Neuroinflammation in Hepatic Encephalopathy: Mechanistic Aspects

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Hepatic encephalopathy (HE) is a major neurological complication of severe liver disease that presents in acute and chronic forms. While elevated brain ammonia level is known to be a major etiological factor in this disorder, recent studies have shown a significant role of neuroinflammation in the pathogenesis of both acute and chronic HE. This review summarizes the involvement of ammonia in the activation of microglia, as well as the means by which ammonia triggers inflammatory responses in these cells. Additionally, the role of ammonia in stimulating inflammatory events in brain endothelial cells (ECs), likely through the activation of the toll-like receptor-4 and the associated production of cytokines, as well as the stimulation of various inflammatory factors in ECs and in astrocytes, are discussed. This review also summarizes the inflammatory mechanisms by which activation of ECs and microglia impact on astrocytes leading to their dysfunction, ultimately contributing to astrocyte swelling/brain edema in acute HE. The role of microglial activation and its contribution to the progression of neurobehavioral abnormalities in chronic HE are also briefly presented. We posit that a better understanding of the inflammatory events associated with acute and chronic HE will uncover novel therapeutic targets useful in the treatment of patients afflicted with HE. (J Clin Exp Hepatol 2015;5:S21–S28)

Pathogenesis

Hepatic encephalopathy (HE) is the major neurological complication of severe liver disease. It presents in two forms, chronic HE and acute HE. Chronic HE (portal-systemic encephalopathy) usually occurs in patients with alcoholic liver cirrhosis and is characterized by impaired neurological function, including changes in personality, altered mood, diminished intellectual capacity, and abnormal muscle tone and tremor.[1] Acute HE (AHE, acute liver failure, ALF; fulminant hepatic failure) generally occurs following massive liver necrosis due to viral hepatitis (hepatitis B and C), hepatic neoplasms, vascular causes, or exposure to acetaminophen and other hepatotoxins. AHE is associated with the abrupt onset of delirium, seizures, and coma.

The principal pathological change in chronic HE is characterized by Alzheimer type II astrocytosis,[2,3] which is characterized by astrocytes possessing enlarged, pale nuclei, often occurring in pairs, with the nuclei frequently displaying prominent nucleoli. Cerebral edema and associated increase in intracranial pressure leading to brain herniation are the characteristic features of AHE which occurs in upto 80% of patients with AHE[4–6] and represents the most frequent cause of death in these patients (70% mortality).[4,7] While the basis for the edema in AHE is poorly understood, astroglial swelling (cytotoxic edema) dominates the pathology in experimental animals,[8–11] as well as in humans.[12] Of interest, no significant or consistent morphologic changes have been identified in neurons or other neural cells. Such findings prompted the suggestion that HE fundamentally represents a primary "astrogliopathy".[13]

While the precise involvement of astrocytes in HE is incompletely understood, it is known that the enzyme responsible for ammonia metabolism in brain, glutamine synthetase, is exclusively found in astrocytes.[14] Such metabolism in the setting of elevated ammonia levels elicits a number of untoward events in astrocytes which exerts negative consequences on other neural cell. For review, see Norenberg[13]; Norenberg et al, 1992.[15]

While the molecular basis for the neurological disorder in acute and chronic liver failure remains incompletely understood, elevated blood and brain ammonia levels have been strongly implicated in its pathogenesis. Factors that lead to increased levels of blood or brain ammonia have

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Abbreviations: HE: hepatic encephalopathy; AHE: acute hepatic encephalopathy; ALF: acute liver failure; LPS: lipopolysaccharide; ONS: oxidative/nitrative stress; NF-κB: nuclear factor-kappaB; FHF: fulminant hepatic failure; TNF-α: tumor necrosis factor-alpha; IL: interleukin; HO: hemoxygenase; iNOS: inducible nitric oxide synthase; BBB: blood–brain barrier; BDL: bile duct ligation; cNOS: constitutive nitric oxide synthase; NOX: NADPH oxidase; RONS: reactive oxygen and nitrogen species; MAPK: mitogen-activated protein kinases; PLA2: phospholipase-A2; ECs: endothelial cells; COX2: cyclooxygenase-2; Tg: transgenic; WT: wild type; TLR: Toll-like receptor
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been shown to worsen HE, whereas reducing blood ammonia levels alleviate HE.[16] Additionally, clinical, pathological, and biochemical changes observed in HE are reproduced by increasing blood or brain ammonia in experimental animals,[2] while exposure of cultured astrocytes to ammonium salts reproduces the morphological and biochemical findings.[17–20]

Recent studies have shown a significant role of inflammation in the mechanism of HE, in particular, the involvement of cytokines and lipopolysaccharide (LPS; endotoxin) in the pathogenesis of acute and chronic HE.[21,22] The focus of this review is to emphasize the involvement of ammonia in stimulating an inflammatory response in brain endothelial cells, microglia and astrocytes, in both acute and chronic HE.

