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CONFERENCE PROCEEDINGS

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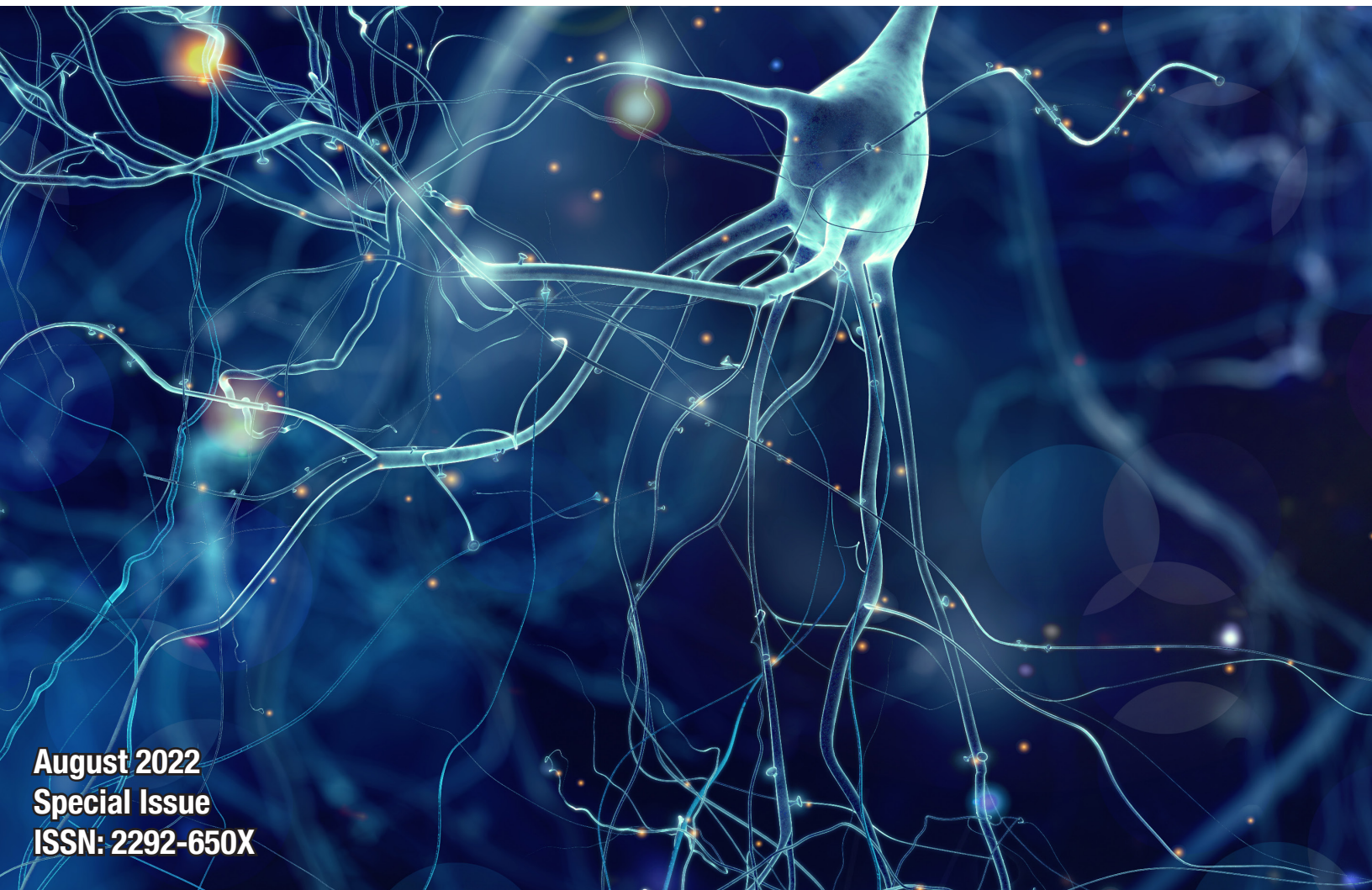
Faculty of Social Sciences

BRAIN HEALTH RESEARCH DAY 2022

Institut de recherche Bruyère Research Institute · CHEO · Montfort · The Ottawa Hospital | L'Hôpital d'Ottawa · The Royal's Institute of Mental Health Research affiliated with the University of Ottawa · Carleton University



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BRAIN HEALTH RESEARCH DAY 2022

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UOJM: PREFACE

The University of Ottawa Brain and Mind Research Institute (uOBMRI) hosted its annual Brain Health Research Day on Friday, June 3, 2022. This year's conference was proudly co-hosted with the University of Ottawa, Faculty of Social Sciences with the theme of Mental Health and Comorbidity at the forefront. This research day marked the institute's first in-person event since 2019 before the onset of the global pandemic and we're proud to welcome back 170 registrants safely onsite. A special thank you to those who participated in making this research day a continued success since its inception in 2009.

The research day began with welcoming remarks from Dean Victoria Barham at the Faculty of Social Sciences, and the uOBMRI Director, Dr. Ruth Slack. The participants received a dynamic talk from our keynote speaker, Dr. Roger McIntyre, Professor of Psychiatry and Pharmacology at the University of Toronto, and Head of the Mood Disorders Psychopharmacology Unit at the University Health Network provided the keynote address. His lecture focused on comorbidity in psychiatry with a concentration on public health, clinical and research implications that led into the local talks from leading experts in mental health research in the Ottawa area.

Trainees from undergraduate, to post-doctoral and clinical fellows within the Ottawa area, shared three oral presentations and 73 poster presentations. Each exhibition emphasising the research excellence that is taking place at the University of Ottawa and Carleton University, specifically.

