Early cognitive decline after bilateral subthalamic deep brain stimulation in Parkinson’s disease patients with GBA mutations.

Abstract
BACKGROUND: Subthalamic nucleus deep brain stimulation (STN-DBS) has demonstrated its efficacy on motor complications in advanced Parkinson’s disease (PD) but does not modify disease progression. Genetic forms of PD have been associated with different cognitive progression profiles.

OBJECTIVE: To assess the effect of PD-related genetic mutations on cognitive outcome after STN-DBS.

METHODS: Patients with STN-DBS were screened for LRRK2, GBA, and PRKN mutations at the Pitié-Salpêtrière Hospital between 1997 and 2009. Patients with known monogenetic forms of PD from six other centers were also included. The Mattis Dementia Rating Scale (MDRS) was used to evaluate cognition at baseline and one-year post-surgery. The standardized Unified PD Rating Scale (UPDRS) evaluation On and Off medication/DBS was also administered. A generalized linear model adjusted for sex, ethnicity, age at onset, and disease duration was used to evaluate the effect of genetic factors on MDRS changes.

RESULTS: We analyzed 208 patients (131 males, 77 females, 54.3 ± 8.8 years) including 25 GBA, 18 LRRK2, 22 PRKN, and 143 PD patients without mutations. PRKN patients were younger and had a longer disease duration at baseline. A GBA mutation was the only significant genetic factor associated with MDRS change (β = -2.51, p = 0.009). GBA mutation carriers had a more pronounced post-operative MDRS decline (3.2 ± 5.1) than patients with LRRK2 (0.9 ± 4.8), PRKN (0.5 ± 2.7) or controls (1.4 ± 4.4). The motor response to DBS was similar between groups.

CONCLUSION: GBA mutations are associated with early cognitive decline following STN-DBS. Neuropsychological assessment and discussions on the benefit/risk ratio of DBS are particularly important for this population.

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Localization of motor and verbal fluency effects in subthalamic DBS for Parkinson’s disease.

Abstract
INTRODUCTION: Subthalamic nucleus deep brain stimulation (STN DBS) improves cardinal motor symptoms of Parkinson’s disease (PD) but can worsen verbal fluency (VF). An optimal site of stimulation for overall motor improvement has been previously identified using an atlas-independent, fully individualized, field-modeling approach. This study examines if cardinal motor components (bradykinesia, tremor, and rigidity) share this identified optimal improvement site and if there is co-localization with a site that worsens VF.

METHODS: An atlas-independent, field-modeling approach was used to identify sites of maximal STN DBS effect on overall and cardinal motor symptoms and VF in 60 patients. Symptom severity was assessed with the MDS-UPDRS part III and established VF scales.

RESULTS: Sites for improved bradykinesia and rigidity co-localized with each other and the overall part III site (0.09 mm lateral, 0.93 mm posterior, 1.75 mm dorsal). The optimal site for tremor was posterior to this site (0.10 mm lateral, 1.40 mm posterior, 1.93 mm dorsal). Semantic and phonemic VF sites were indistinguishable and co-localized medial to the motor sites (0.32 mm medial, 1.18 mm posterior, 1.74 mm dorsal).

CONCLUSION: This study identifies statistically distinct, maximally effective stimulation sites for tremor improvement, VF worsening, and overall and other cardinal motor improvements in STN DBS. Current electrode sizes and voltage settings stimulate
all of these sites simultaneously. However, future targeted lead placement and focused directional stimulation may avoid VF worsening while maintaining motor improvements in STN DBS.

Comprehensive Structural and Thermodynamic Analysis of Pre-Fibrillar WT α-Synuclein and its G51D, E46K and A53T Mutants by a Combination of Small-Angle X-Ray Scattering and Variational Bayesian Weighting.

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Comprehensive Structural and Thermodynamic Analysis of Pre-Fibrillar WT α-Synuclein and its G51D, E46K and A53T Mutants by a Combination of Small-Angle X-Ray Scattering and Variational Bayesian Weighting.

