Chronic Stress and Parkinson's Disease

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Sustained stress leads to series of changes in the brain, firstly through the activation of hypothalamus–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) axis, then the release of glucocorticoid (GCs) and catecholamines (CAs), respectively. The circulating GCs can cause neuronal injury and even the loss of neurons, accompanying the increased level of proinflammatory cytokines in the circulation. Chronic stress has been linked to various diseases, especially mood disorders and neuropsychiatric disorders, mainly mediated by the limbic system. Yet the relationship between chronic stress and neurodegenerative disorders such as Alzheimer disease (AD) and Parkinson's disease (PD) is unknown. It has been found that depression often precedes PD symptoms in clinical subjects [1], while many PD patients present with depression symptoms as well [2,3]. A recent study published in *Molecular Psychiatry* by Hemmerle et al. [4] addressed this point by subjecting 6-OHDA-lesioned rats to the chronic stress, and they found that chronic stress exacerbates the loss of dopamine neurons induced by 6-OHDA injection. The results strongly argued that chronic stress may function as an important factor in the development of PD and potentially other neurodegenerative diseases.

Hemmerle et al. generated a rat model of PD by unilateral 6-OHDA injection, which produces selective toxicity to dopamine neurons, especially in substantia nigra. The dopamine neuron loss leads to motor behavior deficits, as reflected by the forelimb asymmetry test, because the loss of dopamine neurons would lead to impaired usage of the contralateral limb, while the severity of dopamine neuron loss was histologically examined by TH staining [4]. When the rats were subjected to chronic unpredict-

able stress, the authors found that the rats would demonstrate increased forelimb asymmetry (suggestive of worse behavior), which correlated with increased dopamine neuron loss (decreased TH staining). Interestingly, the chronic stress alone did not induce loss of dopamine neurons, and the stress had to occur simultaneously with toxin exposure [4], suggesting that the stress might act adjuvantly with the toxin or increase the vulnerability of the neurons.

In clinical studies, depression as the most common disease caused by chronic stress may occur prior to PD symptoms [1] and may indicate worse prognosis for PD patients [5]. Yet it should be noted that the loss of dopamine neurons could occur much earlier to the motor symptoms [6] and therefore may be concurrent with the depression as well.

What are the potential mechanisms linking stress and increased dopamine neuron loss? It is possible that glucocorticoid contributes to this process, partly through the glucocorticoid receptors (GRs) on the microglia, because MPTP-induced neurotoxicity was less in mice whose GRs were knocked down selectively on microglial cells [7]. In addition, GRs on dopamine neurons regulate the activity of the cells and might sensitize the neurons through excitotoxicity [8].

On the other hand, there is evidence suggesting that the depression can be caused by loss of dopaminergic innervation during PD progression [2], acting as the downstream of PD pathology. It is believed that the mesolimbic and mesocortical dopaminergic pathways that are disrupted in PD would contribute to the depression symptoms [3]. Indeed, a recent study has shown that selective activation of midbrain dopamine neurons with optogenetic tech-

niques could immediately restore the depressive behavior of mice in forced swimming test [9], revealing an unappreciated role of dopamine neurons in mood disorders.

Therefore, the underlying mechanisms of PD progression and depression might interact with each other; for instance, antidepressant treatment was found to delay the need for dopaminergic therapy in early stage PD patients [10]; while selective enhancement of endogenous dopaminergic signaling (rather than pharmacology) could reverse the depression-like behavior in animal models [9]. In future studies, it will be important to fully understand the effects of chronic stress on dopamine neuron loss caused by other challenges, such as ischemia insults or normal aging processes. In addition, given the heterogeneity of midbrain dopamine neurons (connectivity and functional plasticity) and their distinct sensitivity to external toxins, it will be useful to dis-

sect the roles of dopamine neuron subpopulations in PD/depression symptoms of the comorbidities. Last but not least, targeting stress-related disorders and preventing stress-enhanced PD exacerbation will be important in clinical management of PD patients at all stages.

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Conflict of Interest

The authors declare no conflict of interest.

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