We wish to congratulate the following award recipients at this year's event:

NAME	AWARD
Meggan Porteus	Oral Trainee Exposé Award
Allison Loan	Oral Trainee Exposé Award
Nikita Koziel Ly	Oral Trainee Exposé Award
Amélie Gauthier-Beaupré	Postdoctoral Fellow/Research Associate Poster Award
Bianca Bono	Masters Poster Award – Basic Research
Sara Siddiqi	Masters Poster Award – Clinical Research
Éloïse Giraud	PhD Poster Award – Basic Research
Angela Boland	PhD Poster Award – Clinical Research
Mikaela Ethier-Gagnon	Undergraduate Poster Award

Please enjoy this special issue of the University of Ottawa Journal of Medicine, celebrating the collaborative efforts taking place at the uOBMRI and its partnering institutions. We hope that you find this special issue as impactful as the day's events and look forward to sharing with you.

Sincerely,

Nafissa Ismail, PhD, Co-Chair, BHRD Planning Committee

Jennifer Phillips, PhD, Co-Chair, BHRD Planning Committee

BHRD Planning & Trainee Committees

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Influence of gut microbial dysbiosis on acute immune responsivity in pubertal male and female CD-1 mice

M Gandelman[1], P Esposito[2], J Liang[3], N Ismail[3]

[1]Department of Cellular Molecular Medicine, University of Ottawa
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ABSTRACT

The relationship between the gut microbiota and the host plays an integral role in biological homeostasis. Microbial dysbiosis during critical periods of development, including puberty, disrupts brain function and immune responsivity. Furthermore, microbial dysbiosis contributes to various pathologies such as inflammatory bowel disease, irritable bowel syndrome and coeliac disease. Currently, the mechanisms underlying the effects of gut dysbiosis on immune responsivity are poorly characterized. Therefore, the objective of this study was to further elucidate the impact of pubertal microbial dysbiosis (induced by antimicrobial consumption) on acute lipopolysaccharide (LPS)-induced immune response in male and female mice. At five weeks of age, male and female CD-1 mice were treated with a combination of antimicrobial agents or water, twice a day for seven days. At six weeks of age, the mice received an intraperitoneal injection of LPS or saline, and were euthanized 8 hours later. Following euthanasia, blood samples were collected for plasma extraction and analysis with multiplex bead-based Luminex immunoassay. Plasma concentrations of cytokines granulocyte-macrophage-colony-stimulating-factor (GM-CSF), interleukin-2 (IL-2), interleukin-23 (IL-23), interleukin-12p70 (IL-12p70), interleukin-17A (IL-17A), and interleukin-10 (IL-10) were analyzed. Results revealed that antimicrobial treatment increased LPS-induced plasma cytokine concentrations in a sex-dependent manner. Specifically, male mice displayed greater pro-inflammatory cytokine concentrations, while female mice exhibited increased anti-inflammatory cytokines. These findings show important modulatory effects of antimicrobial-induced gut dysbiosis on immune responsivity, demonstrating that microscopic alterations to the gut composition during puberty may have macro-level effects on brain development and function.

Characterization of amygdala neurons activated by sleep deprivation

N Koziel Ly[1], C Leu[2], RH Williams[2], MJ Chee[1]

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ABSTRACT

Background: Chronic sleep deprivation (SD) is associated with worsened health outcomes, including increased risk for mental health disorders. The amygdala supports emotional-processing and is activated by sleep loss, therefore it may link mood changes seen with SD. However, the spatial distribution and electrical properties of SD-activated amygdala cells are yet unresolved.

Methods: Male wildtype mice were sleep deprived or allowed to sleep undisturbed from ZT0 to ZT4 and were then sacrificed for histology or electrophysiological recordings. To map the distribution of amygdala cell activation, we quantified the number of c-fos immunoreactive cells in the amygdala and parcellated amygdala subregions from dual c-fos-labelled and Nissl-stained coronal sections in control and SD mice. We then performed electrophysiological recordings in the basolateral (BLA) and central amygdala (CEA) from a separate set of mice to determine if changes in cell excitability or current-voltage relationships underlie neuronal activation after SD.

Results: SD robustly increased c-fos expression in select amygdalar nuclei, including the BLA and CEA, and this increase appeared anteroposteriorly. BLA cells from SD mice were more excitable compared to control, and CEA cells had reduced current flow after SD.

Limitations: WT cells selected for electrophysiological recordings may include cells those that were not SD-sensitive.

Conclusion: We defined novel populations of amygdalar cells with unique electrophysiological properties following SD. As an overactive amygdala may lead to the exaggeration of emotional cues and heightened anxiety or stress, preserving the cellular function of amygdala cells during SD may mitigate decision-making, mood disturbances, and overall health

Retrospective cohort study to examine disease progression in retinitis pigmentosa patients at the University of Ottawa Eye Institute

L Kandakji[1], M Dollin[2]; S Coupland[3]; C Gottlieb[2], M Lalonde[4]; C Tsilfidis[5]

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[4]University of Ottawa Eye Institute
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ABSTRACT

This is a retrospective chart review of patients with retinitis pigmentosa seen at the University of Ottawa Eye Institute. The purpose is to determine the rate and patterns of disease progression and use this information to help guide the timeline and determine eligibility criteria for a clinical trial aimed at examined gene therapy for the treatment of RP. To optimize our chances for detecting disease progression within a relatively short timeframe (2-3 years), we identified patients that have had multiple structural and functional tests over the past 10 years, have been followed on an annual or biannual basis, and have shown measurable declines in vision based on visual field (VF) testing, electroretinograms (ERG) and/or optical coherence tomography (OCT). We have examined the electronic medical records of 85 RP patients between January 2011 and May 2021. They range in age from 17-91 years and represent 36 men and 49 women. Of those, 11 have confirmatory genetic testing with varied inheritance patterns of RP. Ellipsoid zone measurements via OCT suggest disease progression over subsequent scans with an average of 7-8% loss per year. Mean deviation changes via automated VFs show progression in the range of -0.41 to -0.60 dB per year. Additional diagnostic tests are currently being examined to determine their efficacy in predicting disease progression and their correlation to the OCT data, including manual VFs and ERGs. This data will be combined to inform the protocol for a future gene therapy Phase I clinical trial for the treatment of RP.

