path effect. As predicted, results demonstrated electrophysiological correlates of implicit prosody in Korean garden-path sentences. The Closure Positive Shift at the end of the long subject-NP suggested that long (but not short) subject sentences were read with a prosodic boundary in silent reading (Steinhauer & Friederici, 2001). At the disambiguating second dative-NP, the garden-path effect was indicated by a P600-like positivity, whose amplitude decreased in the long as compared to the short condition. This finding provides direct and cross-linguistic evidence for implicit prosody: Long subject-NPs caused readers to establish a prosodic boundary, which then affected the syntactic analysis of the remaining sentence.

4-2-A

Transforming growth factor-?1 impairs neuropathic pain through pleiotropic effects

Stefania Echeverry*, Xiang Qun Shi, Alexandra Haw, Hong Liu, Zhong-wei Zhang and Ji Zhang

Background Understanding the underlying mechanisms of neuropathic pain caused by damage to the peripheral nervous system remains challenging and could lead to significantly improved therapies. Disturbance of homeostasis not only occurs at the site of injury but also extends to the spinal cord and brain involving various types of cells. Emerging data implicate neuroimmune interaction in the initiation and maintenance of chronic pain hypersensitivity. Results In this study, we sought to investigate the effects of TGF-?1, a potent anti-inflammatory cytokine, in alleviating nerve injury-induced neuropathic pain in rats. By using a well established neuropathic pain animal model (partial ligation of the sciatic nerve), we demonstrated that intrathecal infusion of recombinant TGF-?1 significantly attenuated nerve injury-induced neuropathic pain. TGF-?1 treatment not only prevents development of neuropathic pain following nerve injury, but also reverses previously established neuropathic pain conditions. The biological outcomes of TGF-?1 in this context are attributed to its pleiotropic effects. It inhibits peripheral nerve injury-induced spinal microgliosis, spinal microglial and astrocytic activation, and exhibits a powerful neuroprotective effect by preventing the induction of ATF3+ neurons following nerve ligation, consequently reducing the expression of chemokine MCP-1 in damaged neurons. TGF-?1 treatment also suppresses nerve injury-induced inflammatory response in the spinal cord, as revealed by a reduction in cytokine expression. Conclusion Our findings revealed that TGF-?1 is effective in the treatment of neuropathic by targeting both neurons and glial cells. We suggest that therapeutic agents such as TGF-?1 having multipotent effects on different types of cells could work in synergy to regain homeostasis in local spinal cord microenvironments, therefore contributing to attenuate neuropathic pain.

4-2-B

Neurocognition of Language (NCL) Laboratory (Ongoing Research Projects 2009/2010)

Karsten Steinhauer*, John E. Drury, Hyekyung Hwang, Shani H. Abada, Nicolas Bourguignon, Kristina Kasparian, Jen Mah, Monika Molnar, Efrat Pauker, Erin J. White, Masha Westerlund

The NCL lab focuses on the use of event-related brain potentials (ERPs) to investigate the neural underpinnings of a number of different domains of human language and cognition. The primary topics under investigation are clustered around the following topics: (1) second language acquisition, (2) bilingualism, (3) prosodic processing (in speech, music, and during silent reading), and (4) logical semantics. (1) Projects related to second language acquisition examine the question as to whether loss of brain plasticity after a presumed ‘critical period’ (Penfield, 1959) prevents late language learners from relying on the same brain mechanisms used by native speakers and early bilinguals. Current data support our hypothesis that proficiency level – rather than age of acquisition – predicts the brain mechanisms employed by late language learners, at least in the domain of morpho-syntax. (2) Our bilingual projects investigate the speech perception abilities of English and French simultaneous bilinguals, and second language speakers of English. One series of projects studies the ‘trouble’ Francophone learners of English have with phoneme /h/ (e.g., “It’s cold, let’s (h)EAT the room”). We also found that simultaneous bilinguals develop a unique system of speech sound representations that is not just the sum of English and French monolingual systems. (3) Another set of experiments investigates the contribution of prosody to language comprehension in younger and older adults, as well as in native Korean speakers. Current findings indicate that prosody has an immediate impact on syntactic parsing; and that both inappropriate and missing boundaries lead to miscomprehensions, even in silent reading. We also compare neurocognitive mechanisms of prosodic phrasing in speech and music and study how the brain integrates various types of musical accents. (4) Ongoing work on logical semantics seeks to better understand the patterns of violations in certain syntactic constraints and their linguistic and neurocognitive significance. Our poster will introduce the lab members and present a selection of recent findings related to these research programs and their relevance to neuroscience. More detailed information will be available on additional posters presented by lab members.

4-3-A

MAPPING THALAMIC NUCLEAR PATHOLOGY IN TEMPORAL LOBE EPILEPSY

Bernhardt, B. C.*; Kim, H.; Natsume, J.; Bernasconi, A.

Ample data from animal models and humans suggest a pivotal role of the thalamus in the epileptogenic network of temporal lobe epilepsy (TLE), a finding that may relate to fronto-central cortical thinning observed in this condition. Our purpose was to analyze thalamo-cortical network pathology using MRI-based spherical harmonics shape mapping (SPHARM) on manual thalamus segmentations in 37 patients with TLE and 19 age-and sex-matched healthy controls. Compared to controls, TLE patients had local volume changes predominantly in ipsilateral medial thalamic divisions. Local atrophy was more marked in patients with a longer duration of epilepsy or a history of febrile convulsions. In controls, medial fronto-central cortical thickness was positively correlated with volume of medial and ventral thalamic divisions, whereas in TLE patients the same divisions showed decreased pattern of correlations. Although we found widespread thalamic atrophy in TLE, common damage was found in limbic divisions ipsilateral to the seizure focus. This pattern may reflect effects of mesiotemporal degeneration and seizure spread, as the pulvinar and mediodorsal nuclei participate in the generalization of limbic seizures. On the other hand, decreased morphometric coupling between medio-ventral divisions and the fronto-central neocortex suggests alternative pathological interactions between mesiotemporal and fronto-central regions.

4-3-B

Influence of glial factors on B-cell biology: implication in Multiple Sclerosis pathogenesis.

Antonia Kobert*, Nathalie Lebeurrier, Ichiro Nakashima, Aja Rieger, Philippe Saikali, Jack Antel, Yasuto Itoyama, Amit Bar-Or

Objective: Examine how glial factors produced in the inflamed MS CNS contribute to disease-relevant human B-cell responses. Introduction: MS-relevant B-cell responses within the CNS could include immunoglobulin (Ig) production, APC function and release of inflammatory molecules. B-cell persistence in the CNS may reflect a ‘permissive’ environment provided by local glial factors, but whether specific B-cell antigens and/or T-cell help are absolute requirements is unknown. Methods: CD19+ B cells were studied in co-culture/transwell with astrocytes, or with astrocyte-conditioned media or combinations of IL-6 and BAFF in serum-free media. Astrocytes were either not stimulated, or pre-stimulated with pro-inflammatory cytokines (IFN?+IL1?). B-cell survival and expression of APC-related molecules (e.g. CD80/CD86, MHCI/II) were measured by FACS, IgG/M concentrations by ELISA, and APC function using allogeneic T-cell proliferation assays. Results: Stimulated astrocytes (co-culture/transwell) and astrocyte-soluble products promoted B-cell survival, significantly increased their CD86, MHC-I and MHC-II expression, and enhanced their ability to induce allogeneic T-cell proliferation. Astrocytic factors BAFF and IL-6 induced secretion of both IgG and IgM. Ig responses were synergistically increased upon addition of IL-10 and IL-15, but no antigen or T-cell help was required. Conclusion: Activated human astrocytes produce factors (including BAFF, IL-6, and IL-15) that can promote B-cell survival, APC phenotype and function, pro-inflammatory cytokine secretion and Ig production - all in absence of specific B-cell antigens, and without requirement for T-cell help. These glial-immune interactions may be relevant to ongoing CNS-compartmentalized inflammation.

4-4-A

Astrocytes modulate activity-dependent dendritic spine remodeling in mature hippocampal slice cultures

David Verbich*, George A Prenosil, Pico Caroni, Keith K Murai & R Anne McKinney

Structural plasticity at synapses and dendrites is central for defining neural circuits during development. In the mature brain, other activity-dependent changes occur and are important for synaptic plasticity. We are interested in studying activity-dependent structural remodeling of mature dendritic spines, the recipients of the majority of excitatory glutamatergic synapses in the hippocampus. Recently, the laboratory has shown that under cases of reduced neural activity, subsets of mushroom spines in hippocampal slices send out glutamate receptor-dependent directional protrusions from their spine heads toward active presynaptic terminals. How do these protrusions extend directionally in a dense neuropil to locate an active presynaptic partner? Emerging evidence now suggests astrocytes are important for synaptic plasticity. We have investigated the dynamic interactions between dendritic spines and astrocytes, labeled with a membrane-targeted GFP and fluorescent protein-expressing virus or dextran electroporation, respectively, in hippocampal slices. By reducing synaptic activity (1 ?M tetrodotoxin), we have observed that neuron-glial interactions at mature synapses are spine-subtype specific. When spine head protrusions are formed, astrocytes form a pore or channel, which seems to be responsible for the directionality and stability of these protrusions. Our results suggest that astrocytes are sensitive to synaptic activity, and direct spine head protrusions to active presynaptic boutons. Astrocytes are able to sense the strength of the many synapses they encompass, and thus seem to control the extent of mature synapse remodelling. This may be an important mechanism for modifying local connectivity in the mature hippocampus.

