Programme et résumés
Program and abstracts

EARLY
TRIGGERS
OF PARKINSON'S
DISEASE

MAY
21-22
MAI

ÉLÉMENTS
DÉCLENCHEURS
DE LA MALADIE
DE PARKINSON

Montréal 2019
41e Symposium international en neurosciences de l'Université de Montréal
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Département de neurosciences
Faculté de médecine
Université de Montréal
et du monde.

La tenue de ce symposium est rendue possible grâce à l'appui financier des organismes suivants :

- Abbvie
- UBC
- Fonds Ginette Prémont et Michel Phaneuf pour la recherche en Parkinson
- Chaire Power Corporation du Canada en neurosciences de l'Université de Montréal
- Groupe de recherche sur le système nerveux central (GRSNC)

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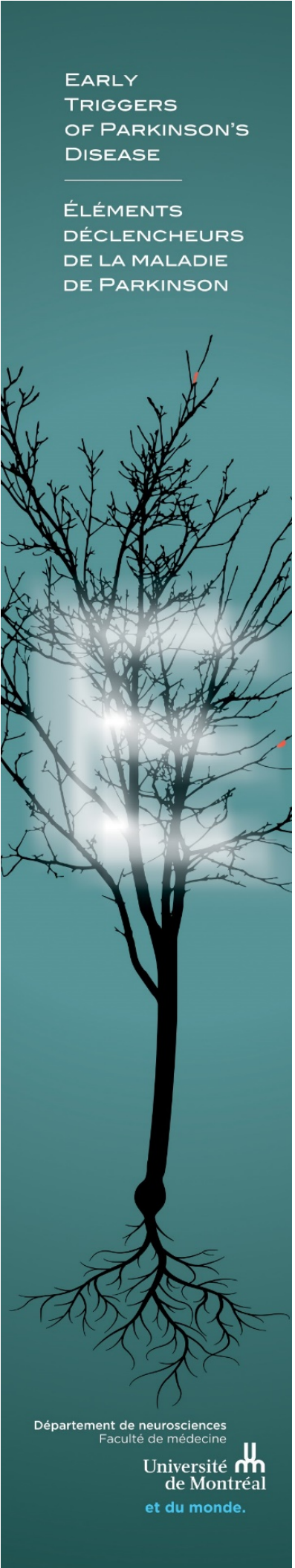

41e Symposium international en neurosciences de l'Université de Montréal

Pavillon 3200, rue Jean-Brillant, local B-2245

Programme / Program

Ce programme vise les scientifiques en neurosciences, les neurologues avec un intérêt en troubles du mouvement et en maladies neurodégénératives, les résidents de neurologie, les étudiants en neurosciences.

Comité organisateur / Organizing committee

Antoine Duquette
Alexandru Hanganu
Nicole Leclerc
Daniel Lévesque
Diana Matheoud
Michel Panisset
Martine Tétreault
Louis-Eric Trudeau

SESSION 1

EARLY PHENOTYPING AND DETECTION OF PARKINSON'S DISEASE

Objectifs d'apprentissage :

- Pouvoir discuter des différents sous-types de maladie de Parkinson
- Acquérir de nouvelles connaissances sur le syndrome prodromal de la maladie de Parkinson
- Acquérir de nouvelles connaissances sur l'imagerie inflammatoire de la maladie de Parkinson

Learning objectives:

- Discuss different subtypes of Parkinson's disease
- Acquire new knowledge about the prodromal syndrome of Parkinson's disease
- Acquire new insights into inflammatory imaging of Parkinson's disease

SESSION 2

PATIENT-DERIVED SYSTEMS TO STUDY EARLY TRIGGERS AND NOVEL THERAPEUTICS

Objectifs d'apprentissage :

- Acquérir de nouvelles connaissances sur les modèles expérimentaux de l'heure pour la maladie de Parkinson
- Acquérir de nouvelles connaissances sur les possibilités de greffes cellulaires

Learning objectives:

- Acquire new knowledge on current experimental models for Parkinson's disease
- Acquire new knowledge on the possibilities of cellular transplants

SESSION 3

EARLY PATHOPHYSIOLOGICAL TRIGGERS AND BIOMARKERS OF PARKINSON'S DISEASE

Objectifs d'apprentissage :

- Acquérir de nouvelles connaissances sur le rôle de l'inflammation dans l'étiologie de la maladie de Parkinson
- Acquérir de nouvelles connaissances sur le rôle des mitochondries dans la maladie de Parkinson
- pouvoir discuter de la thérapie génique dans la maladie de Parkinson

Learning objectives:

- Acquire new knowledge on the role of inflammation in the etiology of Parkinson's disease
- Acquire new knowledge on the role of mitochondria in Parkinson's disease
- Be able to discuss gene therapy in Parkinson's disease

SESSION 4

INFLAMMATION AND IMMUNE RESPONSES AS EARLY TRIGGERS OF PARKINSON'S

Objectifs d'apprentissage :

- Acquérir de nouvelles connaissances dans l'interaction entre l'alpha-synucléïne et l'inflammation
- Acquérir de nouvelles connaissances dans le rôle du microbiote dans la maladie de Parkinson

Learning objectives:

- Acquire new knowledge in the interaction between alpha-synuclein and inflammation
- Acquire new insights into the role of the microbiota in Parkinson's disease

Mardi, 21 mai 2019 Tuesday, May 21, 2019

A.M.	7 h 30 – 8 h 30	Accueil / Arrival of participants
	8 h 30 – 9 h	Mots de bienvenue / Opening statements
		Christian Baron, vice-doyen, recherche et développement, Faculté de médecine
		Patrick Cossette, directeur, Département de neurosciences
		Michel Panisset, professeur, Département de neurosciences

SESSION 1

EARLY PHENOTYPING AND DETECTION OF PARKINSON'S DISEASE

Modérateur / Moderator: ***Antoine Duquette***

A.M.	9 h – 9 h 30	**Roger Barker, Ph.D.** Department of Clinical Neurosciences University of Cambridge, Cambridge, UNITED KINGDOM **Parkinson's Disease- one disorder or many?**
	9 h 40 – 10 h 10	**Andrew D. Siderowf, M.D.** Department of Neurology University of Pennsylvania, Philadelphia, PA, USA **Prodromal Parkinson's Disease: Lessons from PARS and PPMI**
	10 h 40 – 11 h 20	**Antonio P. Strafella, Ph.D., M.D.** Campbell Family Mental Health Research Institute Department of Medicine's Division of Neurology University Health Network, Toronto, ON, CANADA **Neuroimaging biomarkers for early detection of Parkinsonism**
	11 h 30 – 13 h	Repas / Lunch: Cafétéria Jean-Brillant
	13 h – 14 h	Session d'affiches / Poster session

SESSION 2

PATIENT-DERIVED SYSTEMS TO STUDY EARLY TRIGGERS AND NOVEL THERAPEUTICS

Modérateur / Moderator: ***Martine Tétreault***

P.M.	14 h – 14 h 30	**Thomas M. Durcan, Ph.D.** Department of Neurology and Neurosurgery Montreal Neurological Institute and Hospital McGill University, Montreal, QC, CANADA **Developing new models of Parkinson's through stem cells**
	14 h 40 – 15 h 10	**Janelle Drouin-Ouellet, Ph. D.** Faculté de pharmacie Université de Montréal, Montréal, QC, CANADA Groupe de recherche sur le système nerveux central (GRSNC) **Direct neuronal reprogramming to study sporadic Parkinson's disease**
	15 h 15 – 15 h 35	Pause-café / Coffee break
	15 h 40 – 16 h 10	**Michela Deleidi, Ph.D.** Department of Neurodegenerative Diseases University of Tübingen, Tübingen, GERMANY **Innate immunity and immune cell metabolism: links to Parkinson's disease**
	16 h 15 – 17 h 15	Session d'affiches / Poster session
	18 h	**Cocktail et banquet / Cocktail and banquet** Restaurant Le Cercle 3000, chemin de la Côte-Sainte-Catherine, 6e étage

Mercredi, 22 mai 2019 Wednesday, May 2, 2019

SESSION 3

EARLY PATHOPHYSIOLOGICAL TRIGGERS AND BIOMARKERS OF PARKINSON'S DISEASE

Modérateur / Moderator: ***Daniel Lévesque***

A.M.	8 h 45 – 9 h 15	**Richard Youle, Ph.D.** Biochemistry section National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA **Neuroinflammation stemming from mitochondrial DAMPs linked to Parkinson's disease genes and mitophagy defects**
	9 h 20 – 9 h 50	**Francesca Cicchetti, Ph. D.** Département de psychiatrie et de neurosciences Université Laval, Québec, QC, CANADA **Erythrocytes derived microvesicles: a new biomarker of Parkinson's disease**
	9 h 55 – 10 h 10	Pause-café / Coffee break
	10 h 10 – 10 h 30	**Louis-Eric Trudeau, Ph. D.** Département de pharmacologie et de physiologie Université de Montréal, Montréal, QC, CANADA Groupe de recherche sur le système nerveux central (GRSNC) **Axonal arbor size and bioenergetics a determinants of early vulnerability**
	10 h 35 – 11 h 05	**Anurag Tandon, Ph.D.** Department of Medicine University of Toronto, Toronto, ON, CANADA **Gene therapy for synucleinopathies**
	11 h 05 – 12 h 05	Session d'affiches / Poster session
	12 h 05 – 13 h	Repas / Lunch: Cafétéria Jean-Brillant