Brain-wide projections from dopaminergic cells in the zona incerta

BS Bono[1], K Negishi[2], Y Dumiaty[1], M Ponce[2], TC Akinbode[1], E Mejia[2], KS Schumacker[1], DP Spencer[1], M Guirguis[1], AJ Hebert[1], AM Khan[2], MJ Chee[1]

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[2]Department of Biological Sciences and Border Biomedical Research Center, University of Texas at El Paso

ABSTRACT

Background: The zona incerta (ZI) is a predominantly GABAergic region implicated in feeding, hunting, fear, and motor control. ZI GABA neurons co-express tyrosine hydroxylase (TH) and produce dopamine, however the role of dopamine in the ZI is lesser known. We determined the distribution of dopaminergic projections from Th-cre cells to elucidate possible roles of ZI dopamine release.

Methods: We generated the Th-cre;L10-Egfp mouse and validated Th-cre expression in the ZI by the colocalization of Gfp and Th mRNA with TH-immunoreactivity. To visualize dopaminergic projection targets, we delivered a cre-dependent adeno-associated virus encoding mCherry or tdTomato to the medial ZI of Th-cre or Th-cre;L10-Egfp mice and mapped the distribution of dsRed-immunoreactive fibers onto Allen Reference Atlas brain templates.

Results: Only 10% of Gfp cells did not express Th mRNA or TH-immunoreactivity. Ectopic Gfp cells were largely restricted to the lateral ZI, as nearly all (96%) Gfp cells in the medial ZI co-expressed Th mRNA and/or TH-immunoreactivity. We transfected 80% of medial ZI Th-cre cells and found widespread dsRed-immunoreactive projections within the reticular thalamus, nucleus of reunions, periaqueductal grey area, and motor-related layers of the superior colliculus.

Limitations: The transfection of Th-cre cells may spill outside the medial ZI because it is a narrow brain region. However, projections common to both injection cases likely reflect robustly ZI innervation.

Conclusion: The projection targets of medial ZI TH neurons were most abundant within motor-related regions and were consistent with known functions of ZI GABA neurons in motor control.

Influence of type- and timing-specific trauma exposures on symptoms of depression and anxiety

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[2]University of Ottawa Institute of Mental Health Research at the Royal

ABSTRACT

Background: Early life stress is a significant risk factor for the development of psychopathology in adulthood. Recent evidence suggests that both type and timing of trauma exposures before the age of 18 influence mental health outcomes. Yet, how these variations may differentially confer vulnerability to later psychopathological symptom dimensions remain unclear. This study aimed to delineate specific types and sensitive periods of trauma exposure that map onto distinct depressive and anxious symptom dimensions.

Methodology: The association between trauma type and timing, and symptoms of depression and anxiety was examined among first- and second-year university students (N=238, Mage=19.0, 19.7% males, 80.3% females). Participants completed online questionnaires, including the Maltreatment and Abuse Chronology of Exposure scale, Beck Depression Inventory, Beck Anxiety Inventory, and Brief Resilience Scale.

Results: Non-verbal emotional abuse was predictive of overall and atypical depressive symptoms, while parental verbal abuse was associated with overall depressive and somatic anxious symptoms. Emotional neglect predicted symptoms of overall and psychological anxiety. While, sexual abuse was predictive of all outcomes, except for atypical depression. Trauma exposure between the ages of 13-18 was most strongly related to all mental health symptom dimensions assessed.

Limitations: The cross-sectional nature of this study precluded any causal relationships.

Conclusions: The present study suggests that both type and timing of trauma exposures in early life influence diverse depressive and anxious symptom profiles. Exposure to certain trauma types during critical periods of development should be considered in the development of early mental health interventions, particularly among adolescents.

Catecholaminergic neurons innervating the superior colliculus

CJ Onyegbule[1], KS Schumacke[1], MJ Chee[1]

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ABSTRACT

Background: The superior colliculus (SC) integrates sensorimotor information and encodes aversive stimuli, and dopaminergic afferents in the medial SC mediate avoidance behaviors. The zona incerta (ZI) comprises a major source of dopaminergic input to the SC, but the origins of other dopaminergic projections to the SC are largely unknown. We labeled catecholaminergic neurons that project to the SC by retrograde tracing from nerve terminals expressing tyrosine hydroxylase (TH) in the medial SC.

Methods: We delivered a cre-dependent retrograde adeno-associated virus expressing mCherry (50 nl) into the medial SC of a Th-cre mouse. The tissue was processed for dsRed-immunoreactivity and visualized by 3,3'-diaminobenzidine (DAB) staining. DAB-labeled tissue was aligned to an adjacent Nissl-stained series to define the brain region and atlas level containing dsRed-immunoreactive cells.

Results: Retrograde tracing from Th-cre nerve terminals in the medial SC labeled 113 dsRed-immunoreactive cells, which spread across 27 brain regions. Most cells were found in the ZI (30%), optic nerve (12%), lateral division of the parabrachial nucleus (7%), middle cerebellar peduncle (5%), and subparabrachial nucleus (4%). The other half of cells were spread over 22 brain regions.

Limitations: The retrograde virus did not label cell bodies at the injection site so viral spread in this area was not clear. Though catecholaminergic, we have not yet confirmed that dsRed-labeled cells are dopaminergic.

