PROGRAMME

Mardi 8 novembre 2022 à l'amphithéâtre du CRCHUM
900, rue Saint-Denis, 5e étage

07h45 **Accueil des participants**

08h30 **Mot de bienvenue**
Alexandre Prat, directeur Departement de Neurosciences

Présentations orales I
Modérateur: Nathalie Arbour

08h40 **Audrey Hector, étudiante au doctorat**
« Electroencephalographic activity during wakefulness and sleep, a potential new biomarker of amyloid-beta pathology »

08h55 **Moustafa Nouh Badr Elemeery, étudiant au doctorat**
«An adoptive transfer strategy to evaluate the role of mitochondria-specific T-cells in the establishment of Parkinson's disease-like symptoms in PINK1 KO mice »

09h10 **Ali Kassab, étudiant au doctorat**
« Cortical hemodynamic changes associated with status epilepticus in critically ill patients »

09h25 **PAUSE ET PRÉSENTATIONS PAR AFFICHE – SESSION 1**

Présentations orales II
Modérateur: Christine Vande Velde

10h40 **Vidya Jadhav, étudiante au doctorat**
« Understanding the role of SYNGAP1 in Parvalbumin-expressing GABAergic circuit development and function »

10h55 Tanya Leduc, étudiante au doctorat
« The synaptic adhesion molecule Neuroligin-2 modulates vigilance state duration and quality under both baseline and sleep deprived conditions »

11h10 Conférencier d'honneur : Ciaran Murphy-Royal, professeur-chercheur adjoint, Département de neurosciences
« Stress, astrocytes, and cognition »

11h45 Conférencière d'honneur : Elsa Rossignol, professeur clinicienne adjointe, Département de neurosciences
« Exploration des mécanismes neurobiologiques des épilepsies infantiles

12h20 LUNCH

Présentations orales III
Modérateur: Jannic Boehm

13h30 Katarzyna Ochenkowska, étudiante au doctorat
« Investigating mutations in THAP12 as a novel genetic etiology of Lennox Gastaut syndrome »

13h45 Lewis Rhys-Depauw-Holt, étudiant au doctorat
« The effects of Early Life Stress on lateral hypothalamic astrocytes and sleep-wake behaviours »

14h00 Sebastien Audet, étudiant au doctorat
« Long-read sequencing: A powerful tool to improve the diagnosis of complex ataxias »

14h15 PAUSE ET PRÉSENTATIONS PAR AFFICHE – SESSION 2

Présentations orales IV
Modérateur : Richard Robitaille

15h30 Conférencier d'honneur : Jean-Claude Lacaille, professeur titulaire, Département de neurosciences
« Interneurones inhibiteurs, plasticité synaptique et mémoire »

16h15 Remise de prix

LIVRET

DES

RÉSUMÉS

Présentateur/ Présentatrice	Présentation orales	Numéro d'affiche	Séance d'évaluation	Page
Adrien Rihoux		18	Matinée	30
Alex Tchung		23	Après-midi	35
Alexandre Emond		15	Matinée	27
Alexie Gagné		16	Matinée	28
Ali Kassab	C		Matinée	7
Ali Falaki		11	Matinée	23
Amandine Even		19	Après-midi	31
Anne-Catherine Chouinard		8	Matinée	20
Audrey Hector	A		Matinée	5
Aveeva Herold		20	Après-midi	32
Ben Rogers		5	Matinée	17
Braxton Phillips		27	Après-midi	39
Catherine Albert		7	Matinée	19
Dar'ya Sas		28	Après-midi	40
Dominic Falardeau		25	Après-midi	37
Eve Honore		4	Matinée	16
Fiona Henderson		3	Matinée	15
Ikram Toudji		6	Matinée	18
Inoussa Balma		1	Matinée	13
Isley De Jesus		10	Matinée	22
Katarzyna Ochenkowska	F		Après-midi	10
Laurianne Zana		29	Après-midi	41
Lewis Depaauw-Holt	G		Après-midi	11
Lovatiana Andriamboavonjy		13	Matinée	25
Manon Duquenne		2	Matinée	14
Moustafa Nouh Badr Elemeery	B		Après-midi	6
Nab Legault-Cadieux		17	Matinée	29
Ndeye Aissatou Ndiaye		26	Après-midi	38
Poune Mirzazadeh		12	Matinée	24
Raphaëlle Denis		24	Après-midi	36
Roxanne Drainville		9	Matinée	21
Saiyet Baez		14	Matinée	26
Sebastien Audet	H		Après-midi	12
Tanya Leduc	E		Matinée	9
Timothe Langlois-Therien		21	Après-midi	33
Victoria Hannah Mamane		22	Après-midi	34
Vidya Jadhav	D		Matinée	8

RÉSUMÉS DES PRÉSENTATIONS ORALES DES ÉTUDIANT(E)S

PRÉSENTATION ORALE A – Audrey Hector

Electroencephalographic activity during wakefulness and sleep, a potential new biomarker of amyloid-bêta pathology

Audrey Hector[1, 2], Chloé Provost[2], Jonathan Brouillette[1, 2], Valérie Mongrain[2, 3]
[1]Département de pharmacologie et physiologie, Faculté de médecine, Université de Montréal, [2]Centre de recherche du CIUSSS-NIM, [3]Département des Neurosciences, Faculté de médecine, Université de Montréal

Synapse loss and ensuing neuronal death are the best predictors of memory deficits in Alzheimer's disease (AD). There is mounting evidence from recent studies that soluble low-molecular-weight amyloid-beta oligomers (Aβo), especially oligomers derived from $A\beta_{1-42}$ peptides, are the most neurotoxic species in AD patients and animal models. It is also well-established that sleep affects the function of the hippocampus, and that sleep alterations are among the first clinical symptoms observed in AD. Moreover, sleep disturbances enhance the risk to develop AD. There is a connection between sleep and AD but the role of Aβo on the sleep/wake cycle is unknow. The main objective of this project is to determine the impact of soluble Aβo on sleep in a rat model of amyloid pathology. We performed chronic hippocampal injections of soluble $A\beta_{1-42}$ oligomers in rats and electroencephalographic (EEG) measurements were performed to define wake/sleep alteration. Time spent in wakefulness, slow-wave sleep (SWS) and paradoxical sleep was preserved in Aβo-injected rats. However, EEG spectral activity measured during wakefulness was increased by Aβo for slow-wave activity (SWA; 0.5-5 Hz) and low-beta activity (16-20 Hz), whereas it was decreased by Aβo during SWS for theta activity (5-9 Hz) and alpha activity (9-12 Hz). Moreover, the theta activity/SWA ratio was decreased during wake and SWS. These differences were significant for the frontal cortex but not for a central recording site. Identifying the specific signature of hippocampal neurodegeneration on sleep features might serve as a non-invasive marker of early AD.

PRÉSENTATION ORALE B - Moustafa Nouh Badr Elemeery

An adoptive transfer strategy to evaluate the role of mitochondria-specific T-cells in the establishment of Parkinson's disease-like symptoms in PINK1 KO mice.

Moustafa Nouh Badr Elemeery[1, 2, 3], Jean Francois Daudelin[3, 4], Alex Tchung[1], Nicolas Giguère[1], Louis-Eric Trudeau[1], Nathalie Labrecque[3, 4]

[1]1 Department of pharmacology and physiology, Department of Neurosciences, Université de Montréal, Montréal, Quebec, Canada., [2]2 Medical Biotechnology Department, National Research Centre, Dokki, Giza, Egypt., [3] 3 Centre de recherche de l'hôpital Maisonneuve-Rosemont, , [4]4 Department of medicine and Department of microbiology, infectiology et immunology, Université de Montréal, Montréal, Quebec, Canada.

Background:
Growing evidence suggests that PINK1 acts as a negative regulator of innate and adaptive immunity, in addition to its role in mitophagy. The presentation of mitochondrial antigens (MitAP) can lead to the establishment of autoreactive mitochondrial specific T-cells in PINK1-KO mice after infection. However, the specific role of MitAP in neuronal dysfunction in these mice is presently unknown. The present study aimed to decipher the role of mitochondria-specific T-cells in the establishment of PD like symptoms in PINK1-KO mice.

Methods:
To directly assess the role of MitAP and mitochondrial antigen-specific T-cells, we adoptively transferred activated mitochondria-specific CD8+ T cells or control CD8+ T cells recognizing ovaalbumin into wild-type or PINK1-KO mice. To allow these cells to infiltrate into the brain, 20µg/kg of pertussis toxin was injected 48h after adoptive-transfer. The frequency and level of activation of these T-cells was assessed using flow-cytometry. PD-like symptoms were assessed using the pole test, the grip strength test, and the open field.

Discussion:
The current study results show that activated mitochondrial antigen specific CD8+ T cells developed into central memory T-cells after adoptive transfer. A subset of the mice died after a delay of 3 weeks. Many of the surviving PINK1-KO and WT mice showed impaired performance in the pole test, open field and rotarod. We are now extending these results by evaluating the integrity of the dopamine (DA) system in both the striatum and ventral midbrain using immunostaining and stereological counting methods.

Conclusion:
the present work supports the hypothesis that MitAP plays a role in the establishment of PD-like pathology via mitochondria-specific T-cells. Additional work will be required to evaluate the possibility of using mitochondrially-directed T-cells as early PD biomarkers.

PRÉSENTATION ORALE C – Ali Kassab

Cortical Hemodynamic Changes Associated with Status Epilepticus in Critically Ill Patients

Ali Kassab[1, 2], Dènahin Hinnoutondji Toffa[1], Manon Robert[1], Frédéric Lesage[3], Ke Peng[1], Dang Khoa Nguyen[1, 2, 4]
[1]CRCHUM, [2]Université de Montréal, [3]Polytechnique Montréal, [4]CHUM

Rationale. Functional near-infrared spectroscopy (fNIRS) is a non-invasive imaging technique that measures changes in oxyhemoglobin ([HbO]) and deoxyhemoglobin concentrations ([HbR]) with a high temporal resolution, which can be used to infer changes in cerebral blood volume (CBV) and cerebral blood flow (CBF). fNIRS is currently the only modality that can continuously and non-invasively monitor brain hemodynamics over all the superficial cortex in patients with SE. The current use of combined video electroencephalography and fNIRS (vEEG-fNIRS) in critical care seizures and status-epilepticus (SE) have been limited to only a few short recording cases in the pediatric setting.