J Chem Inf Model. 2020 Aug 31;:
Authors: Moretti P, Mariani P, Oratore MG, Plotegeh N, Bubacco L, Beltramini M, Spinozzi F

Abstract
In-solution synchrotron Small-angle X-ray Scattering (SAXS) technique has been used to investigate an Intrinsically Disordered Protein (IDP) related to Parkinson’s disease, the α-synuclein (α-syn), in pre-fibrillar diluted conditions. SAXS experiments have been performed as a function of temperature and concentration on the Wild-Type (WT) and on the three pathogenic mutants G51D, E46K and A53T. To identify the conformers that populate the WT α-syn and the pathogenic mutants in pre-fibrillar conditions, scattering data have been analyzed by a new Variational Bayesian Weighting method (VBWSAS) based on an ensemble of conformers, which includes unfolded monomers, trimers and tetramers, both in helical-rich and strand-rich forms. The developed VBWSAS method uses a thermodynamic scheme to account for temperature and concentration effects and considers long-range protein-protein interactions in the framework of the random phase approximation. The global analysis of the whole set of data indicates that the WT α-syn is mostly present as unfolded monomers and trimers (helical-rich trimers at low T and strand-rich trimers at high T), but not tetramers, as previously derived by several studies. On the contrary, different conformer combinations characterize mutants: in α-syn G51D mutant, the most abundant aggregates at all the temperatures are strand-rich tetramers; strand-rich tetramers are also the predominant forms in the A53T mutant, but their weight decreases with temperature; only monomeric conformers, with a preference for the ones with the smallest sizes, are present in the E46K mutant. The derived conformational behavior then suggests a different availability of species prone to aggregate, depending on mutation, temperature and concentration and accounting for the different neurotoxicity of α-syn variants. Indeed, this approach may be of pivotal importance to describe conformational and aggregational properties of other IPDs.

Interaction of α-Synuclein with Phospholipids and the Associated Restructuring of Interfacial Lipid Water: An Interface-Selective Vibrational Spectroscopic Study.

Related Articles

Interaction of α-Synuclein with Phospholipids and the Associated Restructuring of Interfacial Lipid Water: An Interface-Selective Vibrational Spectroscopic Study.

Angew Chem Int Ed Engl. 2020 Aug 31;:
Authors: Biswas B, Roy S, Mondal JA, Singh PC

Abstract
Interaction of α-Synuclein (αS) with biological lipid is crucial for the onset of its fibrillation at the cell membrane-water interface. Here, we probe the interaction of αS with membrane mimicking lipid monolayer-water interfaces using surface-selective heterodyne-detected vibrational sum frequency generation (HD-VSFG) spectroscopy. Our results depict that αS interacts negligibly with zwitterionic lipid, but strongly affects the pristine air-water and charged lipid-water interfaces by perturbing the structure and orientation of the interfacial water. Specifically, the net negative αS (-9 in bulk water; pH 7.4) reorients the water as hydrogen-up (H-up) at the air-water interface; electrostatically interacts with positively charged lipids, making the interface nearly net neutral. Strangely, αS also interacts with negatively charged lipids: the net H-up orientation of the interfacial water decreases at anionic lipid-water interface, revealing a domain-specific (positively charged N-terminal) interaction of net negative αS with the negatively charged lipids at membrane surface.

Blood Flow as a Route for Bidirectional Propagation of Synucleinopathy in Parkinson’s Disease?

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Blood Flow as a Route for Bidirectional Propagation of Synucleinopathy in Parkinson’s Disease?
Antioxidant Modulation of mTOR and Sirtuin Pathways in Age-Related Neurodegenerative Diseases.

