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Letter to Editor Open Access

Effect of Chronic Stress in the Onset of Parkinson's Disease: Possible Role of Microglial Cells in Neuroinflammation

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For many years, several studies have been conducted to investigate the effect of stress on the onset of Parkinson's disease (PD), which is characterized by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc). de Pablos et al. reported that stressed animals were associated with a higher rate of death of dopaminergic neurons in the substantia nigra, and that this effect was dependent on glucocorticoids [1]. In addition, Smith et al. reported that stress accelerates neural degeneration in the SNpc, further demonstrating that elevated corticosterone levels can exaggerate nigral neuronal loss and motor symptoms in a rate of rat analogue of PD [2]. These studies demonstrated the progression of nigral DA neuronal loss which is primarily triggered by extrinsic neurotoxins, such as Lipopolysaccharide (LPS) and 6-hydroxydopamine (OHDA). In this regard, it was not fully understood whether solely exposure to stress could induce DA neuronal loss in the SNpc.

To answer this question, we conducted experiments by employing stress regimens, 8 h/day, 5 days/week, for pro-longed time up to 16 weeks. The results demonstrated that the DA neurons in the SNpc started to decrease after 2 weeks of stress exposure and further progressed in a time dependent manner reaching 61% at 16 weeks [3]. Of significant importance, it was shown that reduction was accompanied with activated microglia and increased levels of oxidative stress, as shown with nitrotyrosine (NT), in the midbrain [3]. Cellular source of NT appears to be activated microglia. The reduction of DA and 5-HT was also confirmed by HPLC experiment. To the best of our knowledge, this is the first study to demonstrate that solely exposures to chronic stress induce significant DA neuronal loss in the SN. This result, together with previous studies, demonstrated that exposures to stress for longer period could either trigger the DA neuronal loss or further facilitate the progress of the neuronal degeneration in the SNpc.

Concerning to the effect of elevated corticosterone on the progression of DA neuronal loss, however, there have been several studies showing the controversial results. Ros-Bernal et al. reported that mice with selective inactivation of glucocorticoid receptors (GRs) of the GR gene in macrophages/microglia showed increased loss of DA neuronal loss after MPTP intoxication [4]. This result is consistent with our previous study reporting that DA neuronal loss is further increased in the adrenalectomized mice, a condition of GC depletion, following MPTP intoxication [5]. These results indicate that elevated levels of glucocorticoids may play neuroprotective roles, possibly via inhibiting microglial activation. The discrepancy with respect to the effect of corticosterone on the progression of DA neuronal loss, and neuroinflammation, should be further studied by using various experimental models.

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