Methods. To assess large-scale cortical hemodynamics during recurrent and/or prolonged seizures, we performed simultaneous whole-head and long-term vEEG-fNIRS recordings in the intensive care unit at our institution and measured hemodynamics changes of 11 critically ill patients admitted with (or later developed) SE.

Results. More than 200h of monitoring and 1000 seizures were recorded. We observed that most short-duration seizures in a patient were associated with an increase in [HbO], CBV, and CBF and a decrease in [HbR]. However, while a similar increase in [HbO] and a reduction in [HbR] could also be seen at the beginning of long-duration seizures (e.g., > 100s), such hemodynamic change was often followed by a prolonged decline in [HbO] and an increase in [HbR], suggesting an insufficient oxygen supply after the first seconds of the seizure and a hypoxic brain state afterwards.

Conclusions. We observed complex temporal and spatial patterns of the hemodynamic changes induced by seizures, confirming, for the first time in adults, similar observations previously seen only in vitro and in rodents models of SE. vEEG-fNIRS has the potential to offer clinicians a relatively novel, inexpensive, and non-invasive complementary approach to assess cortical hemodynamics during seizures and status epilepticus in the critically ill.

PRÉSENTATION ORALE D – Vidya Jadhav

Understanding the role of SYNGAP1 in Parvalbumin-expressing GABAergic circuit development and function

VIDYA JADHAV[1, 2], BIDISHA CHATTOPADHYAYA[1], MARIA CARRENO-MUNOZ[1, 2], JACQUES MICHAUD[1, 3], GRAZIELLA DI CRISTO[1, 2, 3]
[1]1.CHU Sainte Justine Research Centre, Montréal, [2]2. Department of Neurosciences, Université de Montréal, [3]3. Department of Paediatrics, Université de Montréal

Haploinsufficiency of *Syngap1* gene encoding the Synaptic Ras-GTPase Activating protein is associated with intellectual disability, autism spectrum disorder and epilepsy. Mouse models of *Syngap1* haploinsufficiency show alterations in synaptic plasticity, behavioural abnormalities and cognitive deficits. Several studies have shown that *Syngap1* regulates the developmental trajectory and function of excitatory neurons; in contrast, the role of *Syngap1* in inhibitory GABAergic neurons is less well understood. GABAergic neurons are a diverse class of neurons with different morphology, connectivity and physiological properties. Parvalbumin (PV)-expressing interneurons, one of the major classes of cortical GABAergic interneurons, form synapses onto the soma and proximal dendrites of pyramidal cells and play an important role in neural circuit development and plasticity. We aim to understand the role of *Syngap1* expressed by PV cells in sensory processing and cognition. We used both a) Nkx2.1 Cre conditional mice to specifically delete *Syngap1* embryonically in interneurons derived from the medial ganglionic eminence (where PV and somatostatin-expressing interneurons originate), and b) PV Cre conditional mice to specifically delete *Syngap1* postnatally in PV cells, respectively. Our results suggest altered social behavior and fear extinction, specifically in *Nkx2.1Cre:Syngap1^{lox}* but not in *PVCre:Syngap1^{lox}* mutant mice. Further we found that *Nkx2.1Cre:Syngap1^{lox}* mice show specific alterations in auditory processing. Haploinsufficiency of *Syngap1* in interneurons can thus contribute to cognitive alterations caused by *Syngap1* mutations during development.

PRÉSENTATION ORALE E – Tanya Leduc

The synaptic adhesion molecule Neuroligin-2 modulates vigilance state duration and quality under both baseline and sleep deprived conditions

Tanya Leduc[1, 2, 3], Khadija Bougadir[4], Hiba El Alami[5], Valérie Mongrain[1, 2, 3]
[1]Département de neurosciences, Université de Montréal, Montréal, QC, Canada, [2]Centre d'études avancées en médecine du sommeil, Centre-intégré-de-santé-et-services-sociaux-du-Nord-de-l'Île-de-Montréal, Montréal, QC, Canada, [3]Axe neuroscience, Centre de recherche du Centre hospitalier de l'Université de Montréal, Montréal, QC, Canada, [4]Faculté de médecine dentaire, Université de Montréal, Montréal, QC, Canada, [5]Ingram School of Nursing, McGill University, Montréal, QC, Canada

Synaptic adhesion molecules (SAMs) modulate vigilance states, possibly via their involvement in neurodevelopment and/or neuroplasticity. Neuroligin-2 (NLGN2) is a SAM expressed at GABAergic, dopaminergic and cholinergic synapses. These neurotransmission systems are greatly involved in shaping vigilance states. Our group has shown that, under baseline (BL) conditions, the knockout (KO) of *Nlgn2* in male mice reduces the overall time spent asleep and increases absolute delta activity (1-4 Hz) during slow-wave sleep (SWS). We here aimed to investigate which slow wave (0.5-4 Hz) properties could explain this increase in delta activity. We also aimed to verify the response of *Nlgn2* KO mice to sleep deprivation (SD). Adult male *Nlgn2* KO mice and wild-type (WT) littermates underwent surgical implantation of electrodes for electrocorticography (ECoG). The ECoG was recorded during 24h of BL, 6h of SD, and 18h of recovery. *Nlgn2* KO mice showed an increased density, amplitude and slope of slow waves during BL and after SD. Furthermore, KO mice had an accelerated PS recovery following SD and showed an impaired response to SD for ECoG activity quantified during wake and PS. Our data support an implication of NLGN2 in shaping slow waves during SWS and the response to sleep loss in male mice. We are now verifying whether a similar function can be observed in females. Preliminary results show that, similarly to males, *Nlgn2* KO female mice have increased time spent awake under BL conditions. Yet, their ECoG activity and response to SD remain to be examined. We are also currently investigating whether these phenotypes involve neurodevelopment or plasticity at the adult stage by respectively overexpressing and rescuing *Nlgn2* in adult WT and KO mice. Preliminary results suggest that NLGN2 might regulate vigilance states mainly through its function in neurotransmission and plasticity rather than in neurodevelopment.

PRÉSENTATION ORALE F - Katarzyna Ochenkowska

INVESTIGATING MUTATIONS IN THAP12 AS A NOVEL GENETIC ETIOLOGY OF LENNOX GASTAUT SYNDROME

Katarzyna Ochenkowska[1, 2], Eric Samarut[1, 2], Uday Kundap[1], Meijiang Liao[1]
[1]CRCHUM, [2]Universite de Montreal

Many epilepsy-suffering children will later develop other types of seizures, such as Lennox-Gastaut syndrome (LGS). The prognosis for LGS is poor, with a 5% mortality in childhood and persistent seizures into adulthood in about 85% of the cases. Various underlying conditions can cause Lennox-Gastaut syndrome, but most importantly, in almost 25% of cases, no cause can be identified. Thus, it is urgently needed to identify new LGS-causing genetic variants and functionally validate their pathogenicity *in vivo*.

Recently, two new variants in the *THAP12* gene have been identified by whole-exome sequencing in two siblings with idiopathic LGS. Their pathogenicity needs to be demonstrated, so the project will expand on two main objectives: (1) to show that LGS patients' mutations in *THAP12* cause a loss-of-function (LoF) using patient-derived fibroblasts and (2) to investigate the consequence of *THAP12* LoF *in vivo* on neurodevelopmental using zebrafish as a model.

The first objective aims to show that the *THAP12* mutations identified in our LGS patients are causing a gene loss of function. To do so, we will investigate the expression of *THAP12* in patients' cells at the transcriptomic and proteomic levels. The second objective is correlating *THAP12* LoF with neurodevelopmental problems and epileptic features *in vivo*. To do so, we generated a THAP12-KO zebrafish model using CRISPR-CAS9 and we will characterize in more detail their epileptic phenotype.

This research project has the potential to unravel a novel genetic cause of LGS and unveil novel molecular mechanisms of epileptogenesis.

PRÉSENTATION ORALE G - Lewis Rhys-Depauw-Holt

The effects of Early Life Stress on lateral hypothalamic astrocytes and sleep-wake behaviours.

Lewis Depaauw-Holt[1, 2, 3]
[1]CRCHUM, [2]Universite de Montreal, [3]Murphy-Royal Lab

Astrocytes regulate many complex behaviours including learning and memory, decision making and even sleep-wake cycles. Intimate structural and functional relationships with neurons permit astrocytes to regulate neuronal activity and excitability through diverse means including the supply of energy substrates. Astrocytes share metabolic substrates though gap-junction channel proteins (e.g connexin 43) to modulate synaptic transmission. Specifically, astrocyte metabolic networks maintain a number of behaviours in the brain including sleep-wake cycles and are incredibly sensitive to peripheral fluctuations in stress hormones (e.g glucocorticoids). Given the overwhelming prevalence of sleep-wake perturbations in stress related psychiatric disorders, **we hypothesise that astrocyte metabolic networks in the lateral hypothalamus are dynamically regulated by glucocorticoid signalling which in turn modulates sleep and wake cycles**.

To test our hypothesis we firstly investigated the effect of an Early Life Stress paradigm (mimicking childhood maternal separation) on key astrocyte proteins (e.g GFAP and Connexin 43) in a sleep-wake centre of the brain (lateral hypothalamus). ELS also impacts 24 hour activity profiles with unique sex differences. To implicate astrocyte glucocorticoid signalling in sleep-wake cycles we selectively deleted astrocyte glucocorticoid receptors in the lateral hypothalamus. We delivered AAV5-GFAP-Cre into the lateral hypothalamus of *Nr3c1* (glucocorticoid receptor)-floxed mice and conducted behavioural and metabolic phenotyping. We observed unique changes in feeding behaviours and 24-hour activity profiles of astrocyte *Nr3c1-KO* mice compared to eGFP-control injected mice.