Abstract
In the human body, cell division and metabolism are expected to transpire uneventfully for approximately 25 years. Then, secondary metabolism and cell damage products accumulate, and ageing phenotypes are acquired, causing the progression of disease. Among these age-related diseases, neurodegenerative diseases have attracted considerable attention because of their irreversibility, the absence of effective treatment and their relationship with social and economic pressures. Mechanistic (formerly mammalian) target of rapamycin (mTOR), sirtuin (SIRT) and insulin/insulin growth factor 1 (IGF1) signalling pathways are among the most important pathways in ageing-associated conditions, such as neurodegeneration. These longevity-related pathways are associated with a diversity of various processes, including metabolism, cognition, stress reaction and brain plasticity. In this review, we discuss the roles of sirtuin and mTOR in ageing and neurodegeneration, with an emphasis on their regulation of autophagy, apoptosis and mitochondrial energy metabolism. The intervention of neurodegeneration using potential antioxidants, including vitamins, phytochemicals, resveratrol, herbs, curcumin, coenzyme Q10 and minerals, specifically aimed at retaining mitochondrial function in the treatment of Alzheimer’s disease, Parkinson’s disease and Huntington’s disease is highlighted.

PMID: 32865663 [PubMed — as supplied by publisher]

Vascular risk factors, white matter lesions and cognitive impairment in Parkinson’s disease: the PACOS longitudinal study.

Abstract
The goal of this protocol is to establish a robust and reproducible model of α-synuclein accumulation in primary dopamine neurons. Combined with immunostaining and unbiased automated image analysis, this model allows for the analysis of the effects of drugs and genetic manipulations on α-synuclein aggregation in neuronal

PMID: 32865628 [PubMed — as supplied by publisher]
cultures. Primary midbrain cultures provide a reliable source of bona fide embryonic dopamine neurons. In this protocol, the hallmark histopathology of Parkinson’s disease, Lewy bodies (LB), is mimicked by the addition of α-synuclein pre-formed fibrils (PFFs) directly to neuronal culture media. Accumulation of endogenous phosphorylated α-synuclein in the soma of dopamine neurons is detected by immunostaining already at 7 days after the PFF addition. In vitro cell culture conditions are also suitable for the application and evaluation of treatments preventing α-synuclein accumulation, such as small molecule drugs and neurotrophic factors, as well as lentivirus vectors for genetic manipulation (e.g., with CRISPR/Cas9). Culturing the neurons in 96 well plates increases the robustness and power of the experimental setups. At the end of the experiment, the cells are fixed with paraformaldehyde for immunocytochemistry and fluorescence microscopy imaging. Multispectral fluorescence images are obtained via automated microscopy of 96 well plates. These data are quantified (e.g., counting the number of phospho-α-synuclein-containing dopamine neurons per well) with the use of free software that provides a platform for unbiased high-content phenotype analysis. PFF-induced modeling of phosphorylated α-synuclein accumulation in primary dopamine neurons provides a reliable tool to study the underlying mechanisms mediating formation and elimination of α-synuclein inclusions, with the opportunity for high-throughput drug screening and cellular phenotype analysis.

PMID: 32865527 [PubMed — as supplied by publisher]

Disruption of neocortical synchronisation during slow-wave sleep in the rotenone model of Parkinson’s disease.

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Increased energy expenditure and activated β3-AR-cAMP-PKA signaling pathway in the intercapsular brown adipose tissue of 6-OHDA-induced Parkinson’s disease model rats.

Related Articles

Increased energy expenditure and activated β3-AR-cAMP-PKA signaling pathway in the intercapsular brown adipose tissue of 6-OHDA-induced Parkinson’s disease model rats.