4-4-B

CD4 T cells cause GFAP fragmentation in primary human astrocytes in a Granzyme B dependent manner

Peter J. Darlington*, Jack P. Antel, Amit Bar-Or

The contribution of CD4 T cells to multiple sclerosis (MS) disease development is not completely understood, both MHC-dependent and MHC-independent mechanisms of tissue injury have been proposed. Previously, we showed that innate immune natural killer cells could target astrocytes leading to bystander injury of neurons in primary neuronal cultures, and found evidence for fragmentation of the astrocytic intermediate filament protein GFAP in MS lesions. Here, we demonstrate that CD4 T cells activated with superantigen cause similar GFAP fragmentation in primary human astrocytes and this occurs in an MHC-independent manner. The GFAP fragmentation is marked by the presence of low molecular weight bands on Western blots, with concomitant loss of high molecular weight polymerized GFAP. Despite having fragmented intermediate filaments, the astrocytes were still viable, suggesting that the overall effect of the T cell is sublethal. Neutralizing antibodies against HLA-DR did not prevent the T cell mediated GFAP-fragmentation, nor did cyclosporin A which attenuates T cell receptor signalling. The superantigen-activated CD4 T cells expressed granzyme B but not other cytotoxic molecules such as granyzme A or perforin. Granzyme B was detected in astrocytes after culture with CD4 T cells, and granzyme B inhibitors blocked GFAP fragmentation in astrocytes. Pretreatment of CD4 T cells with the drug concanamycin A, which inhibits cytotoxic granule release, prevented expression of granzyme B in astrocytes and inhibited subsequent GFAP fragmentation. Our data suggests a novel mechanism by which CD4 T cell can trigger GFAP fragmentation in an MHC-independent manner. Further studies are underway to understand the consequence of such cytoskeletal changes on astrocyte function.

4-5-A

Chronic pain changes the brain

Bushnell Lab, Presented by Marta Ceko

When a person experiences pain, certain areas of the brain are highly activated. This can be investigated using functional magnetic resonance imaging (fMRI). Chronic pain can lead to long-term alterations in both function and structure of the brain. These can include new activation patterns, loss of gray matter and changes in connectivity between certain brain areas.

4-5-B

Post-pubertal expression of the protective phenotype of netrin-1 receptor deficient mice

Alanna Grant*, Zoe Speed, Cassandre Labelle-Dumais, Cecilia Flores

Netrin-1 is a guidance cues involved in the organization of neuronal circuitry. We have shown recently that deleted in colorectal cancer (DCC), a netrin-1 receptor, is expressed in both developing and adult dopaminergic (DA) neurons and is involved in the organisation of mesocorticolimbic DA circuitry. Adult mice heterozygous for dcc (+/-) have sizeable increases in tissue levels of DA in the mPFC and in basal, as well as amphetamine (AMPH)-induced extracellular concentrations of DA, but decreased AMPH-induced DA activity in the nucleus accumbens (NAcc). Concomitantly, these mice exhibit blunted AMPH-induced locomotion and reward, resistance to AMPH-induced deficits in sensorimotor gating, and do not develop sensitization to AMPH when treated repeatedly. To determine whether this ‘protective’ effect of reduced DCC occurs at a specific developmental period, we tested for differences in behavioural responses to AMPH between +/- and wild type (+/+) mice at the post-weanling and peri-pubertal periods. Locomotor activity was measured in post-weanling and peri-pubertal +/- and +/+ mice at baseline and following an i.p. injection of 2.2 mg/kg of AMPH. In contrast to adult animals, post-weanling +/- mice show significant increased locomotion in response to AMPH. Remarkably, this difference is no longer evident in peri-pubertal mice. Consistent with these findings, HPLC analysis of mPFC and NAcc tissue punches of post-weanling and peri-pubertal brains revealed, that, again, contrary to what is observed in adult mice, basal DA and DA metabolite concentrations do not differ between +/- and +/+ mice. Finally, stereological analysis revealed that the 20% reduction in the number of midbrain DA neurons we observed in adult +/- mice is not apparent before puberty. Thus, our findings show that the “protective” dcc-phenotype has a post-pubertal emergence and indicate that DCC may play a role in the normal maturation of the mesocorticolimbic DA system.

4-6-A

Late histological changes in frontal cortical morphology during neuropathic pain

P.S. KOCSIS*, D. SEMINOWICZ, A. C. L. LAFERRIERE, M. C. BUSHNELL

Chronic pain in humans has been associated with gross morphological changes in the prefrontal cortex. However, the cellular correlates of these morphological changes have not been thoroughly investigated. In a recent MRI investigation in our lab, it was reported that a rat model of chronic neuropathic pain (spared nerve injury (SNI)) was associated with decreased frontal cortical volume. The current project investigates the cellular correlates of these MRI findings. In the same rats that underwent MRI, brain tissue was harvested 6 months post-injury and used for histological analysis. The tissue was stained with a neuronal marker (NeuN). Cortical thickness in the frontal cortex was quantified. Preliminary histological analysis indicates an overall trend for decreased frontal cortical thickness for SNI rats compared to sham controls. These results provide preliminary information regarding the cellular changes that occur late in neuropathic pain. Further analys is including cell size, and neuronal and glial density at two post-injury time points are underway.

4-6-B

The Development of a Novel Method of Reversibly Directing Neurite Outgrowth with Light

Miloslav Sailer*, Karen Lai Wing Sun, Jessica Robin, Christopher Barrett, Tim Kennedy.

Anchorage-dependent cellular growth is known to be influenced by surface energy and substratum modulus. The investigation of these factors involves the preparation of gradient films composed of weak polyelectrolytes, Poly(acrylic acid) and Poly(allyl)amine hydrochloride (PAA/PAH) through l-b-l self-assembly on a silicon substrate. During the preparation of the films the pH of PAH was varied throughout the dipping process from 11 to 3, whilst the pH of PAA was kept constant at a pH of 3. The gradual reduction of pH of PAH results in a gradual increase of charge and thus a gradual decrease in film thickness/softness, creating over a 1000 fold gradual difference in the modulus of the films. Using Human Embryonic Kindey 293 (HEK 293) cells we were able to identify that film regions of low modulus were cytophobic, thus determining a threshold modulus in which HEK 293 cells grow, we hope to repeat this experiment with neural cells. Moreover, we have developed a light-sensitive polyelectrolyte (similar to PAA) that has the capability of greatly changing the surface energy of the films after the irradiation of light, by growing neurons on these threshold films we hope to reversibly turn neurite outgrowth on/off.

4-7-A

The impact of long-term yoga practice on the brain and experimental pain perception

Valerie Cotton*, Dr. Chantal Villeneuve & Dr. M.C. Bushnell

Pain thresholds and pain tolerance were tested for 9 yoga practitioners, who had been practicing regularly for at least 8 years, and 8 sedentary control subjects. Using thermal testing procedures, we recorded thermal detection thresholds, hot and cold pain thresholds, and the length of time a subject could keep the hand in a cold water bath. Subjects were asked what mental techniques they used to tolerate the pain so that they could be compared between groups. Yoga subjects were also also to fill out a questionnaire about how strongly they believed yoga affected their pain perception. Using MRI anatomical images gray matter density and white matter tract strength were recorded in all the brains of the subjects. The hypothesis predicts that yoga subjects will require more intense thermal stimuli to elicit a change in thermal sensation and an observation of pain. Yoga practitioners are also expected to withstand the cold water bath for longer periods. These differences in pain perception may also be reflected in increased gray matter density and stronger white matter connections for pain-related areas in the brains of the yoga practitioners.

4-7-B

Perisaccadic compression may be related to neural population interactions on a logarithmic map of visual space

*A. RICHARD, J. CHURAN, C. PACK, D. GUITTON

Perisaccadic compression refers to the transient distortion of perceptual space known to accompany saccadic eye movements wherein visual stimuli briefly flashed near saccade onset are perceived at the saccade endpoint. Target luminance (Michels & Lappe, 2004), eye velocity (Ostendorf et al., 2007), and saccade amplitude (Richard et al., Soc Neurosci Abstr, 2007) have been shown to modulate the magnitude of compression, suggesting that this effect is due to an interplay of retinal and extraretinal signals. Here we investigate the amplitude dependence in more detail and suggest a model that reconciles all observations. RESULTS: The strength of compression increases with saccade amplitude and velocity and, for a given amplitude, as stimulus contrast diminishes. We have been able to reproduce our experimental results with a model of compression that invokes the interaction, on a logarithmic map of retinal space, of populations of neurons that encode saccade (motor) and visual stimulus related activity. We assume that the intensity of motor-related activity increases with saccade velocity and that the intensity of visually-evoked activity increases with contrast. How these two populations interact on a log-map will determine the level of compression for all amplitudes. CONCLUSION: The results are consistent with current ideas about enhanced attention at the saccade end-point and suggest that a transient interaction of the visual locus and the motor-related, attentional locus may be sufficient to account for perisaccadic compression. We corroborate existing models (Hamker et al., 2008; VanRullen, 2004) that emphasize interactive effects on maps that are logarithmic representations of visual space.

4-8-A

Artificial rearing of rat pups reveals the beneficial effect of mother care on neonatal inflammation and adult sensitivity to pain

Cynthia B. de Medeiros*, Alison S. Fleming, Celeste Johnston, & C.-Dominique Walker

OBJECTIVE Evidence suggests that long-term negative consequences result from early, untreated painful procedures received by preterm neonates. Maternal care may help reduce these effects. Using an animal model to mimic early exposure to pain in preterm infants, we tested whether maternal stimulation plays a role in adult pain sensitivity. DESIGN The “pup-in-a-cup” artificial rearing paradigm was used to isolate maternal licking effects. Rats were reared with (maternally reared [MR]) or without (artificially reared [AR]) their mothers. MR control (MR-CON) animals remained undisturbed. AR animals received ‘minimal’ (AR-MIN; 2 anogenital stimulations per day) or ‘maximal’ tactile stimulation (AR-MAX; 2 anogenital and 5 body stimulations per day). Each rearing condition was subdivided into 3 treatments: uninjected, formalin (0.5%-1.0%) and saline injections twice daily from postnatal day (PND) 4-14. Animals were tested for paw withdrawal latency in the Hargreaves Test (PND 70-74) and behavioural pain response to formalin (2.5%) (PND 77-87). RESULTS Hargreaves Test: At a lower intensity, uninjected AR-MAX animals had a shorter latency to lift their paw than AR-MIN or MR-CON animals. At a higher intensity, formalin injected animals displayed the shortest latency to lift the paw compared to animals from other treatments. Formalin Test: Area under the curve was calculated for Phase 1 (1-4 minutes) and Phase 2 (5-60 minutes). In Phase 2, AR-MAX animals exhibited a stronger pain response than AR-MIN or MR-CON animals receiving no injections. CONCLUSION Rats who experience pain early in life may develop a greater sensitivity to reflexive pain. Artificial stimulation may be more detrimental than no stimulation indicating that early pain and artificial rearing may modify how the pain system develops.