Mercredi, 22 mai 2019 Wednesday, May 2, 2019

SESSION 4

INFLAMMATION AND IMMUNE RESPONSES AS EARLY TRIGGERS OF PARKINSON'S

Modérateur / Moderator: ***Michel Desjardins***

P.M.	13 h – 13 h 30	**Marina Romero-Ramos, Ph.D.** Department of Biomedicine Aarhus University, Aarhus, DENMARK **Peripheral Monocytic Cells in Parkinson's Disease**
	13 h 35 – 14 h 05	**Ashley S. Harms, Ph.D.** Department of Neurology University of Alabama at Birmingham, Birmingham, AL, USA **Alpha-Synuclein and the immune response in Parkinson's disease**
	14 h 10 – 14 h 25	Pause-café / Coffee break
	14 h 30 – 15 h	**Malú G. Tansey, Ph.D.** Department of Physiology Emory University School of Medicine, Atlanta, GA, USA **The role of inflammation and immune responses in the gut-brain axis in Parkinson's disease**
	15 h 05 – 15 h 35	**Diana Matheoud, Ph. D.** Département de neurosciences Centre de recherche du CHUM Université de Montréal, Montréal, QC, CANADA **Parkinson's disease related proteins PINK1 and Parkin are major regulators of the immune system**
	15 h 40 – 16 h	Mot de clôture / Closing statements

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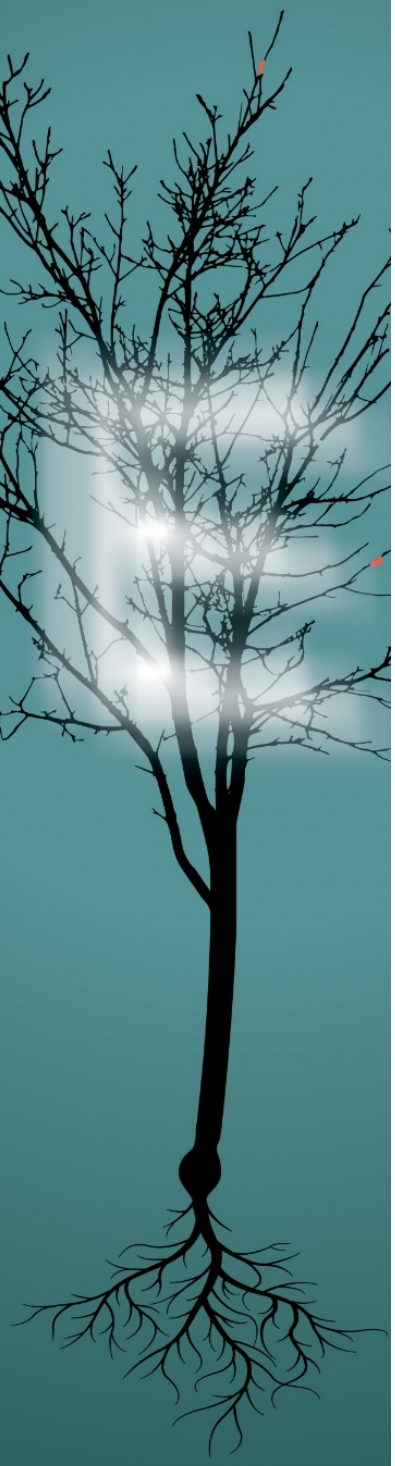

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Résumés / Abstracts

LE PILATES COMME TRAITEMENT ADJUVANT DANS LA MALADIE DE PARKINSON

Andreia Dourado Cunha[1]
Faculté de l'éducation permanente de [1]Université de Montréal

La maladie de Parkinson (MP) est une maladie neurodégénérative progressive qui provoque des troubles cognitifs et moteurs. La thérapie physique cherche à ralentir la progression de la maladie et à retarder le handicap. Actuellement, la méthode Pilates est l'une des ressources utilisées dans le traitement de la MP car elle intègre l'esprit et le corps avec des résultats favorables dans conditionnement, et dans des variables telles que la flexibilité, la force et l'équilibre. Objectifs: Analyser, à travers la littérature, les effets du Pilates dans la réhabilitation du patient atteint de la maladie de Parkinson. MÉTHODES: Il s'agit d'une revue systématique, réalisée de juillet à décembre de 2018. Dans les bases de données PubMed, VHL, SciELO, Papyrus et Science Direct combinant les descripteurs "maladie de Parkinson", "Exercises de Pilates "," Pilates et rehabilitation "en anglais et francais. Essais cliniques randomisés publiés entre 2015 et 2018 qui incluaient la méthode Pilates dans le traitement des personnes atteintes de la MP. RÉSULTATS: Au départ, 80 articles ont été trouvés, dont 20 ont été rejetés parce qu'ils étaient dupliqués ou parce qu'ils ne répondaient pas aux critères d'éligibilité. Équilibre, démarche, stabilité, souplesse et qualité de vie avant et après application de la méthode Pilates. Les protocoles allaient de 6 à 12 semaines de formation. CONCLUSION: Les études indiquent que la méthode Pilates agit dans le système musculaire et nerveux en améliorant l'équilibre dynamique et favoriser l'augmentation de la force des membres inférieurs, équilibre, proprioception et conscience corporelle. La technique s'est révélée efficace et bénéfique, se présentant comme un outil viable pour être inclus dans un plan thérapeutique pour la MP.

IDENTIFICATION D'UN PROFIL OLFACTIF SPÉCIFIQUE À LA MALADIE DE PARKINSON

Émilie Aubry-Lafontaine[1], Cécilia Tremblay[1], Pascali Durand-Martel[2], Nicolas Dupré[3,4], Johannes Frasnelli[1,5]
[1]Chaire de recherche en neuroanatomie chimiosensorielle, Département d'Anatomie, Université du Québec àTrois-Rivières, QC, [2]Département de neurologie, Centre intégré Universitaire de Santé et de Services Sociaux de la Mauricie-et-du-Centre-du-Québec (CIUSSS-MCQ), QC, [3]Faculté de médecine de l'Université Laval, QC, [4]Centre Hospitalier Universitaire de Québec (CHUQ), QC, [5]Centre de recherche de l'Hôpital du Sacré-Cœur de Montréal, QC

PROBLÉMATIQUE : Les maladies neurodégénératives du mouvement, telles que la maladie de Parkinson (MP), touchent 1% des Canadiens de plus de 65 ans. Bien que cette maladie soit une des causes les plus fréquentes des syndromes parkinsoniens, des études anatomopathologiques ont démontré que la précision du diagnostic dépendait principalement de l'expérience du clinicien. Aujourd'hui, le Mouvement Disorder Society a reconnu le trouble olfactif (TO) comme critère diagnostique précoce de la MP. Il est présent chez plus de 90% des patients atteints de la MP et il survient plusieurs années avant les premiers signes moteurs de la maladie. Cependant, la perte olfactive peut avoir diverses causes et elle affecte 20% de la population de plus de 65 ans. Dès lors pour contribuer à améliorer le diagnostic différentiel et envisager du dépistage précoce qui ne soit pas seulement basé sur l'expérience du clinicien, il est nécessaire de différencier les TO associés à la MP, de ceux chez des personnes ayant des TO sans atteintes neurodégénératives. Cependant, l'olfaction comprend une fonction olfactive orthonasale (voie directe par les narines) et une fonction rétronasale (voie indirecte de la bouche par le pharynx) qui seulement partiellement partagent les mêmes structures cérébrales et peuvent être évaluées séparément. Ainsi, il est possible que la MP affecte les deux voies olfactives et son évaluation doit être plus spécifique, afin d'améliorer le diagnostic différentiel, de fournir des outils de dépistage précoce et de mieux comprendre les facteurs qui influencent la perte olfactive dans la MP. L'hypothèse de cette recherche était que les sujets atteints de la MP ont un profil d'atteinte olfactive distinct des sujets ayant un trouble de l'odorat sans atteintes neurodégénératives, comparé aux individus sans atteinte olfactive. Plus spécifiquement, évaluer les voies orthonasale et rétronasale séparément à l'aide de tests comportementaux permettrait d'identifier un profil olfactif spécifique à la MP. APPROCHE EXPÉRIMENTALE : Étude transversale avec groupe témoin. MÉTHODOLOGIE : Patients MP (n=32), TO sans atteintes neurodégénératives (n=25), contrôles (n=15). Les tests comportementaux olfactifs ont été effectuées avec des test d'identification orthonasal et rétronasal. RÉSULTATS : Les deux groupes des patients avaient un odorat atteint; cette atteinte était observable pour la voie orthonasale et la voie rétronasale. Pour les deux groupes la voie orthonasale semble être plus affectée que la voie rétronasale. La fonction olfactive rétronasale était mieux préservée que la fonction orthonasale chez les patients atteints de la MP. Cependant, l'évaluation des voies orthonasale et rétronasale ne permet pas de discriminer un patient ayant la MP, d'un patient ayant un TO sans atteintes neurodégénératives. CONCLUSION : Considérant que l'olfaction rétronasale joue un rôle important dans les comportements alimentaires des patients atteints de la MP et qu'elle est mieux préservée que la fonction orthonasale, elle pourrait contribuer aux conséquences métaboliques de la maladie.