PRÉSENTATION ORALE H - Sebastien Audet

Long-read sequencing: A powerful tool to improve the diagnosis of complex ataxias

Sebastien Audet[1, 2], Valerie Triassi[1, 3], Nab Legault-Cadieux[1, 2], Eric Bareke[1], Antoine Duquette[1, 4], Martine Tetreault[1, 2]
[1]CHUM Research Center, Montreal, [2]Department of Neurosciences, Université de Montréal, [3]Department of Bioinformatics, Université de Montréal, [4]Department of Neurology, CHUM

Despite a rapid evolution of technologies available in clinical settings, such as next-generation sequencing, many patients remain without a molecular diagnosis following standard testing. For rare neurological disorders, standard approaches generally achieve a 20-50% success rate. One of the major obstacles is the complexity of interpreting variants of unknown significance (VUS). Hence, we propose that the versatility of long-read sequencing (LRS) can efficiently bridge the identification of variants and the assessment of their impact. Indeed, allowing the capture of full-length gene transcripts in a quantitative manner generates a great amount of functional information which facilitates VUS interpretation in several manners.

A cohort of eight undiagnosed patients with complex episodic ataxias was recruited following a thorough yet unsuccessful clinical investigation. DNA, RNA and proteins were extracted from peripheral blood mononuclear cells, enabling the combination of whole-genome and RNA-sequencing, as well as validation experiments such as LRS.

The multi-omics approach has allowed the identification of excellent candidates in each patient, four of which have been functionally validated with LRS (4/8; 50%). An interesting aspect of the results is the diverging contexts in which long-reads were used to evaluate the effect of variants: to demonstrate the trans configuration of two *SPG7* variants, to prove the alternative splicing and transcriptome shift of *ELOVL4* and *PMPCB* in two patients, and to precisely quantify the number of *ATXN2* repeats in another case. This adaptability was unsurprisingly a major factor in its capacity to contribute to the functional validation.

These results highlight the potential of multi-omics and LRS in the context of clinical genetics. Additionally, they should have a direct impact on patients through the psychological relief linked to an official molecular diagnosis, a better understanding of the pathology, and better care management. Finally, these findings may hopefully lead to novel therapeutic targets in the future.

LISTE DES RÉSUMÉS DES PRÉSENTATION AFFICHÉES

1 - Altered integration of excitatory inputs onto the basal dendrites of layer 5 pyramidal neurons in a mouse model of Phelan-McDermid syndrome

Inoussa Balma[1], Diana E. Mitchell[1], Sabrina Tazerart[1], Soledad Miranda-Rottmann[1], Roberto Araya[1]
[1]The CHU Sainte-Justine Research Center, Neuroscience department of the University of Montreal

Phelan-McDermid syndrome (PMDS) is a rare neurodevelopmental disease with a high risk of autism spectrum disorder (ASD). Up to 70% of patients with PMDS meet the diagnostic criteria for ASD. Also called 22q13.3 microdeletion syndrome, PMDS is highly associated with *SHANK3* haploinsufficiency. In fact, *SHANK3* is believed to be the main contributor to the neuropsychiatric symptoms of PMDS. *SHANK3* encodes a multidomain protein, Shank3, enriched in the postsynaptic density of excitatory synapses where it interacts with other proteins to promote synapse development and maturation. Excitatory synaptic inputs to cortical layer 5 pyramidal neurons (L5PNs) arrive at dendritic spines where they are processed, computed by dendrites, and integrated. *In vitro* studies in the cortex of Shank3-deficient mice have shown defects in synaptic transmission and plasticity, an impairment in spine density and morphology as well as channelopathies. However, it remains unknown how excitatory inputs are processed and integrated in the dendrites of Shank3-deficient L5PNs.

To uncover how synaptic integration of sensory inputs in the basal dendrites of L5PNs is affected in ASD, we performed two-photon uncaging of caged glutamate to activate single and multiple clustered spines while recording their voltage responses at the soma in wild-type mice and in a mouse model of PMDS. Our preliminary data show that while subthreshold excitatory inputs integrate linearly in wild-type L5PNs, those in *Shank3* heterozygous L5PNs summate supralinearly.

These surprising results suggest sensory inputs are over-represented in the basal dendrites of L5PNs from the cortex of our mouse model of PMDS, which could explain at least in part the sensory hypersensitivity observed in PMDS and in ASD in general.

2 - Implication of astrocytic glucocorticoid signaling pathway in the adaptive response to metabolic stress

Manon Duquenne[1, 2], Sarah Peyrard[1, 2], Lewis Depaauw-Holt[1, 2], Thierry Alquier[1, 2], Ciaran Murphy-Royal[1, 2]
[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), [2]Université de Montréal

In response to stress, glucocorticoids act via their specific glucocorticoid receptors (GRs) to induce metabolic and behavioral adaptation. This GR-dependent adaptation influences energy balance and feeding behavior, notably through the modulation of hypothalamic neuropeptide expression. Chronic glucocorticoids exposure, however, contributes to the development of metabolic disorders that are commonly associated with behavioral deficits. Despite these data, few is known about cellular effectors of metabolic adaptation to stress, particularly in brain regions associated with metabolic regulation, i.e. the hypothalamus. Recent results suggest a relevant role of astrocytic GR activity in regulating the synaptic response to stress. We thus set out to test the hypothesis that astrocytes are involved in the setting-up of adaptive metabolic processes in response to stress via GR activation. First, to evaluate metabolic stress impact on GR-expressing astrocytes plasticity in hypothalamus, we performed immunostaining for astrocytes and GR on mouse brain slices accordingly. Next, to directly implicate astrocytes in metabolic adaptation, we characterized the metabolic phenotype of wildtype and transgenic mice lacking GR specifically in astrocytes (GRfl/fl x Glast-Cre/ERT2) before and after metabolic challenge. This was followed by a battery of behavioural assays to determine whether targeting astrocytic GR signalling could rescue the anxio-depressive-like behaviours associated with metabolic distress. These results are a first step to a highlight of novel stress response mechanisms.

3 - 5-HT raphe - ventral hippocampus pathway: what role in aversion-like behaviors?

Fiona Henderson[1], Félix Perreault[1], Morgane Roger[2], Justine Fortin-Houde[1], Anne-Sophie Simard[1], Suzanne van der Veldt[1], Guillaume Ducharme[3], Bénédicte Amilhon[1]
[1]Université de Montréal, Département de Neurosciences, [2]Université Catholique de Lyon, Institut de Formation de Techniciens de Laboratoire Médical, [3]CHU Sainte-Justine, centre de recherche

Serotonin (5-HT) is clearly involved in modulating emotions but the precise mechanisms through which serotonergic neurons are recruited and how they react to aversive stimuli remains to be characterized. In particular, the ventral hippocampus (vHP) is densely innervated by serotonergic fibers and has also been involved in emotional behavior. Thus, the serotonergic raphe - vHP pathway is ideally positioned to modulate emotional behaviors. This study aims at investigating how the activity of 5-HT neurons changes to adapt to aversive situations.

Our objectives are 1- to analyze the correlation between 5-HT neural dynamics and anxiety-like behaviors and 2- to investigate the impact of optogenetic activation of vHP-projecting serotonergic neurons on these behaviors.

We used viral strategies in SERT-cre mice to enable conditional expression of the calcium sensor GCaMP6s in vHP-projecting 5-HT neurons to perform fiber photometry recordings during exploration of aversive environments. Furthermore, the opsin ChETA was conditionally expressed in SERT-cre mice to photoactivate the 5-HT raphe – vHP pathway during anxiety tests.

We found that the activity of serotonergic neurons is modulated during exploration of an aversive environment and that activation of vHP-projecting 5-HT neurons increases anxiety-like behaviors in female but not male mice. The results generated by this project will provide a deeper insight into the neuronal circuits underlying emotional behaviors to adapt to aversive situations.

4 - Object Location Learning Requires Hippocampal CA1 Somatstatin Interneuron Activity And Is Facilitated By Optogenetic Long-Term Potentiation Induction.

Eve Honoré[1], Jean-Claude Lacaille[1]
[1]Université de Montréal

Hippocampus-dependent learning and memory originate from long-term synaptic changes in hippocampal networks. The activity of CA1 somatostatin interneurons (SOM-INs) during aversive stimulation is necessary for contextual fear memory formation. In addition, mTORC1-dependent long-term potentiation (LTP) of SOM-IN excitatory input synapses from local pyramidal cells (PC-SOM synapses) contributes to the consolidation of fear motivated spatial and contextual memories. Although, it remains unknown if SOM-IN activity and LTP are necessary and sufficient for novelty motivated spatial episodic memory such as the object location memory, and if so when it is required. Here we use optogenetics to examine whether dorsal CA1 SOM-IN activity and LTP are sufficient to regulate object location memory. First, we found that silencing SOM-INs during object location learning impaired memory. Second, optogenetic induction of PC-SOM synapse LTP (TBS_{opto}) given 30 minutes before object location training, resulted in facilitation of memory. However, in mice with mTORC1 pathway genetically inactivated in SOM-INs, which blocks PC-SOM synapse LTP, TBS_{opto} failed to facilitate object location memory. Our results indicate that SOM-IN activity is necessary during object location learning and that optogenetic induction of PC-SOM synapse LTP is sufficient to facilitate consolidation of object location memory. Thus, hippocampal somatostatin interneuron activity is required for object location learning, a hippocampus-dependent form of novelty motivated spatial learning that is facilitated by plasticity at PC-SOM synapses.

5 - The role of astrocyte glucocorticoid receptors in stress-induced synaptic plasticity deficits

Ben Rogers[1, 2], Anthony Bosson[2], Sarah Peyrard[2], Ciaran Murphy-Royal[1, 2]
[1]Centre de Recherche du Centre Hospitalier de l'Univeristé de Montréal (CRCHUM), [2]Département de Neurosciences, Université de Montréal

Glucocorticoid receptors (GRs) are key elements in the central response to stress. The assumption in most studies investigating the central effects of glucocorticoids is that this stress hormone activates neuronal receptors to elicit synaptic effects. Recent evidence challenges this idea suggesting that the effects of stress on synapses are mediated through astrocytes. Despite these data highlighting stress sensitivity in astrocytes, whether the stress-induced impairments of synaptic function occur through direct activation of GRs on astrocytes remains unknown. Thus, we aim to understand the role of astrocyte GR signalling in mediating the effects of stress on synaptic function. To accomplish this, astrocyte GRs will be genetically ablated in mice, and subsequently mice will be subjected to a swim-stress paradigm. We have found that in naïve conditions, acute stress impairs hippocampal long-term potentiation (LTP). We are now carrying out experiments in Nr3C1 (GR-flox) mice injected with AVV2/5-GfaABC1-cre into the hippocampus to elucidate the role of astrocyte GR signalling in stress-induced astrocyte dysfunction and synaptic plasticity. These data will elaborate on the role of astrocyte GR signalling in stress-induced synaptic dysfunction, further emphasizing the pivotal role of neuronal-glial interactions in mediated the central effects of stress.

