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Editorial: Neuroprotection and Disease Modification in Parkinson's Disease

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Editorial on the Research Topic

Neuroprotection and Disease Modification in Parkinson's Disease

Parkinson's disease (PD) is the second prevailing neurodegenerative disease in the world after Alzheimer's. It affects about 1% of adults over 65 years old, with a growing incidence as the global population ages. Bradykinesia, tremor, and rigidity are the typical symptoms of PD. Yet, a myriad of non-motor symptoms like mood, sleep, and autonomic alterations impair patients' life quality. Current treatments focus on PD symptoms but do not slow disease progression, and no preventing treatment is yet available against PD.

Identifying drugs and therapies that can change the course of PD is one of the most critical yet unmet needs in current pharmacological approaches to this disease. Past efforts have been ineffective in identifying these desired pharmaceuticals. Therefore, basic studies aiming at testing the potential neuroprotective properties of new molecules are needed.

This Research Topic focuses on addressing new pharmacological neuroprotective and disease-modifying strategies for PD, their target pathways, and their effects on humans. The goal is to contribute with updated information to developing new therapeutic strategies to prevent PD and halt its progression.

The topics covered are as follows:

Acylated Ghrelin protects Against 6-OHDA-induced Neurotoxicity by Regulating Autophagic Flux (He et al.). The authors show that ghrelin inhibits apoptosis and regulates autophagic flux thus protecting from 6-OHDA-induced neurotoxicity in rats and SH-SY5Y cells. Despite an action of autophagy activation, the neuroprotective effect of ghrelin is more reliant on restoration of TFEB level and relief of autophagic flux dysfunction. The importance of preserving functional autophagic flux against neurodegeneration is suggested, providing further basis for ghrelin as a potential drug for PD treatment (Jiang et al., 2008; Suda et al., 2018; He et al., 2018).

A Ketone Ester Drink Enhances Endurance Exercise Performance in PD (Norwitz et al.). Consumption of a ketone ester drink increased 24 ± 9% the time PD individuals sustained an 80-rpm cycling cadence compared with performance after drinking an isocaloric control beverage. Possible neuroprotective mechanisms are discussed. Ketone ester might synergize with exercise practice, holding potential as an indirect disease-modifying therapy in PD (Norwitz et al., 2019; Clarke et al., 2012).

Contributive Role of TNF-α to L-DOPA-Induced Dyskinesia in a Unilateral 6-OHDA Lesion Model of Parkinson's Disease (Pereira et al.). Chronic L-dopa treatment induced a sustained glial inflammatory response, increasing the pro-inflammatory cytokines TNF-α and IL-1β in the striatum of 6-OHDA-lesioned dyskinetic mice. The antidyskinetic treatment combining capsazepine + cannabidiol prevented TNF-α production but not IL-1β in the dopamine-

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denervated striatum and glutamate-induced TNF-α release in astrocyte cultures. TNF-α release by glutamate-activated astrocytes may contribute to L-dopa-induced dyskinesia in a unilateral 6-OHDA PD lesion model, exacerbating corticostriatal glutamatergic input excitability and maintaining astrocytes activated via a self-reinforcing mechanism (Dos-Santos-Pereira et al., 2016; Del-Bel et al., 2016).

Dl-3-n-Butylphthalide Alleviates Behavioral and Cognitive Symptoms Via Modulating Mitochondrial Dynamics in the A53T-α-Synuclein Mouse Model of Parkinson's Disease (Li et al.). The authors investigated whether Dl-3-n-butylphthalide (NBP), safe and effective in improving the non-tremor-dominant PD, could decrease dopaminergic neurons' loss and α-synuclein deposition. NBP treatment partially preserved mitochondrial homeostasis by yet unknown mechanisms (Huang et al., 2018; Wang et al., 2016).

Melatonin as a Chronobiotic and Cytoprotective Agent in Parkinson's Disease (Pérez-Lloret and Cardinali). The role of melatonin in PD prevention and treatment is discussed. Non-motor symptoms like hyposmia, rapid eye movement sleep behavior disorder (RBD), or depression may precede motor symptoms onset in PD for years and predict worse prognosis. Melatonin is cytoprotective and of mighty clinical usefulness in neurodegenerative disorders.

Daily bedtime administration of 3–12 mg of melatonin is effective in RDB treatment and might halt neurodegeneration to PD. Experimentally, melatonin curtailed PD symptomatology in doses, allometrically projected to humans, in the 40–100 mg/day range, rarely employed clinically. Double-blind, placebo-controlled clinical studies are needed to clarify and define melatonin neuroprotection (Cardinali 2019; Gilat et al., 2020).

Endonasal CNS Delivery System for Blood-Brain Barrier Impermeant Therapeutic Oligonucleotides Using Heterotopic Mucosal Engrafting (Pawar et al.). The blood-brain barrier (BBB) prevents 98% of all potential neuropharmaceuticals from reaching the brain. Brain derived neurotrophic factor (BDNF) has been reported to reverse PD progression. The authors investigated the distribution of BDNF AntagoNAT's (BDNF AT's), synthetic oligonucleotide-like compounds capable of upregulating endogenous BDNF expression, using an extra-cranial graft model in naïve rats using an innovative heterotopic mucosal engrafting technique. BDNF AT cationic liposomes (ideal size range 200–250 nm) were developed and characterized to enhance the delivery to rat brain. The delivered BDNF AT's encapsulated in liposomes conferred neuroprotection in a rat 6-OHDA model of PD. (Pawar et al., 2018; Bleier et al., 2015).

Edaravone Plays Protective Effects on LPS-Induced Microglia by Switching M1/M2 Phenotypes and Regulating NLRP3 Inflammasome Activation (Li et al.). Inhibition of the NLRP3 inflammasome activation could protect dopaminergic neurons. The authors investigated the potential effects of edaravone on M1/M2 polarization of microglia in rats with dopaminergic damage induced by lipopolysaccharide (LPS). They found that edaravone improved neurobehavioral functions and played an anti-neuroinflammatory role in PD rats, possibly by inhibiting NLPR3 inflammasome activation and regulating microglia M1/M2 polarization (Gao et al., 2002; Liu et al., 2019).

AUTHOR CONTRIBUTIONS

All authors made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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