occlusion of the MCA in adult male Lewis rats (250–400 g). Temperature was monitored by rectal probe, and normothermia was maintained using a warming blanket during the course of the operative procedure. After 24 hours, rats were euthanized by decapitation and brains were removed and cut into 1-mm saggital sections. The resulting slices were stained with 2,3,5,-triphenyl tetrazolium chloride, and planimetric analysis was performed using National Institutes of Health Image-mate software to estimate infarct volume. In selected experiments, the carotid artery was cannulated to measure blood pressure and heart rate.

RESULTS AND DISCUSSION

Administration of PICVA-13 (600 mg/kg) 2 hours after the onset of ischemia significantly reduced infarct volume (control, 30.3 ± 27.1 mm^3, $n = 13$; PICVA-13, 6.1 ± 4.11 mm^3, $n = 9$; $P < 0.05$). The reduction in infarct size was dose dependent; infarct volume after PICVA-13 treatment with 400 mg/kg did not differ statistically from that in controls (17.0 ± 15.3 mm^3, $n = 8$, $P = 0.22$). The neuroprotective effects seen with PICVA-13 were not attributable to differences in several physiologic variables known to influence stroke size (heart rate, blood pressure, or arterial blood gas values; data not shown).

Development of new therapies to prevent ischemic cell death in stroke may be accelerated by an understanding of the underlying pathogenic mechanisms at the molecular level. We propose that a metabolic byproduct of polyamine oxidation (3-aminopropanal) is a major mediator of cell death in parenchyma of the ischemic brain and, furthermore, show that a compound that chemically inactivates 3-aminopropanal significantly attenuates infarct volume in experimental stroke. 3-Aminopropanal accumulates to cytotoxic levels within 2 hours after the onset of ischemia and continues to rise for at least 25 hours.[1] This suggests that treatment with PICVA-13 might be of therapeutic benefit at even later time points. The cytotoxic role of 3-aminopropanal in the evolving ischemic infarct has several particularly appealing features for the development of future therapeutics. It is hoped that these results may lead to the design of pharmacologic agents to treat stroke based on inhibiting 3-aminopropanal toxicity.

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DIFFERENTIAL DISPLAY OF GENE EXPRESSION IN CEREBRAL EDEMA INDUCED BY FULMINANT HEPATIC FAILURE

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BRAIN EDEMA, leading to intracranial hypertension and brain herniation, is a leading cause of death in fulminant hepatic failure (FHF).[1] Although these neuro-

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logic complications present a challenge in the management of FHF, the mechanism of brain edema remains poorly understood. Two types of mechanisms are generally indicated in the development of brain edema, vasogenic and cytotoxic.[2] Vasogenic edema occurs as a result of the disruption of the blood-brain barrier, allowing uncontrolled access of plasma components to the brain compartment, whereas cytotoxic edema is most likely the consequence of impaired osmoregulation in the brain. Evidence from experimental animals and postmortem human brain support aspects of each of these mechanisms in FHF.[3,4] The goal of this study was to identify genes involved in the development of brain edema.

MATERIALS AND METHODS

FHF was surgically induced in male Sprague-Dawley rats (200–250 g) by a previously published method.[5] Briefly, the anterior liver lobes were removed through a midline incision in the abdomen, and the common pedical to the right liver lobes was ligated. The 2 omental lobes were left intact. Sham operations consisted of a laparotomy and mobilization of the liver ($n = 5$). To prevent hypothermia, all rats were placed under a heating lamp after the surgical procedure, and body temperature was monitored with a rectal thermister probe. Rats were euthanized 2, 6, and 12 hours after induction of FHF and when they had reached stage IV hepatic encephalopathy (HE) (30–36 hours after FHF induction) ($n = 6$ per group). Cerebral hemispheres were rapidly removed. One cortex sample per rat was flash frozen for RNA isolation, and the other was used to measure edema. The percentage of water in the brain was calculated by a gravimetric technique. Changes in gene expression in the cortex between control, sham-operation, and FHF-induced edema groups were analyzed by differential display reverse transcription–PCR (DDRT-PCR). All DDRT-PCR procedures were performed in duplicate to verify reproducibility, and cDNA fragments were electrophoretically separated on a polyacrylamide gel. Differentially expressed gene fragments were excised from the gel, confirmed by an RNase protection assay, sequenced, and analyzed through GenBank for homology.

RESULTS

Cerebral edema, defined as a statistically significant increase in water content relative to that in control cortex, was confirmed in rats studied 30–36 hours after FHF induction (those with stage IV HE). The percentage of water in the cortex from rats in this group was 81.5% ± 0.41%, compared with 79.5% ± 0.1% ($P < 0.01$) in control cortex. Cerebral edema was not detected in the brains of rats studied at earlier time points after FHF induction. The body temperature of all animals ranged from 36.4 to 36.8°C.

Using the DDRT-PCR technique, we identified 55 cDNAs that are differentially expressed in the cortex of rats with FHF-induced edema. Although most of these cDNAs represent unknown genes, we identified a number of known genes that had altered expression patterns during the development of cerebral edema. Expression of the astrocyte-specific glutamate transporter (*GLT-1*) gene (previously reported by Knecht et al,[6]) the GluR2 subunit of the AMPA/glutamate receptor gene, the carbonic anhydrase II gene, and the transcription factor (nuclear factor kappa B [NF-κB]) gene were downregulated between 6 and 12 hours after FHF induction. The expression of these genes remained downregulated through stage IV HE. Expression of the genes for glycine- and glutamate-thienylcyclohexylpiperidine–binding protein and interleukin 1 receptor type I was upregulated in rat cortex as early as 12 hours after FHF induction.

DISCUSSION

It has been suggested that the accumulation of glutamine within the brain as a result of ammonium detoxification by astrocytes is involved in the formation of cerebral edema in FHF. Related to this hypothesis is the implication of the glutamate neurotransmitter system in HE. The decrease in mRNA levels of GLT-1, GluR2, and NF-κB found in this study support the concept that glutamate plays a role in the development of edema and/or hepatic encephalopathy. Identification and characterization of the novel genes differentially expressed in FHF may provide additional insight into the basic mechanism of brain edema.

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EFFECT OF STANDARD AND ALTERNATIVE PREHOSPITAL RESUSCITATION IN A PORCINE MODEL OF HEMORRHAGIC SHOCK AND HEAD INJURY

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STANDARD PREHOSPITAL RESUSCITATION (SPR) of trauma patients with isolated penetrating torso injuries does not improve survival and may increase blood loss by raising the blood pressure.[1] SPR is advocated for patients with head injury because of the devastating effects of hypotension on outcome.[2] There are no prospective data supporting the efficacy of SPR in patients with hemorrhagic shock (HS) and head injury. We hypothesized that in a pressure-driven model of uncontrolled hemorrhagic shock, SPR would reduce secondary cerebral injury. Our objective was to determine the effects of SPR, delayed resuscitation (DR), and diaspirin cross-linked hemoglobin resuscitation (DCLHb) on lesion size (LS) and surrogates of secondary cerebral injury: intracranial pressure (ICP), cerebral perfusion pressure (CPP), regional cerebral blood flow (CBF), and cerebral oxygen delivery (COD).

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