MECHANISMS OF AMMONIA NEUROTOXICITY

Impaired bioenergetics, electrophysiological defects, changes in intracellular pH, altered glutamateric and GABAergic neurotransmission, excitotoxicity, involvement of the peripheral benzodiazepine receptor,[23] oxidative/nitrative stress (ONS) and induction of the mitochondrial permeability transition, have all been identified as major mechanistic events triggered by ammonia.[24,25] Additionally, activation of intracellular signaling systems, including c-fos,[26] mitogen-activated protein kinases,[26] protein kinase G,[27] Src kinase family,[28] ciliary neurotrophic factor,[26] and the transcription factors p53,[29] SP-1[26] and nuclear factor-kappaB (NF-κB)[30–32] have all been shown to be involved in the mechanism of ammonia neurotoxicity, particularly in neuroinflammation.

Recently, the stimulation of ion transporters, including the Na^+-K^+-Cl^- cotransporter-1[33,34] and the nonselective cation (NCCa-ATP) channel,[35] as well as an increase in the level of the astrocytic plasma membrane protein aquaporin-4,[36] have all been shown to be involved in the mechanism of ammonia neurotoxicity, particularly in the development of the cytotoxic brain edema associated with acute HE. While the signaling systems that are stimulated in acute HE are well established, evidence for the involvement of signaling factors in chronic HE remains sparse.

INFLAMMATION IN HEPATIC ENCEPHALOPATHY

A growing body of evidence suggests that inflammation plays an important role in the development of HE. The concept that inflammation is involved in HE was first proposed by Gans et al, 1971,[37] based on findings that peripheral infections and inflammation were associated with fulminant hepatic failure (FHF). This aspect was further elaborated upon by Wilkinson et al, 1974; Liehr et al, 1976; Wyke et al, 1982.[38–40] Izumi et al 1995[41] documented increased levels of IL-6 in plasma in both FHF and in chronic HE. Subsequently, Wigmore et al, 1998[42] and Wright et al 2007[43] reported increased levels of serum tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) and their arterio-venous differences, consistent with a brain cytokine efflux in patients with acute HE, supporting the presence of a central nervous system inflammatory component (neuroinflammation) in HE when associated with peripheral infections. Noteworthy, blood-derived cytokines, likely arising from necrotic liver and/or from sepsis, are well-known to freely cross blood–brain barrier under normal conditions.[44]

a. Role of inflammation in the brain edema associated with acute HE

As noted above, a major complication of acute HE is the development of cytotoxic brain edema. The involvement of neuroinflammation in acute HE was established by Chung et al, 2001,[45] who showed a protective effect of the anti-inflammatory agent, indomethacin (a potent inhibitor of cyclooxygenase-2), against the development of brain edema in rats with a portacaval anastomosis that were infused with ammonia[45]; indomethacin also normalized the intracranial pressure in patients associated with acute HE.[46] Subsequently, Jiang et al, 2009[47] documented that a member of the tetracycline class of antibiotic, minocycline, also attenuated the encephalopathy grade and prevented brain edema formation in experimental ALF. It should noted, however, that minocycline itself induces liver damage,[48,49] which precludes its possible therapeutic use for the treatment of acute HE.

It was further shown that AHE results in a lesser degree of brain edema in transgenic mice deficient in TNF-α, IL-1β and IL-6 receptors, as compared to wild type mice,[50] and that etanercept, a TNF-α neutralizing molecule, prevented the onset of coma stages of HE as well as liver injury induced by AOM (Chastre et al, 2012).[51] Induction of endotoxemia with LPS in rats was subsequently shown to aggravate the brain edema and encephalopathy associated with ALF.[43] Collectively, these findings suggest an important role of "central" inflammation in the development of the brain edema in ALF. For general reviews on neuroinflammation, see references.[21,52]

Consistent with the role of inflammation in the brain edema associated with AHE, we previously reported that treatment of cultured astrocytes with inflammatory cytokines (TNF-α, IL-1β, IL-6 and IFN-γ) caused astrocyte swelling.[53] Moreover, the swelling caused by these cytokines was markedly potentiated when astrocytes were pre-treated with ammonia for 24 h, and then exposed to cytokines for an additional 24 h. Additionally, astrocyte cultures exposed to a combination of cytokines (TNF-α, IL-1β, IL-6 and IFN-γ) were recently shown to activate NF-κB and that such effect was potentiated by ammonia,[53] while

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