Neuroinflammation in experimental Parkinson's disease

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Parkinson's disease (PD) is one of the most common neurodegenerative disorders, yet the etiology of the disease is still poorly understood. Recent studies indicate a regional, time-dependent degeneration of neurons in PD; before overt nigrostriatal degeneration becomes apparent, neuronal pathology can be observed in a few specific areas, such as the olfactory bulb, locus coeruleus and dorsal motor nucleus of the vagus nerve.
Activation of microglia, a major hallmark of a neuroinflammatory process, has been increasingly associated with the pathogenesis of degenerative neurological disorders, including PD. Blockade of microglial activation has been shown to be protective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mouse model of PD, implicating a role for microglia-derived factors in promoting neurotoxicity in this model.
Activated microglia produce multiple factors, including the cytokine IL-1β, that can contribute to either a neurotoxic or a neuroprotective milieu. At present, the precise role of microglia-derived IL-1β in regulation of the neurodegenerative process in different brain region affected during PD is largely unknown. Therefore, we are currently studying the region-specific (and time-dependent) occurrence of reactive microgliosis and IL-1β expression in substantia nigra/striatum, bulbus olfactorius and locus coeruleus of MPTP-lesioned mice. Preliminary results using a sub-chronic model of MPTP-induced neurotoxicity indicate that dopaminergic cell damage in the substantia nigra is accompanied by a reactive microgliosis, suggesting that microglial activation occurs as a consequence of neurodegeneration. After evaluating the expression of IL-1β in the different brain areas mentioned above, we will subsequently assess the possible neurotoxic or neuroprotective effects of IL-1β in the MPTP model by pharmacological modulation of its expression/activity. Ultimately, these studies will help to assess the possibility of neuroinflammatory factors as targets for neuroprotective strategies in PD.

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