Conclusion: The SC may also integrate inputs from catecholaminergic cells throughout the brain that support anxiety-like behaviors, visual processing, arousal, locomotion, and nociception to mediate avoidance behaviors or mount threat-driven defensive responses.

The development of a cognitive health clinic: an innovative program combining cognitive remediation therapy and research

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ABSTRACT

Cognitive health has a fundamental impact on the life of individuals living with a mental health disorder. Cognitive remediation therapy has been shown to be an effective treatment at improving cognition and functional outcomes in various mental health disorders, including major depressive disorder and schizophrenia. Despite this evidence, it is currently not broadly accessible. Our team has developed an innovative plan to solve this problem by creating a Cognitive Health Clinic at The Royal. Our mission is to: provide cognitive evaluations and evidence-based treatments to the patients at The Royal (while collecting outcome data to determine the feasibility and efficacy of providing such services); and develop and test novel treatments through a clinical research platform, including cognitive remediation therapy delivered through virtual reality technologies and remotely with iPads, as well as combining cognitive remediation with brain stimulation and physical activity programs. The Cognitive Health Clinic will provide added clinical value by providing access to novel, state-of-the-art treatment services, which are not widely available nor routinely integrated into clinical management plans. We will also provide a cognitive assessment battery to many patients at The Royal (which will relieve a significant burden from the current services); provide findings from these assessments to the referring clinicians to help guide and monitor treatment; and provide patients with the possibility to receive evidence-based interventions. Our development and implementation of this Clinic will be evaluated and refined, and may serve as a model for other institutions to implement similar initiatives within their care services.

Sex differences in homeostatic sleep regulation in adolescents with depression: preliminary findings

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ABSTRACT

Background: Sex differences in homeostatic sleep regulation, as indexed by slow wave activity (SWA), have been reported in adolescents with depression; males showing lower sleep pressure and dissipation but not females. Since adolescence is marked by prominent brain changes in the frontal cortex, this study assessed the topography of SWA dissipation in depressed adolescent males and females. **Methods:** Forty-five outpatients with depression (64% females; mean+SD: 16.8+0.8 y.o.) and 39 healthy controls (48% females, mean + SD=17.3+0.8 y.o.) completed the Quick Inventory of Depressive Symptomatology (QIDS-SR) and underwent polysomnography. SWA was modeled using an exponential decay function. The y intercept, decay rate and plateau were compared across groups using corrected Akaike's information criterion (AICc).

Results: Compared to controls, the depression group had higher y intercepts for both females and males in F4 (AICc differences: 1.74-0.68, probability: 70.5%-58.4% respectively), and for females in C4 (AICc difference: 0.12, probability: 51.5%). There were no other significant group differences. In depressed females, QIDS-SR scores correlated with SWA in the first sleep cycle for C4 ($r=.41$, $p=.026$) and in the fourth sleep cycle for F4, C4 and P4 (all $r>.40$, $p<.050$).

Conclusions: These preliminary findings suggest that depressed adolescents present elevated initial levels of SWA in anterior cortical regions at the beginning of the sleep period, which may reflect increased sleep pressure. This may be more pronounced in females than in males. In females, higher depression severity may be linked to higher sleep pressure at the beginning of the night and poorer subsequent sleep recovery.

Association between sleep and brain GABA levels in trauma-exposed veterans: preliminary results from a magnetic resonance spectroscopic study

C Leveille[1,2], R Taylor[1], M Porteous[1,2], M Lanthier[1], C Richard-Malenfant[1,2], C Cassidy[1], Z Kaminsky[1], N Jaworska [1], R McQuaid[1], J Shlik[3], C Higginson[1], R Robillard[1,2]

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[2]School of Psychology, University of Ottawa
[3]Operational Stress Injury Clinic, Royal Ottawa Mental Health Center

ABSTRACT

Objective: While there are indications of a GABA deficiency in trauma-related illnesses, findings have been inconsistent. Since GABA is involved in the generation of deep slow wave sleep and elevated GABA levels have been observed in people with insomnia, it has been hypothesized that chronic hyperarousal linked to sleep disturbances may lead to an adaptive increase in GABA. Considering that sleep is commonly disrupted following trauma exposure, this preliminary report aimed to evaluate whether GABA levels in trauma-exposed veterans may relate to the level of sleep abnormalities in addition to psychiatric symptoms severity.

Method: Nineteen trauma-exposed veterans underwent a structured psychiatric interview and completed the post-traumatic stress disorder (PTSD) Checklist (PCL-5). GABA in the anterior cingulate cortex was quantified using magnetic resonance spectroscopy on the same day where in-lab polysomnography was recorded. The relationships between GABA levels, sleep architecture variables and total scores on the PCL-5 were analyzed using Spearman correlations.

Results: Psychiatric interviews confirmed that all participants in this sample met DSM5 criteria for PTSD (n=15) or major depressive disorder (n=4). There was a negative correlation between GABA levels and the percentage of slow wave sleep (NREM3; rs =-47, p =.042). Lower GABA levels also tended to correlate with more severe PTSD symptoms on the PCL-5 (rs=-44, p =.058).

Conclusions: Corroborating previous reports, these preliminary findings suggest that low GABA levels are associated with more severe PTSD symptoms in trauma-exposed individuals. We provide the first evidence that this neurochemical abnormality may be linked to the amount of deep sleep.

Expression of melanin-concentrating hormone receptor 1 in the ventral tegmental area

J Williams-Ikhenoba[1], D Spencer[1], MJ Chee[1]

[1]Department of Neuroscience, Carleton University

ABSTRACT

Background: Melanin-concentrating hormone (MCH) is a key regulator of energy expenditure. Both MCH and MCH receptor (MCHR1) deletion leads to hyperactivity, which is mediated by a hyperdopaminergic state within the mesocorticolimbic pathway originating from the ventral tegmental area (VTA). We showed that MCH can decrease dopamine release, but it is not known if MCH action occurs at the level of the VTA. We thus determined if the VTA expresses the MCHR1 gene and protein.