6 - PIGB loss-of-function alters interneuron migration dynamics in a novel mouse model of epileptic encephalopathy

Ikram Toudji[1, 2], Praveen K. Raju[1, 2], Karolanne Toulouse[1, 2], Tuyet M. Nguyen[1], Lara Eid[1, 2], Alexis Lupien-Meilleur[1], Mathieu Lachance[1], Marisol Lavertu-Jolin[1], Philippe Campeau[1, 3], Elsa Rossignol[1, 2, 3]

[1]Centre de recherche du CHU Sainte-Justine, [2]Département de neurosciences, Université de Montréal, [3]Département de pédiatrie, Université de Montréal

Rationale

Autosomal-recessive pathogenic variants in *PIGB* were recently identified in children with epileptic encephalopathy, a severe neurological disorder characterized by refractory seizures with cognitive impairment.

The *PIGB* gene encodes an enzyme, mannosyl transferase III, which is implicated in the glycosylphosphatidylinositol (GPI) anchor biosynthesis pathway. These anchors are critical for the membrane attachment of many proteins including cell adhesion and signaling proteins, both essential for proper neuronal migration. Although GPI anchor deficiency had previously been associated with epilepsy, little is known about its neurodevelopmental consequences.

Methods

Using Cre-loxP technology, we generated a novel conditional knock-out mouse model (*Nkx2.1^{Cre};Pigb$^{c/c}$;RCE^{EGFP}*), which was characterized using several behavioral tests and EEG recordings. At the cellular level, we quantified the number of medial ganglionic eminence (MGE)-derived interneurons at different postnatal ages (P0, P21) using immunohistochemistry on brain slices. We also prepared MGE explants and used time-lapse microscopy to examine the impact of *PIGB* loss-of-function on interneuron migration and branching dynamics during embryonic development.

Results

Our mutant mice show spontaneous seizures and behavioral deficits, such as anxiety-like hyperactivity and altered spatial learning. In addition, we observed a reduction in the number of GABAergic interneurons in the postnatal somatosensory cortex, which suggested a migration deficit. Further analysis of different migration parameters showed a reduction in the distance, displacement, speed as well as nucleokinesis impairments in mutant interneurons compared to controls. Neuronal reconstructions revealed a complexification of mutant interneuron morphology, in comparison with controls.

Conclusion

This study will clarify the pathophysiology underlying *PIGB*-associated epileptic encephalopathy as well as deepen our understanding of the role of GPI anchors in neurodevelopment and more specifically, in the migration of GABAergic interneurons.

7 - Jeter un coup d'œil à la réorganisation fonctionnelle dans le cortex visuel de souris après une lésion ischémique

Catherine Albert[1], Bruno Oliveira [2], Solenn Tissier[2], Jean-François Bouchard[2], Matthieu Vanni[2]

[1](1) Département de neurosciences, Université de Montréal. (2) Neurosciences de la vision, École d'optométrie, Université de Montréal., [2](2) Neurosciences de la vision, École d'optométrie, Université de Montréal.

Les accidents vasculaires cérébraux ischémiques (AVCi) revendiquent un haut taux d'invalidité, car un AVCi provoque des pertes fonctionnelles liées aux aires corticales touchées en bloquant leur apport sanguin. Une récupération partielle, spontanée et limitée survient grâce à des mécanismes de réorganisation fonctionnelle impliquant des modifications de la connectivité et des propriétés fonctionnelles des aires saines. Majoritairement observés dans le cortex moteur chez la souris, ils pourraient être aussi présents dans le cortex visuel. Cette étude s'intéresse donc à la création d'un modèle animal reproductible et fiable pour étudier les différents facteurs pouvant influencer la réorganisation fonctionnelle longitudinale après un AVCi dans le cortex visuel de souris à l'aide de l'imagerie calcique.

L'implantation d'une fenêtre crânienne chez des souris Thy1-GCaMP a permis l'enregistrement des variations de fluorescence associées à l'activité calcique des neurones au repos et lors de stimulations visuelles pendant plusieurs semaines. L'analyse de la connectivité entre les aires corticales, de la cartographie des aires visuelles et de leur sélectivité fonctionnelle au contraste avant et après l'induction d'un AVCi a été utilisée pour révéler le degré de réorganisation fonctionnelle. L'activité calcique au repos des aires visuelles et des aires rétrospléniales des deux hémisphères est initialement fortement corrélée. Lors de stimulations visuelles, la réponse calcique observée dans le cortex visuel droit augmente graduellement en fonction des niveaux de contraste. Une semaine après l'induction de l'AVCi dans le cortex visuel droit, une perte de la corrélation et de la réponse calcique sont observées dans les aires visuelles affectées.

La connectivité et la sélectivité des aires visuelles droites sont initialement perturbées par la lésion ischémique. Ce projet fournira un modèle animal approprié pour étudier les mécanismes de plasticité dans le cortex visuel de souris. Éventuellement, il sera utilisé pour définir la contribution du système des endocannabinoïdes dans la réorganisation fonctionnelle après un AVCi.

8 - Effets chroniques de la stimulation bicorticale sur la récupération locomotrice chez le chat avec une contusion spinale

Anne Catherine Chouinard[1, 2], David Bergeron[1], Hugo Delivet-Mongrain[1], Marina Martinez[1, 2, 3]
[1]Département de Neurosciences, Université de Montréal, [2]CIUSSS du Nord-de-l'Île-de-Montréal, [3]Centre interdisciplinaire de recherche sur le cerveau et l'apprentissage, Groupe de Recherche sur la signalisation neurale et la circuiterie, Université de Montréal

La réadaptation physique après une blessure médullaire favorise la récupération de la locomotion, bien que des déficits persistent. Chez le rat présentant une paralysie motrice d'un membre postérieur, la récupération du contrôle volontaire de la locomotion est facilitée par des microstimulations du cortex moteur appliquées pendant l'entraînement locomoteur. Le but de cette étude est de tester cette stratégie de neurostimulation sur un modèle animal de paraplégie cliniquement pertinent, le modèle félin de contusion spinale. Afin de réduire les déficits locomoteurs bilatéraux associés à la contusion spinale, nous avons développé une neuroprothèse permettant d'appliquer des stimulations corticales alternées dans les deux cortex moteurs durant la locomotion. Dans cette étude, nous évaluons l'impact de la neuroprothèse corticale sur la récupération à long terme du contrôle volontaire de la marche.

Les chats sont d'abord familiarisés à différentes tâches locomotrices. Des électrodes sont ensuite implantées dans les muscles des membres postérieurs et dans les cortex moteurs primaires. Une contusion spinale au niveau T10 est ensuite réalisée et les chats sont entraînés sur tapis roulant 20 minutes par jour pendant trois semaines (avec ou sans microstimulation corticale ; 2 groupes de 8 chats). Hebdomadairement, nous examinons les paramètres de marche sur tapis roulant et la capacité à réaliser des tâches de contrôle moteur volontaire (échelle horizontale et évitement d'obstacles), et ce jusqu'à quatre semaines après l'arrêt du traitement. Basé sur nos résultats antérieurs chez le rat, nous prédisons que l'entraînement avec stimulation corticale favorisera la récupération du contrôle volontaire de la marche, et que les performances seront maintenues après l'arrêt de la stimulation.

Un important potentiel de cette recherche est sa traduction en clinique puisque le cortex moteur est une structure accessible qui peut être la cible de thérapies chez l'humain. Des protocoles de stimulation similaires pourraient être déployés pour favoriser la récupération de la marche.

9 - Combining a cortical and spinal neuroprosthesis to restore walking deficits and improve recovery of leg control after incomplete spinal cord injury in the rat.

Roxanne Drainville[1, 2], Marco Bonizzato[1, 2], Rose Guay-Hottin[1], Alexandre Sheasby[1], Marina Martinez[1, 2]
[1]1. Département de Neurosciences, Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Groupe de Recherche sur la Signalisation Neurale et la Circuiterie, Université de Montréal, Québec, Canada, [2]2. CIUSSS du Nord-de-l'Île-de-Montréal

Incomplete spinal cord injuries (SCI) are associated with chronic motor deficits. Neuroprosthetic therapies can target remaining pathways to treat walking deficits. Because no study has directly compared the single and combined effect of spinal and cortical stimulation over restoration of walking, our lab recently developed a novel neuroprosthesis that stimulates the brain and spinal motor circuits in synchrony with walking. In n=6 rats, we implanted electromyographic electrodes (EMGs) within hindlimb muscles, a multi-electrode array within the hindlimb motor cortex and epidural electrodes over the lumbar (L2) and sacral (S1) spinal segments. After obtaining baselines for kinematics/EMGs on a treadmill, rats received a spinal hemisection at T9 that paralyzed one leg. We evaluated the immediate effects of cortical and/or spinal stimulation over treadmill locomotion in the intact state and after SCI. Gait analysis showed that combined cortical and spinal stimulation delivered during walking are more effective in reducing foot drop caused by SCI than cortical or spinal stimulation alone. All rats were then trained on a treadmill for 3 weeks with cortical and/or spinal stimulation. Control rats did not receive stimulation. The ladder task was used to test the recovery of voluntary control of leg movement. Rats trained with cortical stimulation, with or without spinal stimulation, displayed a higher success rate. These experiments demonstrated that cortico-spinal neuroprosthesis has the potential to reduce motor deficits and to enable targeted rehabilitation protocols after SCI.

