Ammonia Attenuates LPS-Induced Upregulation of Pro-Inflammatory Cytokine mRNA in Co-Cultured Astrocytes and Microglia

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Hepatic encephalopathy (HE) is associated with cerebral microglia activation. Ammonia, a major toxin of HE, activates microglia in vitro but does not trigger pro-inflammatory cytokine synthesis. In the present study we analysed effects of ammonia on lipopolysaccharide (LPS)-induced upregulation of microglia activation and cytokine mRNA as well as on cytokine secretion in mono-cultured microglia and co-cultured astrocytes and microglia. In mono-cultured microglia LPS (100 ng/ml, 18 h) strongly elevated mRNA levels of the microglia activation marker CD14 and the pro-inflammatory cytokines IL-1α/β, IL-6 and TNF-α. NH4Cl (5 mmol/l) had no effect on LPS-induced upregulation of CD14, IL-1α/β and IL-6 mRNA but enhanced LPS-induced upregulation of TNF-α mRNA in mono-cultured microglia. In co-cultured astrocytes and microglia, however, LPS-induced upregulation of IL-1α/β, TNF-α, IL-6, CD14 but not of IL-10, IL-12A/B or TGFβ1-3 mRNA was attenuated by NH4Cl. LPS-induced upregulation of IL-1α/β, IL-6 and TNF-α was also diminished by the TGR5-ligands allopregnanolone and taurolithocholic acid in mono-cultured microglia. NH4Cl also attenuated LPS-induced release of MCP-1, IL-6 and IL-10 in mono-cultured microglia. mRNA level of surrogate marker for microglia activation (CD14) and for the anti-inflammatory M2-type microglia (CD163, CXCL1, CXCL2) were also elevated in post mortem brain tissue taken from the fusiforme gyrus of patients with liver cirrhosis and HE. The findings suggest that ammonia attenuates LPS-induced microglia reactivity in an astrocyte-dependent way. One may speculate that these anti-inflammatory effects of ammonia may be triggered by neurosteroids derived from astrocytes and may account for absence of microglia reactivity in cerebral cortex of cirrhotic patients with HE.

KEYWORDS: Ammonia; Hepatic encephalopathy; Neuroinflammation; Neurosteroids; TGR5.