28

DEFINING "NEUROINFLAMMATION": LESSONS FROM MPTP- AND METH-INDUCED NEUROTOXICITY

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"Neuroinflammation" is a hot topic in contemporary neuroscience. Abstracts to the 2007 Annual Meeting of the Society for Neuroscience could be submitted in several sub-categories of neuroinflammation, a clear signal of the growth in this research area. While it is becoming clear that activation of microglia and astroglia and the attendant expression of proinflammatory cytokines and chemokines often are associated with disease-, trauma- and toxicant-induced damage to the CNS, it is by no means clear that a cause-and-effect relationship exists between the presence of a neuroinflammatory process and neural damage. We have explored this issue with two models of dopaminergic neurotoxicity. We used a single low-dose regimen of MPTP or METH, a paradigm that causes selective degeneration of striatal dopaminergic nerve terminals without affecting the cell body in the substantia nigra. Both compounds increased the expression of the microglia associated factors, F4/80, Il-1α, Il6 Ccl2 and Tnf-α and also elicited morphological evidence of microglial activation prior to induction of astrogliosis. Pharmacological antagonism of MPTP and METH neurotoxicity prevented these proinflammatory responses, findings suggestive of a link between neuroinflammation and the observed neurotoxic outcomes. Nevertheless, when we used minocycline to suppress the expression of all these mediators, with the exception of Tnf-α, we failed to see neuroprotection. Likewise, when we examined the effects of MPTP or METH in transgenic mice lacking Il6, Ccl2 or Tnfr1/2 genes, deficiency of either Il6 or Ccl2 did not alter neurotoxicity, whereas deficiency in Tnr1/2 was neuroprotective. Although these observations pointed to a role of the proinflammatory cytokine, TNF-α, in the neurotoxic effects of MPTP and METH, other observations did not support this argument. For example, induction of iNOS or activation of NF-κB, known components of inflammatory responses and free radical formation, were not observed. Moreover, immunosuppressive regimens of glucocorticoids failed to suppress TNF-α or attenuate neurotoxicity. Taken together, our observations suggest that MPTP and METH neurotoxicity are associated with the elaboration of a "neuroinflammatory" response, yet this response lacks key features of inflammation and, with the exception of TNF-α, neurotoxicity appears to be the cause rather than the consequence of proinflammatory signals.

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