Methods: We determined the expression of Mchr1 mRNA in the VTA relative to the hypothalamus, striatum, hippocampus, and cerebellum of male and female wildtype mice. We then assessed MCHR1 protein expression in the VTA of wildtype and MCHR1 knockout mice.

Results: Relative gene expression of Mchr1 mRNA in the VTA was lower than in the striatum but comparable to that in the hypothalamus and hippocampus of male and female mice. Interestingly, VTA Mchr1 mRNA levels was higher in female than male mice. We also detected MCHR1 protein expression throughout the VTA, as MCHR1-immunoreactive cilia was seen on VTA cells of wildtype but not MCHR1 knockout mice.

Limitations: Our analyses thus far have not accounted for the cellular heterogeneity and subpopulations of VTA.

Conclusions: The VTA comprises robust gene and protein expression of MCHR1, thus suggesting that MCH may act directly on VTA neurons to inhibit dopamine release.

Electrophysiological characterization of two melanin-concentrating hormone cell subpopulations

P Miller[1], A Sankhe[1], J Williams-Ikhenoba[1], M Chee[1]

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ABSTRACT

Background: Melanin-concentrating hormone (MCH) cells form a small subset of hypothalamic neurons that mediate complex behaviours including feeding, arousal, maternal behaviour, and stress. MCH cells are also neurochemically diverse, and one distinct subpopulation of MCH cells coexpresses cocaine- and amphetamine-regulated transcript (CART). Currently, the functional distinctions between MCH/CART+ and MCH-only cells are unknown, thus we analyzed the electrical signature of these two cell subpopulations to elucidate their contribution to network excitability.

Methods: We performed whole-cell patch-clamp electrophysiology on male and female Mch-cre; L10-Egfp cells expressing native EGFP fluorescence, and determined their passive and active membrane properties. Cells were biocytin-filled and processed for CART immunoreactivity to match their neurochemical phenotype to their electrophysiological properties post hoc.

Results: There were no differences in passive membrane properties between MCH/CART+ and MCH-only cells. A comparison of active membrane properties showed that hyperpolarization elicited a larger inward current in MCH/CART+, and that male MCH/CART+ cells were less excitable than MCH-only cells.

Limitations: A broad age range (4–52 weeks) was included in our recordings, thus an age effect may be a confounding variable given that MCH cells experience an age-dependent decrease in excitability.

Conclusion: This work defined electrophysiological properties that may underlie the neurochemical and functional diversity of MCH cells. MCH/CART+ cells displayed unique electrical characteristics in a sex-dependent manner, thus they may have specialized roles in MCH-mediated behaviors. We will extend this work by analyzing the putative effects of sex on synaptic strength and the downstream connectivity of MCH/CART+ cells.

Caregivers' attitudes towards using driving simulators to assess driving fitness of older adults with dementia

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ABSTRACT

Background: Driving risk in the context of cognitive decline is typically measured through paper-based cognitive assessments. On-road tests and driving simulations can also be used. This study investigates how caregivers perceive the potential use of driving simulators for assessing driving fitness.

Methods: Family members of patients of the Bruyère Memory Clinic who were reported to the Ministry of Transportation (MOT) between January 2020 and June 2021 were contacted. Semi-structured virtual interviews were conducted with questions covering their caregiving experiences and the potential use of driving simulators. Analysis consisted of transcribing the interviews, coding the data, and identifying themes.

Results: Two males and one female, a child and two spouses, were interviewed. Their ages ranged from 55 to 75. Regarding the visit when the driving risk was discussed, the caregivers felt relieved, whereas the people living with dementia (PLWD) typically were angry but believed they may possibly regain their licenses. Regarding addition of the simulator to the assessment, positives were the structure of the testing, using objective data and safety as well as the ability to repeat the test. On the other hand, negatives included not feeling the machine reflected real driving, stress caused by additional testing, worrying that not understanding the technology would affect results, logistics around repeat visits and potential costs.

Conclusion: In this pilot study, caregivers of older adults assessed for driving risk thought that using driving simulators would, overall, be a valuable addition to the assessment process. However, more research is needed to confirm these preliminary findings.

Application of blood brain barrier models in preclinical assessment of glioblastoma-targeting cart based immunotherapies

J Huang[1], B Li[1], C Charlebois[1], E Baumann[1], D Bloemberg[1], T Nguyen[1] , A Zafer[1], Z Liu[1], Q Liu[1], DB Stanimirovic[1], S McComb[1], A Jezierski[1]

[1]National Research Council of Canada

ABSTRACT

Human blood brain barrier (BBB) models derived from induced pluripotent stem cell (iPSC) have become an important tool for discovery and preclinical evaluation of CNS targeting cell and gene -based therapies. Chimeric antigen receptor (CAR)-T is a revolutionary form of gene-modified cell-based immunotherapy with potential for targeting solid tumors, such as glioblastomas. Crossing the BBB is an important step in the systemic application of CAR-T therapy for the treatment of glioblastomas and other CNS malignancies. In addition, CAR-T therapies are known to trigger CNS side-effects, including brain swelling due to BBB disruption. In this study, we used iPSC-derived brain endothelial cell (iBEC) transwell co-culture model to assess BBB extravasation of CAR-T based immunotherapies targeting U87MG human glioblastoma (GBM) cells overexpressing EGFRvIII (U87vIII). Two types of anti-EGFRvIII targeting CAR-T cells (CAR-F263 and CAR-F269) and control Mock T cells applied on the luminal side, triggered a decrease in transendothelial electrical resistance (TEER) and an increase in BBB permeability. CAR-T cell extravasation and U87vIII cytotoxicity were assessed from the abluminal compartment using flow cytometry and IncuCyte real-time viability imaging, respectively. A significant decrease in U87vIII cell viability was observed over 48hrs, with the most robust GBM cytotoxicity response observed for CAR-F263. CAR-F269 and Mock T cells showed a similar cytotoxic profile but were collectively approximately 4-fold less efficient at killing the U87vIII cells than CAR-F263, despite similar transmigration rates. Visualization of CAR-T cell extravasation across the BBB was further confirmed using iBEC-on-CHIP models. The BBB assay was able to discriminate the cytotoxic efficacies of the two different EGFR-CARs and to provide a measure of potential alterations to BBB integrity. Collectively, we illustrate how BBB models in vitro can be a valuable tool in deciphering the mechanisms of CAR-Tâ€“induced BBB disruption, accompanying toxicity and effector function on post-barrier target cells.