10 - Étude de la période optimale pour l'application d'une thérapie de neurostimulation corticale chez le rat blessé médullaire

Isley De Jesus[1]
[1]Département de Neurosciences, Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Groupe de Recherche sur la Signalisation Neurale et la Circuiterie, Université de Montréal, Québec, Canada

Chez les personnes atteintes de lésions de la moelle épinière (LME), la restauration de la marche est citée comme une priorité. Malheureusement, la récupération est rarement satisfaisante et de multiples déficits persistent tout au long de la vie. Une question de longue date dans le domaine de la réadaptation est: quand devons-nous initier les interventions thérapeutiques pour obtenir une récupération optimale ? Pour adresser cette question, nous avons développé la première stratégie de neurostimulation qui cible directement le cortex moteur en synchronie avec le mouvement et avons fait varier le début de notre intervention thérapeutique. Chez le rat, la stimulation corticale a été appliquée 30 min/jour pendant 3 semaines lors de l'entraînement sur tapis roulant, débutant à une (groupe aigu, n=2), quatre (groupe sous-chronique, n=2) ou huit semaines (groupe chronique, n=1) après une LME incomplète. La récupération de la locomotion a été évaluée pendant 15 semaines sur tapis roulant et lors de la traversée d'une échelle horizontale. Nos résultats préliminaires montrent une amélioration des performances locomotrices (diminution du pied tombant et du nombre de fautes au test de l'échelle) dès la première semaine de traitement, peu importe le délai d'initiation de la thérapie de stimulation corticale. Plus important, les performances pour le groupe aigu et sous-chronique étaient maintenues un mois après l'arrêt de la thérapie. Ces données préliminaires suggèrent que notre intervention thérapeutique est efficace même lorsqu'initiée dans la phase chronique après une LME, un résultat encourageant considérant que la neuroréadaptation est généralement débutée tardivement en clinique.

11 - Differential patterns of local field potential activity in premotor and motor cortices during ipsilateral vs. contralateral hand movements in macaque monkeys

Ali Falaki[1], Hugo Delivet-Mongrain[1], Stephan Quessy[1], Numa Dancause[1]
[1]Département de neurosciences, Université de Montréal

In primates, each of the primary motor cortex (M1) and the ventral and dorsal premotor cortices (PMv and PMd, respectively) contributes to unique aspects of motor planning and execution. Although, several studies have used local field potentials (LFPs) to decode the activity of M1, PMv and PMd during contralateral hand movement, no study has compared the activity of these areas using simultaneously recorded LFP data. Our objective was to compare the pattern of neural activity in M1, PMv and PMd at different stages of ipsilateral and contralateral hand movements using LFPs.

Two monkeys were trained to reach a force sensor and pressed it using precision grips. LFPs were recorded simultaneously from PMv and PMd in both hemispheres and left M1 using implanted microelectrode arrays. We calculated amplitude modulations, around each behavioral event, in delta, theta & alpha, beta, and gamma rhythms for each brain area during ipsilateral and contralateral hand movements. Behavioral events included the time when monkeys received a visual cue about the upcoming trial, were allowed to initiate reach, started grasping, and applied the maximal force.

Pronounced differences were observed in the activity of M1, PMd, and PMv. Most strikingly, in comparison to PMv and PMd, M1 exhibited more increased delta and theta power during the reach and early grasp, which was more prominent for ipsilateral hand movements. While we observed increased delta activity in PMd at Grasping and mostly for contralateral hand movements, PMv showed remarkably increased delta power at this epoch mainly for ipsilateral hand movements.

Results suggest different synaptic inputs to these areas depending on the hand and phase of movement. These differences likely support distinct functions each area undertakes for the control of ipsilateral vs. contralateral hand movements that might be used to guide developing more effective neuromodulatory protocols.

12 - A Computational Model for the Distributed Brain Circuits of Deciding Between Reaching Actions

Poune Mirzazadeh[1], Paul Cisek[2], David Thura[3]
[1]University of Montreal, [2]Université de Montréal, [3]Lyon Neuroscience Research Center

Classical decision-making theories consider the deliberation process separated from action planning. However, neural data strongly suggests that decisions unfold within the same distributed brain circuits implicated in sensorimotor processes and action planning. This makes sense from an evolutionary perspective, where the most fundamental decisions are between actions currently possible in the world, such as running left or right to escape a predator. In such scenarios, deliberation and action planning must take place in parallel, calling for theories that provide a unified view of these processes.

Our studies have yielded a rich data set from both cortical regions and interconnected nuclei in the basal ganglia, suggesting a hypothesis on how deliberation and commitment occur in decision-making between multiple reaching actions. In brief, we suggest that sensory information (from the prefrontal cortex) is combined with a context-dependent signal related to the rising urgency to decide (from the basal ganglia) to bias a competition unfolding in the dorsal premotor and primary motor cortex. Once a critical contrast between a “winning” and “losing” action is achieved in the cortex, a positive feedback occurs through the basal ganglia, producing a “winner-take-all” process that is the neural equivalent of volitional commitment.

Here we describe a computational model of this process, expressed in the language of dynamical systems. We show how potential reaching actions can be simultaneously encoded in the parietal and premotor cortex, and how sensorimotor regions integrate all decision factors that influence potential actions and bias the competition between them.

13 - Variant analysis of disease-causing genes and risk factor genes in patients with Parkinson's Disease

Lovatiana Andriamboavonjy[1], Marjorie Labrecque[1], Sébastien Audet[1], Valérie Triassi[1], Camille Michaud[1], Michel Panisset[2], Martine Tétreault[1]
[1]CRCHUM, [2]CHUM

Although extensively studied, the complex interaction of environmental and genetic components that drive Parkinson's disease (PD) development is still poorly understood. Only 30% of familial and 3-5% of sporadic cases can be explained by genetic mutations. While over a hundred risk factor loci have been described as PD development contributors, no accurate disease predictor markers exist. Hence, studying the interaction of PD gene polymorphisms could help better understand the molecular pathways involved in the progression of the pathology.

We conducted the whole-exome sequencing (WES) on the DNA extracted from peripheral blood mononuclear cells in 13 parkinsonian patients, who did not have access to genetic screening prior to their recruitment.

Our approach led to the identification of at least one variant in PD-related genes in all 13 patients; six single-nucleotide variants (SNV) in disease-causing genes 54 in risk factor loci. A gene clustering analysis identified significant enrichment of mutations linked to pathways such as transcription regulation.

We also identified homozygous variants of interest in our population, which can potentially be Parkinson-related and need further experiments for validation.

While the results are still preliminary, it should be interesting to validate the implication of the VUS in the pathogenesis of these patients. Another main takeaway from our findings is the apparent clustering of variants that may affect transcription regulation. Therefore, future transcriptomic sequencing may further our understanding regarding how VUS in risk factor genes could directly affect disease progression through the regulation of gene expression.

14 - Identification of novel biomarkers on transcriptome and proteome profile of Parkinson's Disease Patients

Lovatiana Andriamboanovjy [1], Camille Michaud[1], Diana Matheoud[1], Michel Panisset[1], Martine Tetreault [1], Saiyet Baez[1]
[1]Universite de Montreal

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1-2% of the population over 65 years of age. PD is characterized by a complex of symptoms caused by a preferential and massive loss of dopaminergic neurons (DN) in the *substantia nigra*. The lack of predictive and diagnostic biomarkers can lead to misdiagnosis in the critical early phases of the disease. Even though the exact causes of DN loss in the *substantia nigra* of PD patients are unclear, several lines of evidence support the involvement of autoimmune mechanisms in the etiology of PD. Our central hypothesis is that PD can impact the inflammatory/immune response of patients, which in turn can be reflected as change in their transcriptomic and proteomic expression profile. Our objectives are i) to determine the immune profile of antigen-presenting cells from PD patients; ii) to assess if an inflammatory/immune signature is present in blood or serum of PD patients and thus, serve as a disease biomarker. We will perform RNA-sequencing to determine which genes are differentially expressed, and proteomic assays (Olink's immune panels) to define inflammatory and immune signatures at the protein levels. Using a system biology approach, transcriptomic and proteomic data will be integrated to define multi-omic signatures associated with the disease, and if the identified signatures can discriminate between PD and atypical PD subtypes. We expect to identify potential biomarkers that could easily be implemented in a clinical setting and contribute to the early diagnosis of PD and atypical PD patients.

15 - Génération et caractérisation d'une lignée de poissons-zèbres dont le gène C9orf72 a été invalidé par CRISPR-Cas9 afin de modéliser la sclérose latérale amyotrophique.

Alexandre Emond[1, 2], Carl Laflamme[3], Alex Parker[1, 2]
[1]CRCHUM, [2]Université de Montréal, [3]Université McGill

Des répétitions GGGGCC dans le premier intron du gène C9orf72 (C9) sont une cause prépondérante de la sclérose latérale amyotrophique (SLA). C9 est un gène hautement conservé évolutivement dont les fonctions demeurent incertaines. Des modèles knockout (KO) de C9 chez le C. elegans et de knockdown chez le poisson-zèbre présentent des phénotypes associés à la SLA. Ceux-ci incluent entre autres : une diminution de l'activité motrice, une perturbation de l'organisation des motoneurones, des difformités morphologiques importantes et une mortalité accrue. Nous cherchons alors à générer et caractériser le premier modèle KO stable de C9 chez le poisson-zèbre.

Le KO a été généré par CRISPR/Cas9 puis confirmé par séquençage et western blot. La caractérisation initiale du modèle se fait notamment par des tests d'activité de nage autonome et une observation de la morphologie ainsi que l'organisation des motoneurones par croisement avec une lignée dont les motoneurones expriment GFP. La mortalité ainsi que la taille/morphologie des spécimens ainsi que leur susceptibilité à divers stress (chaleur et immunitaire) sont aussi évaluées.

Nos spécimens C9KO démontrent jusqu'à présent au stade larvaire des déficits moteurs, une mortalité accrue, une absence de difformité morphologique évidente et une réduction de leur croissance.

Des expériences de caractérisations additionnelles sont envisagées, dont aux niveaux de processus dans lesquelles C9 est proposé d'être impliqué (métabolisme, réponse immunitaire, etc.) et l'évaluation de l'intégrité de la jonction neuromusculaire. Ce modèle de KO stable de C9 sera un nouvel outil puissant pour approfondir nos connaissances sur l'expression et la fonction de C9 en plus de modéliser sa perte de fonction/haploinsuffisance observée chez les patients atteints de SLA qui sont porteur des répétitions GGGGCC. Si notre modèle présente un ou plusieurs phénotypes robustes associés à la SLA, notamment une dysfonction motrice, il pourra alors servir au criblage de médicaments pour son traitement.

