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MILD HYPOTHERMIA IN THE PREVENTION OF BRAIN EDEMA IN ACUTE LIVER FAILURE: MECHANISMS AND CLINICAL PROSPECTS

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ABSTRACT

Mild hypothermia (32 C–35°C) reduces intracranial pressure in patients with acute liver failure and may offer an effective adjunct therapy in the management of these patients. Studies in experimental animals suggest that this beneficial effect of hypothermia is the result of a decrease in blood–brain ammonia transfer resulting in improvement in brain energy metabolism and normalization of glutamatergic synaptic regulation. Improvement in brain energy metabolism by hypothermia may result from a reduction in ammonia-induced decrease of brain glucose (pyruvate) oxidation. Restoration of normal glutamatergic synaptic regulation by hypothermia may be the consequence of the removal of ammonia-induced decreases in expression of astrocytic glutamate transporters resulting in normal glutamate neurotransmitter inactivation in brain. Randomized controlled clinical trials of hypothermia are required to further evaluate its clinical impact.

Key words:
Hypothermia; acute liver failure; brain edema; ammonia; glutamate; glutamine; lactate; cerebral blood flow.

INTRODUCTION

The major cause of mortality in patients with acute liver failure (ALF) is brain herni-ation, a complication which results from increased intracranial pressure caused by pro-gressive brain edema. Although the precise mechanisms responsible for brain edema in ALF have not been fully elucidated, ammonia toxicity continues to attract a great deal of attention.

Hyperammonemia is encountered in experimental ALF resulting from both ischemia and toxic liver injury and, in all cases, brain edema is a characteristic feature. Brain am-monia concentrations at coma/edema stages of encephalopathy in experimental ALF may reach concentrations as high as 5 m*M* (Swain et al., 1992a,b). Hyperammonemia of a similar magnitude to that seen in ALF is observed in patients with Reye's syndrome or urea cycle enzymopathies (Brusilow, 1985; Jenkins et al., 1987) and, in both cases, brain edema is a significant feature. Furthermore, exposure of brain cells to millimolar concentrations of ammonia *in vitro* leads to significant cell swelling (Norenberg et al., 1991). More recently, a positive correlation was reported between arterial ammonia con-centrations and the incidence of brain herniation in patients with ALF (Clemmensen et al., 1999). >

The mechanisms responsible for the deleterious effects of ammonia on central ner-vous system function are multiple involving effects on both energy metabolism, astrocytic function, and neurotransmitter regulation (Hazell and Butterworth, 1999).

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Mild hypothermia of 33 C–35°C is protective in both experimental ischemic and trau-matic brain injury (Busto et al., 1989; Dietrich et al., 1994) and, in these cases, the beneficial effects were deemed to result from improvement in neurotransmitter-related mechanisms rather than brain energy metabolism. Mild hypothermia has recently been shown to be ef-fective in the reduction of intracranial pressure in patients with ALF and some potential mechanisms have been forwarded on the basis of the results of studies in experimen-tal ALF. This paper will review these mechanisms and the potential for mild hypother-mia to offer a useful approach to the management of intracranial hypertension in patients with ALF.

HYPOTHERMIA IN EXPERIMENTAL ALF

Studies by Traber et al. (1989) reveal that hypothermia leads to a significant delay in the onset of encephalopathy and brain edema in rats with ALF resulting from hepatic devascularization. These findings have since been replicated by others (Chatauret et al., 2001; Rose et al., 2000). In a comprehensive study of the mechanisms responsible for the beneficial effects of mild hypothermia in experimental ALF, groups of rats were subjected to hepatic devascularization while maintaining their body temperatures at either 37°C (normothermic) or 35°C (hypothermic). Mild hypothermia resulted in a significant delay in the onset of severe encephalopathy in these animals (Chatauret et al., 2001; Rose et al., 2000), a delay which was accompanied by a significant reduction of brain water content (Fig. 1).

EFFECTS OF HYPOTHERMIA ON BRAIN AMMONIA IN ALF

Pioneering studies by Schenker and associates in the 1960s showed that hypothermia extended the survival time in rats administered lethal doses of ammonia (Schenker and War-ren, 1962). More recent studies in experimental ALF demonstrated that cerebrospinal fluid concentrations of ammonia are significantly reduced by mild hypothermia (Table 1) (Rose et al., 2000). Decreases in cerebrospinal fluid ammonia concentrations occurred in the absence of any significant fall in blood ammonia (Rose et al., 2000). Three possible mechanisms could be responsible for the reduction in ammonia in brain due to hypothermia, namely,

1. Decreased brain ammonia uptake,
2. Decreased production of ammonia in brain *in situ*, and
3. Improved removal of ammonia in brain (stimulation of glutamine synthesis).

In favor of mechanism (1), studies in human patients with ALF reveal that hypothermia results in a decrease in cerebral blood flow, an action which could result in decreased brain ammonia extraction (Jalan et al., 1999). However, earlier studies suggest an inverse relationship between cerebral blood flow and brain ammonia extraction rates (Phelps et al., 1977). Further studies are necessary to resolve this issue. Hypothermia could theoretically result in decreased brain ammonia production. However, this is probably a small entity compared with uptake of ammonia from the circulation. Furthermore, the finding of a lack of change in brain glutamine by hypothermia in rats with ALF (Table 2) suggests that neither ammonia production from glutamine nor increased ammonia removal as glutamine is significantly altered by hypothermia.

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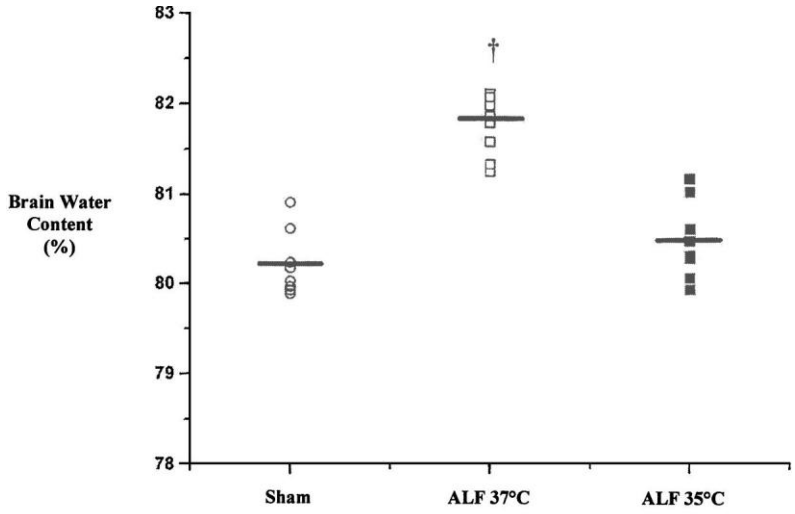
Table 1. Effects of Mild Hypothermia on Blood and CSF Ammonia Concentrations in Rats with ALF

		Acute liver failure	
	Sham-operated	Normothermic	Hypothermic
Blood ammonia (μg/dL)	64.7 ± 9.5	640.4 ± 33.8*	585.7 ± 34.2*
CSF ammonia (μg/dL)	52.4 ± 9.5	1007.3 ± 77.8*	671.0 ± 72.8*,†

Note: Mild hypothermia results in a reduction of CSF but not blood ammonia. Values represent mean ± SE of duplicate determinations in six animals per group.
*$p < 0.01$ compared with sham-operated group.
†$p < 0.01$ compared with normothermic ALF group (data from Chatauret et al., 2001).



Mild hypothermia results in prevention of the increase in brain water associated with ALF. Values represent mean ± S.E. of triplicate determinations in 8 animals per treatment group. Values significantly different from sham-operated group (sham) indicated by *p<0.01. Acute liver failure (35°C) values were not significantly different from sham-operated controls (NS)

Figure 1. Effect of mild hypothermia ($35^{\pm}$C) on brain water content of rats with acute liver failure due to hepatic devascularization versus sham-operated controls.

