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HYPOTHERMIA IN ACUTE LIVER FAILURE

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ABSTRACT

The development of encephalopathy in patients with acute liver injury defines the occurrence of liver failure. The encephalopathy of acute liver failure is characterized by brain edema which manifests clinically as increased intracranial pressure. Despite the best available medical therapies a significant proportion of patients with acute liver failure die due to brain herniation. The present review explores the experimental and clinical data to define the role of hypothermia as a treatment modality for increased intracranial pressure in patients with acute liver failure.

Key words: Acute liver failure; hepatic encephalopathy; intracranial pressure; hypothermia; liver transplantation.

INTRODUCTION

Brain edema resulting in increased intracranial pressure (ICP) and brain herniation is a major cause of mortality in patients with acute liver failure (ALF). Increased ICP is a key event that defines their prognosis (Ascher et al., 1993; Hoofnagle et al., 1995; Makin et al., 1995; O'Grady et al., 1989; Trey and Davidson, 1970). Over 90% mortality is expected in patients with ALF in whom ICP cannot be controlled. In addition, 30–40% of patients with ALF die while waiting for a donor organ to become available, primarily due to the effects of increased ICP. In our unit, we treated 315 patients with acute liver injury due to paracetamol overdose. In those patients that fulfilled the Kings College criteria for poor prognosis and who were not transplanted, a mortality of about 90% was observed. The immediate cause of death in these patients was uncontrolled intracranial hypertension in about 30%. In 24 patients who underwent successful orthotopic liver transplantation (OLT), two died in the early posttransplant period from the effects of increased ICP. These results suggest that despite our best efforts in management, a significant proportion of patients continue to die from the effects of increased ICP (Jalan, 2003).

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HYPOTHERMIA

THE PATHOPHYSIOLOGY OF HYPOTHERMIA-EFFECT ON THE BRAIN

The pathophysiological mechanisms responsible for the development of brain edema and increased ICP in ALF have not been fully elucidated. However, ammonia remains a prime candidate. Hyperammonemia is a consistent finding in different experimental animal models of ALF which result in increased brain ammonia concentrations (>1 mM) and consequently the development of brain edema and ICP. Furthermore, a positive correlation has been reported between arterial ammonia concentrations and the appearance of brain stem herniation in patients with ALF (Clemmensen et al., 1999). Therefore, ammonia toxicity, directly or indirectly, is a major factor involved in the development of brain edema and increased ICP in ALF.

Deep hypothermia (<32°C) has been demonstrated to extend the survival time and prevent an increase in brain water content in rats with ALF (Traber et al., 1989). Recently, a more defined mild hypothermia (33–35°C) showed a beneficial effect in prolonging the time of onset of hepatic encephalopathy (HE) and preventing brain edema in rats with liver devascularization (Rose et al., 2000). These data support earlier stud-ies where hypothermia prevented CNS consequences of pure hyperammonemia (Schenker and Warren, 1962), hepatectomy (Peignoux et al., 1982), and more recently, the delay in ammonia-induced brain edema in rats following portacaval shunting (Cordoba et al., 1999).

We have demonstrated the beneficial effects of hypothermia are not mediated by an effect on blood ammonia, but on cerebral spinal fluid (CSF) ammonia where in hypothermic rats with ALF at times when blood ammonia levels were unchanged, CSF ammonia concentrations were significantly less (Rose et al., 2000). These findings suggest that one of the beneficial mechanisms of action of mild hypothermia in ALF may be to limit blood–brain barrier transfer of ammonia.

Increased CBF resulting in cerebral hyperemia has been strongly suggested to be implicated in the development of brain edema and increased ICP. Hyperemia consequently results in higher ammonia “delivery” to the brain. Cordoba et al. (1999) demonstrated with mild hypothermia a delay in ammonia-induced brain edema and increased ICP in rats with portacaval shunt. This was accompanied with a beneficial reduction in CBF. Mechanisms responsible for increased CBF in ALF are elusive however the vasodilator nitric oxide (NO) is thought to play a stimulating role. The source of NO remains unknown however it has been suggested through clinical studies that NO productions arises as a result in inflammation and subsequently increased cytokine production. Furthermore, increased activation of NMDA receptors due to ammonia toxicity in brain results in increased NO synthase and NO production (Hermenegildo et al., 2000).