4-8-AII

Blame it on your mom! Early nutritional environment and adult dopamine function

Lindsay Naef*, Luc Moquin, Alain Gratton, Claire-Dominique Walker

The term ‘metabolic imprinting’ suggests that the perinatal nutritional and hormonal environment of developing young can produce long-lasting consequences on metabolic function, which have been linked to permanent alterations in the hypothalamic areas involved in the homeostatic control of feeding behavior. These experiments examine the long-term consequences of early exposure to high-fat on the functioning of the dopamine system, involved in the rewarding aspects of feeding behavior. Methods: In our model, rat dams are placed on either a high-fat diet (30% fat) or a control diet (5% fat) from gestational day 14 to postnatal day 22 when male offspring are weaned and maintained on the control diet until time of testing in adulthood. Results: Offspring of mothers exposed to high-fat display decreased locomotion in response to acute amphetamine administration and decreased behavioral sensitization to repeated amphetamine administration. Using in-vivo microdialysis, we found that animals exposed to high-fat have blunted amphetamine-induced increases in dopamine concentrations in both the nucleus accumbens and prefrontal cortex compared to animals exposed to control diet conditions. To examine the behavioral consequences of these changes, we used a conditioned-place preference paradigm with amphetamine as the conditioning drug. In a drug-free state following conditioning, high-fat and control offspring did not differ in their time spent on the drug-paired side. However, following extinction, reinstatement with amphetamine was increased in the offspring exposed to high-fat compared to control animals. Discussion: These studies suggest that early nutritional environment can have long-lasting consequences on dopamine function and these changes could impact drug-seeking behavior. We are currently investigating how these changes influence feeding behavior, in particular, with respect to the response to palatable high-fat foods. Supported by CIHR (Canada)

4-8-B

Mathematical modeling of intracellular signal transduction involved in neural plasticity

Faisal Naqib*, Christopher C. Pack, Wayne S. Sossin.

Facilitation of sensory neuron synapses in Aplysia californica is induced by the neurotransmitter serotonin (5-HT). This strengthening of synaptic transmission can be mediated by the activation of protein kinase C (PKC), which regulates transmitter release, ion channel function, cytoskeletal rearrangement and gene expression. PKC activation is sensitive to the method of 5-HT application. Spaced application of 5-HT (five 5-min applications of 5-HT with an inter application interval of 15-min) strongly desensitizes PKC activation, while prolonged application of 5-HT leads only to weak desensitization of PKC. Inhibition of protein kinase A (PKA) results in a decrease of PKC desensitization for both spaced and massed application of 5-HT. In contrast, applying a protein translation inhibitor drastically increases the desensitization seen after massed application of 5-HT, but decreases desensitization during spaced application of 5-HT. We present a mathematical model describing how the molecular components of this signaling pathway are connected and regulated in order to elicit the previously described dynamics. This model contains two proteins differentially produced by massed or spaced training as well as a PKA-dependent cycling step. The model is capable of reproducing experimental observations with high accuracy and makes several predictions on the mechanism of desensitization as well as its long-time behavior.

4-9-A

Low cost nanopatterning of protein arrays and digital gradients of one-hundred-nanometer spots for studying neuronal navigation

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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 novel microcontact printing technology that we developed. We introduce a double nanoreplication method that allows for the creation of multiple copies of a single e-beam patterned Si masters into photopolymerized epoxy polymers. These photopolymer masters were subsequently used as lift-off stamps for microcontact printing of proteins by placing them in contact with a flat PDMS inked with the protein – the contacted proteins are then lifted-off by removing the stamp. The flat PDMS stamp is then printed onto the target substrate and the remaining proteins are transferred. We patterned 400 million 200-nm-wide spots with fibronectin on an area of 1 cm2 and showed that it could be recognized by an anti-fibronectin antibody as well as by human embryonic kidney cells which formed focal adhesions on these spots. Next, we formed digital gradients of fluorescent antibodies patterned as 100 nm spots over a distance of 400 micrometers with a variable spacing between 100 nm to 10 micrometers, thus spanning 4 orders of magnitude in density compared to only 2 in previous studies. 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 digital gradients.

4-9-B

McGill University Life Sciences Complex Imaging Facility

Aleksandrs Sprumanis and Claire M. Brown*

The Imaging Facility provides the research community at McGill University and outside of McGill with access to advanced imaging equipment for cellular and tissue imaging, as well as technical support from our facility staff with over 35 years of combined microscopy experience. The facility offers thirteen microscope platforms for such things as: confocal microscopy, laser micro-dissection, total internal reflection fluorescence (TIRF) microscopy, live cell imaging, spectral imaging, FRET, FRAP, photoactivation, fluorescence correlation spectroscopy (FCS), high content and high throughput automated imaging (HCS), automated image processing assays (cell cycle, mitotic index, translocation), multi-photon microscopy, FLIM, image correlation spectrosopy and advanced image processing and analysis. Basic and advanced training is available and users have ongoing support for all of the equipment and analysis workstation in our facility. The facility also provides advice on specific applications such as fluorescent dyes, live cell imaging, cameras, appropriate imaging platforms for given applications and image analysis.

4-10-A

The role of TNF? in homeostatic plasticity, developmental plasticity, and behaviour

G. Lewitus*, M. Kaneko, M. Stryker, R. Malenka, and D. Stellwagen

The cytokine TNF?, while primarily known for its role in inflammation, also serves important roles in nervous system function. Through activation of neuronal TNF-R1 receptors, TNF? causes the exocytosis of GluR2-lacking AMPA receptors and results in an increase of excitatory synaptic strength. Concurrently, TNF? application leads to an endocytosis of GABA-A receptors, and a decrease in inhibitory synaptic strength. TNF? is released by glia and this release is increased when neural activity is reduced. The increase in glial TNF? release mediates homeostatic synaptic plasticity, where the nervous system compensates for a long-term reduction in neural activity levels by increasing the excitation and reducing the inhibition in the neural circuit. Blocking TNF? signaling prevents the activity-blockade-induced homeostatic plasticity, which is also absent in tissue from TNF? deficient mice. TNF? deficient mice are also lacking in one component of the in vivo visual cortical plasticity induced by monocular deprivation, a standard model of developmental plasticity. Specifically, TNF? is required for the strengthening of inputs from the open eye, following the closure of the other eye during a critical period of development. Further, TNF? deficient mice lack the normal response to the chronic administration of anti-depressants, judged in two behavioral assays of anti-depressant function. TNF? deficient mice also demonstrate increased sensitivity to cocaine in assays of behavioural sensitization. Based on these results, we can use the TNF? -/- mice to explore the role of homeostatic plasticity in the nervous system.

4-10-B

A NOVEL TRANSGENIC RAT MODEL WITH A FULL ALZHEIMER'S-LIKE AMYLOID PATHOLOGY DISPLAYING INTRACELLULAR A?-ASSOCIATED COGNITIVE IMPAIRMENT

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Alzheimer's disease (AD) is a neurodegenerative pathology in which amyloid-beta (A?) peptide accumulates in different brain areas, leading to the deposition of plaques and to a progressive decline of the cognitive functions. A few rat models of AD-like pathology have recently been reported, developing intracellular and/or extracellular A? accumulation and displaying memory impairment. All these models are based on the co-expression of at least two mutated genes to obtain a full amyloid pathology. Here we describe the generation and characterization of a new transgenic rat line, coded McGill-R-Thy1-APP, developed to express the human amyloid precursor protein (APP) carrying both the Swedish and Indiana mutations under the control of the murine Thy1 promoter. The selected mono-transgenic line displays an extended phase of intraneuronal A? accumulation, which is widespread throughout different cortical areas and the hippocampus (CA1, CA2, CA3 and dentate gyrus), developing as early as at one week after birth. The cognitive functions in transgenic McGill-R-Thy1-APP rats, as assessed with the Morris water maze task, were impaired as early as at 3 months of age, when no CNS plaques are present. Extracellular amyloid deposits, in the form of both diffused A? aggregates and fibrillar (Thioflavine S-positive) plaques, were found from the age of 11 months, and occasionally at earlier stages. They appear first in the subiculum, spreading with time to the hippocampus formation and finally to cortical areas. Glial reactivity is associated with plaques deposition, as measured by MHCII and GFAP immunoreactivity. Dystrophic neurites are also found surrounding the A? deposits.

4-11-A

Novel Experience-dependent Changes in the Developing Retina

Patricia Brown, Ingrid Osswald, Mabel Chong, Beibei Zhao, Fiona Bedford & Derek Bowie

Ionotropic glutamate receptors (iGluRs) are pivotal to CNS development and are implicated in several childhood neurological disorders. Almost all attention has focused on the N-methyl-D-aspartate (NMDA) receptor since appreciable Ca2+ transport through this channel drives many maturation processes. However, not all neurons express NMDARs, suggesting that other Ca2+-permeable iGluRs may also be important. Recently, we have identified a developmental mechanism in the rat retina whereby light entering the eye triggers the insertion of novel Ca2+-permeable AMPA receptors (CP-AMPARs) that are uniquely insensitive to external polyamine blockers. Furthermore, dark rearing abolishes the developmental switch in their expression. As yet, the mechanisms underlying this permanent switch in receptor expression are unknown. We hypothesize that this event occurs as a result of several factors in development, some of which may also be involved in other known activity-dependent mechanisms. We characterized the developmental profile of spontaneous synaptic patterns in AII amacrine cells. We observed an increase in AMPAR-mediated synaptic acticity after eye opening. In addition, Western blot analysis revealed that the developmental expression and phosphorylation of iGluR subunits is disrupted in dark-reared animals. These results provide insight into the underlying molecular components of these developmental changes, such as protein trafficking and post-translational modifications. Potential candidates are neurotrophic factors, including brain-derived neurotrophic factor (BDNF), protein kinases and transcription factors. Since developmental processes are conserved throughout many structures, our findings in the retina can be extrapolated to the brain. Understanding how the permanent switch in receptor expression affects maturation processes will drive the direction of research on childhood neurological disorders, such as Fragile X Syndrome.