Tamoxifen's impact on pericyte reprogramming into neural stem cells in vitro

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ABSTRACT

Pericytes are cells that are a component of the neurovascular unit where they wrap around the endothelial cells lining blood capillaries and overall help maintain blood-brain barrier integrity. It has been found that pericytes have a special ability to reprogram into neural stem cells – this is because pericytes and neural stem cells share a common lineage called the neural crest cell. Prior in-vivo work by our lab shows that drugs such as compound C can promote this reprogramming. When differential growth factors are present, this can trigger differentiation of these cells into neurons. Tamoxifen is widely found in research labs as it is involved in the Cre-LoxP system – a system used to control transcription of genes. Delivering a higher concentration of tamoxifen in mice results in higher reprogramming of pericytes into neural stem cells following stroke, but with a lower concentration of tamoxifen in mice there is less reprogramming of pericytes into neural stem cells. Thus, it is being investigated whether tamoxifen can enhance pericyte reprogramming into neural stem cells using an in-vitro cell culture model. Preliminary findings show that there is a degree of enhanced reprogramming with the addition of tamoxifen as there is a greater number of nuclear SOX2+ and total SOX2+ cells in the tamoxifen groups implying increased reprogramming into neural stem cells. This is significant because it not only shows that tamoxifen has functions other than controlling gene transcription, but also that it can act as a potent drug that can contribute to neural regeneration through neurogenesis.

Wistar-kyoto rats exhibit decreased serotonin/dopamine neuronal activity but enhanced norepinephrine tone

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[2]Institute of Mental Health Research Ottawa
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ABSTRACT

Introduction: Antidepressants increasing serotonin (5-HT), norepinephrine (NE) and/or dopamine (DA)-levels are demonstrated to be effective in treating major-depressive-disorder. Wistar-Kyoto rats (WK) represent an animal model of depression, exhibiting similar deficits in behavioural, neurochemical, and endocrine parameters to clinical patients. These include lower 5-HT levels/transporters in the Dorsal-Raphe-Nucleus (DRN), decreased concentration of NE in the Locus-Ceruleus (LC) and attenuated tissue DA-levels in the Ventral-Tegmental-Area. There is scant electrophysiological evidence supporting this model, so this study aims at characterizing basal firing, burst and population activity of the monoaminergic regions.

Methods: Male Wistar (W)/WK rats were anesthetized with chloral-hydrate/mounted in stereotaxic apparatus. Single-glass micropipettes were used for in-vivo extracellular recordings.

Results: DRN 5-HT neuron firing-activity was significantly decreased in WK compared to W rats, with no change in the percentage of neurons firing in burst-mode. In LC, the firing/burst-activity of NE neurons were significantly enhanced in WK compared to W rats. In VTA, preliminary data show there is a significant decrease in DA neurons firing, but no significant alteration in bursting (% Spikes in bursts or neuron quantity per electrode descent.

Conclusion: The decrease in 5-HT and DA neuron firing in WK rats would be consistent with the hypothesis of a decreased/altered 5-HT/DA neurotransmission in depression, and the NE neuron firing increase may be due to decreased NE levels previously reported. These results show important alterations to the monoamine systems in WK rats and support its use in testing mechanisms of antidepressants.

Effect of pubertal gut dysbiosis and LPS treatment on neuroinflammation and dopaminergic markers in male and female mice

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ABSTRACT

During puberty, the central nervous system (CNS) is vulnerable to stressors that may have long-term consequences, impacting the immune system, cognitive functioning, and behaviours later in life. Exposure to stress also alters the composition of the gut microbiome, which in turn also impacts the immune system, the brain, and various behaviours. However, it is unclear whether stress-induced gut dysbiosis can increase the susceptibility to neurodegeneration. Therefore, the goal of this study was to examine the effect of pubertal gut dysbiosis (induced by antimicrobials) and lipopolysaccharide (LPS) treatment on cellular mechanisms of neurodegeneration, which was assessed by examining the expression of Complement 3 (C3) and tyrosine hydroxylase (TH) in the caudate-putamen (CP) and substantia nigra (SN). At 5 weeks of age, male and female CD1 mice were administered mixed antimicrobial solution or water. At 6 weeks (pubertal sensitive period), mice received an intraperitoneal injection of LPS or saline. Western blot was used to examine C3 and TH expression in the CP and SN. Contrary to our hypothesis, LPS-treated males displayed reduced C3 expression in the SN. Additionally, there were no significant changes in TH expression in the CP or SN. These results suggest that C3 expression is reduced in the SN of LPS-treated male mice which can indicate reduced synaptic pruning that occurs during adolescence and is associated with neurological disorders such as Alzheimer's disease (AD), autism, or schizophrenia.

