Hypoxia-inducible factor-1α protects cultured cortical neurons from lipopolysaccharide-induced cell death via regulation of NR1 expression

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Lipopolysaccharide (LPS), which is present in the outer layer of the cell wall in gram-negative bacteria, induces innate immune responses via toll-like receptor (TLR)-4 and is recognized by monocytes/macrophages. LPS is associated with many neurodegenerative diseases, including Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis (1-3). In the central nervous system (CNS), LPS-induced chronic inflammation in the rat brain leads to the degeneration of hippocampal CA3 pyramidal neurons and impairs spatial memory (4). Recent studies indicate that both microglial cells and astrocytes are activated during inflammation and release cytokines that cause neuronal damage, including TNF-α (5). TLR-3 or TLR-4 is also expressed in neurons (6;7); however, the detailed processes regulated by these receptors remain unknown.

The N-methyl-D-aspartate glutamate receptor (NMDAR) is a tetramer formed by interaction between an obligatory NR1 subunit and NR2A–NR2D. NR1 expression is regulated by physiological conditions in the CNS, including those associated with neuronal plasticity, learning, and memory (8;9). However, inappropriate NMDAR activation is involved in the etiology of several human diseases, including acute insults such as hypoxia (10), ischemia (11), trauma (12), epilepsy (13) and in the pathology of various chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (14-17). Although accumulated evidence indicates that NR1 expression is altered during neuroinflammation (18;19), the precise role played by NR1 in neuroinflammation remains unknown.

Here, we show that NR1 expression in the cerebral cortex and primary neurons of rats was upregulated following lipopolysaccharide (LPS) treatment. This increase in NR1 expression was considered to be strongly associated with hypoxia-inducible factor (HIF)-1α activation because the treatment of primary neurons with either echinomycin or small interference RNA (siRNA) targeting HIF-1α could block NR1 expression. HIF-1α could be induced by an increase in the translational efficiency of the cells. Following this, it was transported into the nucleus where it bound to the NR1 promoter and regulated the induction of NR1 transcriptional activity by LPS. LPS injection into the
prefrontal cortex caused neuronal death, and this condition was aggravated by intracerebroventricular injection of echinomycin. Further, knockdown of HIF-1α and NR1 by the appropriate siRNAs reduced the neurite outgrowth and viability of the primary neurons. These results are summarized in Fig.1: LPS selectively induces NR1 expression in neurons via HIF-1α activation and that NR1 play a protection role against LPS challenge.

These results represent the first evidence that HIF-1α activation in neurons is essential during neuroinflammation. Furthermore, the identification of HIF-1α as a molecular substrate during the development of inflammation provides a more selective and potentially more productive target for the treatment of neurodegenerative diseases.

References: