NEUROINFLAMMATORY RESPONSE IN THE ACUTE MPTP RODENT MODEL OF PARKINSON'S DISEASE: TIME-DEPENDENT CORRELATION WITH HISTOPATHOLOGICAL, NEUROCHEMICAL AND BEHAVIORAL RESPONSE TO NIGROSTRIATAL INJURY AND REPAIR

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Selective degeneration of dopaminergic (DA) neurons in the subtantia nigra pars compacta (SNpc) and astrogliosis are pathological hallmarks of Parkinson's disease (PD) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) animal model of PD. In PD and its experimental animal models, an inflammatory process within the striatum and mesencephalon has been suggested to contribute to the demise of nigrostriatal DA neurons. Activation of microglia, a hallmark of neuroinflammation, has been demonstrated in the SN of PD patients, in human patients exposed to MPTP and in experimental models of PD. To further assess the relevance of the neuroinflammatory response, we have correlated temporal changes in gene transcript levels of major chemokines/cytokines, neurotrophic and DA-specific transcription factors in striatum and ventral midbrain, to neuropathological, neurochemical and behavioral changes in male C57BL mice receiving the well established acute MPTP protocol (four i.p. injection of 20 mg/kg 2 h apart in one day). Mice (12/experimental group) were sacrificed at different time intervals (3 hr-42 days) after MPTP discontinuation, the striatum and ventral midbrain quickly dissected and processed for determinations of gene expression and dopamine neurochemistry and changes correlated with immunohistochemical determinations in striatum and SNpc. Behavioral impairment was monitored by rotarod performance. The analysis of 100 gene transcript indicate discrete time- and region-dependent changes in gene expression associated with DA denervation and recovery from MPTP neurotoxicity. Temporal patterns of transcript levels differed in the striatum versus the ventral midbrain, sometimes in opposite directions, and within different windows (i.e. 3-24 hrs; 7-14 d, or 21-42 d post-MPTP). Concerning inflammatory response, the phase of nigrostriatal DA neurotoxicity and motor behavior deficit (1-7 d post-MPTP) were associated to an acute and sharp increase of chemokines of the CCL and CXCL families, including the proinflammatory CCL3/MIP-1α and CXCL10/IP-10 peacking in striatum (+15-30-fold)between 6-24 hrs, remaining elevated (+2-4-fold) for 7d and coinciding with maximal astrocyte and microglia activation, followed by an acute drop thereafter. By 14 d, behavioral motor recovery was observed, and from 21through 42 d striatal DA functionality started to increase with a progressive histopathological recovery associated with a substantial increase of the cytokine G-CSF (+10-20-folds) both in striatum and midbrain was observed. These results have implications for the understanding of pathogenesis and potential therapeutical strategies in Parkinson's disease.