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Purpose: To test for sustained ammonia-induced impairment of astrocyte function by analyzing expression levels of senescence biomarkers following ammonia treatment of astrocytes cultured from newborn Wistar rats, and in postmortem brain samples from patients with cirrhosis with or without hepatic encephalopathy (HE).

Key takeaways:
- When compared to untreated controls, cultured rat astrocytes exposed to ammonia for 72 hours exhibited impaired proliferation without induction of apoptosis.
- Ammonia treatment was shown to induce senescence in cultured astrocytes, suggesting that this process underlies the established proliferation arrest.
- Inhibition of glutamine synthetase (GS) largely prevented both the defect in astrocyte proliferation and induction of senescence that resulted from ammonia treatment.
- Cultured astrocytes exposed to ammonia exhibited activation of the tumor suppressor p53 and multiple downstream genes that inhibit the cell cycle, an effect that was also shown in postmortem human brain samples from patients with cirrhosis and HE.
- Formation of reactive oxygen species was increased in ammonia-treated cultured astrocytes; this induction of oxidative stress could be localized to mitochondria, which showed prominent swelling.

Discussion:
- The dependence on GS activity for ammonia-induced senescence and decreased proliferation suggests that these effects are dependent on glutamine synthesis, which has been previously shown to increase in astrocytes exposed to ammonia.
- The prolonged occurrence of cognitive deficits seen in patients with cirrhosis and HE following liver transplant could potentially be explained by ammonia-induced astrocyte senescence.
- The previously observed downregulation of glutamate transporter EAAT1 in cultured astrocytes exposed to ammonia could also arise from the induction of senescence detailed in this study.