Anat Rec (Hoboken). 2020 Aug 31;:

Authors: Lian H, Zhou L, Zhang Y, Song YH, Zhang YM, Cao ZH, Wang ZY

Abstract

OBJECTIVE: To explore the possible mechanism of weight loss in Parkinson’s disease (PD) METHODS: Bilateral injections of 6-hydroxydopamine (6-OHDA) into substantia nigra (SN) were performed to induce the PD model rats. The rotared test, food intake, body weight and intercapsular brown adipose tissue (IBAT) weight were recorded 6 weeks postoperation. HE staining was performed to observe the morphology of multilocular adipose cells in IBAT. Immunohistochemistry and western blot were used to determine the protein levels of tyrosine hydroxylase (TH) in the SN, and the levels of uncoupling protein 1 (UCP1), peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), phosphorylated-hormone sensitive lipase (p-HSL), HSL, TH, β3-adrenergic receptor (β3-AR), cyclin adenosine monophosphate (cAMP) and protein kinase A (PKA) in IBAT.

RESULTS: After treatment with 6-OHDA for 6 weeks, 6-OHDA rats exhibited decreased TH expression in SN accompanied with shortened staying time on the rotating rod. This motor impairment paralleled with no significant alteration in body mass, IBAT weight and food intake until the end of the experimental protocol. However, the decrease diameter of single fat vesicle in IBAT was observed in 6-OHDA group. Meanwhile, compared with the control group, the protein expression of UCP1, PGC-1α, p-HSL, TH, β3-AR, cAMP and PKA in IBAT were increased significantly in 6-OHDA group whereas no obvious change in the expression of HSL.

CONCLUSION: The present study suggested an increased energy expenditure and activation of β3-AR-cAMP-PKA signaling pathway in the IBAT after the destruction of dopamine system in the SN of rat. This article is protected by copyright. All rights reserved.

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Disruption of neocortical synchronisation during slow-wave sleep in the rotenone model of Parkinson’s disease.

J Sleep Res. 2020 Aug 31;e13170

Authors: Dos Santos Lima GZ, Targa ADS, de Freitas Cavalcante S, Rodrigues LS, Fontenele-Araújo J, Torterolo P, Andersen ML, Lima MMS

Abstract

Parkinson’s disease motor dysfunctions are associated with improperly organised neural oscillatory activity. The presence of such disruption at the early stages of the disease in which altered sleep is one of the main features could be a relevant predictive feature. Based on this, we aimed to investigate the neocortical synchronisation dynamics during slow-wave sleep (SWS) in the rotenone model of Parkinson’s disease. After rotenone administration within the substantia nigra pars compacta, one group of male Wistar rats underwent sleep-wake recording. Considering the association between SWS oscillatory activity and memory consolidation, another group of rats underwent a memory test. The fine temporal structure of synchronisation dynamics was evaluated by a recently developed technique called first return map. We observed that rotenone administration decreased the time spent in SWS and altered the power spectrum within different frequency bands, whilst it increased the transition rate from a synchronised to desynchronised state. This neurotoxin also increased the probability of longer and decreased the probability of shorter desynchronisation events. At the same time, we
observed impairment in object recognition memory. These findings depict an electrophysiological fingerprint represented by a disruption in the typical oscillatory activity within the neocortex at the early stages of Parkinson’s disease, concomitant with a decrease in the time spent in SWS and impairment in recognition memory.

PMID: 32865294 [PubMed — as supplied by publisher]

Leveraging sequence-based faecal microbial community survey data to identify alterations in gut microbiota among patients with Parkinson’s disease.

Related Articles

Leveraging sequence-based faecal microbial community survey data to identify alterations in gut microbiota among patients with Parkinson’s disease.

Eur J Neurosci. 2020 Aug 31;:

Abstract
Parkinson’s disease is a common degenerative disease of the elderly. Although the majority of studies have focused on the central nervous system (CNS) features of Parkinson’s Disease, recent findings suggest there is a functional link between the gut microbiome and the hallmarks of the disease. PubMed, Web of Science, EMBASE, and other Chinese and English databases were searched for relevant literature. Studies on changes to intestinal microbiota in Parkinson’s patients were retrieved and systematically reviewed. Alpha diversity indices and a random effect model were used to analyse significantly altered microbiota. A total of nine studies were included in this retrospective analysis, four of which contained raw data. Alpha diversity was significantly different between control and Parkinson’s Disease patients in two of the four studies. Using the raw data from four individual studies, we observed differences in the phyla Bacteroidetes and Actinobacteria. Additionally, differences were observed between control and Parkinson’s Disease patients at the level of family (Prevotellaceae and Lactobacillaceae) and genus (Bifidobacterium and Clostridium). This study confirmed that changes in the microbiome are a consistent feature of Parkinson’s Disease patients and therefore may contribute to the onset of disease.

