Ammonia-induced senescence in cultured rat astrocytes and in human cerebral cortex in hepatic encephalopathy.

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Hepatic encephalopathy (HE) is a frequent complication of liver cirrhosis and is due to a low-grade cerebral edema associated with oxidative/nitrosative stress. Recent reports suggest that cognitive impairment in cirrhotic patients may not resolve completely after an attack of manifest HE. As astrocyte dysfunction is central to the pathogenesis of HE and astrocytes are critically involved in synaptic plasticity, we tested for sustained impairment of astrocyte function by analyzing expression levels of senescence biomarkers in ammonia-treated cultured rat astrocytes and in postmortem brain samples from cirrhotic patients with or without HE. NH4 Cl time- and dose-dependently inhibited proliferation of cultured astrocytes by up to 45% (5 mmol/L, 72 h) and strongly increased senescence-associated β-galactosidase activity. Inhibition of astrocyte proliferation by ammonia was mediated by a l-methionine sulfoximine-, oxidative stress-, and p38(MAPK) -dependent activation of p53 associated with enhanced transcription of cell cycle inhibitory genes GADD45α and p21. Mitochondria and the nucleus were identified as sources of oxygen radical formation after prolonged NH4 Cl exposure. Concurrently, NH4 Cl (5 mmol/L) treatment inhibited both epidermal growth factor- and brain-derived neurotrophic factor (BDNF)-induced proliferation as well as BDNF-mediated astrocyte morphology changes through downregulation of the respective growth factor receptors epidermal growth factor receptor and truncated tyrosine receptor kinase B. Increased mRNA expression levels of senescence-associated genes were also found in post mortem brain samples from patients with liver cirrhosis with HE, but not in those without HE. The data suggest that ammonia toxicity and HE are associated with premature astrocyte senescence, which may impair neurotransmission and contribute to persistence of cognitive disturbances after resolution of episodes of overt HE.

KEYWORDS: ammonia; astrocytes; glutamine; senescence