RÉPONSE ÉLECTROPHYSIOLOGIQUE TRIGÉMIALE SPÉCIFIQUE DANS LA MALADIE DE PARKINSON

Cécilia Tremblay[1], Rosa Emrich[2], Annachiara Cavazzana[2], Thomas Hummel[2], Antje Haehner[2], Johannes Frasnelli[1,3]
[1]Université du Québec à Trois-Rivières, [2]Technical university of Dresden, [3]centre de recherche de l'hopital Sacré-coeur de Montréal

Le trouble de l'odorat est un symptôme non-moteur fréquent observé chez 90 à 96% des patients atteints de la maladie de Parkinson. Il apparaît tôt dans le développement de la maladie, jusqu'à 20 ans avant l'apparition des troubles moteurs et du diagnostic. D'où l'intérêt d'étudier l'odorat pour aider au diagnostic précoce de la maladie. Toutefois, le trouble olfactif n'est pas spécifique de la maladie, il est très fréquent et touche environ 20% de la population générale avec de nombreuses causes possibles (infection virale, troubles sinu-nasaux, trauma, etc.) Il est donc important de différencier un trouble de l'odorat associé à la maladie de Parkinson à d'autres troubles de l'odorat d'origine différente. Une avenue potentielle est l'étude du système trigéminal, il est intimement lié au système olfactif et permet la perception des sensations de piquant, brûlure, chaleur, rafraîchissant des odeurs. Le système trigéminal est typiquement affecté dans les autres troubles de l'odorat.Toutefois, il semble que le système trigéminal n'est pas affecté de la même façon dans la maladie de Parkinson. Le but de cette étude est d'étudier la sensibilité trigéminale chez des patients atteints de la maladie de Parkinson et les comparer avec des patients présentant d'autres troubles de l'odorat non-Parkinsonniens et des participants contrôles. Nous avons donc mesuré des réponses électrophysiologiques de la muqueuse nasale et du cerveau en réponse à un stimulus trigéminal. Nos résultats ont démontré que les patients avec des troubles de l'odorat non-parkinsonien présentent des latences prolongées comparativement aux patients avec la maladie de Parkinson et aux contrôles pour la mesure de la réponse de la muqueuse nasale. De plus, les patients atteint de la maladie de Parkinson ont de plus grandes amplitudes de la réponse centrale que les patients avec un trouble de l'odorat. Nos résultats suggèrent un patron d'atteinte chimiosensoriel spécifique dans la maladie de Parkinson avec un système olfactif atteint et un système trigéminal qui semble intact. L'étude du système trigéminal est une avenue prometteuse pour différencier un trouble de l'odorat spécifique à la maladie de Parkinson et mener ultérieurement au développement d'outils de diagnostic précoces de la maladie.

STRUCTURAL BRAIN ALTERATIONS IN PARKINSON'S DISEASE PATIENTS WITH POLYSOMNOGRAPHY-CONFIRMED RBD

Shady Rahayel[1,2,3], Malo Gaubert[1,2], Ronald B. Postuma[1,4], Jacques Montplaisir[1,5], Julie Carrier[1,3,6], Oury Monchi[3,4,7,8], David Rémillard-Pelchat[1,2], Pierre-Alexandre Bourgouin[1,2], Michel Panisset[9], Sylvain Chouinard[9], Sven Joubert[3,6], Jean-François Gagnon[1,2,3]

[1]Centre for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur de Montréal, Montreal, Canada, [2]Department of Psychology, Université du Québec à Montréal, Montreal, Canada, [3]Research Centre, Institut universitaire de gériatrie de Montréal, Montreal, Canada, [4]Department of Neurology, Montreal General Hospital, Montreal, Canada, [5]Department of Psychiatry, Université de Montréal, Montreal, Canada, [6]Department of Psychology, Université de Montréal, Montreal, Canada, [7]Department of Radiology, Radio-Oncology, and Nuclear Medicine, Université de Montréal, Montreal, Canada, [8]Departments of Clinical Neurosciences, Radiology, and Hotchkiss Brain Institute, University of Calgary, Calgary, Canada, [9]Unité des troubles du mouvement André-Barbeau, Centre Hospitalier de l'Université de Montréal, Montreal, Canada

INTRODUCTION: Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of muscle atonia and the presence of abnormal motor activity during REM sleep. The gold standard to diagnose RBD is through video-polysomnography (PSG), which allows detecting excessive tonic and phasic activity during REM sleep. PSG-confirmed RBD affects 33% to 46% of Parkinson's disease (PD) patients and the presence of RBD in PD is associated with a more severe clinical phenotype. However, the structural brain abnormalities associated with RBD in PD patients remain poorly understood. Only a few studies investigated brain structural metrics in PD with RBD and they had some methodological issues such as a questionnaire-based diagnosis of RBD, the use of an uncorrected statistical threshold for neuroimaging analysis, and the lack of surface-based analyses. Here, we performed whole-brain mapping of cortical and subcortical tissues in PD patients with PSG-confirmed RBD, PD patients without RBD, and healthy subjects using surface-based cortical thickness analysis, voxel- and deformation-based morphometry (VBM and DBM), and subcortical shape and volume analyses. METHODS: Thirty PD patients, including 15 patients with RBD, were recruited and compared to 41 healthy controls. All participants underwent sleep laboratory, neurological and neuropsychological exams, and a 3T MRI acquisition of T1-weighted images. Surface-based cortical thickness, VBM, and DBM analyses were performed using CAT12 toolbox for SPM12. Subcortical structures were also investigated for shape and volume using FSL-FIRST. Group-based analyses were performed using general linear modeling, with age, sex, and education (and total intracranial volume for volume-based analysis) used as covariates. PD subgroups were compared with UPDRS-III and MCI status also added as covariates. We also performed regression analysis between phasic and tonic motor activity during REM sleep and structural metrics. Results were considered significant when below the familywise error-corrected threshold of $p<0.05$. RESULTS: Patients with RBD showed cortical thinning in the perisylvian and inferior temporal cortices and shape contraction in the putamen compared to patients without RBD. Compared to controls, patients with RBD had extensive cortical thinning and volume loss, brainstem volume was reduced, and shape contraction was found in the basal ganglia and hippocampus. Patients without RBD showed more restricted thinning in the sensorimotor, parietal, and occipital cortices, reduced volume in the midbrain as well as in temporal and more posterior areas, and shape contraction in the pallidum and hippocampus. Moreover, tonic REM sleep motor activity was associated with extensive thinning in frontal, temporal, parietal and occipital cortex and shape contraction in the left thalamus, whereas phasic REM sleep motor activity was associated with thinning in more restricted areas of the frontal, temporal, and parietal cortices and with surface contraction in the left thalamus. CONCLUSIONS: The presence of RBD in PD was associated with extensive cortical and subcortical structural abnormalities, suggesting more severe neurodegeneration in PD patients with RBD.This is in line with the more severe and aggressive clinical phenotype generally found in this population. Our study also suggests that surface-based cortical and subcortical investigations may reveal more structural abnormalities in this population than would other methods such as volume-based approaches previously used in the literature.

INVESTIGATING THE MICRORNA-PROTEIN NETWORK REGULATING ALPHA-SYNUCLEIN

Alix Salvail-Lacoste[1], Caudèle Lemay-St-Denis[1], Pascale Legault[1]
[1] Département de biochimie et médecine moléculaire de l'Université de Montréal

MicroRNAs (miRNAs) are small non-coding RNAs that silence gene expression by targeting complementary sequences within mRNA molecules. In Parkinson's disease (PD), decreased levels of select miRNAs that target the α-synuclein mRNA have been observed, which directly correlate with increased levels of α-synuclein. Given that the accumulation and aggregation of the α‑ synuclein protein is one of the major contributors to PD pathogenesis, it is of critical importance to better understand how the levels of α-synuclein-targeting miRNAs are regulated. We hypothesize that select proteins interact with the immature forms of a-synuclein-targeting-miRNAs to regulate their maturation, which leads to increased levels of a‑ synuclein in affected neurons. To investigate miRNA processing in a cellular model relevant to PD, we established in our laboratory the human SH-SY5Y neuroblastoma cell line, which is commonly used in PD research. For our investigations, the SH‑ SY5Y cells are grown under three different conditions to generate: 1) control undifferentiated cells; 2) differentiated cells and 3) differentiated cells treated with the MPP+ neurotoxin (PD model cells). To identify a-synuclein-targeting miRNAs that undergo post-transcriptional regulation, we are measuring levels of immature and mature miRNA forms by qPCR under the three different growth conditions. We are also identifying candidate proteins that may regulate the maturation of each of these miRNAs by performing affinity purification and quantitative mass spectrometry (MS) studies with the stem-loop that is common to immature miRNA forms. Once these candidate proteins are identified, we will use in vitro and in vivo assays to determine if and how candidate proteins regulate miRNA maturation. All together, our results will provide a deeper understanding of the RNA-protein network controlling α-synuclein levels.

B-NEUREXIN CONTRIBUTES TO A-SYNUCLEIN PATHOLOGY IN PARKINSON'S DISEASE

Aurélie Fallon[1,3], Alfred Lee[2,3], Yusuke Naito[2,3], Hideto Takahashi[1,2,3]
[1]Université de Montréal, [2]McGill University, [3]IRCM

Parkinson's disease (PD) is a neurodegenerative disease associated with an α-synuclein (α-syn) pathology, but its underlying molecular mechanisms remain unknown. α-syn is the primary component of Lewy bodies and Lewy neurites, both present in PD and Dementia with Lewy body (DLB). α-syn can form oligomers and fibrils, which are toxic for neurons and synapses. Yet, little is known about how it leads to synaptic pathology. Involving still unidentified mechanisms, α-syn could be released and uptaken from neuron to neuron, resulting in spreading of α-syn pathology which could be linked to the disease's progression in PD and DLB. We have recently found that α-syn interacts with the β-isoform of the neurexin (NRX) family members (β-NRXs). NRXs are presynaptic cell adhesion molecules that regulate synapse formation, plasticity, neurotransmitter release and cognitive function. My project is to evaluate how the α-syn-β-NRX interaction contributes to α-syn pathology and spreading. We hypothesize that this interaction affects synaptic function and composition of NRXs and mediates neuron-to-neuron transmission of α-syn. To test our hypothesis, I will first characterize α-syn-NRX interaction by performing cell surface binding assays and pull-down assays. Second, I will characterize the effects of α-syn on NRX trafficking and functions by performing an internalization assay and an artificial synapse formation assay, respectively. Finally, I will elucidate if NRXs mediate the uptake and the propagation of α-syn by performing respectively pH-Rodo uptake assays and microfluid three chamber assays. This work will contribute to our better understanding of molecular mechanisms of α-syn pathology and spreading, providing new molecular insight into PD dementia.

