PRE-EXISTING INFLAMMATORY STATUS, GENDER AND ESTROGEN DEFICIENCY: THE NEUROINFLAMMATORY WINDOW OF OPPORTUNITY FOR PHARMACOLOGICAL TARGETING OF PARKINSON'S DISEASE

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Over the past decade neuroinflammation has been increasingly recognized as a crucial contributory factor to neurodegeneration in normal aging, as well as in age-related neurodegenerative diseases, including Parkinson's diseases. Neurodegeneration caused by chronic inflammation involves activation of the brain's resident immune cells, the microglia, which produce a large number of pro-inflammatory factors. Systemic inflammation also impacts on local inflammation in the diseased brain, leading to over-production of inflammatory mediators, which may, in turn, influence neuron survival, plasticity and repair. The female hormone estrogen criticalyl modulates both central and systemic inflammation, with important implications for the brain's ability to mount an efficient beneficial and protective response to injury. The main pathological hallmark of PD is a selective and progressive death of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and astrogliosis with loss of DA afferents to basal ganglia and motor dysfunction, including tremor, rigidity, and bradykinesia, with a prevalence in male gender. The onset of menopause is associated with spontaneous increases in cytokine production, whereas cytokine levels are lower in post-menopausal women on hormone replacement therapy. However, whether estrogen effects on inflammation have therapeutical potentials for neuroprotection, still remains to be elucidated. Using the subchronic (30 mg/kg/day per 5 days) MPTP mouse model of PD we here underscore that longterm estrogen deficiency (by mean of bilateral ovariectomy, OVX) significantly activates both peripheral and central innate immune response to the neurotoxic MPTP challenge, as revealed by selected changes in a number of pro-/anti-inflammatory mediators by peripheral and CNS macrophage/microglia. By contrast, in intact female mice with highest plasma estrogen levels (proestrous) or in OVX mice receiving chronic administration of 17-β but not 17-α estradiol starting 24 h after OVX, a sharp counteraction of the exacerbated pro-inflammatory status associated with resistance to MPTP neurotoxicity were observed. In vitro experiments in peritoneal macrophages and brain macrophage/microglia activated with the inflammogen, lipolysaccharide (LPS) documented estrogen receptor alpha (ER-α) mediation of estrogen effects. Together these results indicate that estrogen triggers a beneficial crosstalk between central and peripheral immunity underlying neuroprotection from MPTP neurotoxicity, and highlight neuroinflammation as a window to develop therapeutical strategies for neuroprotection in PD.