Systematic approach to define common neuroanatomical targets of dopaminergic zona incerta cells

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ABSTRACT

Background: Cre-dependent tracing strategies are commonly used to track nerve fibers of pre-defined cell groups. However, it is inherently challenging to control viral spread, which can obscure the common fiber projection pattern across injection cases. In this project, we developed an unbiased approach to map the brain regions commonly innervated by two stereotactic injection cases targeting dopaminergic cells in the zona incerta (ZI).

Methods: We manually traced nerve fibers from medial ZI cells in two Th-cre mouse brains. One mouse received a focused injection (25 nl) of a cre-dependent adeno-associated virus encoding mCherry or tdTomato, while the second mouse received a larger injection volume (75 nl), which may spill outside the ZI. We overlaid the projection maps from each injection case in Adobe Illustrator, then applied the Intersect tool in the Pathfinder panel to map the areas receiving fibers from both injection cases.

Results: Intersecting maps highlighted brain regions comprising high fiber density in both ZI injection cases, including the midbrain motor-related regions like the periaqueductal gray and the superior colliculus. Fiber projections arising from only one injection case were not represented in intersected maps.

Limitations: Resultant traces in intersected maps appear when fibers from separate injection cases overlap in space, thus do not reflect the actual fiber density in the region.

Conclusion: The Intersect tool detected the common brain regions innervated by two injection cases and can be an unbiased tool to establish a consistent pattern of fiber projections among two or more brains.

Functionally distinct NPAS4-expressing somatostatin interneuron ensembles critical for motor skill learning

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ABSTRACT

Local GABAergic inhibitory neurons are known to play an essential role in memory formation and allocation by modulating the level of inhibition to downstream excitatory neuronal ensembles. During motor learning dendritic spines on pyramidal neurons (PNs) undergo reorganization, which coincides with subtype-specific axonal bouton changes in somatostatin-expressing inhibitory neurons (SOM-INs) and parvalbumin-expressing inhibitory neurons (PV-INs). Moreover, SOM-mediated inhibition has been shown to regulate spine reorganization on PNs. However, the molecular mechanisms that underlie changes in inhibition, and whether the changes arise from all SOM-INs remain unclear. Here, we identified that the immediate-early gene transcription factor, NPAS4, is selectively expressed in a subset of SOM-INs, but not in PV-INs or PNs, during motor learning. Combining in vivo two-photon imaging with a head-fixed pellet reaching motor learning task, we found that activity was reduced among NPAS4-expressing SOM-INs during task-related movements compared to other SOM-INs. Region- and cell-type specific deletion of Npas4 within SOM-INs in the motor cortex disrupted the spine elimination process and impaired new motor skill aquisition. Strikingly, chemogenetic activation of the NPAS4-expressing ensembles was sufficient to impair motor learning and also alter the spine elimination process. Together, our results reveal an instructive role of NPAS4 within the microcircuits, in which it modulates the inhibition of a distinct subset of SOM-INs during motor learning to promote spine stabilization of downstream task-related PNs that are important for motor skill acquisition.

Impact of gestational hyperglycaemia on the development of the rat fetal hypothalamic melanocortin system

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ABSTRACT

Gestational Diabetes (GD) is associated with adverse metabolic outcomes in offspring, such as increased vulnerability to develop obesity and type 2 diabetes. Prior research has attributed obesity and other metabolic disorders by a dysregulation of the melanocortin system. Indeed, it is possible that GD may influence the development of this system and confer this vulnerability. We employed an experimental model of GD to examine how a maternal hyperglycemic state impacts the development of this system in the arcuate nucleus (ARC) in the developing fetus. To do this, we induced a mild diabetic state by injecting intraperitoneally pregnant Wistar rats with a low dose of streptozotocin (STZ; a pancreatic beta cell toxin), inducing a mild hyperglycemic and insulin deficient state. The injection of vehicle or 35 mg/kg of STZ was given (N=8/group) one week after impregnation was confirmed. GD was confirmed with a glucose tolerance test on day 15 and following this confirmation, on day 19, pregnant females were deeply anesthetized, and their fetuses were extracted via c-section. Fetuses were rapidly decapitated, and their heads were immediately submerged in 4% paraformaldehyde for fixation. Sections from these brains containing the ARC were processed for immunohistochemistry detecting the pro-opiomelanocortin (POMC) peptides. Results showed that pups harvested from STZ-treated rats had lower number of ARC POMC stained cells, suggesting that maternal hyperglycemia may be influencing the development of the melanocortin system, conferring vulnerability to metabolic disorders.

Chronic stress increases ghrelin entry into the arcuate nucleus of the hypothalamus

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ABSTRACT

Ghrelin is a stomach-derived peptide hormone that increases food intake through central activation of the growth hormone secretagogue receptor (GHSR). Circulating ghrelin levels also rise in response to stressors and plays an important role in the regulation of feeding behavior and metabolism in the face of stress. The mechanisms by which ghrelin regulates such behaviors is still being elucidated, as ghrelin movement into and throughout the brain is extremely limited by the blood brain barrier. Notably, social stressors have been found to increase blood brain barrier permeability and therefore may increase the ability of large peptide hormones, like ghrelin, to enter the brain. To investigate if stress influences blood brain barrier permeability to ghrelin, male mice were subjected to 21-days of chronic social defeat stress then subcutaneously injected with 300pmol/g of fluorescently labelled ghrelin, Cy5-ghrelin. Mice were then sacrificed 7-, 15-, 30-, or 60-minutes following injection, to monitor ghrelin movement throughout the brain. The results showed that stress exposure increased Cy5-ghrelin fluorescence in the arcuate nucleus of the hypothalamus, compared to non-stressed controls. This was accompanied by a decrease in astrocyte expression and end-feet branching, as determined by glial fibrillary acidic protein (GFAP) immunohistochemistry. These results suggest that increased food intake during stress may be due to the reduction in astrocyte coverage of the blood brain barrier, facilitating an increase of ghrelin accumulation in the arcuate nucleus of the hypothalamus.