Effects of Hypothermia on Brain Glutamate in ALF

Extracellular brain glutamate concentrations (measured using the technique of *in vivo* microdialysis) are increased in a wide range of experimental animal models of ALF (de Knegt et al., 1994; Michalak et al., 1996; Tossman et al., 1983). On the basis of these reports, it was suggested that increased glutamate in the brain extracellular space is implicated in the pathogenesis of encephalopathy and brain edema in ALF (Butterworth, 1997). In favor of this possibility, it is well established that exposure of astrocytes (the cells which preferentially manifest edema and swelling in ALF) to glutamate leads to significant cell swelling. One possible explanation for the increase in extracellular glutamate in brain in ALF is ammonia-induced reductions in expression and activity of astrocytic glutamate transporters (Chan et al., 2000; Knecht et al., 1997). Mild hypothermia in animals with ALF prevents the accumulation of glutamate in the extracellular space of brain (Table 2) (Rose et al., 2000). However, whether this effect of hypothermia results from normalization of glutamate transporter expression awaits further studies.

Table 2. Effects of Mild Hypothermia on Extracellular (Microdialysate) or CSF Concentrations of Glutamate, Glutamine, and Lactate in Rats with ALF

			Acute liver failure	
		Sham-operated	Normothermic	Hypothermic
Glutamate (μM)	Microdialysate	1.0 ± 0.4	2.7 ± 0.5*	1.4 ± 0.3†
Glutamine (μM)	Microdialysate	51.0 ± 10.1	226.0 ± 42*	231.6 ± 70*
Lactate (mM)	CSF	0.9 ± 0.1	7.8 ± 1.2*	1.8 ± 0.6†

Note: Mild hypothermia prevents the increase in extracellular glutamate and CSF lactate characteristic of ALF. Values shown represent mean ± SE of duplicate determination in six animals per treatment group.

* $p < 0.01$ compared with sham-operated controls.

† $p < 0.01$ compared with normothermic ALF group (data from Rose et al., 2000 and Chatauret et al., 2001).

Effects of Hypothermia on Brain Lactate in ALF

Increased brain lactate is a consistent finding in experimental ALF (Chatauret et al., 2001; Deutz et al., 1988; Mans et al., 1994) and increased in brain lactate parallel EEG changes in these animals (Deutz et al., 1988). Increased lactate in brain in ALF is generally considered to reflect decreased brain glucose (pyruvate) oxidation re-sulting from ammonia-induced decreases in activity of the tricarboxylic cycle enzyme α-ketoglutarate dehydrogenase (Lai and Cooper, 1986) (Fig. 2). It is unlikely that increased brain lactate in ALF results from increased circulating levels of lactate since Posner and Plum (1967) reported an independence of blood and CSF lactate over a wide range of concentrations. Moreover, Jalan et al. (1999) found no significant changes in brain lactate uptake associated with the beneficial effects of hypothermia in patients with ALF.

HYPOTHERMIA IN THE MANAGEMENT OF PATIENTS WITH ALF

With the advent of orthotopic liver transplantation, survival rates of up to 80% have been achieved in patients with ALF. However, up to half of these patients die while wait-ing for a donor organ, mostly because of the deleterious effects of increased intracranial pressure (Jalan et al., 1999). For these patients, there are few therapeutic options available. Hyperventilation may be of some value in delaying the onset of brain herniation but does not prevent edema (Ede et al., 1986). Mannitol has limited value particularly in patients with associated renal failure (Canlese et al., 1982) and relapses of increased intracranial pressure occur in up to 80% of patients treated with hyperventilation or mannitol (Jalan et al., 1999). Two pilot (uncontrolled) studies in small numbers of patients have assessed the use of mild hypothermia in the management of patients with ALF.

