Review

Pathophysiology of cerebral edema in fulminant hepatic failure

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Fulminant hepatic failure (FHF) is a devastating disease and is still associated with a high mortality (1). FHF results in progressive multi-organ failure with a dramatic impact on the brain. Indeed, development of intracranial hypertension (IH) is a leading cause of death in FHF. During this decade two theories have independently emerged to explain the pathogenesis of cerebral edema and intracranial pressure in FHF.

The glutamine hypothesis is based on the fact that ammonia is detoxified in the brain to glutamine, whose osmotic effects in astrocytes may account for the development of brain edema (2). Astrocyte swelling is a prominent neuropathological feature in FHF (3). In humans, hyperammonemia induces brain edema in several medical conditions (4). Experimentally, inhibition of glutamine synthesis with methionine-sulfoximine (MSO) prevents the development of ammonia-induced brain edema in normal rats (5), decreases astrocyte swelling (6) and ameliorates brain edema in rats after portacaval anastomosis (PCA) receiving an ammonia infusion (7).

A second hypothesis suggests that cerebral edema arises as a consequence of cerebral vasodilatation (8). Physiological studies in patients with FHF (9,10) and in experimental models (11) indicate that cerebral arterioles are dilated. Furthermore, patients with signs of cerebral edema and IH have a higher cerebral blood flow (CBF) compared to patients without brain swelling (12,13).

Two recent experimental studies suggest that development of brain edema may depend both on glutamine accumulation in astrocytes and changes in CBF. First, Córdoba et al. (14) found in PCA rats receiving an ammonia infusion that an increase in brain glutamine was associated with a marked rise in CBF at the time of an increase in brain water and intracranial pressure. Mild hypothermia ameliorated the degree of brain edema by reducing CBF rather than glutamine accumulation in the brain (14). In addition, Master et al. (15) have shown in the same model that MSO ameliorates brain edema by inhibiting both glutamine synthesis and the development of cerebral vasodilatation.

This review will first describe the background for the two theories suggested to be involved in the genesis of brain edema. Based on this critical appraisal, a unified theory for the development of cerebral edema is outlined.

Background

The glutamine hypothesis

Astrocytes are located between the cerebral blood vessels and neurons. This central position favors their function in securing adequate balance between neuronal energy consumption and glucose uptake from the capillaries, i.e. the metabolism-blood flow coupling. Indeed, astrocytes surround virtually all capillaries though end-feet processes and exhibit an increased uptake of glucose during increased synaptic activity (16). Astrocytes also maintain a constant composition of the extracellular fluid and are involved in the re-uptake of neurotransmitters, such as glutamate (17), and ions, such as potassium (18), from the synaptic cleft after depolarization.

Astrocytes are the site of ammonia detoxification in brain (19). Since the brain lacks a complete urea cycle, ammonia is eliminated via amidation of glutamate to form glutamine, an action catalysed by glutamine synthetase located exclusively in glial cells (20). Glutamine efflux from the astrocyte into the extracellular fluid and CSF occurs by passive diffusion, a process that may be affected by changes in intracellular pH (21). Thus, glutamine accumulates during induction of acute hyperammonemia and causes astrocytes to swell, i.e. the glutamine hypothesis (22). Indeed, pre-treatment with MSO, an irreversible glutamine synthetase inhibitor, prevents glutamine accumulation in the setting of ammonia intoxication (23). It also prevents ammonia-
induced mortality (24). Cerebral edema induced by acute ammonia intoxication can be prevented by MSO pretreatment in normal (5) and PCA (7) rats.

A recent study has demonstrated that the arterial ammonia concentration is related to cerebral herniation in patients with FHF (25) (Fig. 1). These observations require confirmation by other centers. In any case, they support the concept that ammonia uptake in the brain is of direct importance for cerebral edema and IH. They may also provide an explanation for the development of cerebral edema in cirrhosis (26), as well as differences in the evolution of FHF from that of patients with acute-on-chronic liver failure (25).

Further support for the role of glutamine as a brain osmolyte is derived from the behavior of other brain organic osmolytes. In humans who receive an acute ammonia load (as seen with TIPS), glutamine increases while myo-Inositol and choline peaks are reduced, as seen with brain spectroscopy (27). The maintenance of a constant level of brain organic osmolytes has been shown in rats 6 weeks after PCA, where glutamine rises while myo-Inositol and taurine are decreased (28). Thus, the brain in chronic liver disease appears to undergo osmotic compensation.