4-11-B

Circadian and homeostatic regulation of heart rate

Philippe Boudreau*, Guy Dumont, Diane B. Boivin

Recent evidence suggests that the sleep-wake cycle and circadian rhythms modulate cardiac function in humans. Using an ultra-rapid sleep-wake procedure (URSW), we investigated the interaction between circadian and homeostatic processes on heart rate variability (HRV). After an 8-hour baseline sleep episode, 6 men and 2 women healthy (mean age ± SD: 26.3 ± 4.6 years) underwent a 72-hour URSW consisting of 60-min waking episodes in dim light (<10lux) alternating with 60-min nap episodes in darkness. Throughout the experiment, participants remained in time isolation, in a semi-recumbent position and were served iso-caloric snacks. HR was monitored 200Hz and RR interval, high and low frequencies (absolute: HF, LF; normalized: nHF, nLF), and the LF/HF ratio were calculated using wavelet transform. Data were binned per subject per waking and napping episode, then averaged per time-of-day. A dual-harmonic mixed model was used to compare the circadian amplitude and phase of HR parameters during sleep and wake periods. The sleep has a significant effect on all HR parameters ($p<0.01$). We observed a significant circadian amplitude during wakefulness for all parameters (p?0.035). Similarly, we observed a significant circadian amplitude during sleep periods for all parameters (p?0.079). Circadian amplitude was significantly different between sleep and wake for RR ($p=0.004$) only with greater circadian amplitude during sleep. Also, circadian phase was significantly different between sleep and wake for RR ($p=0.006$), LF ($p=0.006$), LF/HF ratio ($p<0.001$), nHF ($p<0.001$) and nLF ($p<0.001$). The present study reveals a significant effect of sleep-wake state and circadian phase on cardiac rhythm as well as a significant interaction between homeostatic and circadian processes on several indexes of HRV. Sleep stages will be analysed to further address the interaction between sleep-wake state and circadian phase on HRV.

4-12-A

WILL UNIVERSITY STUDENTS FEEL FREE TO USE PRESCRIPTION DRUGS AS 'COGNITIVE ENHANCERS'? PERSPECTIVES FROM A QUALITATIVE STUDY

Cynthia Forlini* and Dr. Eric Racine

There is mounting evidence that methylphenidate (MPH; Ritalin) is being misused by healthy university students to improve concentration, alertness, and academic performance, a phenomenon often described as “cognitive enhancement” (CE). One of the key concerns associated with the spread of the use of pharmaceuticals to improve cognition in healthy individuals is the degree of freedom they have to engage in or abstain from performance enhancement. However, it remains unclear whether CE is viewed as 1) an individual’s autonomous decision; 2) the result of external coercion or 3) a combination of both scenarios. This qualitative study aimed to examine stakeholder perspectives on autonomy, informed consent, and coercion relating to non-medical use of MPH for enhancement purposes.We examined the perspectives of three stakeholder groups (university students, parents of university students, and healthcare providers; n=65) during focus groups (n=9). The focus group content was coded systematically for statements relating to the autonomy of individuals, social pressure to succeed and feelings of coercion to engage in CE. Our study revealed that focus group participants had mixed opinions about whether the decision to use MPH for CE was autonomous or coerced. Stakeholder perspectives tended to reflect that despite beliefs in autonomous choice, students are subject to enormous social pressures that may ease the social acceptance of cognitive enhancement.Our data indicate the need to understand perspectives of stakeholders and non-experts on key issues like cognitive enhancement to fully grasp moral insights in pluralistic societies and prepare sound public health responses.

4-12-B

THE CIRCADIAN AND MENSTRUAL VARIATION OF SLEEP INERTIA: CORRELATION WITH SLEEP STAGE AND CORE BODY TEMPERATRURE

Ari Shechter, B.Sc.* and Diane B. Boivin, M.D., Ph.D.

Alertness is reduced after awakening from sleep, a phenomenon called sleep inertia (SI). SI varies across the circadian cycle, with greatest SI observed after awaking at night when core body temperature (CBT) is low. SI is also affected by sleep structure, with reduced SI observed when awaking from REM sleep. Our aim was to investigate the circadian and menstrual variation of SI, and its relationship with CBT and sleep stage. Eight women were studied during the mid-follicular (MF) and mid-luteal (ML) menstrual phases, with a 72-hour ultra-rapid sleep-wake cycle procedure (36 cycles of 60-min wake episodes alternating with 60-min naps). CBT and sleep were recorded throughout naps, and SI was assessed upon awakening from each nap. Statistics included two-way repeated measures ANOVA (factors: menstrual phase x time) and Pearson's correlation. At both menstrual phases, a circadian variation was observed for SI, CBT, REM sleep and non-REM sleep. During ML compared to MF, SI was increased at 08:00 and 10:00, and reduced at 24:00. Additionally, during ML, REM sleep was reduced at 01:00 and 05:00 and CBT was increased throughout nighttime hours. Regression analyses revealed positive correlations between sleep stage (REM- and non-REM sleep) and SI, which were similar at MF and ML. A negative correlation between CBT and SI was observed, though during ML compared to MF, the slope of the regression line was increased ($p<0.01$) and the y-intercept was reduced ($p<0.01$), suggesting a greater effect of temperature change in SI during ML. SI varied across the circadian cycle, with increased SI found during the nighttime in both menstrual phases. During ML compared to MF, SI was increased at times of habitual awakening and reduced near times of habitual sleep onset, indicating a menstrual modulation of SI. Sleep stage does not seem to produce these changes, since correlations were unchanged between menstrual phases despite altered REM sleep in ML. Altered CBT during ML may contribute, however, since correlations were differentially affected by menstrual phase.

4-13-A

PHENOTYPIC VARIABILITY IN THE COURSE OF EPM1-UNVERRICHT-LUNDBORG DISEASE (ULD) IN TWO SIBLINGS

Dina Amrom, Mohsen Talani, Frederick Andermann, Anna-Elina Lehesjoki & Eva Andermann

Objective: To present the difference of the clinical course in two siblings with molecularly confirmed ULD. Background: ULD or progressive myoclonic epilepsy type I (EPMI) is a neurodegenerative, autosomal recessive disorder, caused by mutations in the cystatin B gene. Methods: Review of medical records and investigations of two siblings. Patients reports: A 30-year-old woman presented her first seizure at the age of 8 years. She had tonic-clonic, atonic and myoclonic seizures. She was treated with valproic acid and various add-on medications, but developed ataxia, and over the past few years, her seizures have worsened. Since the last 2 years, she has improved on an add-on study medication given in the context of a clinical trial. She has mild mental retardation, a history of adjustment disorder and drug abuse, and receives treatment for a depressive disorder. A 31-year-old man, the older brother of patient 1, presented his first myoclonus at the age of 9 years. He had a few tonic-clonic attacks, and short clusters of myoclonic seizures on a few days monthly. He receives valproic acid with some benefit, does not have any ataxia. He drinks alcohol feeling it has an antimyoclonic effect, has a history of drug abuse, and is treated for mood disorder. Both patients are born to non-consanguineous Caucasian-American parents. DNA analysis showed compound heterozygosity with a dodecamer repeat expansion on one allele and a c.67-1G>C mutation on the other allele. Conclusions: These siblings show a great difference in terms of age of onset, symptomatology, disease course and medication. The severity and the rate of progression of ULD are known to be variable, both between and within families, and seem to be independent of the type of mutation. Alcohol has been reported to temporarily relieve myoclonus when used in moderation. In these patients, the difference in symptomatology and disability was striking and unexplained.

4-13-B

Functional Diversification of Glial Cell Subtypes Through Neuron-Glia Interactions via Notch Signalling

Stephanie Stacey, Graham B. Thomas, Nara Muraro, Richard Baines, and Donald J. van Meyel*

Glial cells are essential components of every complex nervous system and it is important to study the differentiation and diverse roles of glia in order to gain a complete understanding of nervous system development and function. An important challenge is to understand the extent of the functional diversity among glial cells, and to discover how functionally diverse glial cell subtypes arise during development. Our work focuses on a subtype of glial cells called the longitudinal glia (LG). LG reside within the ventral nerve cord (VNC) of Drosophila embryos and larvae and lie close to axon projections, dendrites and synapses. The anterior 6 comprise a subtype well equipped to modulate glutamatergic neurotransmission in the CNS because they specifically express a glutamate transporter, Eaat1, and a glutamate recycling enzyme, Glutamine synthetase 2 . We created mutants of Eaat1 and found it is required for correct motor neuron output, larval locomotion and viability. Restoration of Eaat1 expression in the LG is sufficient to rescue larval locomotion while Eaat1 expression in all CNS glia also rescues lethality. Additionally, we found that differential levels of N signaling in the LG promote Eaat1 expression in the anterior subtype. Currently, we are using larval crawling assays to further characterize motor phenotypes in these mutants. We are determining whether Eaat1 is necessary for the development of motor circuits or if it is required more acutely during larval locomotion. Finally, we are studying developmental interactions that promote LG subtype differentiation during embryogenesis.

4-14-A

DEVELOPMENTAL DELAY AND LATE ONSET MYOCLONUS IN A PATIENT WITH INTERSTITIAL DELETION OF CHR 6Q21Q22.3.

Andermann, E.*, Lavoie, J., Andermann, F.

Rationale: Chromosomal abnormalities are often associated with mental retardation, dysmorphic features and seizures. Interstitial deletions of the long arm of chromosome 6 (chr 6q) are relatively rare, and usually not associated with epilepsy. Adult onset myoclonus has not been reported, to our knowledge. Methods: A 30-year-old patient had a history of a single febrile seizure at the age of 8 months. He had mild to moderate developmental delay, dysmorphic features and no further history of seizures. In his late twenties, he developed jerky movements with some features of low amplitude myoclonus and a possible intentional component. Detailed examination and family history was performed. The patient had prolonged day and night telemetry recording, as well as MRI studies. Karyotype was performed, as well as FISH studies and array comparative genomic hybridization (array CGH) Results: On examination, the patient has mild dysmetria and frequent myoclonic jerks involving the upper extremities. According to the parents, there has been no evidence of recent cognitive deterioration. Prolonged video-telemetry revealed extremely frequent myoclonic jerks arising from the right or left upper extremity, with occasional eye closure and head deviation, at times occurring in small runs. Some of these jerks were elicited by startle, and some involved axial musculature as well. The jerks were associated with muscle artifact on the EEG, but no epileptiform abnormality was noted during these events or interictally. Background rhythm showed mild to moderate persistent dysfunction of cerebral activity. MRI showed mild cerebellar vermian atrophy or hypoplasia with slight dilatation of the fourth ventricle. Karyotype revealed a subtle interstitial deletion of chr 6q. This was at the limit of detection at the level of resolution obtained by conventional cytogenetics. Array CGH employing an oligonucleotide array confirmed a deletion of chr 6q at 6q21-6q22.31. The extent of the deletion is estimated to be 7.6 Mb. Family history revealed no neurological disorders except for a few distant relatives on the paternal side with developmental delay or mental retardation Conclusions: Although deletions of chromosome 6q are usually not associated with epilepsy, one patient with a different deletion had intractable seizures. Phenotypic variation is in large part due to differences in size and location of the segmental aneuploidy. The exact deletion described in our patient has not been reported previously, to our knowledge. However, overlapping deletions without a history of seizures or myoclonus have been described. Thus the relationship between the patient’s late-onset myoclonus and the deletion must await further reports of similar deletions. The patient does not have evidence for progressive myoclonus epilepsy, although Kufs’ disease cannot be entirely ruled out.

