pressure elevation via a mechanism that is distinct from the renin-angiotensin-aldosterone system.

CELL VOLUME AND HEPATIC ENCEPHALOPATHY

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Hepatic encephalopathy (HE) defines a reversible neuropsychiatric syndrome frequently associated with acute and chronic liver failure. Current evidence suggests that HE in cirrhotic patients reflects the clinical manifestation of a low grade cerebral edema which exacerbates in response to a variety of precipitating factors (infections, sedatives, bleeding, high protein intake, electrolyte disturbances etc.) after an ammonia-induced exhaustion of the volume-regulatory capacity of astrocytes. Evidence for such low grade cerebral edema in HE came from *in vivo* proton magnetic resonance (^{1}H-MRS) studies on human brain and also by quantitative water mapping of the human brain *in vivo*. The cerebral edema accompanying HE is largely due to astrocyte swelling triggered by an oxidative/nitrosative stress response together with ammonia-induced glutamine accumulation in astrocytes. However, astrocytes not only swell in response to ammonia, but also in response to hyponatremia, benzodiazepines and inflammatory cytokines, all of which induce the rapid formation of reactive oxygen and nitrogen species through *N*-methyl-D-aspartate (NMDA)-receptor- and Ca^{2+}-dependent mechanisms in cultured astrocytes and in rat brain *in vivo*. NMDA receptor activation under these conditions is thought to result from a depolarization-induced removal of a Mg^{2+}-blockade from the receptor and a prostanoid-dependent autocrine amplification of NMDA receptor activity by ammonia-induced astroglial vesicular glutamate release. There is an *auto*-amplificatory signalling loop between astrocyte swelling and oxidative/nitrosative stress: astrocyte swelling induces oxidative/nitrosative stress through NMDA receptor- and Ca^{2+}-dependent mechanisms on the one hand and on the other, NMDA receptor activation and oxidative stress trigger astrocyte swelling. Activation of NADPH oxidase isoforms and of Ca^{2+}/calmodulin-dependent isoforms of nitric oxide synthase in response to hypoosmotic astrocyte swelling or ammonia exposure are the major sources of the early ROS and NO formation.

Functional consequences of the ammonia- and astrocyte swelling-induced oxidative/ nitrosative stress response in HE are protein tyrosine nitration, RNA oxidation and effects on zinc dependent gene transcription. Such phenomena may alter synaptic plasticity and lead to disturbances of oscillatory networks in the brain, which finally trigger HE symptoms. Mobilization of zinc from zinc-sulfur clusters in proteins stimulates Zn^{2+}-dependent gene transcription, which may explain the upregulation of the peripheral benzodiazepine receptor (PBR) in the brain of cirrhotic patients with HE. Upregulation of PBR triggers enhanced formation of neurosteroids, which are not only positive modulators of $GABA_A$ receptors, but also are high-affinity ligands for TGR5 which acts as a neurosteroid receptor in astrocytes, neurons and microglia. Hepatic encephalopathy is also associated with an activation of microglia, but this is not associated with increased synthesis of *pro*-inflammatory cytokine mRNA. This suggests that in HE microglia becomes activated but is not reactive. Most importantly, the above-described hallmarks of HE pathophysiology, such as astrocyte swelling, oxidative/nitrosative stress, protein tyrosine nitration and RNA oxidation have also been identified in human brain.

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