Ammonia removal in the brain is solely accomplished by the production of glutamine through the astrocyte-specific enzyme glutamine synthetase. It has been pro-posed that ammonia-induced brain edema in ALF involves alterations in astrocytic in-tracellular osmolarity resulting from glutamine accumulation (Cordoba et al., 1996). This is supported by studies demonstrating the administration of the glutamine synthetase inhibition, methionine sulfoximine, reduces ammonia-induced brain edema both in vitro (Norenberg and Bender, 1994) and in vivo (Chodobski et al., 1986; Takahashi et al., 1991). However, recently hypothermia-induced reductions in brain water content in ALF rats were not accompanied by significant reductions of microdialysate (extra-cellular) brain glutamine (Rose et al., 2000) or brain glutamine (Chatauret et al., 2003) at time points associated with brain edema. This suggests that mild hypothermia's ma-jor protective effect on brain edema is not mediated via an effect on brain glutamine synthesis.

A consistent finding in experimental animal models of ALF is that of increased extra-cellular brain glutamate (Bosman et al., 1992; de Knegt et al., 1994; Hilgier et al., 1999; Michalak et al., 1996). This increased extracellular brain glutamate leads to increased glutamatergic neurotransmission which has been suggested to be implicated in the pathogenesis of CNS complications of ALF (Butterworth, 1997). Furthermore, a noncompetitive antagonist (memantine) of glutamate receptor (NMDA) in brain reduces the severity of neurological signs of HE in rats with ALF (Vogels et al., 1997). Mild hypothermia revealed a significant lowering of extracellular brain glutamate concentrations in rats with ALF, concomitant with the delay in the onset of severe encephalopathy and of brain edema and a reduction in CSF ammonia. It is therefore strongly suggested that increased extracellular brain glutamate is implicated in the pathogenesis of HE and brain edema in ALF. An increase in extracellular brain glutamate results from increased glutamate release or decreased glutamate uptake (clearance) from the extracellular space (see review, Rose, 2002). Knecht et al. (1997) found increased extracellular glutamate concentrations in brain are the consequence of loss in expression of the astrocytic glutamate transporter, EAAT-2 (GLT-1). This is supported in vitro with cultured astrocytes, where the loss of glutamate transporter expression on astrocytes is thought to be mediated from exposure to ammonia (Chan et al., 2000). These findings suggest that reduction in the effect of ammonia on EAAT-2 expression resulting in normalization of glutamate uptake into astrocytes is the mechanism responsible for the effect of hypothermia on extracellular brain glutamate.

There has been evidence that ammonia may have an effect on cerebral energy metabolism (Rao and Norenberg, 2001). Ammonia when applied to cultured astrocytes stimulates lactate production and lactate dehydrogenase activity in cultured astrocytes (Belanger et al., 2001). Chatauret et al. (2001) found an increase in CSF lactate during se-vere encephalopathy and brain edema in rats with ALF. Clinically, extracellular brain lactate concentrations were found to increase in association with increased ICP in patients with ALF (Tofteng et al., 2002). It has also been demonstrated that alanine is elevated in the hyperammonemic brain (Hilgier et al., 1999; Mans et al., 1994; Swain et