**The gradual vasodilatation hypothesis**

This hypothesis is based on experimental studies demonstrating that cerebral vasodilatation develops in the rat after PCA (29) and in the cat during ammonia infusion (11). Also, clinical studies in severe FHF by Ede & Williams in 1986 (30) showed a high CBF in a few patients. These measurements were performed at a late stage of the disease but well before development of cerebral herniation. The authors noted an absence of the ability of cerebral arterioles to constrict in response to a decrease in PaCO$_2$ (i.e. hypocapnic CO$_2$-reactivity). Subsequent studies in patients with FHF could not reconfirm these high CBF values (31) and the issue of cerebral hyperemia was not pursued. However, we now know from several large studies that not only is CBF associated with a wide interindividual variation in patients with FHF (12,13) but a high CBF seems also to be associated with a poor prognosis (12). The mechanisms responsible for this wide variation in CBF are still unclear, but the data support an abnormal vascular regulation in the brain.

Normally brain metabolism is closely related to blood flow (32). Since, the cerebral metabolic rate for oxygen (CMRO$_2$) is invariably reduced in FHF to a level of $\sim$1.0 ml · 100 g$^{-1}$ · min$^{-1}$ [normal CMRO$_2$ is 3.0 ml · 100 g$^{-1}$ · min$^{-1}$ (33)], a low CBF would be expected in such patients. Thus, an increase in flow under these circumstances indicates an abnormal regulation of CBF. Indeed, studies in the rat with thioacetamide-induced acute liver failure (34) as well as in patients with FHF (9,10) evaluating the relation between arterial pressure and CBF, could not identify any autoregulation of CBF. This loss implies that arterial blood pressure can directly influence the CBF (Fig. 2). This failure of autoregulation appears to arise from cerebral arteriolar dilatation, a view supported by studies of CBF in FHF. The CO$_2$-reactivity coefficient is reduced in FHF (35), especially during hypercapnia (8,36). Furthermore, profound hyperventilation restores normal autoregulation in patients with FHF (37). The loss of arteriolar tone in these circumstances may unbalance the Starling forces in the brain capillaries, i.e. the hydrostatic pressure may overcome the osmotic pressure and result in water accumulation in the extracellular space. The possibility that cerebral hyperemia may be involved in the genesis of brain edema is further supported by studies reporting selective abnormalities of the blood-brain barrier in FHF (38).
Mechanisms of Vasodilatation
Since cerebral edema appears closely related to the development of cerebral vasodilatation, two mechanisms could account for the change in CBF. The first is that cerebral vasodilatation results from changes in the peripheral circulation, i.e. systemically related cerebral vasodilatation. The second possibility is that vasodilatation in the brain arises from substances produced within the brain itself, i.e. locally-induced cerebral hyperemia. This latter view would suggest that cerebral circulatory alterations in FHF result from metabolic changes in astrocytes and/or neurons, whose net result is an increase in cerebral blood volume.

Systemically-related cerebral vasodilatation
In patients with FHF, leakage of endotoxins from the gut to portal blood (and/or lymph nodes) may result in elevated systemic endotoxin levels as portal blood bypasses the non-functional liver. Endotoxin may increase the plasma concentration of tumor necrosis factor (TNF-alfa) and IL16 and 6 in the inflammatory host defence response (39,40). Cytokines are potent stimulators of nitric oxide synthase. The hyperdynamic systemic circulation with high cardiac output and low systemic vascular resistance in FHF may result from the production of excessive amounts of nitric oxide (NO) in the endothelium (41), as suggested by studies examining cGMP levels in these patients (41). However, the cerebral circulation does not participate in the systemic vasodilatation in cirrhosis (42) where a hyperdynamic state is also seen.

Patients with severe FHF who are awaiting emergency liver transplantation stabilize systemic hemodynamics after hepatectomy (43). Also, cerebral edema and IH appeared to be reduced in a few patients by hepatectomy (44). It is not clear why systemic and cerebral hemodynamic patterns improve after hepatectomy. The failing liver per se may release pro-inflammatory substances that result in cerebral hyperemia and impaired cerebrovascular reactivity. However, patients with acute-on-chronic liver failure (31) and patients with sepsis have low CBF and normal cerebrovascular reactivity in spite of their vasodilated state (45). In addition, patients with cirrhosis and brain edema do not always have ongoing hepatic necrosis (26). Thus, the role of the necrotic liver in the pathogenesis of cerebral edema and vasodilatation is still uncertain.