EXTRACELLULAR VESICLES DERIVED FROM ERYTHROCYTES: BIOMARKER AND VEHICLE FOR PATHOLOGICAL PROTEIN SPREAD IN PARKINSON DISEASE

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Background. Parkinson's disease (PD) is a complex disorder of which the clinical profile includes motor symptoms and a wide range of cognitive and non-motor features. The last few years of research has seen our understanding of PD change dramatically. One very important realization that has been agreed upon by the scientific community is that PD is a heterogeneous pathology with an equally heterogeneous clinical course. This observation has highlighted how the search of biomarkers is crucial as they could serve to rapidly and accurately confirm diagnosis, predict disease evolution and validate treatment efficacy. Recently, this growing field of research has included the investigation of extracellular vesicles (EV); small entities that carry critical molecules and which mediate cell-to-cell communication in both physiological and disease conditions. Their protein cargo, cell signature and availability in all bodily fluids make EV very attractive candidate biomarkers. Of significance importance in our understanding of the disease has also been the observation of Lewy body pathology in healthy fetal ventral mesencephalic transplants implanted into the brains of PD patients. This discovery has led to a whole new theory on the prion-like behaviour of α-Synuclein (α-Syn). Interestingly, α-Syn is also present in EV, which could represent a route by which the pathological protein propagates between cells. Objectives. Based on these observations, we designed a study to undertake two specific objectives. 1) We sought to characterize the nature, profile and protein signature of EV in the plasma of PD patients vs age- and sex-matched healthy individuals (Controls) and how they correlate to clinical measures of disease state. 2) Ongoing pre-clinical work aims at determining if/how EV, with their pathological protein load, can cross the blood brain barrier (BBB) and thereby contribute to dissemination of pathology. Methods. Blood samples were collected from 60 PD as well as 37 Controls. The patients, at the time of blood sampling, also underwent a battery of clinical tests. An additional and independent cohort of 42 PD patients was recruited to validate our findings. EV were isolated from plasma samples and exhaustively analyzed using flow cytometry and proteomics. We further used transmission electron microscopy and commercial ELISA kits to quantify their load in α-Syn and phosphorylated (serine 129) forms of the protein. The capacity of fluorescently-tagged EV to cross the BBB was evaluated using a Boyden chamber composed of primary human brain endothelial cells. Results. The most striking observation we made was that the number of plasma EV derived from erythrocytes (EEV) strongly correlated with disease states, as assessed using the total Unified Parkinson Disease Rating Scale (UPDRS) scores; findings which were validated in a second independent cohort. We also identified that out of the 818 proteins found in the proteome of EEV, 8 had expressions that were significantly different in patients with various stages of PD and Controls. We detected the presence of total/phosphorylated (serine 129) α-Syn in EEV by transmission electron microscopy and ELISA, but no differences between groups were detected. In preliminary Boyden chamber experiments, we observed that the tagged EEV added to the "luminal" side of the model could move across the endothelial barrier into the "abluminal side" and that some EEV could also be found within endothelial cells. We noted that this transport was not altered using samples derived from PD patients. It should be noted that, prior to the initiation of these studies, flow cytometry was used to demonstrate that released EEV retained the fluorescence from the labeled human erythrocytes. Conclusion and perspectives. We have identified a novel biomarker in the blood of patients with PD that correlates with disease stage and which is derived from 2 measures: the number of EEV and the expression of 8 different proteins. We planned to replicate these results in a larger cohort of patients (200 controls and 200 patients at various stages of PD). We also showed the presence of both normal and pathological forms of α-Syn in EEV and the transport of EEV across an in vitro model of BBB. Future experiments will use 1) a 3D in vitro BBB model which includes microfluidic, endothelial cells, astrocytes and pericytes as well as 2) an in situ brain perfusion (ISBP) approach applied to parkinsonian mice and controls. These combined methods will shed light on new pathogenic processes and possibly identify EEV as an important novel therapeutic target.

SPHINGOSINE-1-PHOSPHATE RECEPTORS MODULATORS DECREASE NEUROINFLAMMATION AND PREVENT PARKINSON'S DISEASE SYMPTOMS IN THE MPTP MOUSE MODEL

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Sphingosine-1-phosphate (S1P) is a potent bioactive lipid mediator that acts as a natural ligand upon binding to five different receptors that are located in astrocytes, oligodendrocytes, microglial and neuronal cells. Recently, global activation of these receptors by FTY720 (Fingolimod) has been suggested to provide neuroprotection in animal model of Parkinson's disease (PD). Among S1P receptors, the subtype 1 (S1P1R) has been linked to features of neuroprotection and, using the selective agonist SEW2871, the present investigation assessed potential benefits (and mechanisms) of this receptor subtype in an established animal model of PD. We demonstrated that oral treatments with SEW2871 are able to provide protection to the same levels than FTY720 against loss of dopamine neurons and motor deficits in the MPTP (30 mg/kg, i.p., 5 days) mouse model of PD. At the molecular level, we observed that the beneficial effects of both S1PR agonists were not associated with alterations in ERK and Akt levels, two markers of molecular adaptations in the striatum neurons. However, these compounds have the capacity to fully prevent neuroinflammation such as the activation of astrocytes and glial cells, as well as MPTP-incuded reduction of BDNF levels in key regions of the brain implicated in motor functions. These findings suggest that selective S1P1R modulation has the ability to attenuate devastating brain inflammation and provide neuroprotection in response to MPTP neurotoxicity. Targeting S1P1R in PD therapy may represent a prominent candidate for treatment of this neurodegenerative conditions. KEYWORDS S1P receptors; FTY720; SEW2871; MPTP; Neuroinflammation; Neuroprotection

THE THERAPEUTIC POTENTIAL OF CYSTEAMINE TO TREAT VARIOUS FEATURES OF PARKINSON'S DISEASE

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To date, medical and surgical interventions offered to patients with Parkinson's disease (PD) serve only to manage clinical symptoms; they have not shown the capacity to halt nor reverse degenerative processes. There is thus an urgent need to identify and/or develop therapeutic strategies that will demonstrate 'disease modifying' capacities. The molecule cystamine (Cys), and its reduced form cysteamine (Cye), act via a number of pathways targeted in PD pathogenesis. They are capable of promoting the secretion of neurotrophic factors, the inhibition of oxidative stress, the reduction of inflammatory responses but of critical importance, they can cross the blood brain barrier and are already in use for a number of clinical indications. In the last decade, our laboratory has accumulated compelling evidence that both Cys and Cye can halt, and possibly reverse, ongoing neurodegenerative processes in the classic 6-hydroxydopamine (6-OHDA) mouse model. Additional experiments conducted in dopaminergic explants demonstrated the effects of Cye on axogenesis and neurite sprouting following exposure to 6-OHDA. More recently, we have assessed the therapeutic potential of Cye using Thy-1 a-synuclein (a-syn) mice over-expressing full-length human wild-type a-syn given the obvious need to target Lewy bodies in any future therapies. Two-month (pre) and 8-month old (post) a-Syn and age- sex-matched control mice were treated once daily with Cye (i.p. 20mg/kg) for a period of 6 weeks at the end of which they were assessed using a battery of well-established motor tests (open field, cylinder, challenging beam, pole test and inverted grid). At sacrifice, a series of western blots (WB) were performed on brain extracts for neuronal and synaptic markers (TH, Snap 25, PSD-95, Drebrin, Septin-3, Synaptophysin and VGlut-1), neuroinflammatory signs (GFAP and Iba-1), neurotrophic factors (pro-BDNF, BDNF), TGase-2, and levels of different forms of a-Syn (Human a-Syn, S-129-p- a-Syn and S-87-p- a-Syn). Both pre- and post a-syn mice treated with Cye showed significant improvements in muscle strength, fine motor coordination and balance. WB results revealed an overall reduction in a-Syn levels in a-Syn mice treated with Cye. Moreover, these mice displayed increased levels of TH, pro- and mature BDNF levels after treatment with Cye. Neuroinflammation in treated mice was also attenuated as seen by lowered Iba-1 levels compared to those treated with saline; results corroborated with immunohistochemical analysis of the number and morphology of Iba1 labelled microglia. TGase 2 levels were also significantly reduced in α-syn mice treated with Cye. Our findings show that Cye is both neuroprotective in young adults and neurorestorative in aged a-Syn mice with a full-blown motor phenotype, as seen in the behavioural and post-mortem readouts. To mimic, as closely as possible, a clinical context, the benefits of cysteamine were additionally tested in differentiated induced pluripotent stem cells (iPSCs) derived from PD and matched Control subjects. In vitro screens of various doses of Cye (200, 300, 400 and 500μM) in 6-OHDA treated DAergic neurons derived from iPSCs were performed. Neurons were cultured for 4 weeks before exposure to toxins and cysteamine treatments was commenced. After 24 hours, the cultures were fixed, immunolabeled for a-syn, TH, microtubule associated protein 2 (Map2) and hoechst (nuclei) and imaged. Following exposure to 6-OHDA alone, the cultures depicted significant blebbing and fragmentation. In cultures of SNCA neurons treated with Cye, intact/healthy neurites were more frequently observed. Overall, our in vivo and in vitro findings support the hypothesis that Cye can act as a disease-modifying molecule by rescuing/restoring motor abilities via, in part, enhanced DAergic neurons survival. With our preliminary in vitro results bolstering our in vivo findings, we make the case for advancing Cye to clinical trials aimed at testing the efficacy, safety and disease-modifying properties of Cye in cohorts of early-stage PD patients.