16 - Impact sur la fonction musculaire d'une mutation homozygote non-sens dans MLIP

Alexie Gagné[1, 2], Jean Mezreani[1, 2], Sébastien Audet[1, 2], Adrien Rihoux[1, 2], Erin O'Ferrall[3, 4], Martine Tétreault[1, 2]
[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Canada, [2]Département de Neurosciences, Faculté de Médecine, Université de Montréal, Montréal, Canada, [3]McGill University Health Centre, Montréal, Canada, [4]Rare Neurological Disease Research Group, Université McGill, Montréal, Canada

Malgré l'avancement des technologies de séquençage, plusieurs maladies neuromusculaires héréditaires restent sans diagnostic moléculaire. Ainsi, nous sommes incapables d'interpréter les variants de 25 à 30% des patients atteints de myopathie. Pour mettre en œuvre une méthode de diagnostic plus efficace afin d'améliorer le taux de diagnostic et de déterminer plus précisément l'impact fonctionnel des variants, certains laboratoires, dont le nôtre, ont combiné le séquençage de l'ADN et de l'ARN. En utilisant cette approche, nous avons identifié un variant homozygote non-sens dans l'exon 5 de MLIP (Muscular LMNA-interacting protein) chez un patient atteint de myopathie distale adulte et présentant un phénotype plus tardif et moins sévère que les cas précédemment décrits. Nous avons également démontré une diminution de l'expression de certains transcrits de MLIP et une augmentation de l'expression du LMNA (lamin A/C), un interacteur connu de MLIP et une cause importante de maladies musculaires. Outre l'interaction avec LMNA, la fonction exacte de MLIP est encore largement inconnue. Cependant, la littérature indique un rôle dans la régulation de certains activateurs transcriptionnels, tels que Akt/mTOR/FOXO1. Pour approfondir l'étude du rôle de MLIP dans des contextes pathologique et physiologique, nous établirons un modèle cellulaire à l'aide de CRISPR/cas 9 sur les myoblastes. Ce modèle cellulaire est un outil essentiel pour étudier l'impact des variants MLIP sur la prolifération cellulaire, la différenciation et la localisation cellulaire de MLIP et de son partenaire LMNA. Nos résultats contribueront non seulement à améliorer le diagnostic moléculaire des patients atteints de myopathie, mais aussi à améliorer notre compréhension sur la fonction de MLIP dans les muscles.

17 - Investigation du rôle de nouveaux variants du gène ITPR1 dans les ataxies tardives

Nab Legault-Cadieux[1], Sébastien Audet[1], Marjorie Labrecque[1], Valérie Triassi[1], Jean Mezreani[1], Lovatiana Andriamboavonjy[1], Annie Laplante[1], Eric Bareke[1], Adrien Rihoux[1], Alexie Gagné[1], Saiyet De La Caridad Baez Llovio[1], Laura Hamilton[1], Martine Tétreault[1]
[1]CRCHUM

L'identification des causes génétiques de nombreuses pathologies pose un défi de taille pour la communauté scientifique. Ceci est particulièrement vrai pour les maladies présentant une grande hétérogénéité étiologique et phénotypique, comme les ataxies, des maladies neurodégénératives habituellement causées par une dégénérescence du cervelet et qui affectent la coordination motrice.

Notre hypothèse est qu'une démarche alliant des approches de génétique moléculaire (génomique, transcriptomique) et de génomique fonctionnelle (modèles cellulaires) permettrait de déceler les causes sous-tendant les phénotypes ataxiques chez les patients pour qui les analyses traditionnelles (séquençage d'exome ou panel) n'ont pas abouti à un diagnostic moléculaire. En effet, certaines limitations réduisent l'efficacité de ces méthodes, telles que l'interprétation de la pathogénicité de variants qui n'ont pas encore été reportés dans la littérature et la limitation des résultats à une liste de gènes prédéterminés (panel) ou à la région codante (exome).

Nous investiguons actuellement trois nouveaux variants du gène ITPR1 découverts par analyse WGS chez des patients cliniquement ataxiques. Il s'agit d'un variant faux-sens, d'un variant d'épissage et d'un variant synonyme dont les prédictions in silico prédisent un épissage alternatif. En l'absence d'évidence supportant un impact délétère de ces variants, une validation fonctionnelle est nécessaire. Celle-ci passera par la détermination de leur impact sur l'expression transcriptomique (qRT-PCR) et protéique (WB) ainsi que sur la fonction de relâche calcique du récepteur ITPR1, via des modèles cellulaires modifiés par Crispr-Cas9.

Une approche efficace pour la caractérisation des causes génétiques est essentielle puisque l'étiologie génétique est à la base de notre compréhension des mécanismes moléculaires de ces maladies rares, et pourrait ultimement s'inscrire dans la recherche de stratégies thérapeutiques.

18 - Congenital myopathy caused by a muscle-allelic imbalance in IARS1

Adrien Rihoux[1, 2], Jennifer Hauteclocque[1, 2], Alexie Gagné[1, 2], Stefan Nicolau[2], Audrey Labarre[1, 2], Sarah Duhaime[1], Ericka Guitard[1, 2], J. Alex Parker[1, 2], Bernard Brais[3, 4], Martine Tetreault[1, 2]
[1]Centre de recherche du centre hospitalier de l'Université de Montréal (CRCHUM), Montréal, Québec. Canada, [2]Département de Neurosciences, Faculté de médecine, Université de Montréal, Montréal, Québec, Canada, [3]Rare Neurological Diseases Group, Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, [4]Department of Human Genetics, Montreal Neurological Institute, McGill University, Montreal

It is estimated that 25% of patients with myopathies and muscular dystrophies are without molecular diagnosis, despite several clinical and genetic investigations. Several reasons explain this phenomenon: 1) focus on the study of DNA, which does not allow the identification of intronic-regulatory variants or alternative splicing events; 2) the inability to determine functional impact by studying DNA alone; 3) high frequency of variants of unknown significance during diagnostic testing. Using a combination of omic approaches with functional genomics can overcome these difficulties. Using this approach, we have identified, in patients with congenital myopathy, a muscle-specific allelic imbalance in the IARS1 gene encoding isoleucyl-tRNA synthetase, an enzyme catalyzing the aminoacylation of tRNAs. Patients in our study exhibit only a muscle-level phenotype which is supported by muscle-specific allelic imbalance. This allelic imbalance may be the result of an intronic regulatory variant affecting expression and/or DNA methylation. We therefore sequenced the genome and identified an intronic variant located near a methylated region. Decreased expression of iars-1 in a C. elegans model demonstrated significant muscle fiber disorganization. In order to further our study of the pathological mechanisms associated with IARS1 haploinsufficiency in muscle, we are working to establish primary or genetically edited cellular models. We have established the first association of IARS1 with a myopathic phenotype. These results not only make it possible to establish a molecular diagnosis for this family but also make it possible to characterize a new pathological mechanism involving an epimutation and better understand the role of IARS1 in the muscle.

19 - Comparison of the ability of the pathogen-associated molecular patterns LPS and Poly(I:C) to trigger Parkinson's disease-like pathology in Parkin KO mice

Amandine EVEN[1, 2], Sriparna MUKHERJEE[1, 2], Alex TCHUNG[1, 2], Soraya PAQUEREAU--GABOREAU[1, 2], Marie-Josée BOURQUE[1, 2], Louis-Eric TRUDEAU[1, 2, 3]
[1]Department of pharmacology and physiology, Faculty of medicine, Université de Montréal, [2]SNC and CIRCA research groups, [3]Department of neurosciences, Faculty of medicine, Université de Montréal

The main motor symptoms of Parkinson's disease (PD) are caused by the loss of dopamine (DA) neurons of the substantia nigra. Although growing evidence links inflammation to the onset of the disease, the underlying mechanisms are unclear. An early onset form of PD is associated with mutations of Pink1 or Parkin, proteins involved in regulating mitophagy and repressing the presentation of mitochondrial antigens to the immune system. We have begun to test the hypothesis that repeated exposure to pathogen-associated molecular patterns such as lipopolysaccharide (LPS) or Poly(I:C) mimicking bacterial or viral inflammations, lead to early and exacerbated pathogenesis in Parkin KO mice.

Parkin$^{-/-}$ or WT littermate mice were injected 4 times at 1-week interval with either LPS (1-3mg/kg), Poly(I:C) (20mg/kg), or an alternation of both. Levels of cytokines were measured using a multiplex assay in blood serum 1 or 2 days after a single injection. Behavioral profiling was performed 3 months after the last injection.

Our first results show that LPS-induced and Poly(I:C)-induced elevation of serum IL-6 levels are higher in Parkin$^{-/-}$ mice. We also observe higher microglial activation in the brain of Parkin$^{-/-}$ mice treated with chronic LPS compared to WT. Initial behavioral profiling suggest that at 3 months after the end of the Poly(I:C) treatment, motor impairments can be detected in Parkin$^{-/-}$ but not WT mice nor in saline-treated mice. We are now extending these results in larger cohorts of animals. We are also evaluating the integrity of the dopamine system in these mice and examining the physiological properties of microglia including their phagocytic capacity. Our results support the hypothesis that loss of function of Parkin exacerbates inflammatory responses and microglial activation induced by pathogens.

20 - Developing precision medicine models for Epilepsy using zebrafish

AVEEVA HEROLD[1, 2], Katarzyna Ochenkowska[1, 2], Uday Kundap[1, 2], Meijiang liao[1, 2], Éric Samarut[1, 2]

[1]CRCHUM, [2]University of Montreal

Epilepsy is a widespread neurological disorder characterized by recurrent seizures that affect more than 50 million individuals worldwide. Although more than 30 anti-epileptic drugs (AEDs) are available, treatment response is often unpredictable. There is no “one-size-fits-all” approach applicable to the medical treatment of epilepsy patients. There is a need to better understand the genotype-phenotype-treatment responsiveness correlations to tailor the anti-epileptic medication. In this project, we aim at establishing a proof of concept to generate a patient-specific zebrafish genetic avatar (one patient = one genetic variant = one genetic zebrafish avatar) to test the effect of all available anti-seizure medicines and to identify the best medical treatment for each patient.