4-14-B

The Effects of Simulated and Actual Z-Shifts on FreeSurfer-Segmented Whole-Brain, Lateral-Ventricle, and Hippocampal Volumes

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Accurate quantification of whole-brain-tissue (WBT), hippocampal (HIP), and lateral-ventricle (LV) volumes in patients with multiple sclerosis (MS) is an important goal. Accuracy can be affected, however, by local-volume changes resulting from MRI-scanner-gradient nonlinearities and from inconsistent positioning of subjects within a scanner (particularly along the Z-axis). Furthermore, standard canthomeatal (CM) alignment results in the cerebrum being centered several cms away from the isocenter of the magnet. In MRI data from 9 normal controls, simulated 50-mm Z-shifts into, and out of, the magnet had asymmetric effects on mean WBT volumes [out: decrease of 18.77 cc (-1.49%), p=0.022; in: decrease of 98.75 cc (-7.44%), p < 0.0001) and LV volumes [out: decrease of 0.12 cc (-0.81%), p=0.155; in: decrease of 1.28 cc (-8.24%), p < 0.0001); they had symmetric effects on mean HIP volumes [out: decrease of 0.50 cc (-5.19%), p<0.0001; in: decrease of 0.37 cc (-3.98%), p < 0.0001). These results suggest that Z-shifts can have significant effects on observed tissue volumes. Accordingly, inadvertent Z-shifts should be avoided or corrected for. Such steps should lead to more accurate and precise estimates of brain-related changes in neurodegenerative diseases like MS; and, as a result, should lead to increased statistical power in experimental and clinical studies of patients with such disease.

4-15-A

MUSICOGENIC EPILEPSY WITH INDEPENDENT BILATERAL TEMPORAL SEIZURES

Dina Amrom* Eva Andermann, Benjamin Zifkin, Francois Dubeau & Frederick Andermann

Objective: To present two unrelated patients with musicogenic epilepsy who had bilateral temporal interictal discharges and seizure onsets. In these two patients surgical treatment was not considered possible as they had no atrophy and no convincing lateralization. This conundrum is the reason for this presentation. Background: A recent review of musicogenic epilepsy included 110 patients reported since 1884. Most had unilateral epileptic discharges, with an overwhelming preponderance in the non-dominant hemisphere; only 3 had bitemporal discharges. Methods: Review of medical records and investigations of two patients. Results: Patient 1, a 52-year-old woman, has had temporal lobe seizures since the age of 8 years. Some of her attacks, those with a d

4-15-B

GABA, GLUTAMATE AND ASTROGLIAL MEDIATORS IN THE CORTICAL NEUROVASCULAR COUPLING RESPONSE TO BASAL FOREBRAIN CHOLINERGIC INPUT

Clotilde Lecrux, Ara Kocharyan, Claire Sandoe, Edith Hamel

Background and aims: Neurovascular coupling or the tight adjustment of cerebral blood flow (CBF) to neurons displaying increased activity is widely used in functional neuroimaging techniques to map changes in neuronal activity. GABA interneurons contribute to the cortical CBF response to basal forebrain (BF) stimulation (Kocharyan et al., JCBFM. 2008;28:221-31). However, little is known about their interactions with other cortical neurons and astrocytes in this response. Hence, we investigated the neuroglial components involved in the CBF response to BF stimulation by blocking GABA and/or glutamatergic receptors, astroglial function or vasoactive mediators. Methods: Bilateral cortical CBF responses to electrical BF stimulation were measured in urethane-anesthetised rats by Laser-Doppler flowmetry at baseline and after intracisternal (3µl, 10-4M, pH 7.4 buffered solution) injection of vehicles, antagonists of NMDA (MK-801), AMPA (CNQX), metabotropic glutamate (mGluR) (MPEP+LY367385), GABA-A (picrotoxin), epoxyeicosatrienoic acids (EETs) (14,15-EEZE), muscarinic (scopolamine) receptors, blockers of astroglial metabolism (fluorocitrate), or inhibitors of EET-producing P450-epoxygenase (MS-PPOH) or prostaglandin-synthesizing cyclooxygenase-1 and 2 (COX-1 and 2, SC-560 and NS-398, respectively). Body temperature, blood gases and arterial blood pressure were stable throughout the experiments. Changes in CBF, expressed as mean±SEM, were compared by repeated-measures analysis of variance (ANOVA) or by one-way ANOVA for three group comparisons. Results: The role of glutamate and GABA was evidenced by the significant decrease in the CBF response to BF stimulation after MK-801 (-32.2±5.3%, $p<0.01$), CNQX (-30.2±5.5%, $p<0.01$), LY367385+MPEP (-19.6±4.5%, $p<0.05$) and picrotoxin (-24.5±4.1%, $p<0.05$). MK-801 and picrotoxin administered together had an additive inhibitory effect on this response (-45.9±6.2%, $p<0.01$). As previously reported, scopolamine reduced the CBF response (-55.5±4.2%, $p<0.01$), but no further decrease was found when combined with MK-801 (-54.7±9.5%, $p<0.01$), suggesting that the glutamate effect is downstream of muscarinic receptor activation. Inhibition of astroglial metabolism reduced (-43.6±5.9%, $p<0.001$) the CBF response, as did blockade of EET synthesis (MS-PPOH, -44.2±6.2%, $p<0.01$) or receptors (14,15-EEZE, -52.5±3.6%, $p<0.01$). The combined administration of MS-PPOH with MK-801 or picrotoxin had no significant additive effect as compared to MS-PPOH alone (-34.5±3.5%, $p<0.01$ and -35.1±4.3%, $p<0.001$), suggesting that glutamate and GABA act partly through the astroglial EET cascade. In contrast, COX-1 or COX-2 inhibition had no effect on the evoked CBF response (-9.8±10.2%, ns and +6.9±9.5%, ns). Conclusion: Our results demonstrate that (i) specific networks of cortical GABA and glutamate neurons are involved in the cortical CBF response induced by BF stimulation, (ii) these cortical neurons act, at least in part, through vasoactive EETs derived from astroglial arachidonic acid metabolism and (iii) COX-2 derivatives are not involved in the perfusion response to BF stimulation, in contrast to the thalamocortical pathway (Niwa et al., J Neurosci. 2000;20:763-70; Fernandes et al., Brain07, Abstract #BO12-3, and this meeting). Together with previous studies, these results suggest that neurovascular coupling in the cerebral cortex is input-specific, and that different vasoactive mediators are involved depending on the neurons recruited locally by a given afferent pathway.
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4-16-A

The role of neural sirtuins in acute ischemia

Angela O Choi and Dusica Maysinger

Microlesions in the brain, initiated by acute hypoxic-ischemic insults, can develop into a stroke if they remain undetected. At the core of the lesion, neurons undergo necrotic cell death; however, cells in the surrounding penumbra can remain viable for a longer period of time, but will eventually undergo cell death via mechanisms resembling that of apoptosis. Shortly after an ischemic insult, there is a transient increase in insulin-like growth factor-1 (IGF-1) signal transduction near the site of injury. IGF-1-mediated cytoprotection has been suggested to involve a NAD-dependent, class III histone deacetylase, known as sirtuin (or Sir2, named after the yeast silent information regulator 2). The family of Sir2 was first identified as the key link between caloric restriction and life span extension in yeast, worms, fruit flies and more recently, in mice. Sirt1 is the mammalian homolog of the yeast Sir2, and is currently investigated extensively as a neuroprotective factor in several neurodegenerative diseases. Our objective is to identify the role of Sirt1 in regulating neurodegeneration upon ischemic injury. Oxygen-glucose deprivation (OGD) of murine primary cortical cultures was used as an in vitro model of acute ischemic stress. We found that short term OGD, as little as 5 hours, significantly reduced the number of neurons, and completely abolished the expression of Sirt1 in our cultures. More interestingly, at 1-2 hours of OGD, we found that Sirt1 is differentially expressed in neurons and astrocytes, suggesting a dynamic regulation by Sirt1 in both of these neural cell types. These preliminary results indicate that Sirt1 function is impaired under ischemic injury. To detect early minute changes in Sirt1 activity, a sensor is currently being developed based on fluorescent nanoparticles. This sensor consists of a substrate-mimicking peptide (containing an acetylated lysine group) covalently linked with a fluorescent nanoparticle, which is quenched in the presence of the acetylated lysine. Upon deacetylation by Sirt1, the fluorescence of the sensor can be measured in an in vitro assay or be detected in vivo. Identification of early changes in acute ischemia, such as changes in Sirt1 activity, can allow for the design and development of nano-tools and treatments to rescue the viable, but stressed neural cells in the penumbra.

4-16-B

Characterization of c3orf60 (NDUFAF3), a novel Complex I (NADH ubiquinone oxidoreductase) assembly factor.

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Complex I (NADH:ubiquinone oxidoreductase) is a large multimeric enzyme complex of the mitochondrial respiratory chain. Deficiencies in the function of complex I are the most common cause of mitochondrial disease in infants. A failure to correctly assemble the complex appears to be the cause of the deficiency in most cases; however, the assembly pathway is poorly understood. To date, only six genes involved in complex I biogenesis have been identified. In this work we show that previously uncharacterized complex I assembly factor c3orf60 (NDUFAF3) localizes to the mitochondria and is involved in early and late complex I assembly steps, possibly ensuring the correct insertion of ND1 in the inner mitochondrial membrane.

