Deciphering stress-induced immune alterations and their contribution to physiopathological mechanisms in Parkinson’s disease.

https://neurodegenerationresearch.eu/survey/deciphering-stress-induced-immune-alterations-and-their-contribution-to-physiopathological-mechanisms-in-parkinsons-disease/

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Research Abstract

Our proposal is centered on understanding the molecular, cellular and behavioral basis of stress in exacerbating or contributing to progression of Parkinson’s disease (PD). PD is multi-organ disease chiefly characterized by movement symptoms. It is widely acknowledged from clinical

anecdotes that stress can trigger the appearance of the disease as well exacerbate both motor and mood symptoms. However, little is known on underlying processes that are affected by stress.
The disease affects not only brain regions such as substantia nigra (SN) or striatum but also the peripheral organs such as gut or sympathetic nerves. The pathological hall marks from which the symptoms appear are degeneration of dopamine neurons (DNs) in SN, presence of alpha-synuclein (aSyn) containing Lewy bodies in all affected regions and chronic inflammation mediated by activated microglia, astroglia and infiltrating T cells.
Thus, to study the role of stress, the proposal is specifically focused on examining how stress affects a) the immune system and b) the DNs, both in PD-like pathological context. There is ample experimental evidence showing that activated microglia mediating innate immune responses have deleterious effects on diseased neurons. A major effecter system for stress is hypothalamic-pituitary-adrenal (HPA) axis that controls stress-induced glucocorticoid (GC) release from adrenal glands. GCs activate ubiquitously expressed glucocorticoid receptor (GR) that exerts adaptive stress- and ultradian-related changes in the organism. There is a large body of evidence indicating that in chronic stress situations or during dysfunction of HPA axis, the resultant chronically high GC levels are deleterious and therefore are implicated in various diseases. There are several studies including ours showing elevated levels of circulating cortisol and altered ultradian secretory pattern in PD patients, suggesting a deregulation of HPA axis. The impact of stress and sustained high cortisol levels on PD physiopathology remains, however, unknown. Our basic and simplified hypothesis is that de-regulated HPA axis may affect PD patients' responses to stress and negative effects of these alterations could feed into the ongoing degenerative process and disease progression.
The two partners recently reported alterations in GR expression in SN and striatum in PD patients. Moreover, their functional data from conditional knockout mice of GR in microglia/macrophages indicate that GR has a role in regulating the survival of DNs through its regulatory effects on activation state of microglia and inflammatory processes (Ros-Bernal et al, PNAS, 108:6632-7). These preliminary observations are promising for undertaking: (i) a more in-depth analysis on the role of peripheral and central immune mechanisms in stress-related modulation of neuronal cell death (ii) the effect of stress on aSyn pathogenecity.
The proposal consists of development of chronic stress model and its consequences on 2 experimental PD models a) Toxin-based i.e. 1-methy-2-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication that selectively triggers degeneration of DNs; b) Genetic-based i.e. viral-driven overexpression of wild type and mutated aSyn. Cell-specific GR functions will be studied in conditional mouse models lacking GR either in microglia/macrophages or DNs. The peripheral contribution of immune cells will be examined by creating parabiosis-based chimeras with GFP mice and mice lacking GR in microglia/macrophages.
The project proposed is novel with not much known on molecular basis of deleterious effects of stress in PD and the interdisciplinary nature of the proposed project brings together the two partners with expertise in the fields of neurodegeneration (S. Hunot, ICM) and stress-related physiopathology (S. Vyas, UPMC-campus Jussieu).

Further information available at:

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