PMID: 32865266 [PubMed — as supplied by publisher]

IGF-1 inhibits MPTP/MPP+-induced autophagy on dopaminergic neurons through the IGF-1R/PI3k-Akt-mTOR pathway and GPER.

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IGF-1 inhibits MPTP/MPP+-induced autophagy on dopaminergic neurons through the IGF-1R/PI3k-Akt-mTOR pathway and GPER.

Am J Physiol Endocrinol Metab. 2020 Aug 31;:
Authors: Wang XW, Yuan LJ, Yang Y, Zhang M, Chen WF

Abstract
Autophagy dysfunctions are involved in the pathogenesis of Parkinson disease (PD). In the present study, we aimed to evaluate the involvement of G-protein coupled estrogen receptor (GPER) in the inhibitory effect of insulin-like growth factor-1 (IGF-1) against excessive autophagy in PD animal and cellular models. 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) treatment significantly induced mice movement disorder and decreased the protein level of tyrosine hydroxylase (TH) in the substantia nigra (SN) and dopamine (DA) content in striatum. Along with the dopamine neuron injury, we observed significant up-regulations of microtubule associated light chain-3 II (LC3-Ⅱ) and α-synuclein as well as a down-regulation of P62 in MPTP-treated mice. These changes could be restored by IGF-1 pretreatment. Co-treatment with IGF-1R antagonist JB-1 or GPER antagonist G15 could block the neuroprotective effects of IGF-1. 1-methyl-4-phenylpyridinium (MPP+) treatment could also excessively activate autophagy along with the reduction of cell viability in SH-SY5Y cells. IGF-1 could inhibit the neurotoxicity through promoting the phosphorylation of Akt and mTOR, which could also be antagonized by JB-1 or G15. These data suggest that IGF-1 inhibits MPTP/MPP+-induced autophagy on dopaminergic neurons through the IGF-1R/PI3k-Akt-mTOR pathway and GPER.

PMID: 32865008 [PubMed — as supplied by publisher]

Synucleinopathy alters nanoscale organization and diffusion in the brain extracellular space through hyaluronan remodeling.

Related Articles

Synucleinopathy alters nanoscale organization and diffusion in the brain extracellular space through hyaluronan remodeling.

Nat Commun. 2020 07 10;11(1):3440
Abstract

In recent years, exploration of the brain extracellular space (ECS) has made remarkable progress, including nanoscopic characterizations. However, whether ECS precise conformation is altered during brain pathology remains unknown. Here we study the nanoscale organization of pathological ECS in adult mice under degenerative conditions. Using electron microscopy in cryofixed tissue and single nanotube tracking in live brain slices combined with super-resolution imaging analysis, we find enlarged ECS dimensions and increased nanoscale diffusion after α-synuclein-induced neurodegeneration. These animals display a degraded hyaluronan matrix in areas close to reactive microglia. Furthermore, experimental hyaluronan depletion in vivo reduces dopaminergic cell loss and α-synuclein load, induces microgliosis and increases ECS diffusivity, highlighting hyaluronan as diffusional barrier and local tissue organizer. These findings demonstrate the interplay of ECS, extracellular matrix and glia in pathology, unraveling ECS features relevant for the α-synuclein propagation hypothesis and suggesting matrix manipulation as a disease-modifying strategy.

PMID: 32651387 [PubMed — indexed for MEDLINE]