4-17-A

NANOTHERAPEUTICS IN ALZHEIMER'S DISEASE: Nanogels Bind A?1-42 and Prevent Cytotoxicity

Sebastien Boridy*,Haruko Takahashi, Kazunari Akiyoshi, & Dusica Maysinger

Polymeric nanoparticles have exhibited much promise as nanomedicines due to their stability and unique amphiphilic properties. Importantly, hydrogel nanoparticles (nanogels; 20-30 nm) composed of pullulans bearing cholesteryl moieties (CHP) interact with soluble proteins through hydrophobic bonding and can restore function to misfolded proteins via artificial chaperone-like activity. The OBJECTIVE of this study was two-fold: (i) Firstly, to investigate whether CHP nanogels can bind to hydrophobic peptides with a known propensity to aggregate, in particular the 42 amino acid ?-amyloid variant (A?1-42) thought to be causal in Alzheimer's disease (AD); and (ii) secondly, to determine whether formation of CHP- A?1-42 oligomer entities will reduce cytotoxicity of A?1-42 in primary cortical cultures and microglia (N9) cell cultures. Our results indicate that (i) CHP nanoparticles interact with the A?1-42 variant in the monomeric and oligomeric forms, (ii) while the neutral derivatives of CHP nanogels are non-toxic, the positively charged derivatives (CHPNH2) are, particularly in primary cell cultures, and finally, (iii) binding of monomeric and oligomeric A?1-42 forms to CHP significantly reduce A?1-42 cytotoxicity in both the primary cortical cultures and microglial cell line. These findings support the principle of using nanogels for a nanotherapeutic-based approach in neurological disorders characterized by formation of soluble toxic aggregates such as those in Alzheimer's Disease (AD) and could provide a valid complementary approach to passive immunotherapies already being studied in this field.

4-17-B

HSP90 INHIBITORS AS POTENTIAL THERAPEUTIC AGENTS IN ALS

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Protein misfolding and aggregation are important features in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS), which is characterized by progressive degeneration of upper and lower motor neurons, leading to paralysis and ultimately death from respiratory insufficiency. Protein chaperones are involved in protein quality control in cells, maintaining unfolded and misfolded proteins in soluble state, refolding them into proper conformation, or promoting degradation through the ubiquitin-proteasome system. Protein chaperones are upregulated by cellular stress, a process called the heat shock response. Upregulation of heat shock proteins (HSPs) was neuroprotective in culture and animal models of familial ALS (fALS) caused by sod1 mutation (Batulan et al., 2006; Bruening et al., 1999; Kieran et al., 2004). Motor neurons have a high threshold for induction of heat shock genes in response to stress, making them resistant to treatments that upregulate HSPs in other cell types through the major heat shock transcription factor Hsf1 (Batulan et al., 2003). However, treatment with Hsp90 inhibitors does upregulate multiple HSPs in motor neurons and treatment with the Hsp90 inhibitor, geldanamycin, protected motor neurons from toxicity of mutant SOD1 in a primary culture model of fALS (Batulan et al., 2003; Batulan et al., 2006). Geldanamycin and other Hsp90 inhibitors have an unfavourable pharmacokinetic and toxicological profile for therapeutic use; 17-AAG and radicicol induced HSPs in neurons, but at cytotoxic concentrations (Batulan et al., 2006). NexGenix Pharmaceuticals is developing novel Hsp90 inhibitors with reduced toxicity and blood-brain barrier permeability. The Durham lab and NexGenix are collaborating in the preclinical assessment of the lead compound, NXD30001. In cancer cell lines, NXD30001 induced HSPs, and promoted degradation of several Hsp90 client proteins by disrupting the Hsp90 complex and making them available for proteasomal degradation. In dissociated spinal cord-DRG cultures, NXD30001 increased expression of HSPs in motor neurons including Hsp70, Hsp40, Hsc70, but not Hsp90, in levels comparable to geldanamycin. Thus, NXD compounds may protect cells from misfolded proteins through the increased chaperoning activity provided by additional HSPs, or by disrupting the association of Hsp90 with misfolded protein and promoting degradation. These hypotheses are being tested in primary culture models of motor neuron disease, i.e., expressing mutant proteins responsible for familial ALS (SOD1, TDP-43 or FUL/TLS) in motor neurons of dissociated spinal cord-DRG cultures and in transgenic mouse models. Preliminary results suggest that NXD30001 does improve protein quality control in mutant SOD1-expressing motor neurons, as observed by reduced inclusion formation in motor neurons treated with NXD30001 compared to control.

4-18-A

CROSS - CULTURAL DIFFERENCES IN VIRTUAL NAVIGATION

Bhairavi Balram* and Veronique Bohbot

Research over the past decade has looked into the influence of culture in modulating the way we perceive our environment. Theories stemming from this research suggest a fundamental difference in the way Asians and Westerners process complex visual scenes. In our study, elderly Canadian and Japanese subjects were asked to perform virtual navigational tasks, in order to determine the navigational strategy that they adopted. The results from our study reveal a significant difference between the navigational strategies employed by the Canadians and Japanese participants. These findings have serious implications on healthy aging as well as age related neurodegenerative disorders such as Alzheimer

4-18-B

Evidence of Altered Polyamine Concentrations in Brains of Suicide Completers

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ABSTRACT Background: Recent mRNA studies have found alterations in the expression of several polyamine metabolic enzymes in the brains of suicide completers, including widespread downregulation of spermidine/spermine N1-acetyltransferase (SAT1), the key enzyme in polyamine catabolism, suggesting compensatory mechanisms attempting to increase brain levels of polyamines. Methods: We developed a method employing high-resolution capillary gas chromatography (GC) in combination with mass spectrometry (MS) for the analysis of polyamines from post-mortem brain tissue, which allowed accurate measurements of spermidine and putrescine. We analyzed polyamine levels in a total of 126 samples from Brodmann areas (BA) 4, 8/9, and 11, from 42 subjects, comprising 16 suicide completers with major depression, 13 non-depressed suicide completers, and 13 controls. Results: Both putrescine and spermidine levels fell within the expected nanomolar ranges. Putrescine concentrations were significantly elevated in all three brain regions from suicide completers compared to controls, whereas spermidine concentrations were significantly increased in BA 11, with a trend for increased levels in BA 4. Conclusions: This is the first GC-MS study to analyze the expression of polyamines in post-mortem brain tissue and confirms the hypothesis raised by previous studies that alterations in brain putrescine and spermidine levels take place in individuals dying by suicide.

4-19-A

Investigating the functional significance of DCC trafficking during axon guidance.

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The netrin-1 receptor Deleted in Colorectal Cancer (DCC) is required for the formation of multiple major axonal projections by embryonic cortical neurons, including the corpus callosum, hippocampal commissure, and cortico-thalamic tracts. The presentation of DCC by axonal growth cones is tightly regulated, but the mechanisms regulating DCC trafficking in neurons, and the functional significance of that regulation, are not well understood. We have demonstrated that protein kinase A (PKA) activation recruits DCC to the axonal plasma membrane of embryonic mouse cortical neurons, and that this enhances axon chemoattraction to netrin-1. Similarly, depolarization, induced by elevated levels of extracellular KCl also recruits DCC to the plasma membrane and increases axon outgrowth evoked by netrin-1. Inhibition of PKA, phosphatidylinositol-3-kinase, protein kinase C, or Tetanus Toxin sensitive exocytosis, blocks the depolarization-induced recruitment of DCC and reduces axon outgrowth in response to netrin-1. Inhibiting protein synthesis does not alter DCC recruitment, nor are the distributions of trkB or NCAM significantly affected, consistent with selective mobilization of DCC. We are currently extending these studies by examining the contribution of DCC trafficking to netrin-1 induced cortical axon branching. Together, these findings identify a role for PKA activation and membrane depolarization modulating the response of axons to netrin-1 by regulating DCC recruitment to the plasma membrane.

4-19-B

Regulation of Protein Phosphatase 1 subcellular localization through interaction with 14-3-3 and its Implication for Alzheimer's Disease.

Myrka Jerome*; Yifan Lu, and Hemant K. Paudel

Background: Alzheimer’s disease (AD) is a neurodegenerative disease characterized by the presence of senile plaques and neurofibrillary tangles (NFTs). NFTs are mainly composed of hyperphosphorylated microtubule associated protein tau. In AD, hyperphosphorylation of tau reduces its affinity for microtubules causing microtubule instability and neurodegeneration. The mechanisms leading to the imbalance between kinases and phosphatases that modulate tau phosphorylation are unknown. In AD brains, 14-3-3 is highly upregulated and found in NFTs. Our previous studies have shown that 14-3-3 promotes tau phosphorylation by kinases. Protein phosphatase 1 (PP1) is a Ser/Thr phosphatase that dephosphorylates tau in the brain. PP1 activity is regulated by its phosphorylation. When PP1 is phosphorylated on Thr320, it is inhibited. Methods: Transient transfections. GST pull-down assay. Immunofluorescence. Western blotting. Results: Using cell extracts of HEK-293 cells overexpressing PP1 and pull-down assay, we showed that PP1 binds to GST-14-3-3. Next, using subcellular fractionation of HEK-293 cells overexpressing PP1, we found that phosphorylated PP1 localized to the nucleus. However, when 14-3-3 is co-expressed with PP1, most of the phosphorylated PP1 localized to the cytoplasm. These results were substantiated by immunofluorescence using undifferentiated PC12 cells. Our data suggest that 14-3-3 regulates PP1’s cellular localization by binding to it. Conclusions: In this study, we found that (1) 14-3-3 binding to PP1 regulates the nuclear shuttling of PP1 and (2) our data imply that upregulated 14-3-3 in AD promotes tau phosphorylation by preventing tau dephosphorylation by PP1, ultimately leading to the accumulation of hyperphosphorylated tau. Relevance/Impact: We have identified 14-3-3 as a modulator of PP1, a protein important for microtubule stability and neuronal maintenance. Understanding how 14-3-3 regulates PP1 could identify new therapies for the treatment of AD.