We will use a Cre-Lox transgenic approach to introduce specific LoxP sites (Lox71 or both LoxP-Lox2272) within the 5’UTR of the endogenous zebrafish *gabra1* gene (an epilepsy-causing gene) that allows stable and irreversible recombination events (with Lox66 or LoxP-Lox2272 sites). Using CRISPR/CAS9, we will generate stable transgenic zebrafish lines carrying Lox71 and LoxP-Lox2272 sites at the 5’UTR of the zebrafish gabra1 gene. Once these lines are established, we will recombine the Lox71 and LoxP-Lox2272 sites with a cDNA encoding GFP (as a negative control), a WT gabra1 cDNA (as a positive control) or a mutant cDNA encoding the precise GABRA1 variant of a particular epileptic patient. Further, we will perform behavioural studies and a light-induced seizure assay to assess the capacity of each AED to alleviate the seizure phenotype. Finally, these models can identify which AED is the most suitable (precision medicine).

21 - Le traitement médical et chirurgical de l'épilepsie chez les vieux adultes : un sondage national

Timothé Langlois-Therien[1], Nafisa Husein[2], Bastien Rioux[2], Colin Josephson[3], Nathalie Jette[3], Mark Keezer[2]
[1]Université d'Ottawa, [2]Université de Montréal, [3]Université de Calgary

Objectif :
Il n'existe aucune ligne directrice spécifique au traitement de l'épilepsie chez les vieux adultes (i.e., de plus de 65 ans). Nous avons sondé l'opinion d'un groupe de médecins canadiens sur leur pratique clinique du traitement de l'épilepsie dans cette population. Nous étions intéressés à voir quelles différences existaient entre les gériatres, les neurologues généralistes et les épileptologues.

Méthode :
Nous avons disséminé notre sondage à travers deux rondes de télécopieur et un envoie par poste conventionnelle à tous les individus éligibles listés dans un répertoire national de médecins canadiens. Nous avons utilisé des statistiques descriptives telles que des tableaux et des histogrammes afin d'illustrer nos résultats.

Résultats :
Cent-quarante-quatre médecins (104 neurologues généralistes, 25 gériatres, et 15 épileptologues) ont répondu à notre sondage (taux de réponse global de 13.2%). Levetiracetam et lamotrigine furent les médicaments antiépileptiques privilégiés pour traiter les vieux adultes avec l'épilepsie. Deux-tiers des épileptologues et près de la moitié des neurologues considéreraient prescrire lacosamide à plus de 50% des personnes de plus de 65 ans; un seul gériatre partageait la même opinion. Plus de 40% des neurologues généralistes et des gériatres croyaient de façon erronée qu'aucun des médicaments antiépileptiques mentionnés dans notre sondage avaient été préalablement étudiés dans des études contrôlées randomisées spécifiques aux traitements de l'épilepsie chez les vieux adultes. Les épileptologues étaient plus ouverts à recommander un traitement chirurgical pour l'épilepsie que les neurologues généralistes ou les gériatres (e.g., 66.6% versus 22.9 à 37.5% chez les vieux adultes).

Conclusion :
Les décisions thérapeutiques chez les vieux adultes avec l'épilepsie varient entre les différents groupes de médecins et parfois dérogent des preuves cliniques disponibles. Les médecins sondés diffèrent dans leur choix de médicaments antiépileptiques ainsi que dans leur perception de la chirurgie pour cette population. Ces résultats pourraient refléter le manque de lignes directrices dédiées à cette population.

22 - Methionine intake modulates neuroinflammatory and neurodegenerative processes in murine models of multiple sclerosis

Victoria Mamane[1], Florence Millette[1], Corentin Richard[1], Olivier Tastet[1], Audrey Daigneault[1], Renaud Balthazard[1], Wendy Klement[1], Clara Margarido[1], Helene Jamann[1], Oumarou Ouedraogo[1], Bertrand Routy[1], Russell Jones[2], Catherine Larochelle[1]
[1]Université de Montréal / Centre de recherche du CHUM, Montréal, Canada, [2]Van Andel Institute, Grand Rapids, United States

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). Dietary methionine restriction (MR) displays anti-inflammatory properties and improves metabolic health through sexually dimorphic mechanisms. We found that methionine pathway is induced upon T cell activation and MR affects the effector function and proliferation of TH17 cells, considered pathogenic in MS and its animal model, experimental autoimmune encephalomyelitis (EAE). Our objective is to study manipulation of T cell methionine metabolism as a new therapeutic avenue for controlling neuroinflammatory diseases such as MS in both sexes. We immunized C57BL/6 mice exposed to MR vs. control diet with MOG35-55 and used transgenic TCR1640 mice exposed to MR vs. control or methionine supplemented (M+) diet to test the impact of methionine intake on clinical course and immune cell distribution and activation. We measured serum neurofilament light chain (sNfL) levels to evaluate neuroaxonal injury. We found that MR delays onset of MOG-induced EAE and this is paralleled by lower numbers of pro-inflammatory immune cells in the spleen at presymptomatic stage, in the spleen and CNS at pre-onset stage and in the CNS at peak stage. Moreover, MR delays onset of spontaneous EAE in TCR1640 mice, with a near complete abrogation in males. This is associated with lower numbers of pro-inflammatory immune cells in the spleen and CNS at presymptomatic and chronic stages. In addition, the elevation of sNfL observed at peak of induced EAE is reduced in both sexes exposed to MR, with a more pronounced impact on females. Similarly, we found reduced levels of sNfL as well in males and females exposed to MR during chronic phase of spontaneous EAE, while M+ diet is associated with increased sNfL levels in females. In conclusion, MR ameliorates EAE clinical course and limits neuroinflammatory processes and neuroaxonal injury in two MS preclinical models.

23 - L'optimisation de l'efficacité mitochondriale à la rescousse des neurones dopaminergiques dans la maladie de Parkinson

Alex Tchung[1, 2], Nicolas Giguère[1, 2], Marie-Josée Bourque[2, 3], Louis-Éric Trudeau[1, 2, 4]
[1]Département de pharmacologie et physiologie, Faculté de médecine, Université de Montréal, [2]Groupe de recherche SNC, [3]Départements de pharmacologie et physiologie, Faculté de médecine, Université de Montréal, [4]Département de neurosciences, Faculté de médecine, Université de Montréal

La maladie de Parkinson (MP) se caractérise par une perte massive des neurones dopaminergiques (DA) dans la substance noire compacte (SNc). La vulnérabilité sélective de ces neurones semble être déterminée par leur très grand axone et leurs besoins énergiques comblés principalement par la phosphorylation oxydative (OXPHOS) mitochondriale. Cette voie étant connue pour produire des réactifs dérivés de l'oxygène (DRO), le stress oxydatif s'ensuivant pourrait être un déterminant de leur vulnérabilité. Notre hypothèse est que des approches réduisant le ratio DRO : ATP, par exemple en augmentant l'efficacité mitochondriale, devraient améliorer la résilience des neurones DA. Afin d'atteindre cet objectif, il est nécessaire de confirmer que la mort cellulaire est causée par les ROS. Par la suite, nous quantifierons la production d'ATP et de DRO à l'aide de sondes encodées génétiquement (ATeam, PercevalHR, mito-roGFP) afin d'évaluer le ratio DRO : ATP. Nous nous attendons à observer un ratio plus grand dans la SNc que dans des neurones DA moins vulnérables, tels que ceux de l'aire tegmentaire ventrale (ATV). Nos résultats indiquent que l'action d'antioxydants augmente la survie des neurones DA, mais uniquement contre certains modèles de vulnérabilité cellulaire, dont celui de la 6-OHDA. À l'avenir, nous nous intéresserons aussi à la défense antioxydante intrinsèque en quantifiant le niveau d'ARNm et l'expression de protéines antioxydantes pour mieux comprendre les mécanismes qui prédisposent les neurones DA de la SNc à être plus vulnérables au stress oxydatif. Par la suite, nous testerons l'hypothèse qu'il existe une relation positive entre la fonction mitochondriale et l'activité électrique et sécrétoire qui seront mesurées à l'aide des senseurs fluorescents GCaMP et synapto-pHluorin. Pour finir, nous partirons à la découverte de petites molécules ou protéines pouvant positivement moduler les paramètres précédemment mentionnés afin d'améliorer la résilience des neurones DA et ouvrir la voie à de nouvelles pistes de traitement de la MP.

24 - Le mystère derrière le développement de l'arborisation axonale des neurones dopamimergiques

Raphaëlle Denis[1, 2, 3], Samuel Burke[1, 2, 3], Alex Tchung[1, 2, 4], Marie-Josée Bourque[1, 2, 4], Nicolas Giguère[1, 2, 4], Louis-Éric Trudeau[1, 2, 3, 4]
[1]Groupe SNC, [2]CIRCA, [3]Département de neurosciences, Faculté de médecine, Université de Montréal, [4]Département de pharmacologie et physiologie, Faculté de médecine, Université de Montréal

Les neurones dopaminergiques (DA) de la substance noire compacte (SNc) et de l'aire tegmentaire ventrale (VTA) sont connus pour leur arborisation axonale très développée et leur nombre de terminaisons axonales plus élevé que la plupart des autres neurones. Les mécanismes moléculaires qui sous-tendent le développement de ces caractéristiques morphologiques des neurones DA sont cependant inconnus. L'objectif principal est de mieux comprendre le développement de l'arborisation des neurones DA de souris ainsi que les mécanismes impliqués. L'hypothèse est que les neurones DA développent une arborisation exceptionnellement développée, parce que la cinétique de croissance et de formation de branches de leur axone est plus rapide comparée à d'autres neurones. Une approche de vidéo-microscopie et l'utilisation de souris transgéniques exprimant la protéine fluorescente rouge TdTomato dans les neurones DA ou dans des neurones glutamatergiques du thalamus seront utilisées pour visualiser cette croissance de façon quantitative. Les résultats jusqu'à maintenant ne démontrent pas de différence importante dans la taille de l'arborisation et la vitesse de croissance à 0 DIV des neurones DA de la SNc en comparaison avec ceux de la VTA ainsi que les neurones glutamatergiques du thalamus. Pour terminer cette partie du projet, nous évaluerons la croissance à 3 et 7 DIV dans les différents groupes de neurones pour les comparer. Par la suite, des sondes seront exprimées à l'aide d'AAV pour examiner les terminaisons axonales établies par les neurones DA et de visualiser les emplacements stratégiques des mitochondries durant la croissance. Ce projet permettra de mieux comprendre le développement des neurones DA, leur cinétique de croissance ainsi que leur vulnérabilité dans la maladie de Parkinson.

