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Abstract 3

Microglia Activation and Neuroprotection During CNS Preconditioning

Walid Jalabi, Ranjan Dutta, Yongming Jin, Gerson Criste, Xinghua Yin, Grahame J. Kidd, and Bruce D. Trapp

Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH

Preconditioning is a phenomenon in which low doses of noxious stimuli shield the brain from future insults. Preconditioning can be induced by a number of stimuli, including hypoxia, ischemia, heat shock, and IP injections of lipopolysaccharide (LPS). While global preconditioning with LPS provides protection against injurious focal ischemia in the brain, the cellular mechanisms involved in LPS neuroprotection are incompletely understood.

In this study, C57BL/6 mice were preconditioned by four daily LPS injections. One day post-LPS treatment, cortical microglia expressed activation markers and directly apposed neuronal cell bodies and proximal dendrites. A 27% reduction in the neuronal circumference occupied by inhibitory GABAergic synapses was observed in preconditioned cortex, and major GABA receptor subunit mRNA and proteins were significantly reduced. In addition, animals preconditioned with LPS showed a significant reduction in the size of cortical induced cryoinjury and the number of apoptotic cells. Cortical mRNA and protein levels of several anti-apoptotic members of the Bcl-2 and the inhibitor of apoptosis (IAPs) families were upregulated and the pro-apoptotic protein BAD was inhibited. Furthermore, the transcription factor cAMP-response-element-binding-protein (CREB) and its regulated neurotrophin brain derived neurotrophic factor (BDNF) were significantly upregulated by LPS preconditioning.

These data support microglia activation as part of a CNS neuroprotective response that involves preferential reductions in GABAergic axosomatic synapses and the activation of anti-apoptotic pathways in cortical neurons through CREB. Reductions in inhibitory innervation may transiently favor neurotrophic activity through synaptic NMDA receptor activation and the subsequent induction of anti-apoptotic pathways in neurons.

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