Using cortical inhibition measured with transcranial magnetic stimulation to better understand electroconvulsive therapy

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ABSTRACT

Background: Despite the therapeutic efficacy of electroconvulsive therapy (ECT), the mechanisms of action are not fully understood and around 35% of individuals will not show response. Thus, understanding how ECT modulates brain activity and finding predictors of response is crucial.

Methods: Sixty individuals with diverse mental health disorders receiving ECT will be recruited. Three transcranial magnetic stimulation (TMS) measures (short- and long-interval intracortical inhibition; SICI, LICI, and cortical silent period; CSP) will be used to explore cortical inhibition 72hrs pre-/post-ECT. The Quick Inventory of Depressive Symptoms (QIDS) will be administered 72 hours pre-/post-ECT. Paired t-tests will be computed to assess changes in cortical inhibition. Spearman rho correlations will be computed between baseline and change in TMS measures, and change in QIDS score.

Results: Preliminary data from 8 participants (Depression: N=6, Bipolar disorder: N=1, Schizoaffective disorder: N=1) show no significant changes in SICI- and CSP-related cortical inhibition post-ECT (p=0.327, p=0.600, respectively), whereas a trend towards increased LICI-related cortical inhibition post-ECT is obtained (p=0.123). While no correlations were significant, a strong positive relationship was obtained between baseline levels of SICI-related cortical inhibition and symptom reduction post-ECT (r=0.48, p=0.23), and between the change in CSP post-ECT and symptoms reduction post-ECT (r=0.60, p=0.21).

Limitations: Small sample size and including a variety of mental health disorders and response rates likely contribute to lack of significance.

Conclusion: Further recruitment is needed to increase statistical power in the hopes to better understand the mechanisms of action and to find a predictor of response to treatment.

Investigating α-synuclein pathology within the murine olfactory system & characterizing the inflammatory response in infected animal models

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ABSTRACT

Background & hypothesis: The relative importance of the olfactory system in PD pathogenesis is supported by the presence of disease pathology (Lewy bodies) in the olfactory bulb at early disease stages and before being found in the midbrain. The Schlossmacher team has published that α-synuclein is highly expressed in the neurons within the olfactory epithelium and that a-synuclein helps to protect mice from nasally acquired viral infections. We hypothesized that viral encounters could act as seeding events that induce changes in α-synuclein metabolism (from transcription to posttranslational modifications) and, by extension, accumulation of toxic oligomeric, pre-amyloid species. Further, this concomitant spread of a disease process involves inflammation and neural injury from the nasal epithelium along the olfactory circuitry and onward into deeper regions of the brain.

Methods: We tested this in vivo using VSV-GFP infectious agent in one α-synuclein mouse model (n=21 C57BL WT mice that express endogenous α-synuclein). Adult mice were infected through an internasal inoculation of this neurotropic virus at dosage predetermined to be LD50. We analyzed skulls sections of mice sacrificed at 2,4,6, and 10 DPI using immunohistochemistry and immunofluorescence to look at temporal progression of VSV-GFP and monitor α-synuclein modifications. Subsequent western blotting for α-synuclein changes and qPCR to measure changes in transcripts of SNCA will ensue.

Results: Mice showed diverse progressive staining of VSV-GFP along the olfactory circuitry, which was variable across different post-infection days indicating an individual-specific inflammatory response outlined by immune-cell markers such as IBA1, GFAP, and TMEM119. A quantitative analysis of signal where it makes sense, along with α-synuclein staining of normal and abnormal species and measurement of viral loads in the brains of infected mice will follow.

Conclusion: Infected animals respond variably and distinctly to VSV, illustrating an individual-specific immune response. The staining patterns describe an overall progressive route of inoculated VSV entry to deeper components in the olfactory circuitry through the olfactory epithelium. Ongoing studies will unveil whether α-synuclein's metabolism, phenotype, and populations are affected.

Emotional inhibition processing is associated with poor sleep in hospitalized adolescents with acute suicidal behaviours

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ABSTRACT

Background: Suicide is the second most common cause of death for adolescents. Previous studies observed lighter sleep in suicidal adolescents compared to healthy adolescents. This could alter inhibitory processes, leading to dangerous behaviours. This study assessed how sleep architecture in suicidal adolescents may relate to inhibition processing in response to stimuli with different emotional valence.

Method: Ten adolescents between 12 and 17 years of age (80% females, Mean+SD = 15.1+1.6 y.o.) who attempted suicide were recruited while hospitalized for a suicidal crisis. All had a diagnosis of depression based on DSM-V criteria. Polysomnography and event-related potentials (ERPs) were recorded in patientsâ€™ bedrooms. ERPs were recorded during a Go/NoGo task involving pictures of emotionally sad, neutral, and happy faces. Pearson correlations evaluated associations between sleep architecture parameters and the P3d, a brain response thought to reflect inhibition processing (i.e. difference waveform calculated as NoGo minus Go trials).

Results: Participants had significant suicidal symptoms on the adolescent version of the Suicidal Ideation Questionnaire (range: 32-82, Mean+SD = 46.3+16.6), and 88.9% were taking psychotropic medications. Higher amounts of NREM2 (r=-.77, p = .010) and lower amounts of NREM3 (r=.64, p=.045) significantly correlated with lower amplitude of the P3d in response to sad stimuli. No such association was found for neutral or happy stimuli.

Conclusion: Our findings suggest that shallower sleep in suicidal adolescents is associated with fewer neural resources mobilized by inhibitory control in emotionally negative context. Thus, addressing sleep disturbances while managing acute suicidal behaviour in adolescents may be clinically relevant.


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