Locally-induced cerebral hyperemia
Evidence to support a vasodilatory signal from the brain arises from experimental studies. Ammonia-induced brain edema in the rat after PCA is an excellent paradigm to study the pathogenesis of cerebral edema, as the development of brain swelling occurs in the absence of acute hepatic necrosis. Cerebral vasodilatation in this model is a selective phenomenon, i.e. there are no systemic hemodynamic changes. However, ammonia per se is not the cause of the vascular change, as MSO, the inhibitor of glutamine synthetase, results in even higher ammonia blood levels, while brain
edema and cerebral vasodilatation are ameliorated (15). What could be the nature of this intracerebral signal?

Hypoxia. Vasoactive factors, such as lactate, released from the brain after a hypoxic event could be responsible for development of vasodilatation and edema in ALF. In fact, glial cells swell within seconds after induction of hypoxia, followed by a phase with “global cerebral hyperemia” and high oxidative metabolism (46). Wendon et al. (13) demonstrated an increased cerebral lactate efflux in patients with severe ALF shortly after episodes of intracranial hypertension. Furthermore, these authors (13) reported a concomitant increase in CBF and metabolism during infusion of N-acetylcysteine, an improvement that would indicate cerebral hypoxia. However, we consider brain hypoxia to be an unlikely explanation for cerebral vasodilatation in FHF, as oxidative metabolism in the brain is always severely reduced regardless of the value of blood flow (47).

Prostaglandins. In patients with FHF and severe IH, iv. injection of indomethacin decreases the intracranial pressure within a few minutes by reducing cerebral blood volume (48). Indomethacin is a potent vasoconstrictor and probably inhibits the cyclooxygenase activity in the cerebral endothelium. However, the effects of indomethacin are not confined to the brain, and the role of an increased cerebral production of prostaglandins in the development of cerebral hyperemia remains to be defined.

A Unified Theory of Brain Edema

A unified theory is based on observations in the model of ammonia-induced brain edema in the rat after PCA. In this preparation, three different approaches have been shown to be effective in reducing the degree of brain swelling: mild hypothermia (14), methionine-sulfoximine (7) and memantine (49) (Fig. 3). This unified theory postulates that the generation of glutamine is a critical step for the development of cerebral circulatory changes.

Glutamine, generated in astrocytes, diffuses to the presynaptic neuron, where it is deaminated by glutaminase to glutamate, a critical excitatory neurotransmitter in brain. \[\text{[Glutamate]}_{\text{EC}}\] is increased in experimental ALF (17) as a result of its release from swollen astrocytes (27) and/or a decreased activity of the glutamate transporter GLT-1 in astrocytes (50). Under normal conditions, activation of neuronal nitric oxide synthase (nNOS) results from NMDA receptor activation, with production of nitric oxide (NO) (51–53). The activity of nNOS is increased in the cerebellum of rats after PCA (54).

Generation of NO via activation of NMDA receptors can result in an increase in CBF (51). Cerebral hyperemia that accompanies several physiological and pathophysiological processes can be prevented by inhibition of nNOS (51–53). An increased production of NO will dilate cerebral arterioles and compromise cerebral vascular reactivity. Studies examining the effects of inhibition of nNOS in experimental paradigms are currently under way.

While recognizing the limitations of studies in a model of brain edema without ALF, the unified hypothesis suggests that two mechanisms need to be present in order for brain edema to develop: an acute osmotic change in the brain coupled with an increase in cerebral perfusion. Other postulated pathogenic mechanisms in ALF can also fit this model, especially their effects on cerebral blood flow.

A Therapeutic Perspective

At a time of numerous attempts to provide artificial/bioartificial support for ALF, research in brain edema has shown alternative avenues to deal with the acute effects of ammonia on the brain. These include the stimulation of ammonia metabolism in muscle with ornithine-aspartate (55), antagonism of glutamate-NMDA receptors as seen with memantine (49) and use of selective nNOS inhibitors, if generation of NO in the brain is critical for the develop-
ment of cerebral hyperemia. Inhibition of glutamine synthetase may not be an attainable goal, as available compounds are not only intrinsically toxic but are non-selective for brain, resulting in even greater hyperammonemia. Elucidation of the pathogenesis of brain edema should open new avenues not only in treating but in preventing the development of this fatal complication.

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References
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