4-20-A

Developing a Method to Transplant Allogenic Oligodendrocytes into Shiverer Organotypic Slices to Study Myelination

Jenea M. Bin*, Sarah-Jane Bull & Timothy E. Kennedy

Netrin-1 and its receptor DCC play an important role in the maintenance of paranodal axoglial junctions in myelin. Due to the fact that both the netrin-1 and DCC knockouts die at birth, organotypic slice cultures have been a valuable method to study myelination in these mutant animals. While it is known that mature oligodendrocytes express both netrin-1 and DCC, it has not been determined whether the paranode phenotype is a consequence of loss of netrin-1 in the oligodendrocytes themselves, the surrounding environment, or both. To investigate the requirement of cell-autonomous expression of netrin-1 by oligodendrocytes for paranode maintenance, we developed a method in which oligodendrocytes from netrin-1 knockouts can be transplanted into organotypic cerebellum slices from Shiverer mice. The advantage of using Shiverer slices is that these mice have a mutation in the MBP gene that prevents MBP protein expression and the formation of compact myelin. Therefore, we are able to visualize myelin produced by the transplanted cells using immunohistochemistry for MBP. With this method we observed significant myelination by the transplanted cells throughout the slice, and the sequestering of caspr indicating the formation of paranodal axoglial junctions. This method could also be used to study oligodendrocyte-specific phenotypes resulting from other genetic mutations in myelin-related genes.

4-20-B

Awareness of deficits during the etomidate speech and memory procedure

Sarah Jane Banks, Rose Debra Golinski, Jelena Djordjevic, Viviane Sziklas, Marilyn Jones-Gotman

Rationale: Intracarotid anaesthetic procedures (IAPs) result in temporary deficits, including contralateral hemiparesis and certain cognitive changes. This procedure provides a model to investigate the hemispheric differences in occurrence of anosognosia, or loss of awareness into symptoms. In various neurological disorders there is a robust association between nondominant hemisphere lesions and anosognosia. Consistent with this, the great majority of patients show no recall of hemiparesis following right hemisphere amobarbital injection. A smaller number of patients do not recall hemiparesis following left hemisphere injection and these patients usually have a seizure focus in their right hemisphere. However, anosognosia is not always a right hemisphere phenomenon. Loss of awareness sometimes occurs in aphasia. Whereas patients with Broca's aphasia are usually aware of their naming deficit, patients with Wernicke's aphasia appear unaware of their comprehension deficit. No previous research has focused on this distinction during the IAP. To date, most of the research on IAPs has been done with amobarbital as the anesthetic agent. We have recently introduced an alternative anesthetic agent, etomidate. It was the drug used in the current study. Our aims were to compare awareness for motor changes after left or right injections, to compare awareness in patients with left vs. right TLE, and to compare awareness for naming vs. comprehension deficits after left injections. Methods: Subjects were 35 unilateral TLE patients, all left hemisphere dominant for language. At the conclusion of etomidate speech and memory (eSAM) testing, patients were asked standard questions probing awareness into motor weakness, dysarthria, naming and comprehension. Their responses were coded as no awareness, partial awareness, or full awareness. Memory scores from the eSAM were also analyzed as related to the awareness scores. The data were analyzed using nonparametric statistics. Results: For motor symptoms, less awareness was seen following right hemisphere injections (56.8% no awareness vs. 43.2% following left hemisphere injections), and injections contralateral to the seizure focus resulted in the least awareness; this was not associated with memory scores. Following right hemisphere injection, awareness for dysarthria was also significantly reduced only when the seizure focus was contralateral to the injection. Following left hemisphere injection, the predicted dichotomy was evident, with 10% of patients not aware of naming deficits, whereas 73% were not aware of comprehension deficits. This result did not differ by side of seizure focus. Conclusions: This study confirmed the difference in awareness between left and right injections seen in earlier studies using amobarbital, but in contrast relatively more awareness overall was evident during the eSAM. In addition, this was the first study to show the striking difference in awareness between comprehension and naming deficits after injection into the dominant hemisphere. Funding: Canadian Institutes of Health Research

4-21-A

Mechanisms Regulating DCC Trafficking in Neurons

Jacklyn Girgis*, Katherine E. Horn & Timothy E. Kennedy

Netrin-1 is a bifunctional axon guidance molecule found in the developing and mature central nervous system. Deleted in colorectal cancer (DCC) is a netrin receptor required for chemoattraction to netrin. In axonal growth cones, activation of Protein Kinase A facilitates chemoattraction to netrin-1 by recruiting DCC from an intracellular vesicular pool to the plasma membrane. How DCC trafficking is regulated is not well understood. To investigate the mechanisms that regulate DCC trafficking, we are characterizing DCC containing cargo vesicles in neurons using biochemical and immunocytochemical methods. These studies aim to determine how DCC trafficking contributes to chemoattractant responses to netrin-1.

4-21-B

A LONGITUDINAL FMRI INVESTIGATION OF EMOTIONAL MEMORY ENCODING DURING RECOVERY FROM PTSD

Erin W. Dickie*, Alain Brunet, Vivian Akerib, and Jorge L. Armony

Background: Post-Traumatic Stress Disorder (PTSD) has be characterized as a disorder of the neural systems that process threat related information and underlie declarative memory formation. However, little is known about how these systems change over time, specifically as one recovers from the disorder. We examined the neural correlates of remission from PTSD using a longitudinal fMRI investigation. Methods: Civilian PTSD patients were scanned within weeks of seeking treatment (time 1) and six to nine months later (time 2), when PTSD symptoms were in remission for 65% of patients. During each scanning session, participants viewed a series of fearful and neutral faces in preparation for a memory test (administered outside the scanner). Results: An improvement in memory performance from time1 to time 2 was correlated with symptom reduction. In addition, memory related fMRI activity of the amygdala and the ventral-medial prefrontal cortex was correlated with current symptoms levels at both time points. Moreover, the change in memory related activity within the hippocampus and the rostral anterior cingulate cortex (rACC) was associated with the degree of recovery. Importantly, in both the hippocampus and the rACC, memory related activity at time 1, when patients were beginning the recovery process, was correlated with the degree of recovery they would receive, and not current symptom levels. Conclusions: Present findings underscore the importance of longitudinal investigations for the identification of factors that are associated with and can predict recovery, a research question of upmost importance to clinicians.

4-22-A

Dissecting the contribution of prenatal hypoferremia induced by turpentine in the development of schizophrenia-like behaviours

Argel Aguilar-Valles* , Cecilia Flores, Giamal & Luheshi

Maternal infection or inflammation during the first 2 trimesters of human pregnancy is associated with greater incidence of schizophrenia (SCZ) in the adult offspring. Interleukin-6 (IL-6), a pro-inflammatory cytokine released during inflammation, is thought to play a central role. IL-6 plays a fundamental role in the decrease of circulating levels of non-heme iron (hypoferremia) in the mother, which is the source of iron for the fetus. Hypoferremia may result in alterations in neurodevelopment, leading to increased risk of SCZ. We investigated the role this factor on the effects of a prenatal aseptic inflammatory insult with turpentine oil (TURP) in an animal model. To elicit an inflammatory response in pregnant rats at gestational day (GD) 15, we injected i.m. 100 ?L of TURP or saline (SAL) as control. One batch of dams was sacrificed 11 h after injection for iron determination. In another batch of dams SAL and TURP were co-administered with iron-sucrose (1 daily i.p. injection of 10 mg/kg from GD 13-14 and 20 mg/kg GD 15-18), in order to test the effect of hypoferremia. Dams were allowed to give birth and the adult (60 days old) offspring were analyzed for either acute or repeated amphetamine (AMPH)-induced locomotion (2 mg/kg, 5 consecutive days, test 7 days after with a dose of 1 mg/kg). TURP treatment induced a significant decrease in serum iron levels in GD 15 mothers. In the adult offspring, those animals whose mothers were treated with TURP presented an increased response to a single injection of AMPH and greater sensitized response to repeated AMPH administration. Interestingly, effects of prenatal TURP on AMPH induced locomotion (acute and repeated) were prevented by prenatal iron co-treatment, supporting a fundamental role of reduced iron supply during gestation in the development of behavioral alterations in the adult offspring.

4-22-B

Differential expression of Slitrk family members in the mouse nervous system

Francois Beaubien* Jean-Francois Cloutier

The development of the nervous system requires a wide variety of processes to take place including cellular differentiation, cell migration, axonal guidance, and synapse formation and refinement. The Slitrks are a large subfamily of LRR-containing transmembrane proteins (Slitrk-1 to 6) composed of an extracellular domain containing two leucine-rich repeats domains (LRR) highly homologous between members of the family and of a cytoplasmic region that varies in size between the six members. The LRR domains of Slitrk family members show a high homology to LRR regions found in members of the Slit family of secreted molecules that have been implicated in the regulation of several biological processes including cell migration, axon pathfinding, and axonal and dendritic branching. In an effort to further understand the roles of the Slitrks during development of the mouse nervous system, we have performed a comprehensive analysis of their expression in the late prenatal and early post-natal period using in situ hybridization. We show that despite some overlap in expression, the Slitrks display distinct patterns of expression in the olfactory system, the eye, in forebrain and midbrain structures, the cerebellum, the spinal cord, and dorsal root ganglia. The partially overlapping yet differential expression of the six Slitrk genes in the nervous system we report suggest they may play different roles in the development of specific regions of the brain.

4-23-A

Not tonight, dear': Sex differences in decreased sexual behavior during genital and non-genital pain

Melissa A. Farmer*, Lindsay J. Chan, Emily Foxen-Craft, Julian Becher, Yitzchak M. Binik, James G. Pfaus & Jeffrey S. Mogil

Pain is thought to impact diverse motivational states in humans and rodents. The relationship between pain and sexual motivation remains largely unexplored, despite the frequent comborbidity between clinical pain conditions and impaired sexual desire. Our study objectives were to a) assess the negative impact of tonic, inflammatory pain on sexual motivation, b) compare the sexual impact of genital versus non-genital pain, and c) determine possible sex differences in pain-influenced sexual behavior. We compared male and hormonally primed female mice experiencing genital (vulvar or penile) or non-genital (dorsal aspect of hindpaw or tail) pain with respective saline controls and a no treatment control group. For pain groups, genital or hindpaw zymosan (0.5 mg/ml in 10 ?L volume) and tail carrageenan (2% in 10 ?L volume saline) injections were given 4 h before sexual behavior testing so that the peak of zymosan or carrageenan-induced hypersensitivity corresponded with the beginning of testing. Results indicate that genital pain reduces sexual behavior in both sexes. However, female sexual behavior is equivalently reduced by hindpaw and tail pain, whereas male sexual behavior remains unaltered, despite evidence that males and females show comparable levels of zymosan-induced hindpaw hypersensitivity. The negative impact of pain on sexual behavior is an intuitive relationship that has not previously been demonstrated experimentally. The sex difference in sexual behavior secondary to non-genital pain points to the robustness of male sexual motivation and/or the context-sensitive nature of female sexual motivation. This work was funded by the National Vulvodynia Association.

