Hypoxia potentiates cytotoxicity of LPS-activated microglial BV2 cells in vitro by synergistic effects on cytokine and nitric oxide secretion

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Background

Microglial activation due to a variety of stimuli results in secretion of high levels of neurotoxic substances including pro-inflammatory cytokines, nitric oxide (NO), and reactive oxygen species. Clinical studies indicate a crosslink between inflammatory and hypoxia-regulated pathways suggesting that bacterial infections may sensitize the immature brain to hypoxic injury.

Methods

BV2 cells were exposed to lipopolysaccharides (LPS, 1×10^5 EU/ml for 24h) and hypoxia (1% O_2 for 6h). Cytokine and NO release was quantified by ELISA and the Griess reaction, respectively. Cytotoxicity was determined in MTS cell viability assays.

Results

Activation of BV2 microglial cells by LPS exposure stimulated significant and persistent production of NO, IL-1β, IL-6, and TNF-α. Even after LPS removal, ongoing NO and cytokine secretion could be observed. While hypoxia alone mediated exclusively a significant, short-term increase of IL-1β, oxygen deprivation enhanced LPS-induced secretion of NO, IL-1β, IL-6, and TNF-α significantly. Surprisingly, pre-stimulation of BV2 cells by hypoxia prior LPS exposure abolished microglial activation suppressing LPS-induced NO production. Hereby, cell-free supernatants derived from LPS-activated microglial cells exhibited a stronger cytotoxic effect in glial and neuronal cells than LPS exposition per se ($P < 0.001$). Again, hypoxia potentiated LPS-induced cytotoxicity.

Conclusion

Present data prove that i) the outcome of hypoxia is determined by the microglial activation status and that ii) LPS-induced soluble factors rather than LPS are mediators of microglial neurotoxicity under conditions of hypoxia in vitro. Activation of pro-inflammatory pathways may sensitize microglial cells to promote hypoxia-induced injury of the developing brain. Consequently, our findings may promote neuroprotective therapeutic strategies in the field of perinatal brain injury.