al., 1992) and more recently in rats with ALF using nuclear magnetic resonance (NMR) spectroscopy (Chatauret et al., 2003). Increased lactate and alanine production indirectly suggest that anaerobic pathways (increased glycolytic activity) may be stimulated to compensate for a decreased pyruvate oxidation (due to ammonia inhibition on the enzyme alpha-ketoglutarate dehydrogenase in the tricarboxylic acid cycle (Lai and Cooper, 1986)) and maintain ATP production. Furthermore, decreased concentrations of the neuronal marker molecule N-acetylaspartate (NAA) have been demonstrated in frontal cortex of rats in coma stages of HE as a result of ALF, reflecting neuronal mitochondrial dysfunction (Chatauret et al., 2003). In addition, increased alanine production could also reflect an increase in alanine aminotransferase (ALAT) activity (ammonia incorporated into alanine after transamination of glutamate) as an additional pathway to remove excess ammonia. Recently, mild hypothermia prevented the increase in brain lactate, alanine, and NAA in frontal cortex concomitant with the prevention of encephalopathy and brain edema (Chatauret et al., 2003). Therefore, one possible mechanism of action of hypothermia in ALF is the facilitation of pyruvate oxidation as a consequence of decreased blood–brain barrier transfer of ammonia. This therefore releases the ammonia inhibition in the TCA cycle and decreases brain lactate, alanine, and NAA and restores neuronal mitochondrial function and, proper energy metabolism within the brain (see Fig. 1).

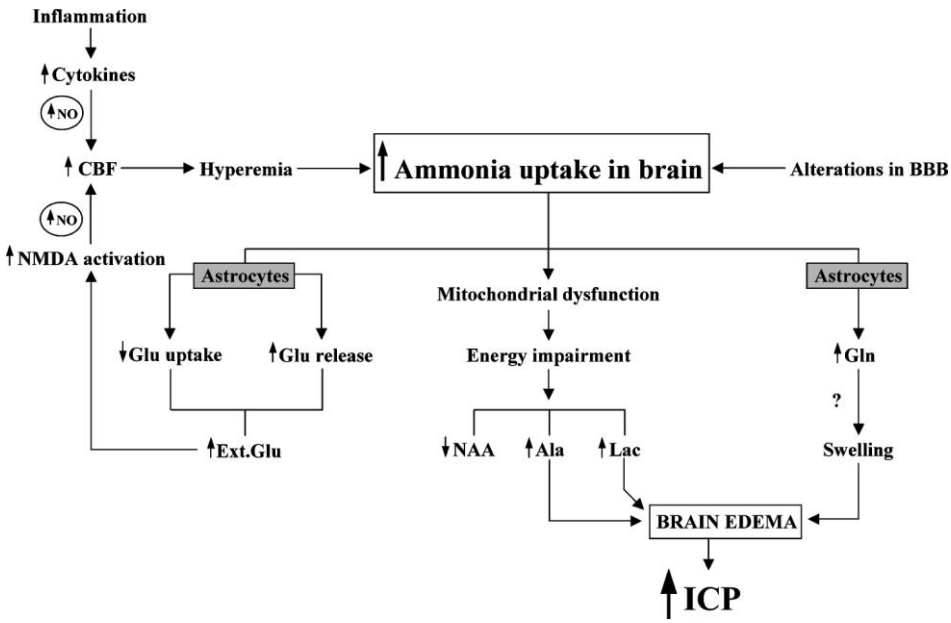

Figure 1. Pathophysiological evidence for increased ICP in ALF from beneficial treatment of mild hypothermia.

CLINICAL EFFECTS OF MILD HYPOTHERMIA

Mild–moderate (32–35°C) hypothermia has been extensively studied in head injured patients. As discussed above, animal studies provided the rationale for the evaluation of the role of hypothermia in patients with ALF however available data on patients treated with hypothermia are limited. We will limit the following section to data acquired in our own unit. We performed three separate studies. Study 1 was performed to ask whether hypothermia could be used as a bridge to transplantation in patients with ALF and uncontrolled intracranial hypertension (defined as persistently elevated ICP to levels of 25 mmHg or more despite treatment with two boluses of mannitol and removal of 500 mL of fluid with haemofiltration). Study 2 was performed to ask whether treatment of patients with ALF and severe HE but ICP < 20 mmHg with mild hypothermia would prevent the occurrence of episodes of increased ICP requiring specific therapy. Study 3 was performed to ask whether hypothermia would prevent the occurrence of episodes of increased ICP during the dissection and reperfusion phases of OLT.