ANOMALIES DE LA MATIÈRE GRISE EN LIEN AVEC LA DÉPRESSION ET L'ANXIÉTÉ DANS LE TROUBLE COMPORTEMENTAL EN SOMMEIL PARADOXAL

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INTRODUCTION: Le trouble comportemental en sommeil paradoxal idiopathique (TCSPi) est un prodrome de la maladie de Parkinson (MP) et la démence à corps de Lewy (DCL). La dépression et l'anxiété sont fréquentes dans la MP, la DCL et le TCSPi. Cette étude vise à évaluer les anomalies de la matière grise associées à la dépression et l'anxiété dans le TCSPi. MÉTHODE: Quarante-six patients ayant un TCSPi et 32 sujets sains (CTRL) ont complété un examen polysomnographique, un examen d'imagerie par résonance magnétique, un examen neurologique et une batterie de tests neuropsychologiques. Ils ont également rempli le Beck Depression Inventory Second Edition (BDI-II) et le Beck Anxiety Inventory (BAI). RÉSULTATS: Les patients ayant un TCSPi avec des symptômes dépressifs cliniquement significatifs présentaient une diminution du volume de matière grise au niveau de l'amygdale, du striatum, des régions frontales et pariéto-occipitales, comparativement aux CTRL ou aux patients ayant un TCSPi sans symptômes dépressifs. De plus, les patients ayant un TCSPi avec des symptômes anxieux cliniquement significatifs présentaient une diminution du volume de matière grise au niveau de l'amygdale et de l'hippocampe, comparativement aux CTRL ou aux patients ayant un TCSPi sans symptômes anxieux. CONCLUSION: La dépression et l'anxiété dans le TCSPi sont associées à des anomalies de la matière grise relativement distinctes.

MAPPING ALPHA-SYNUCLEIN-INDUCED BRAIN PATHOLOGY IN A MOUSE MODEL OF PARKINSON'S DISEASE

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INTRODUCTION: While the mechanism underlying Parkinson's Disease (PD) pathology has not yet been elucidated, recent evidence suggests alpha-synuclein (aSyn) may propagate in a prion-like manner, mediating the spread of pathology and contributing to PD progression. Using a transsynaptic aSyn mouse model of PD, we examined magnetic resonance imaging (MRI)-derived measures to link aSyn aggregates to brain atrophy. METHODS: Intracerebral inoculation of M83 aSynA53T transgenic mice (n=8 mice/group; 4 males and 4 females) was performed where one group received an injection of the pathological form of aSyn (preformed fibrils; PFF) in the right dorsal neostriatum, in order to accelerate the formation of intracellular PD pathology. At 90 days post-injection (the onset of symaptology), the mice were sacrificed and imaged ex-vivo (Bruker 7T; T1-weighted images; 70 µm3 voxels). Whole structure volume differences between the PFF and control (PBS; Phosphate-buffered saline) group were examined using atlas-based segmentation, performed using the MAGeT-Brain algorithm. A general linear model was used to examine brain structure volume differences between the groups, modelling sex as a covariate. False discovery rate (FDR) was used to correct for multiple comparisons. RESULTS: At FDR 15%, smaller volumes for the PFF injected mice were observed for the right thalamus and regions of the frontal cortex (left medial orbital cortex, right primary motor cortex, and left primary somatosensory cortex, hindlimb region) ($t>3.83$). CONCLUSION: The inoculation of aSyn PFF in the striatum showed widespread effects on brain morphology, particularly in regions that project to, or receive input from the injection site. These results are in accordance with immunohistochemistry studies in which showed prominent aSyn pathology in the neurons of these same structures following striatal PFF innoculation. Whole brain longitudinal examination of aSyn spreading, brain structure, and behavioural symptom progression are currently being performed to characterize a signature of network spreading and disease progression.

IDENTIFICATION OF GENETIC MODIFIERS OF ALPHA-SYNUCLEIN AGGREGATES INTRACELLULAR ACCUMULATION

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Parkinsons's disease (PD) is the second most common neurodegenerative disease, causing major motor and non-motor deficits in patients. PD and other neurodegenerative disorders known as synucleinopathies are characterized by the accumulation and propagation throughout the brain of pathological aggregates of the protein alpha-synuclein that cause neuronal dysfunction and death. Understanding how these aggregates propagate from cell to cell in a prion-like fashion thus holds great therapeutic promises. Specifically, our aim is to understand the cellular processes involved in the entry and accumulation of pathological alpha-synuclein in neural cells. To answer this question, we designed an unbiased approach to identify genes that modify the accumulation of fluorescent aggregates made of recombinant human alpha-synuclein. Using a FACS-based genome-wide CRISPR/Cas9 screen in human Retinal Pigmented Epithelial cells (RPE1), we identified key genes and pathways implicated in aggregates accumulation, including heparan sulfate proteoglycans synthesis, Golgi trafficking, and to our surprise, cell cycle/growth. The hits were further validated using targeted CRISPR/Cas9 and high-content microscopy in RPE1 cells. This yielded a list of 8 high-confidence hits specifically regulating the accumulation of alpha-syn aggregates, but not that of other cargoes (dextran, EGF, transferrin). Interestingly, we show that four hits affect heparan sulfate, a post-translational modification previously described as a receptor for proteinaceous aggregates. We are actively trying to decipher the mechanism of action of two other hits: a zinc transporter (SLC39A9) and a putative kinase (C3orf58) located in the endoplasmic reticulum and Golgi apparatus. Future experiments will include the confirmation of validated hits in PD-relevant biological models, including iPSC-derived neurons, and brain organoids and mouse models of alpha-synuclein pathology spreading. Our study provides the first truly unbiased view of the mechanisms underlying accumulation of alpha-synuclein aggregates and uncovers relevant therapeutic targets that could slow or prevent the spreading of PD pathogenesis in the brain.

MECHANISM OF PARKIN SUBSTRATES SELECTIVITY AND RECOGNITION

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RATIONAL: Early onset autosomal recessive form of Parkinson's disease (PD) is caused by a dysfunction of mitochondrial quality control pathways and mutations in key regulatory proteins such as the E3 ubiquitin ligase Parkin and PTEN-induced putative kinase 1 (PINK1). Upon cellular damages, recruitment and activation of Parkin by PINK1 leads to the ubiquitination of outer mitochondria membrane (OMM) proteins, and the subsequent clearance of damaged mitochondria by mitophagy. In the recent years, studies have revealed the hierarchical processes that are essential to drive damaged mitochondria clearance. For instance, PINK1 autophosphorylation in trans is required for ubiquitin (Ub) and Parkin Ub-like (Ubl) domain phosphorylation and activation (Rasool et al. 2018). Phospho-Ub (pUb) binding to Parkin triggers sequential conformational changes, allowing for the release of autoinhibition that Parkin adopts at the basal level to gain its catalytic activity (Tang et al. 2017; Sauvé et al. 2018). However, there is still a gap of knowledge regarding how Parkin dictates its substrate recognition and specificity once it is catalytically active. Many groups have reported Mitofusin 2 (Mfn2) as the preferred substrate of Parkin and indeed, at physiological concentrations, Parkin will selectively ubiquitinates Mfn2 over other OMM substrates. However, the exact molecular mechanism underlying this selectivity is still unknown. OBJECTIVE: Our overall objective is to determine the mechanism underlying Parkin substrate selectivity, more specifically how it preferentially ubiquitinates Mfn2 over other OMM substrates. We hypothesize that Mfn2 is preferentially ubiquitinated by Parkin because it is the first protein to be tagged with pUb moieties due to its proximity to PINK1. METHODS: Parkin's selectivity for Mfn2 will be validated using in organello reconstitution assays to assess the rate of Mfn2 ubiquitination in depolarizing cell culture systems and then compared to other OMM substrates. Subsequently, to demonstrate that Mfn2 is located in proximity to PINK1, an immunocytochemistry assay (i.e a proximity ligation assay (PLA)) will be performed in depolarizing cell culture systems. In order to demonstrate that Mfn2 is decorated with pUb moieties prior to Parkin recruitment, an ESI Q-TOF LC/MSMS mass spectrometry analysis of Ub-enriched mitochondria lysates will be performed. RESULTS: Our in organello assays revealed that out of nine tested OMM substrates, Mfn1 and Mfn2 are both preferentially ubiquitinated by Parkin. In fact, Mfn1 and Mfn2 are ubiquitinated even at low Parkin concentration (0.1 mM) whereas other OMM substrates are unmodified, even at high Parkin concentrations (1-10 mM). Subsequently, we sought to show that this specificity arises from the proximal cellular localization of Mfn2 to PINK1. Indeed, PLA confirmed that Mfn2 is localized in proximity to PINK1 in cell-based assays: PLA showed positive results in conditions where both PINK1 and Mfn2 were present. These findings explain Parkin selectivity towards Mfn2: given that Parkin recruitment is enhanced by the presence of pUb moieties generated by PINK1, any substrate that is located in proximity to PINK1 will be preferentially ubiquitinated by Parkin. Finally, given that Mfn2 is located in proximity to PINK1, we assessed whether Mfn2 is coupled to pUb at the onset of mitochondrial damage. Mass spectrometry analysis revealed the presence of total pUb moieties in the depolarized cell lysates. Various ubiquitinated and phospho-ubiquitinated OMM substrates were elucidated and ongoing optimizations aim to increase the yield of the captured products, which will lead to a better detection of Mfn2 peptides. CONCLUSION: These results altogether provide a better understanding of Parkin substrate selectivity when mitochondria are damaged. The mechanistic model that we propose is the following: Mfn2 is located in proximity to PINK1 in cells, allowing it to be the first protein tagged with pUb moieties at the onset of mitochondrial damages. Those pUb in turn act as signals for Parkin recruitment and thereby facilitating downstream Mfn2 ubiquitination. In the current literature, it is suggested that Mfn2 ubiquitination and degradation act as an important gateway to initiate mitophagy and downstream clearance of other OMM substrates (Mclelland et al. 2018). Therefore, elucidating Parkin's selectivity towards Mfn2 will result in defining a better mechanistic model for substrates clearance, allowing for finding potential therapeutic targets and a better understanding of the pathogenesis of PD.

