Cerebral Blood Flow in Acute Liver Failure: A Finding in Search of a Mechanism

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In the last few years, several abnormalities of cerebral blood flow (CBF), namely loss of cerebral autoregulation, altered reactivity to carbon dioxide, and development of cerebral hyperemia, have been described in patients as well as experimental models of acute liver failure (ALF) and/or hyperammonemia. The development of cerebral hyperemia seems particularly relevant to the pathogenesis of brain edema in ALF. In addition to the potential increase of brain blood volume causing a rise in intracranial pressure, an increase of CBF could facilitate the movement of water across the blood brain barrier in an osmotically altered brain. Because maneuvers that abrogate the rise of CBF have been shown to prevent or ameliorate brain edema in ALF/hyperammonemia, elucidation of the mechanism by which the rise of CBF occurs is important. In the rat after portacaval anastomosis receiving an ammonia infusion, the signal resulting in cerebral hyperemia arises within the brain once maximal glutamine accumulation has occurred in astrocytes. Several mediators potentially involved in the development of cerebral hyperemia in ALF are examined in this review, but further work is needed to assess the role, if any, of each of them.

Key words: Acute liver failure; cerebrovascular circulation; brain edema; ammonia; astrocytes.

NOMENCLATURE

ALF Acute liver failure
CBF Cerebral blood flow
ICP Intracranial pressure
NO Nitric oxide
NOS Nitric oxide synthase (endothelial eNOS, neuronal nNOS, inducible iNOS)
CO Carbon monoxide

A HISTORICAL PERSPECTIVE

The initial focus of research on the neurological repercussions of acute liver failure (ALF) was the study of brain neurochemical abnormalities. This approach was justified by the prevailing concept that brain dysfunction was due to a primary alteration of neuronal transmission, as a result of the exposure of the brain to circulating toxins not cleared by a
failing liver. Animal models of ALF were used, then, to examine neurochemical hypotheses.
In the period from 1960 to 1985, based on experimental studies, theories of energy failure, synergistic toxins (ammonia, mercaptans, phenols, short-chained fatty acids, octanoic acid), and GABA alterations were successively proposed to account for the pathophysiology of brain dysfunction in liver failure.

Brain edema was not accepted as a distinct clinical entity within ALF until 1977 (Berk and Popper, 1978). This recognition provided new perspectives and prompted the adoption of brain water content as a physiological end point for experimental studies. In experimental models of ALF, it was shown that an osmotic disturbance of the brain was an early event, preceding the increase in brain water content (Swain et al., 1992). Later, it was noted that a profound disturbance of brain organic osmolytes was also a common alteration in experimental models of chronic liver failure (Traber et al., 1986; Cordoba et al., 1996) as well as in patients with cirrhosis, demonstrated by in vivo nuclear magnetic spectroscopy techniques (Haussinger et al., 1994; Taylor-Robinson et al., 1994). Some recent clinical studies have taken this logic one step further and have postulated that an increase of brain water content may play a role in the development of hepatic encephalopathy in patients with cirrhosis of the liver (Balata et al., 2003; Cordoba et al., 2001).

In the last decade, several abnormalities of cerebral blood flow (CBF) have been described in patients with ALF. The description of cerebral hyperemia in these patients led us to propose a model for the development of brain edema in ALF, based on the combined effects of an osmotic disturbance, focused on the astrocyte, coupled with the development of cerebral hyperemia (Blei and Larsen, 1999). This hypothesis has been extensively studied in our laboratory using rats with portacaval anastomosis subjected to infusion of ammonium acetate, a model that results in a reproducible rise of CBF at 2 h and evident brain edema at 3 h of infusion (Master et al., 1999). We believe the study of cerebral hyperemia as a physiological end point in this model can provide important insight into the pathophysiology of brain edema in ALF. Furthermore, elucidation of the signal that induces the rise of CBF in this model may have therapeutic implications, given that manipulation of CBF appears to prevent the development of brain edema both experimentally (Cordoba et al., 1999; Traber et al., 1989) and clinically (Clemmesen et al., 1997; Jalan et al., 1999).

RELEVANCE OF CBF TO THE DEVELOPMENT OF BRAIN EDEMA IN ALF

Pathophysiological Concepts

Conceptually, there are three major mechanisms by which an increase of CBF could influence the development of brain edema in ALF:

1. In the first mechanism, the increase of CBF would increase the movement of water across the blood–brain barrier by accelerating the pathologic processes causing brain edema in ALF.
2. In the second mechanism, the increase of blood volume in the brain would lead per se to an elevation of intracranial pressure (ICP).
3. In the third, a rise in CBF increases the exposure of the brain to toxin(s) responsible for the development of brain edema.