4-23-B

Role of Coxsackie and Adenovirus receptor in the Central Nervous System

Luyu Zheng*, Kuo-Cheng Huang, Josephine Nalbantoglu

The Coxsackie and adenovirus receptor (CAR), a newly described regulator of neurite outgrowth in the developing central nervous system (CNS), is an adhesion molecule of the immunoglobulin superfamily1,2. CAR is highly expressed in the developing brain, but its level is down-regulated in adult nervous system. Recently, CAR has been demonstrated to mediate homophilic cell-cell adhesion in tumor cell-lines and to be a transmembrane component of the tight junction in epithelial cells. We observed that neurons grown in the presence of soluble CAR have longer neurites compared to BSA control. Furthermore, the presence of soluble CAR was able to overcome the inhibitory effect of cytokines (TNF?) and restore the neurite length to control level. It has been shown that general knockout of CAR results in embryonic lethality; by breeding CAR-floxed mice (a generous gift of Jeffrey Bergelson, U. Pennsylvania) to synapsin-1-Cre transgenic mice we have developed conditional knockout mice in which CAR is deleted specifically in the nervous system. . We are now characterizing the development of the nervous system in these mice. In addition, using hippocampal neurons, isolated from CAR floxed embryos, and infected with AdV-Cre-GFP or control vector (AdV-BFP), we studied basal neurite formation and outgrowth in the absence of CAR expression. Sholl analysis was performed to measure the complexity of the neurite network at three days post infection time point (PID 3). Preliminary results showed decreased neurite complexity in AdV-Cre-GFP infected neurons at 0.06mm distance from cell soma as compared to both AdV-BFP infected and non-infected controls. In addition, neuron survival seemed to be affected by the deletion of CAR, as we observed a dramatic decrease in cell numbers in AdV-Cre-GFP infected plates compared to both controls. The results of this study will further our understanding on the role CAR plays in developmental processes in the brain as well as axonal sprouting.

4-24-A

Oxytocin-induced analgesia is not mediated by the oxytocin receptor, but rather by the vasopressin-1A receptor: evidence from oxytocin- and vasopressin-receptor knockout mice

Ara Schorscher-Petcu*, Susana Sotocinal, Jacqueline N. Crawley, Larry J. Young, Remi Quirion & Jeffrey S. Mogil

Oxytocin (OXT) and vasopressin (VP) are two closely related hypothalamic neuropeptides. Recently, major discoveries have been made with respect to the role of these peptides for the regulation of complex social and sexual behavior in mammals. There is also evidence for the analgesic effects of OXT and VP in both human and rodent species. Indeed, OXT has been reported to be analgesic in a variety of pain tests when administered directly into the brain, the spinal cord or systemically. In the CNS, OXT and VP exert their effects through binding to the OXT receptor (OTR) and the 1A subtype of the VP-receptor (V1AR), respectively. It is well documented that the strong sequence homology of OXT and VP can lead to the activation of the V1AR by OXT, and vice-versa. Here, we characterized the pain phenotype of mutant mice possessing non functional OTR or V1ARs. Surprisingly, we found that OTR knockout mice display a pain phenotype identical to their wildtype littermates. Moreover, systemic administration of OXT dose-dependently produced analgesia in both OTR knockout and wildtype mice in two different pain tests: the radiant heat paw-withdrawal test of thermal nociception and the formalin assay of inflammatory pain. In contrast, OXT-induced analgesia was completely absent V1AR knockout mice. When injected centrally, both OXT and VP elicit a strong scratching response. Here, we report that OXT-induced scratching is present in both OTR wild-type and knockout mice, but absent in V1AR knockout animals.

4-24-B

Neuropeptide Y Y1 and Y2 receptors reverse behavioral despairs by increasing neurogenesis in dentate gyrus in a rat model of depression

Julio Cesar Morales-Medina*, Yvan Dumont, Wenfeng Yu and Remi Quirion

Depression is a heterogeneous debilitating disorder that will become the world's second leading cause of disabilities by 2020. Available treatments provide only limited effectiveness for a considerable number of patients, along with side effects and long delay before therapeutic efficacy. Therefore new treatments are needed. Interestingly, chronic antidepressant treatments have been shown to induce neurogenesis in the dentate gyrus (DG), this apparently leading to efficacy. The olfactory bulbectomy (OBX) rat model produces a wide array of symptoms that mimics several aspects of the human condition including emotional-like despairs and decreased neurogenesis. Animal and pre-clinical studies have suggested that neuropeptide Y (NPY) and its receptors may be involved in mood-related disorders. Here, we evaluated NPY receptors as candidate targets for depression-like behaviors and substrates for antidepressant-like actions in the OBX model. Apparent levels of NPY receptor sub-types were not significantly altered in the OBX model. However, treatment with the Y1-like agonist [Leu31Pro34] PYY ameliorated the depressive-like and anxiolytic-like behaviors displayed in OBX rats. Interestingly, the Y2 antagonist BIIE0246 also improved depression-like behavior, while having limited efficacy on anxiety-like paradigms in OBX animals. Moreover, [Leu31Pro34] PYY reversed cell proliferation-related deficits whereas the Y2 agonist, PYY3-36, enhanced these losses in OBX animals. These results suggest that the behavioral effects of NPY related analogs in our assays could be at least partly related to increased cell proliferation. Taken together, these results suggest that NPY related molecules could prove useful in the treatment of depressive illness.

4-25-A

Comparison of Effects of Continuous Central Infusion of Obestatin versus Ghrelin on Spontaneous Food Intake and Pulsatile GH Secretion

Zehra J. Khoja*, Juan P. Maianti, Cyril Y. Bowers and Gloria S. Tannenbaum

Ghrelin and its receptor(s) form a novel hormone system that exerts powerful stimulatory effects on GH secretion and energy balance. The recent discovery of a second posttranslational product of the preproghrelin gene, termed obestatin, which was shown to exert opposite actions to ghrelin on food intake, triggered a host of investigations. However, no consensus has emerged regarding obestatin’s biological activity. In this study, we sought to unmask a potential role for obestatin, either as a putative satiety signal or regulator of pulsatile GH secretion at the level of the brain. To this end, we examined the efficacy of continuous intracerebroventricular (icv) infusion of obestatin to decrease food intake or influence spontaneous GH release, as compared to icv-infused ghrelin. Adult male rats received a continuous 7-day infusion of either obestatin, ghrelin or the normal saline vehicle by Alzet osmotic mini pumps. Ghrelin strongly stimulated food intake on day 1 and cumulative food intake remained significantly ($P< 0.001$) elevated throughout the infusion period. By contrast, continuous central infusion of obestatin failed to alter food intake at any time point examined. Interestingly, 7-day central exposure to ghrelin did not augment pulsatile GH secretion; neither ghrelin nor obestatin infusion significantly altered any of the GH pulsatility parameters. Conclusions: 1) The orexigenic effects mediated by central ghrelin circuits are not desensitized. 2) Distinct signaling pathways may exist for the GH-release and orexigenic effects of ghrelin. 3) Obestatin is not an important physiological regulator of energy balance or GH secretion at the level of the brain.

4-25-B

Molecular approaches to identify novel therapeutic strategies for nerve repair

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Spontaneous regeneration of the injured central nervous system (CNS) fails due to the action of outgrowth inhibitors that block growth cone extension. Our lab focuses on identifying inhibitory influences that block nerve cell repair and on the receptors and intracellular signaling proteins through which they act. We use this information to develop therapeutic strategies to promote nerve regeneration. We actively study the influence of myelin-associated inhibitors (MAIs) on nerve cell repair and have found that MAIs and their receptors can be degraded by membrane-type matrix metalloproteinases (MT-MMPs). By overexpressing and knocking down expression of MT-MMPs we are studying their therapeutic potential and their physiologic relevance to nerve injury. We have also discovered that immune cells, which actively invade sites of CNS injury, inhibit nerve cell outgrowth and we are studying their molecular mechanism of action. Intracellularly we have identified CRMP4 as a protein that interacts with RhoA to mediate neurite outgrowth inhibition. We have developed a CRMP4 antagonist and are assessing its role in nerve regeneration. Many neurite outgrowth inhibitors converge to regulate cytoskeletal dynamics and we are studying the influence of inhibitory cues on the cytoskeleton through Spatial Temporal Image Correlation Spectroscopy and through the study of regulatory proteins such as TESK. Finally, we are interested in how axons may find their appropriate targets during regeneration and we have identified 14-3-3s as a family of proteins that regulate directional responses of growth cones. Our goal is to establish novel therapeutic strategies to promote nerve cell repair following CNS injury.

4-26-A

Cortisol levels in response to stressful versus non-stressful testing environments"

Shireen Sindi*, Catherine Lord, Bruce Pike, Jens Pruessner and Sonia Lupien.

Background
Elevated cortisol levels can impair cognitive performance, but do testing environments themselves function as stressors? The goal of this study was to assess whether the cortisol stress response (CSR) differs as a function of testing environments manipulated to induce higher or lower distress.

Methods
Twenty eight adults ages 18 to 35 were each tested in three different conditions: 1) Montreal Neurological Institute (MNI - Low stress) tested on university grounds in the afternoon by a young graduate student; 2) Douglas Hospital (DH -High stress) tested far from the university in the morning by an older adult; 3) Douglas Hospital re-visit (DH-R - High stress) for exposure to a psychosocial stress task. Salivary cortisol was repeatedly measured in all conditions.

Analysis
Area under the curve with respect to ground (AUCg) was calculated for the CSR in each session. One-way repeated measures ANOVA were performed with three levels for the different contexts followed by paired samples t-test for significant effects.

Results:
Results revealed that DH AUCg was significantly higher than the MNI AUCg. DH-R AUCg was also significantly higher than MNI AUCg.

Conclusion
That young adults experienced higher CSRs in both stressful conditions (morning testing) versus the non-stressful condition (afternoon testing) stresses the importance of context.