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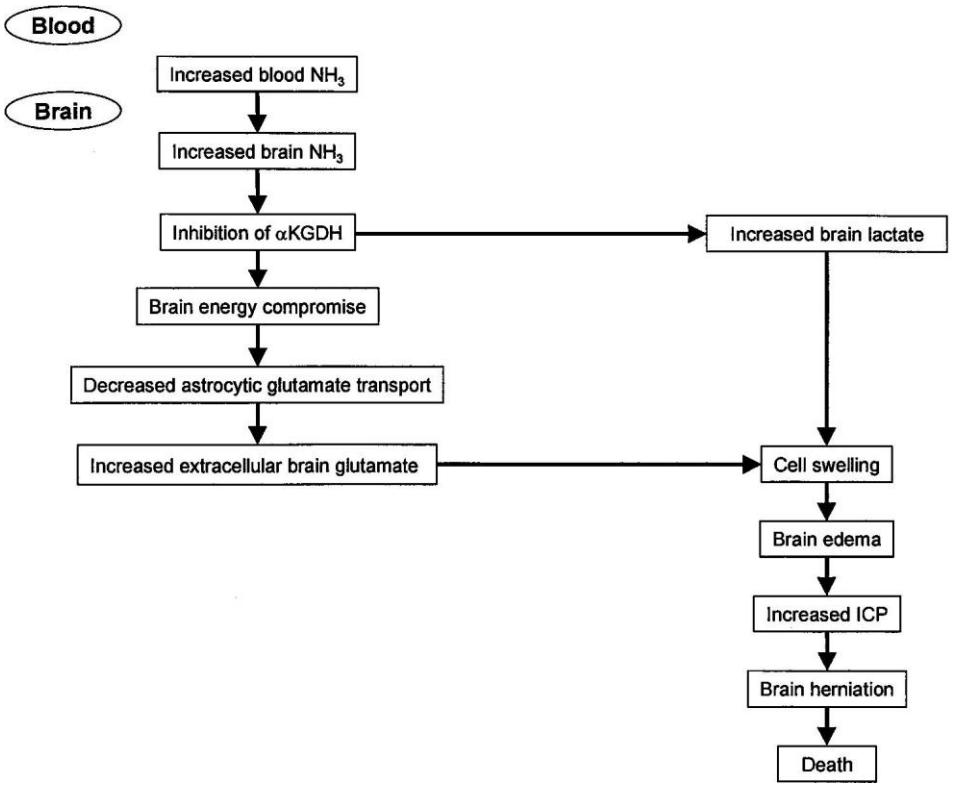

Figure 2. Possible mechanisms whereby ammonia causes increased intracranial pressure and brain herniation in acute liver failure. Mild hypothermia reduces ammonia delivery to the brain resulting in prevention of the increases in lactate and glutamate, two factors potentially involved in the pathogenesis of brain edema.

In a study by Roberts and Manas (1999), the use of hypothermia with temperatures of 32 C–36°C over a 3-day period was found to be beneficial in the management of a patient with ALF due to acetaminophen intoxication. Jalan et al. (1999) initiated a study in seven consecutive patients with ALF aged 16–46 who fitted criteria for poor prognosis ALF and had increased intracranial pressure which was unresponsive to both mannitol and ultra-filtration. Cooling blankets were used to lower patients core temperature to 32 C–33°C. Patients who were not candidates for transplantation were cooled for 8 hr then gradually rewarmed to 37°C; patients on the transplantation waiting list were cooled both before and during the transplant procedure. Cooling resulted in a reduction in intracranial pressure in all patients. The four patients who were candidates for liver transplantation were maintained for up to 14 hr of hypothermia. Both arterial ammonia and cerebral blood flow decreased in these patients leading to the proposal that hypothermia resulted in a decrease in ammonia delivery to the brain and a concomitant decrease in brain ammonia metabolic rates (Table 3).

Table 3. Blood/Brain Ammonia Parameters in Patients with ALF: Effect of Hypothermia

	Prior to cooling	After cooling
$^{[Ammonia]}$Arterial (μM)	343 (109–490)	259 (100–453)*
$^{[Ammonia]}$Jugular venous (μM)	305 (49–477)	268 (85–527)
Brain ammonia extraction (%)	11.0 (1.0–15.0)	–4.6 (–16.3 to 15.4)*
Brain ammonia metabolic rate (μmol/L/100 g/min)	2.6 (0.6–6.3)	–0.3 (–3.1 to 1.4)*

* $p < 0.05$ compared with precooling values (modified from Jalan et al., 1999).

In conclusion, there is a convincing body of evidence that mild hypothermia lowers intracranial pressure in ALF. Studies in experimental animals suggest that these protective effects are the consequence of reductions of blood–brain ammonia transfer leading to normalization of extracellular brain glutamate concentrations and improvement in brain energy metabolism.

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