LRRK2 ALLELES MODULATE INFLAMMATION DURING INFECTIONS

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Variants in the Leucine-rich repeat kinase-2 (LRRK2) gene are associated with Parkinson disease, leprosy and Crohn's disease risk, three conditions that feature inflammation. Due to its high expression in granulocytes and $CD68^{+}$-cells, we hypothesized that LRRK2 has a function in innate immunity. We tested this in two ways: one, by intravenous inoculation of adult mice with Salmonella typhimurium causing sepsis; two, by nasal application of newborn pups with a neurotropic respiratory-enteric-orphan virus (reovirus; serotype-3-Dearing) leading to encephalitis. In both paradigms, wild-type Lrrk2 expression was protective and showed a sex effect: female, Lrrk2-deficient animals controlled these infections less well. Conversely, mice expressing the Parkinson's-linked p.G2019S mutant showed enhanced microbial control with lower viral titres and reduced bacterial growth. The latter resulted in prolonged survival during sepsis. This gain-of-function effect by p.G2019S Lrrk2 was mediated by myeloid cells, and was abolished in animals expressing a kinase-dead variant, p.D1994S. In the context of reovirus encephalitis, p.G2019S mice showed increased mortality, despite lower titres. We attributed this outcome to enhanced host responses: Lrrk2 p.G2019S augmented chemotaxis and generated more reactive oxygen species by infected cells, in septic organs, and even in aseptic brains. Reovirus-infected p.G2019S brains also contained higher concentrations of α-synuclein. In contrast, animals expressing one or two p.D1994S allele(s) showed lower mortality rates from encephalitis. We conclude that Lrrk2 alleles alter the course of infections by modulating inflammation. The variable outcomes of infections are dependent on the host's genotype, pathogen exposure, its organ tropism and sex. Our findings may inform (pre)clinical trials aimed at LRRK2 kinase inhibition.

STRUCTURAL STUDIES OF ACTIVATED PARKIN AND ITS BINDING PARTNERS

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Mutations in the ubiquitin ligase, parkin, are responsible for a familial form of Parkinson's disease. Parkin and PINK1 kinase are the key players in the regulation of the mitochondrial quality control. In its basal state, Parkin is auto-inhibited by intra-molecular interaction, preventing the binding to E2-conjugating enzyme and access to the catalytic cysteine. In order to activate parkin, it is first recruited to the mitochondria by PINK1 through the phosphorylation of ubiquitin on the outer membrane of damaged mitochondria. Once at the mitochondria and binding to pUb, parkin is phosphorylated on its ubiquitin-like (Ubl) domain. Here,we describe the mechanism of parkinactivation after phosphorylation.The crystal structure of phosphorylated Bactrocera dorsalis (oriental fruit fly) parkin in complex with phosphorylated ubiquitin and an E2 ubiquitin-conjugating enzyme reveals the key activating step: the movement of the Ubl domain and the release of the catalytic RING2 domain. Hydrogen-deuterium exchange and NMR experiments with the various intermediates in the activation pathway confirm and extend the interpretation of the crystal structure to mammalian parkin. Our results rationalize previously unexplained Parkinson's disease mutations and the presence of internal linkers that allow large domain movements in parkin.

TARGETING THE ORPHAN NUCLEAR RECEPTOR NURS (NR4A) IN PARKINSON'S DISEASE

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The involvement of the Nurs (Nurr1, Nur77 and Nor1), members of the orphan nuclear receptor family, in dopaminergic neurotransmission is well documented. In particular, Nurr1 and Nur77 have been shown to be associated with Parkinson's Disease (PD) pathophysiology and treatment. However, the molecular mechanisms regulating their activities as yet to be properly characterized. The laboratory research program includes 3 main projects. One project focuses on the single nucleotide polymorphism (SNP) rs2603751 localized in 3'UTR of Nur77 transcript, that is associated with abnormal involuntary movements. We explore the possibility that this SNP regulate Nur77 expression through the modulation of micro-RNA activity and RNA binding protein in the context of PD. Another project aims, through a proteomic approach, to characterize Nur77 interactome and the role post-translational modifications (SUMOylation, acetylation, phosphorylation) on Nur77 activity. A third project consists to a drug discovery program. It aims to find new compounds that can bind Nurr1 and Nur77 because no selective ligand has been discovered for these nuclear receptors so far. Since they can form heterodimers with the Retinoid X Receptor (RXR), we are interested in finding compounds that can bind to Nurr1/RXR and Nur77/RXR nuclear receptor complexes. This project involves development of new assays that can specifically monitor the activity of nuclear receptor complexes in living cells, drug library screening, selectivity investigation and structure-activity relationship analysis. This research program will give us a better understanding of the regulation of Nurs (Nr4a) and will enlighten their potential as therapeutic targets in PD.

NEUROANATOMICAL ALTERATIONS UNDERLYING MILD COGNITIVE IMPAIRMENT IN REM SLEEP BEHAVIOR DISORDER

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Rapid eye movement sleep behavior disorder (RBD) is a sleep condition considered as a major risk factor for Parkinson's disease and dementia with Lewy bodies. We aimed to investigate the neuroanatomical alterations underlying mild cognitive impairment (MCI) in patients with RBD. Fifty-three patients with RBD, including 17 patients with MCI, were recruited and compared to 41 healthy controls. All participants underwent extensive clinical assessments, cognitive testing, and 3--tesla MRI acquisition of T1 anatomical images. Voxel--based morphometry and deformation--based morphometry were performed to investigate brain volume abnormalities between groups. Correlations were performed to investigate associations between MRI metrics and cognitive domains (attention and executive functions, verbal learning and memory, and visuospatial abilities). Patients with MCI had reduced volume throughout the cortex, particularly in the insula and temporal lobes. Volume abnormalities were also found in several subcortical structures including the putamen, amygdala, hippocampus, and cerebellum. Volume contraction in the midbrain was correlated with lower performance in attention and executive functions. Patients without MCI had a less severe pattern of atrophy, which nonetheless included the frontal and insular lobes and the cerebellum. Cortical and subcortical volume reductions were associated with cognitive status in patients with RBD, with more extensive abnormalities in patients with MCI. Our results are in line with the brain structural alterations reported in dementia with Lewy bodies and Parkinson's disease with dementia. Our study highlights the importance of distinguishing between subgroups of RBD patients to better understand the underlying neurodegenerative processes.

EVALUATING INFLAMMATORY STATUS OF T CELLS FROM PARKINSON'S DISEASE PATIENTS

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Immune deregulation plays a central role in the development of age related disorders such as auto-immune diseases and neurodegenerative diseases. Hence, a general inflammatory state may precede the disease onset and favor the progression of neurodegenerative diseases such as Parkinson's disease (PD). Further, impaired blood-brain barrier may allow for the migration of inflammatory immune cells to the brain exacerbating neuroinflammation. However, possible inflammatory status of immune cells, particularly T cells, in the context of PD is not evaluated. In this study, we determined phenotype of T cells isolated from blood of healthy donors (HD) and PD patients by evaluating their cytokine profile, activation status, and expression of the brain localisation markers. Our analysis show that both $CD4^+$ and $CD8^+$ T cells from PD patients express higher levels of inflammatory cytokines such as interferon-γ and GM-CSF. These inflammatory T cells expressed higher level of Survivin, an activation marker. Furthermore, both T cells and antigen presenting dendritic cells from PD patients expressed significantly higher levels of makers favoring brain localisation such as CXCR2. Taken together, these results suggest a possible role for immune inflammation in onset and/or progression of PD, and may serve as basis for use of anti-inflammatory strategies to reduce neuroinflammation in PD patients.

INTERACTION BETWEEN PROPRIOCEPTIVE SENSITIVITY AND THE ATTENTIONAL DEMAND FOR DYNAMIC POSTURAL CONTROL IN SENIORS: A PILOT STUDY

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Postural instabilities and falls among seniors have been attributed to both a decline in proprioceptive function as well as an inability to efficiently allocate attention to balance in multi-task conditions. Growing research has suggested an interaction between both proprioception and attention. However, the relationship between them has yet to be systematically investigated. This study aims to explore the interaction between proprioceptive sensitivity and attentional demand for dynamic postural control in seniors. Old and young sedentary adults will perform a postural stability limit task (maximal leaning in four directions) in five experimental conditions that vary the availability of vision and the presence of a secondary attentional task: (a) attentional task, (b) postural task with eyes open, (c) postural task with eyes closed (d) postural task with eyes open and secondary attentional task and (e) postural task with eyes closed and secondary attentional task. Ground reaction force data will be collected at 200 Hz using an AMTI force platform and center of foot pressure (COP) will be analysed. The functional limits of stability will be quantified as the maximum center of pressure excursion during voluntary leaning in each direction. We hypothesize that the greatest age-related differences in performing this stability limit task will be seen under the dual task condition because of a limitation in attentional resources available for concurrently coping with high proprioceptive and cognitive demands. Young adults showed reduced stability limits in the eyes closed conditions relative to the eyes open conditions ($P<0.05$). However, their stability limits were not significantly degraded with the addition of the attentional task. In contrast, the stability limits of the older adult were greatly affected by the addition of the attentional task, especially in the absence of vision. The preliminary findings indicate that the impact of removing visual information is more important when the older subject is required to perform the attentional task simultaneously with the postural stability limit task. This suggests that increasing the demand for proprioceptive processing increases the attentional cost of postural control. This result is consistent with a significant interaction between proprioception and attention in the postural control of seniors. Future studies will test: a) the attentional demand of proprioceptive processing when there is no postural control requirements and b) the effect of intervention programs aimed at improving proprioception for postural control in complex everyday situations involving varying levels of attentional demand. The development of such intervention programs is important for fall prevention in older adults and in neurological disorders producing proprioceptive processing impairments (e.g. Parkinson's disease).