Study 1: Uncontrolled Intracranial Hypertension

We explored the role of moderate hypothermia in a series of patients with ALF who had uncontrolled intracranial hypertension. The six patients who were not suitable candidates for OLT died following rewarming. Thirteen of the 14 patients who were candidates for OLT were successfully bridged to OLT with a mean of 32 h of cooling. The longest period that a patient could be kept cool without occurrence of increased ICP was 118 h, at which time the patient were successfully transplanted. Prior to cooling, the ICP was high at 36.5 (2.7) mmHg and this was reduced to 17.1 (0.9) mmHg at 4 h, which was sustained at 24 h (16.3 (1.3) mmHg) ($p < 0.001$). Recurrence of episodes of increased ICP to above 20 mmHg responded to additional treatment with mannitol. All the patients who could be transplanted had normal neurological recovery apart from a patient who required prolonged rehabilitation for muscle weakness due to prolonged hospital admission. Hypothermia impacted significantly upon all the crucial pathophysiological mechanisms. Arterial ammonia concentration was reduced by about 30% and ammonia delivery to the brain by 66%. This was coupled with a reduction in extraction of ammonia by the brain from about 11% to values, which were not significantly different from zero (Jalan et al., 1999). The brain produced glutamine prior to cooling and this was reduced to values not different from zero suggesting that hypothermia reduces the activity of the major ammonia metabolizing enzyme, glutamine synthetase. CBF was reduced significantly at 4 h after cooling and this was sustained at 10–24 h ($p < 0.001$). CBF autoregulation was restored with cooling (Jalan et al., 2001). In addition, hypothermia reduced proinflammatory cytokines TNFa, IL-1b, and IL-6 significantly [unpublished data]. These effects on ICP and CBF were associated with significant improvement in cardiovascular hemodynamics manifested by increased mean arterial pressure and systemic vascular resistance and reduced noradrenaline requirements.

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Study 2: Prevention of Rise in ICP

We studied five patients with ALF who fulfilled criteria for poor prognosis and had Grade IV HE but an ICP of <20 mmHg. They were cooled to 35°C from the time of mechanical ventilation until OLT, spontaneous recovery or death. Three of the four patients were successfully bridged to OLT with a mean cooling period of 54 h. The longest period that a patient was cooled was 120 h. One of the patients recovered without need for OLT and one patient died 120 h after inclusion into the study from sepsis and multiorgan failure. Prior to cooling, the ICP was elevated at a mean of 17.6 (2.7) mmHg and this was reduced to 15.2 (0.9) mmHg at 4 h, which was sustained at 24 h (15.9 (1.3) mmHg) ($p < 0.05$). There were no significant changes in CBF during the cooling period [unpublished data].

Study 3: Prevention of Increase in ICP During OLT

During the dissection and reperfusion phases of the OLT in ALF patients, increases in ICP are inevitable and current therapies are limited to using barbiturates as treatment with its attendant difficulties. In this study, we compared the changes in ICP between a group that was maintained hypothermic and another group that was maintained normothermic during OLT. There were significant increases in ICP in the normothermic group during the dissection and reperfusion phases of the operation, which was not observed in the hypothermic group. The rise in the ICP in the normothermic group was associated with significant increase in CBF, which was not observed in the hypothermic patients (Jalan et al., 2003).

CONCLUSIONS

Although the data on the use of hypothermia as therapy for increased ICP in ALF and during OLT are not from randomized controlled studies they provide evidence of efficacy and safety in patients with uncontrolled ICP and those that are undergoing OLT. In patients who have severe HE but do not have increased ICP, mild hypothermia reduces the risk of developing increases in ICP. The mechanisms in which hypothermia is beneficial are multi-factorial as hypothermia acts nonspecifically both peripherally and centrally. Hypothermia is an excellent treatment against elevated ICP and in addition is a useful therapeutic tool to help explore and understand the pathophysiology of ALF. Hypothermia displays many beneficial effects on brain water and ICP which seem to be related to decreased brain ammonia concentrations, cerebral blood flow and the mediators of inflammation, which together are thought to underlie the pathophysiology of severe increases in ICP in patients with ALF.

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