25 - Effects of modulating the Trigeminal principal sensory nucleus on masticatory movements

Dominic Falardeau[1], Ohini Yanis Sanvi[1], Sophia Dubois[1], Arlette Kolta[1]
[1]Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage (CIRCA)

Chewing is produced by a central pattern generating circuitry which output is rhythmic. Previous work from the laboratory has identified a population of neurons in the dorsal part of the trigeminal principal sensory nucleus (NVsnpr) which firing pattern changes from tonic to rhythmic when the extracellular Ca^{2+} concentration decreases. The Ca^{2+} decrease acts by enhancing a sodium persistent current (I_{NaP}) that involves Nav1.6 channels and results from activation of astrocytes and subsequent release of S100b, an astrocytic Ca^{2+} binding protein. However, these findings were obtained in *in vitro* slice preparations. Therefore, the main objective of this project is to validate *in vivo* whether dorsal NVsnpr is sufficient and necessary to produce masticatory movements and whether astrocytes play an essential role in this process. We used transgenic mice expressing channelrhodopsine-2, under the control of neuronal promoters VGluT2 or Thy1 in which we can induce mastication by optogenetic stimulation of the cortical masticatory area (CMA) while pharmacologically or optogenetically manipulating the NVsnpr. Photostimulating the CMA (2.5 mm anterior to Bregma, 2.0 mm lateral to the midline and 0.75 mm in depth) induced rhythmic (7-9 Hz) mastication movements in most animals (12/16) that were tested awake using right unilateral 10-40 Hz stimulation (2.5 ms, pulse duration). In two animals, movements elicited by stimulation of the CMA were either transiently abolished or greatly reduced in amplitude and frequency after local injection of an I_{NaP} or an Nav1.6 channels blocker (Riluzole, 20 µM, unilateral injection; 4,9-anhydroTTX, 10µM, bilateral injection respectively) in dorsal NVsnpr. Further, bilateral, but not unilateral, optogenetic stimulation of NVsnpr at a frequency of 40 to 60 Hz induced masticatory movements (n=1). These preliminary data suggest that the NVsnpr is involved in the genesis of masticatory movements. Future experiments will involve manipulation of astrocytic networks in NVsnpr to assess their role.

26 - Trajectoires de rechute : impact des stimuli associés à la consommation de cocaïne sur l'abstinence chez le rat

Ndeye Aissatou NDIAYE[1], Sema ABU SHAMLEH[2], Sol'Abraham CASTANEDA OUELLET[1], Mike J. F. ROBINSON[2, 3], Anne-Noël SAMAHA[3, 4, 5]
[1]Département de Neurosciences, Université de Montréal, [2]Department of Psychology, Concordia University, [3]Département de Pharmacologie et Physiologie, Université de Montréal, [4]Groupe de recherche sur la signalisation neurale et la circuiterie (SNC), Université de Montréal, [5]Centre Interdisciplinaire de Recherche sur le Cerveau et l'Apprentissage, Université de Montréal

Dans l'addiction à la cocaïne, la rechute après abstinence est un obstacle au rétablissement. Les stimuli (objets, odeurs, sons) associés à la consommation provoquent l'envie de consommer, et la rechute. Ceci inclut les stimuli conditionnés (SCs) et les stimuli discriminatifs (SDs). Les SCs apparaissent simultanément avec les effets de la drogue et y deviennent associés (odeur de la cocaïne fumée). Les SDs quant à eux informent de la disponibilité (SD^+) ou non-disponibilité (SD^-) de la drogue. Une partenaire de consommation est un SD^+. Un collègue est un SD^-.

Ici nous avons comparé la rechute provoquée par un SC *vs*. SD. Des rats ont appuyé sur un levier pour des infusions de cocaïne (14 sessions). Des lumières signalaient la disponibilité (SD^+) ou non-disponibilité (SD^-) de la cocaïne. Une 3^e lumière (le SC, pendant 5 s) était présentée avec chaque infusion. Ensuite, nous avons comparé la rechute provoquée par ces stimuli. La rechute est indiquée lorsqu'un rat revient appuyer sur le levier après abstinence.

Après 1 et 20 jours d'abstinence, la présentation du SD^+ seul ou combiné au SC (mais pas le SC seul) a augmenté le comportement de rechute. Après 20 jours d'abstinence, les rats pouvaient appuyer sur le levier pour se faire présenter chaque stimuli. Ils ont autant appuyé pour obtenir le SD^+ seul, le SD^+ avec le SC^+ et le SC^+ seul. Tous ces stimuli avaient donc des effets de récompense comparables.

En conclusion, un SD^+ est un stimulus plus puissant pour induire la rechute compare à un SC, même si les deux ont une valeur récompensante équivalente. Ce travail informera les théories sur la rechute, les modèles animaux de rechute, et les cibles biologiques pour le traitement.

27 - Store-Operated Ca2+ Channels Mediate Microdomain Ca2+ Signals and Amplify Gq-Coupled Ca2+ Elevations in Capillary Pericytes

Braxton Phillips[1], Jenna Clark[1], Éric Martineau[1], Ravi Rungta[1]
[1]Université de Montréal

Pericytes are multifunctional cells of the vasculature that are vital to brain homeostasis, yet many of their fundamental physiological properties remain unexplored. Ca^{2+} is a ubiquitous second messenger across cell-types, where it mediates diverse functions such as contractility and gene transcription. It is therefore important to understand the cellular mechanisms underlying Ca^{2+} signalling in capillary pericytes. Here, we performed pharmacological and ion substitution experiments to investigate the mechanisms underlying pericyte Ca^{2+} signaling in acute cortical brain slices of PDGFRβ-GCaMP6f mice. We report that in mid-capillary bed pericytes (≥ 4^{th} branch order), spontaneous microdomain Ca^{2+} signals are dependent on extracellular Ca^{2+}, but largely independent of depolarization, L- and T-type voltage-gated calcium channels (VGCCs), and TRPC3/6 channels. In contrast, these microdomain signals were inhibited by multiple Orai channel blockers, including the specific antagonist GSK-7975A. Furthermore, capillary pericytes exhibited classical store-operated calcium entry (SOCE) following store depletion that was sensitive to GSK-7975A and required for amplification of intracellular Ca^{2+} increases evoked by the vasoconstrictor endothelin-1. These results suggest that Orai SOCE mediates microdomain Ca^{2+} signals at rest and amplifies Gq-GPCR coupled Ca^{2+} elevations in capillary pericytes. Thus, SOCE is a major regulator of pericyte Ca^{2+} and a target for manipulating their function in health and disease.

28 - Évaluation de la réactivité astrocytaire au niveau du système trigéminal dans un modèle de myalgie orofaciale chronique

Dar'ya Sas[1], Arlette Kolta[2], Fanny Gaudel[1], Dorly Verdier[1]
[1]Université de Montréal, [2]Faculté de Médecine

Les conditions de douleur chronique s'avèrent être la plus grande cause d'invalidité, la douleur musculo-squelettique étant la plus commune. Par contre, à ce jour, les mécanismes moléculaires sous-jacents à la douleur chronique sont peu connus, les traitements sont peu efficaces et les coûts du secteur de santé sont alarmants. Les syndromes de douleurs sont souvent associés aux afférentes sensorielles primâtes de petit calibre. Cela dit, plusieurs études supportent l'implication des afférentes sensorielles primaires de gros calibre. Des études antérieures du laboratoire utilisant un modèle de douleur chronique au niveau oro-facial démontrent une augmentation de longue durée de l'excitabilité des afférentes des fuseaux neuro musculaires qui est dépendante d''un courant sodique persistant. Parmi plusieurs études sur la douleur chronique indiquant une implication astrocytaire, une étude du laboratoire démontre une modulation astrocytaire de l'excitabilité neurone par la libération d'un chêlateur de calcium. L'objectif principal de ce projet est de déterminer si les astrocytes causent l'hyperexcitabilité mentionné ci-haut. Cela est étudié dans un modèle de myalgie chronique au niveau du système trigéminal et des afférentes sensorielles primaires de gros calibre. Cette étude aidera à la compréhension des mécanismes impliqués dans le développement de la myalgie chronique et pourrait mener à l'identification d'une approche thérapeutique potentiellement intéréssante.

29 - Spatial analysis of interneuron activity during neurovascular coupling

Laurianne Zana[1, 2], Eric Martineau[1, 3], Isabel Laplante[1, 3], Jean-Claude Lacaille[1], Richard Robitaille[1], Ravi L. Rungta[2]
[1]Department of Neurosciences, University of Montreal, QC, Canada, [2]Department of Stomatology, University of Montreal, QC, Canada, [3]Department of Pharmacology and Physiology, University of Montreal, QC, Canada

Brain activity triggers increases in local energy supply by sending signals to blood vessels that increase blood flow in activated regions of the cortex. This process, known as neurovascular coupling, is used to map human brain activity in health and disease. However, mounting evidence suggests that inhibitory interneurons can also modulate blood flow by releasing vasoactive compounds such as nitric oxide, raising the question of how different interneuron subtypes interact and control blood flow during sensory processing. Here, we perform optical imaging in mice expressing the calcium indicator GCaMP6f, in either somatostatin or parvalbumin-expressing interneurons. Using a single whisker stimulation model, we measure the spatial tuning of these different inhibitory neuron subtypes across the barrel cortex in relation to changes in blood volume and compare them to excitatory neuronal activity. This work sheds light on the intricate relationship between cell-type specific activity and blood flow control in the healthy brain and is important for interpretation of non-invasive hemodynamic imaging signal, such as BOLD fMRI.