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Endotoxin Preconditioning of the CNS: Microglia Activation and Neuroprotection

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Preconditioning by subthreshold stress can protect the brain from subsequent injury. Preconditioning can be induced by a number of mechanisms including hypoxia, ischemia, heat shock and intraperitoneal injection of the endotoxin lipopolysaccharide (LPS). While global preconditioning with low doses of LPS provides protection against injurious focal ischemia in the brain, the cellular mechanisms involved in LPS neuroprotection are incompletely understood. C57BL/6 mice were injected with four intraperitoneal injections of LPS, 24 hours apart. This LPS paradigm reduced the size of cortical cryoinjury by 60%. In this study, we examined the response of activated microglia to intraperitoneal injection of LPS and investigated the mechanisms by which the CNS is protected. One day after LPS treatment, cortical microglia expressed activation markers and ensheathed neuronal cell bodies and proximal dendrites. Electron microscopy analysis demonstrated that activated microglia directly apposed neuronal plasma membranes. Quantification of confocal microscopy images immunostained for neurons and GAD67-positive presynaptic terminals shows a 27% reduction ($P < .001$) in the neuronal circumference occupied by inhibitory GABAergic synapses. In addition, GABA receptor transcripts were significantly reduced 1 day after LPS treatment. mRNA and protein levels of the anti-apoptotic molecule Bcl-2 were increased in LPS-treated animals and highly enriched in neurons. Furthermore, LPS treatment inhibits the pro-apoptotic protein BAD. These data support the hypothesis that LPS induces an anti-apoptotic pathway in cortical neurons. Similar to the neuroprotective effects of LPS, microglia activation, reductions in inhibitory innervation of cortical neurons, and cortical Bcl-2 upregulation were transient and returned to control levels at 14 days post-LPS treatment. In summary, microglia activation is a surrogate marker for LPS-induced CNS protection. It remains to be determined if these activated microglia are actively stripping synapses from cortical neurons. These data support microglia activation as part of a CNS neuroprotective response that involves preferential reductions in GABAergic axosomatic synapses. Reductions in inhibitory innervation may transiently favor neurotrophic activity of excitatory NMDA agonists and induction of anti-apoptotic pathways in neurons.

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