Effects of Simulated Upper Gastrointestinal Hemorrhage on Ammonia and Related Amino Acids in Blood and Brain of Chronic Portacaval-shunted Rats

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Gastrointestinal (GI) hemorrhage during compromised liver function is known to precipitate portal-systemic encephalopathy (PSE). Hypothetically, the induced hyperammonemia depletes cerebral glutamate pools. To investigate this hypothesis, rats were studied 14 days after portacaval shunt (PCS) or sham surgery (SHAM). Rats received 3 mL bovine erythrocytes or saline at t= 0, 1, 2, and 3 h via a previously placed gastrostomy catheter. At t= 0, 2, 4, 6 and 8 h arterial blood and at t=8 h cerebral cortex were sampled for determination of ammonia and amino acids. Control rats (NORM) were sampled without previous surgery. Repeated intragastric blood administration increased the already elevated arterial ammonia levels in PCS rats further. This resulted in higher cerebral cortex ammonia and glutamine levels after blood administration. Despite the accumulation of ammonia and glutamine, cerebral cortex glutamate concentrations remained unaltered. Yet, PCS rats became more encephalopathic after blood gavages, suggesting that there is not a clear-cut relation between cerebral cortex glutamate concentrations and degree of PSE. Interestingly, cerebral cortex concentrations of GABA, tyrosine and phenylalanine were markedly increased. Whether these observations are pathogenetically related to PSE remains to be established. The present model of simulated GI hemorrhage in PCS rats seems to be a suitable, clinically valid model for future research regarding hepatic encephalopathy.

Keywords: Ammonia; glutamine; glutamate; portacaval shunting; hepatic encephalopathy; brain; gastrointestinal bleeding

Abbreviations: PCS: portacaval shunt GI: gastrointestinal; PSE: portal-systemic encephalopathy; GS: glutamine synthetase

INTRODUCTION

Liver insufficiency is known to be associated with the occurrence of portal-systemic encephalopathy (PSE). The precise pathogenesis of PSE is unknown, but ammonia is considered to be an important factor (Cooper and Plum, 1987; Zieve, 1987; Mousseau and Butterworth, 1994). Thus, it has been hypothesized that ammonia arising in the intestines...
escapes hepatic clearance due to intra- and extrahepatic portasystemic shunting, while the hepatic capacity of urea and glutamine synthesis is reduced (Zieve, 1987), resulting in elevated plasma ammonia concentrations (Meijer et al., 1990). Because the blood-brain barrier is freely permeable to ammonia, elevated systemic ammonia levels have been shown to result in net ammonia uptake and elevated brain ammonia levels (Dejong et al., 1992b; Dejong et al., 1993c and references cited in there), which are neurotoxic (Mousseau and Butterworth, 1994).

Because brain is devoid of a complete urea cycle, the glutamine synthetase reaction (GS; EC 6.3.1.2: amidation of glutamate to glutamine) has been viewed as the most important alternative ammonia detoxification pathway in brain (Duda and Handler, 1958; Lockwood et al., 1979). The GS reaction consumes glutamate and therefore cerebral ammonia detoxification via glutamine formation has been suggested to deplete cerebral glutamate pools (Cooper et al., 1985; Cooper and Plum, 1987; Meijer et al., 1990). Because glutamate is the principal excitatory neurotransmitter in several regions of the CNS, including the cerebral cortex (Cooper and Plum, 1987), this could disturb glutamatergic neurotransmission, subsequently inducing PSE (Cooper et al., 1985; Cooper and Plum, 1987; Mousseau and Butterworth, 1994).

Recently, we showed that chronic liver insufficiency-induced hyperammonemia in rats resulted in decreased total cerebral cortex tissue glutamate levels if the experimental groups were compared with normal unoperated control rats fed ad libitum (Dejong et al., 1993c). However, when the chronic liver failure groups were compared with sham-operated pair-fed control rats, such a decrease could not be demonstrated, suggesting that this finding was primarily related to diminished food intake and/or surgical trauma (Dejong et al., 1993c). Despite similar glutamate concentrations in the cerebral cortex, there were apparent differences in encephalopathy stage between sham operated and liver failure rats. These observations made a clear-cut relation between total cerebral cortex glutamate concentrations and encephalopathy stage less likely during chronic liver insufficiency in rats.

Whole brain glutamate concentrations have been reported to be decreased or remain unchanged during liver failure (reviewed in Cooper and Plum, 1987). Most of these studies reviewed by Cooper and Plum (1987) used some form of portacaval shunting in rats either with or without ammonia administration as a model of PSE. Although portacaval shunting in rats probably is the best model of PSE currently available, its clinical relevance has been questioned (Mullen, 1995), especially if used in combination with ammonia administration. Because it is well known that upper gastrointestinal (GI) hemorrhage from esophageal varices in patients with liver cirrhosis often is accompanied by the precipitation of encephalopathy, simulation of upper GI hemorrhage by administration of blood protein during chronic portacaval shunting in rats could be a clinically more valid model of PSE. Despite the enormous amount of research on hepatic encephalopathy to our knowledge no experiments have been performed, in which cerebral cortex ammonia and related neurotransmitter amino acids have been studied after such an intervention.