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Subtle BBB alterations in brain edema associated with acute liver failure

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Abstract

Vasogenic mechanism of brain edema in acute liver failure (ALF) remains poorly understood. Recent work demonstrates that matrix metalloproteinase-9 (MMP-9) contributes to the development of brain edema in experimental ALF (*J Hepatol* 44:1105, 2006). Importantly, MMP-9 blockage with specific monoclonal antibodies and/or synthetic inhibitor, the edema is attenuated. Specifically, ultrastructural evaluations demonstrate intact blood-brain barrier and its tight junction. These results suggest that subtle alterations in BBB are likely to involve in the brain edema associated with ALF.

Keywords

Blood-brain barrier; Brain edema; Acute liver failure

Dear Editors,

I have read the article (Sawara et al., 2009) with great interest. However, I would like to call your attention to the statement in the article, “In contrast to the present study, azoxymethane-treated mice manifest clear signs of physical breakdown of the BBB including extravasation of sodium fluorescein and Evans blue.” We believe this is an incorrect interpretation of the cited work.

In our report, “Matrix metalloproteinase-9 contributes to the brain extravasation and edema in fulminant hepatic failure mice,” (Nguyen et al., 2006) we demonstrated the first evidence that a vasogenic mechanism takes part in the development of brain edema in acute liver failure (ALF). The original characterization of this mouse model of ALF by Matkowskyj et al. (1999) and recent further examination of this model by Dr. Butterworth’s lab confirmed that this mouse model recapitulates the ALF in humans (Belanger et al., 2006). We further demonstrated the increased BBB permeability to Evans blue dye and water in azoxymethane-induced ALF in mice (Nguyen et al., 2006). The leakage of Evans blue was visualized as brain extravasation. When we examined the brains under fluorescent microscopy, the extravasated dye was observed in the immediate surrounding region of the brain capillary. More importantly, the electron microscopic evaluations showed intact BBB (Fig. 1). The evidence of astrocytic swelling is obvious. We did not observe any significant structural alterations of the brain capillaries of the azoxymethane-induced ALF mice under electron microscopy (Fig. 1a) as compared to the brain of the normal control mice (Fig. 1b). The tight junction was intact. The results from our lab are consistent with the previous

reports on the brains from humans and animals with ALF (Potvin et al., 1984; Traber et al., 1987; Kato et al., 1992; Gove et al., 1997). These findings collectively corroborate that BBB dysfunction is associated with increased permeability only to small molecules like water and ammonia but is not necessarily associated with a structural breakdown. Recent data from other laboratories have demonstrated that a leaky BBB could result from subtle alterations in the tight junction (Wong and Gumbiner, 1997; Tavelin et al., 2003; Nusrat et al., 2000; Nitta et al., 2003).

Therefore, our results suggest that the pathogenesis of ALF-induced brain edema is unlike the brain edema caused by brain ischemia and traumatic brain injury, which result from complete BBB breakdown associated with the vasogenic mechanism, but likely involves a rather subtle disruption in the BBB. Clearly, understanding ALF-induced brain edema will require additional research, and the best options for its therapeutic intervention may not be the same as in other types of brain injury.

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Fig. 1.
 (a, left) Electron micrographs showed the lucent cytoplasm of astrocyte (Ast) abutting a capillary (Cap) with its swollen astrocytic endfoot processes (*) present in ALF mice. (b, right) In contrast, we observe astrocytes with normal endfoot process and capillary in the normal control mice. Bars represented 1 μm.