EXOCYTOSIS OF MITOCHONDRIAL PROTEINS REQUIRES MITOCHONDRIA-DERIVED VESICLES

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Recently, Cell-Cell communication has emerged as an important tool in understanding disease mechanisms, and a therapeutic target. Specifically, cells secrete a range of extracellular vesicles (EV), that act as communication devices by transferring proteins, DNA and RNA between cells. Several studies have reported that mitochondrial proteins accumulate in these vesicles, but their role or mechanism through which this occurs remain poorly understood. Here we show that mitochondria derived vesicles (MDVs) play an important role in the selective release of mitochondrial proteins in EVs. MDVs are small vesicles that carry specific mitochondrial cargo destined to be degraded in peroxisomes and lysosomes. MDVs are also involved in immune regulation thought MHC I antigen presentation, which requires the protein Snx9. We demonstrate that Snx9 is also involved the inclusion of some mitochondrial proteins in EVs. Specifically, knockdown of Snx9 inhibited the formation of MDVs positive for the mitochondrial matrix protein mtHSP70, and their release as EVs. In contrast, MDVs and EVs positive for the outer mitochondrial membrane TOM20 were not affected, demonstrating the selective, MDV-dependent incorporation of mitochondrial cargo in EVs. Importantly, deletion of OPA1, an inner membrane protein required for mitochondrial fusion and maintenance of cristae structure, selectively caused loss of MDVs and prevented the exocytosis of inner membrane proteins. Our findings indicate that MDVs selectively target mitochondrial proteins towards EV formation in a process that is dependent on the presence of Snx9 and OPA1. These results could thus provide important insight into the mechanisms regulating cell to cell communication by EVs.

DETECTING THE COGNITIVE PRODROME OF DEMENTIA IN PARKINSON'S DISEASE

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OBJECTIVE: More than 75% of patients with Parkinson's disease (PD) will develop dementia during the course of the disease. Non-invasive and non-expensive tools to predict dementia in PD are important to identify in clinical setting individuals at high risk of dementia in this population. This study aims to identify some cognitive tests as predictors of dementia in patients with PD. METHODS: At baseline (T0), 100 PD patients without dementia were recruited. They underwent polysomnography, a neurological exam, and a complete neuropsychological evaluation to assess attention, executive functions, episodic memory, visuospatial abilities, and language. At follow-up (T1, mean follow-up of 4.3 years), 80 of these patients underwent cognitive and neurological assessments. Cognitive performance and proportion of patients with clinically impaired performance (zscore < -1.5) were compared at T0 between patients who developed dementia and patients who remained dementia-free, using Student's ttests and Chi-square tests. Moreover, PD patients who developed dementia were pair-matched at T0 according to age, sex, and education to healthy controls (2:1) and receiver operating characteristic curves were calculated to identify the psychometric properties of cognitive tests to predict dementia. RESULTS: At T1, 23 patients developed dementia and 57 were still dementia-free. At T0, PD patients who developed dementia had poorer performance and a higher proportion of clinically impaired performance on several cognitive tests assessing attention, executive functions, episodic memory, and visuospatial abilities. Two cognitive tests assessing executive functions (Trail Making Test part B and semantic Verbal Fluency) were the best predictors of dementia in PD compared to controls (area under the curve > 0.90). CONCLUSION: This study shows that cognitive tests assessing executive functions strongly predict conversion to dementia in PD patients.

LES SYMPTÔMES MOTEURS EN LIEN AVEC LA SÉVÉRITÉ DE L'ATTEINTE COGNITIVE DANS LA MALADIE DE PARKINSON

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OBJECTIF : Cette étude vise à caractériser les symptômes moteurs à l'éveil et en sommeil dans la maladie de Parkinson (MP) en lien avec la sévérité de l'atteinte cognitive. MÉTHODOLOGIE : Cent-trois sujets avec la MP ont complété une polysomnographie, un examen neurologique et une évaluation neuropsychologique complète. Quatre profils cognitifs ont été définis sur la base de l'évaluation neuropsychologique : cognition normale, plainte subjective cognitive (PSC), trouble cognitif léger à domaine unique (TCL-1) et trouble cognitif léger à domaines multiples (TCL-2). Plusieurs variables mesurant les symptômes moteurs à l'éveil et en sommeil, dont la présence d'un trouble comportemental en sommeil paradoxal (TCSP), ont été comparés entre les 4 groupes en utilisant une ANOVA univariée ou le test du Chi-carré selon le cas. RÉSULTATS : La présence d'un TCSP varie significativement entre les groupes : le groupe TCL-2 présente davantage de sujets avec un TCSP (22/27, 81%) comparativement au groupe TCL-1 (10/16, 62.5%), PSC (10/22, 45.5%) et cognition normale (6/18, 33%). Au niveau des symptômes moteurs à l'éveil, les patients du groupe TCL-2 ont une présentation plus souvent bilatérale des symptômes moteurs en début de maladie, signe d'un parkinsonisme plus sévère. CONCLUSION : Cette étude montre que les symptômes moteurs à l'éveil et en sommeil dans la MP sont plus manifestent chez les individus qui ont une atteinte cognitive plus sévère.

EFFECTS OF PARKINSON'S DISEASE ON COGNITION AND SELF-REPORTED COMPLAINTS ON MOOD AND SLEEP

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INTRODUCTION: Approximately 50% of patients with Parkinson's disease (PD) will have cognitive decline in the first five years after diagnosis. PD patients often exhibits deficits in executive functions (EF), visuospatial abilities (VA) and episodic memory. They also tend to complain about their mood (e.g., anxiety and depression) and their sleep (e.g., excessive daytime sleepiness (EDS) and insomnia). This study evaluated cognitive impairments and self-reported complaints (EDS, insomnia, depression and anxiety). Our objective is to identify factors using a data-driven approach in which we could discriminate Parkinson's patients from healthy elderly subjects. METHODS: To do so, 112 participants with PD (65.9 ± 8.8 yrs; 73 men) and 51 healthy elderly controls (63.8 ± 10.1 yrs; 28 men) underwent a comprehensive neuropsychological assessment and filled out self-reported questionnaires. A principal component analysis (PCA) was computed on all z scores associated to the tests in order to identify factors that are specific to the sample. To evaluate the difference between PD patients and healthy elderly controls, analysis of variance and covariance were performed on each of the six identified factors by the PCA. RESULTS: Four factors presented a significant group difference: two factors including cognitive tests measuring EF and VA, one memory factor, and the last factor included questionnaires related to self-reported complaints. These factors were controlled for age, sex, and education. Compared to healthy elderly controls, PD patients showed lower cognitive performances on factors associated to memory, EF and VA. Altered performances exclusive to PD combined both EF and VA whereas memory impairment was an isolated factor. As for self-reported complaints, it formed a distinct factor from cognitive performances where PD patients reported more complaints related to mood and sleep as compared to healthy elderly controls. CONCLUSION: As contrary to the classical view of cognitive functions as being separate entity working together to explain cognitive functioning, our results suggest an overlap between classical cognitive functions when impaired by Parkinson's disease. This data-driven approach, allowing data reduction, gives a new way of conceptualizing cognitive impairment in the context of a neurodegenerative disease. This study also highlights the importance to consider cognitive impairments and self-reported complaints as two distinct levels of impairments in PD.

THE INTRANASAL MPTP ADMINISTRATION IN RATS: AN ANIMAL MODEL TO STUDY NOCICEPTIVE ALTERATIONS IN THE EARLY STAGES OF PARKINSON`S DISEASE

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Pain is a non-motor alteration present in a large proportion of Parkinson's disease (PD) patients and has a significant negative impact on their quality of life. Although this symptom occurs secondarily to the motor alterations of PD, about 40% of PD patients experience pain in the early stages of PD. Considering that the pathophysiology is not well understood and there is not appropriate management for this symptom, it is important to define these alterations in rodent models of PD. Therefore, our aim was evaluated the nociceptive alterations followed the intranasal administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a model of the early stages of Parkinson's disease. For this, 32 male Wistar rats (90 days) were treated with a single i.n. infusion of MPTP (1 mg/nostril) or saline. At 7, 14 and 21 days later 20 rats (10 per group) were evaluated in von Frey and hot plate tests, and 12 rats (6 per group) were evaluated in acetone and tail flick tests. In another experiment, 24 rats (6 animals per group) also received i.n. MPTP or saline, and 14 days later received a single intraplantar administration of capsaicin (20 µL, 5 mM, right hind paw) or vehicle (0.15% ethanol in saline) and was measured the time spent licking the injected paw. In order to evaluate the motor alterations, 48 rats (8 per group) animals received MPTP or saline and were independently evaluated at 7, 14 and 21 days later in the pole test and cylinder test. The evaluators were blinded with regard to the experimental groups. (CEUA 1454/2017) Our results indicated that the MPTP induces mechanical and hot hyperalgesia at 14 and 21 days after i.n. infusion, and also increases the nociceptive responses followed the intraplantar capsaicin 14 days later. The MPTP administration did not modify the nociceptive responses followed the intraplantar acetone test and increase the latency of response to the tail flick test 14 days later. In relation to motor evaluations, the MPTP did not modify the turn time in the pole test and the rearing behavior in the cylinder. This study demonstrates that intranasal MPTP administration, an experimental model of early PD, induced nociception alterations in rats earlier than motor disabilities.

CHARACTERIZATION OF THE MITOCHONDRIAL PROCESSING PEPTIDASE IN PARKINSON'S DISEASE

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Although mitochondria contain their own genome, most mitochondrial proteins are encoded in the nucleus and translocated into mitochondria via an N-terminal mitochondrial targeting signal (MTS). In order for these proteins to localize, fold, and function correctly, their MTS must be cleaved by the mitochondrial processing peptidase (MPP) in the matrix. Recently, mutations in both MPP and its substrates MTS's have been implicated in neurodegenerative diseases, including Parkinson's disease (PD). However, beyond siRNA knockdowns and genetic studies, the structural and mechanistic implications of MPP processing in these diseases remain uncharacterized. This work focuses on the MPP processing of PINK1, a kinase whose mutations are known to cause early onset PD. In healthy mitochondria, PINK1 is imported, cleaved first by MPP, next by PARL, and is sent back to the cytosol to be degraded. Upon mitochondrial damage, PINK1 accumulates on the outer membrane to initiate mitochondrial degradation. This accumulation hinges on MPP: it has been shown that even partial knockdowns of MPP induce PINK1 OM accumulation while leaving most other substrates unaffected. Still, many questions remain: where does MPP cleave PINK1? How does MPP uniquely regulate PINK1 accumulation? How might MPP cleavage regulate the downstream proteolysis of PINK1? To answer these, we have purified the recombinant human MPP heterodimer, reconstituted its activity in vitro, and developed a mass spectrometry based platform to measure its proteolytic activity. Using synthetic MTS peptides, we have determined the MPP cleavage site on PINK1 and have probed its cleavage kinetics. Our current model highlights PINK1 as a non-canonical MPP substrate that binds tightly within the MPP active site, yet is cleaved on a distinctly slow timescale. Our cell-based assays are currently investigating this model, as well as the implications of perturbed MPP processing by monitoring the rates of PINK1 accumulation following mitochondrial damage in both PD-linked and designer MTS mutant backgrounds. Crystallization trials with human MPP both alone and in complex with substrate MTS are ongoing in our laboratory.

ASSESSING THE IMPACT OF EXCESSIVE DAYTIME SLEEPINESS ON COGNITION IN PARKINSON DISEASE

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INTRODUCTION. Excessive daytime sleepiness (EDS) is a common complaint in individuals with Parkinson's disease (PD), affecting 20 to 60% of them. Some studies in PD suggest that subjective EDS is associated with lower cognitive performance; nonetheless, this association is not always corroborated. Part of this controversy could be explained a variability in the use of less sensitive cognitive tests between studies, and the presence of a great heterogeneity of the clinical profile in PD. Hence, this study aims at assessing the impact of subjective EDS on an extensive neuropsychological evaluation in PD patients. METHODS: One hundred and thirteen participants with PD were included in the present study. They completed a comprehensive neuropsychological assessment that included attention, executive function, episodic memory and visuospatial testing. They also completed the Unified Parkinson 's Disease Rating Scale (UPDRS-III) to assess motor impairment, and the Epworth Sleepiness Scale (ESS). The participants were separated into two groups on the basis of the presence or absence of an EDS via a score higher than 11 on the ESS. Variances analyzes were subsequently performed to measure any group difference. RESULTS: The two groups did not differ in age, sex, level of education and duration of PD. No significant difference was observed between the two groups on all cognitive performance. In contrast, compared to subjects without subjective sleepiness, subjects with EDS had a higher score at UPDRS-III, suggesting a higher motor impairment. CONCLUSIONS: Although PD participants with EDS report more severe motor impairment, complaints of subjective daytime sleepiness do not appear to discriminate objective cognitive performance. Future studies could objectively evaluate EDS and its possible impacts on cognition.

INVESTIGATION OF THE DEVELOPMENTAL DOWNREGULATION OF VGLUT2 EXPRESSION IN DEVELOPING DOPAMINEA NEURONS: IMPLICATION OF THE DORSAL STRIATUM

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In Parkinson's disease, the most vulnerable neurons are found in the ventral tier of the substantia nigra (SN), while the adjacent dopamine (DA) neurons of the ventral tegmental area (VTA) are mostly spared. Although a large proportion of adult VTA DA neurons express Vglut2, a vesicular glutamate transporter, and release glutamate as a second neurotransmitter in the striatum, adult SN DA neurons typically do not have this capacity. To better understand the contribution of Vglut2 expression to the functions and vulnerability of DA neurons, we aim to better understand the developmental expression pattern of Vglut2 in DA neurons and the mechanisms that regulate expression of this transporter in DA neurons. Using an intersectional genetic approach based on Vglut2-Cre and TH-Flpo drivers, we first find that a large majority of dopaminergic neurons expressed Vglut2 at some point in their development. Using fluorescent in situ hybridization, we found that already at E14.5, subset-specific differences can be found, with Vglut2 transcript still found in caudomedial DA neurons, but with very limited expression in rostrolateral DA neurons. We are presently looking at the time course of this developmental downregulation of Vglut2. Together, these data suggest that the glutamatergic neurotransmitter identity of DA neurons is gradually suppressed during late embryonic development a finding that is in line with our previous observations showing that the percentage of DA neurons expressing Vglut2 decreases from E16.5 to P0 (Fortin et al., 2012). Intriguingly, a substantial component of the innervation of the striatum by DA neurons develops just before birth, and as such temporally overlaps with the repression of Vglut2 expression in a large portion of DA neurons. We therefore hypothesize that innervation of the striatum by DA neurons provides a signal required for postnatal repression of Vglut2. To test this hypothesis, we are presently taking advantage of a primary DA neuron striatal co-culture system, in combination with single-cell qPCR or fluorescence-activated cell sorting and population-based qPCR to examine signals that regulate Vglut2 expression. We find that Vglut2 expression is globally repressed when DA neurons are co-cultured with dorsal striatal cells, but not with ventral striatal cells. The contribution of contact-dependent and secreted signals is presently being investigated. These experiments shed new light on the mechanisms that regulate the neurochemical identity of DA neurons during development. Ongoing experiments might also provide new insights into the plasticity of the neurochemical identity of DA neurons during pathological conditions.

PHYSIOLOGY AND MORPHOLOGY OF PARKINSON'S DISEASE-VULNERABLE NEURONAL POPULATIONS IN VITRO TO BETTER UNDERSTAND SELECTIVE VULNERABILITY

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There is a growing body of evidence exploring the causative factors rendering neurons vulnerable in Parkinson's disease (PD). Much of this work posits that chronic mitochondrial oxidative stress and impaired proteostasis are driving the cellular pathological mechanisms. One key distinguishing characteristic of PD-vulnerable neurons is their vast projecting axonal arborizations, a factor thought to contribute significantly to their elevated bioenergetic needs, increased basal oxidative stress and ensuing vulnerability. Recent work in our group has provided evidence for a tight link between neuronal vulnerability, basal bioenergetics and axonal arbor size, when comparing dopaminergic (DA) neurons of the substantia nigra (SNc), ventral tegmental area (VTA) and olfactory bulb. To further strengthen and extend this hypothesis, we now aim to determine if a similar link between axonal arbor size and vulnerability can be found in other long-range projection neurons. We used a mouse primary culture system to compare noradrenergic neurons of the locus ceoruleus, serotononergic neurons of the raphe nuclei and cholinergic neurons of the dorsal motor nucleus of the vagus and pedunculopontine nucleus. We find that these neurons possess an intrinsic capacity to establish a long and complex axonal arbor that is larger than that of VTA neurons but comparable to that of SNc DA neurons. We are presently extending this comparison by evaluating mitochondrial density and polarity as well as oxidative stress in the axonal domain of these same neuronal populations. Finally, we are comparing and contrasting the relative vulnerability of these PD-vulnerable nuclei to PD-relevant in vitro stress assays including oxidative stress and proteosomal stress. Preliminary results suggest that LC neurons are surprisingly less vulnerable to hydrogen peroxide than SNc DA neurons. These data are expected to further contribute to the hypothesis that the bioenergetic phenotype of neurons plays an important role in determining their vulnerability in PD.

IN VITRO MODELS OF PARKINSON'S DISEASE AND ITS IMPACT OF NEUROPROTECTION STRATEGIES

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Parkinson's disease (PD) is a neurodegenerative disease characterized by the abnormal accumulation of proteins, such as α-synuclein, and by the substantial loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) of the brain, which then leads to the emergence of motor dysfunctions. Previous researches, some performed by our lab, suggest that the loss of DA neurons might be the results of multiple sources, such as mitochondrial dysfunction, and/or a malfunctioning protein elimination system, caused by toxins and/or genetic dispositions. However, despite the extensive literature on the subject, science is no closer to a cure than it was decades ago. One of the major obstacles in this pursuit is the transfer of therapeutic effects from in vitro models to the human body. Even though our lab focuses more on the mitochondrial dysfunction axis of PD research, to ease the identification process of neuroprotection treatments (by heightening mitochondrial efficiency), we have optimised an in vitro approach that combines the different facets of PD, in order to form a better model of the disease. This consists of a systematic comparison between 3 different stress models: an induction of mitochondrial dysfunction using MPP+ (a neurotoxin frequently used to model PD in vitro due to its specificity towards DA neurons), a perturbation of the ubiquitin-proteasome system using lactacystin (a proteasome inhibitor used to increase protein accumulation), and a knock-out (KO) of the Parkin gene (a gene highly linked to the familiar form of PD). Using these 3 complementary models, we will evaluate the therapeutic effects of multiple approaches which will increase the mitochondrial efficiency of DA neurons in order to protect them from degeneration, such as honokiol, nicotinamide riboside, and an overexpression of MCL-1 matrix.