intravenously, and the extravasation of tracers was analyzed.

Results: Results disclosed that treatment of RBMECs with 5 mM ammonia increased intracellular Ca^{2+} accumulation, while pretreatment with MK-801 or memantine attenuated such Ca^{2+} accumulation. As expected, ammonia increased total ROS production by 75%. Pretreatment with MK-801 or memantine decreased ROS accumulation in ammonia-treated cells, strongly suggesting that the ONS induced by ammonia in RBMEC is, in part, mediated by activation of NMDA-R. BBB permeability to 10 kDa FITC-dextran was increased 2-fold in rats with ALF, when compared to controls. Memantine prevented the ammonia-induced changes in permeability, resulting in a return of 10 kDa dextran extravasation to basal levels.

Conclusion: In summary, these results provide novel and important information on the role of endothelial NMDA receptors in BBB dysfunction associated with HE that will bring us closer to a better understanding of the mechanisms involved in the development of the brain edema in acute liver failure.

CONFLICTS OF INTEREST

The authors have none to declare.

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6

NEURONAL DYSFUNCTION IN CHRONIC HEPATIC ENCEPHALOPATHY: ROLE OF ASTROCYTIC MATRICELLULAR PROTEINS

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Chronic hepatic encephalopathy (CHE), due to chronic liver failure, is characterized by confusion, disorientation, behavioral changes, impaired cognition, and motor disturbances. It is associated with defective neuronal integrity, leading to neurobehavioral and cognitive impairments. The mechanisms responsible for the neurological abnormalities in CHE, however, remain largely unknown. Since a reduction in astrocytic secretion of matricellular proteins (MCPs), including thrombospondin-1 (TSP-1), Hevin, Glypicans 4 and 6, and the CCN family of proteins (CYR61/CTGF/NOV), have been implicated in the neuronal dysfunction associated with various neurological conditions (e.g., ischemia, Alzheimer's disease, Down's syndrome), we examined whether astrocytic MCP synthesis and release may likewise be affected in CHE, and whether this event contributes to the defective neuronal integrity and associated neurobehavioral and cognitive impairments that occur in CHE. Exposure of cultured astrocytes to ammonia (NH_4Cl, 1 mM) for 10–15 days resulted in a decrease in intra- and extracellular levels of TSP-1, Hevin, Glypicans 4 and 6, nerve growth factor, as well as in basic fibroblast growth factor. These changes were associated with a decrease in levels of specificity protein-1, activator protein-1, Forkhead box O, and transforming growth factor-beta, factors known to enhance the synthesis and release of MCPs. Exposure of cultured neurons to conditioned media (CM) from ammonia-treated astrocytes showed a decrease in synaptophysin, PSD95 and synaptotagmin levels. CM from TSP-1 overexpressing astrocytes (by the addition of TSP-1 cDNA) that were treated with ammonia, when added to cultured neurons, reversed the decline in synaptic proteins. We also found a significant decline in TSP-1, Glypicans 4 and 6, CCN1 and CCN4 levels in cortical astrocytes, as well as a reduction in levels of synaptic proteins in an *in vivo* rat model of CHE (treatment with the liver toxin, thioacetamide). Additionally, treatment of rats with Metformin, an agent known to increase levels of MCPs in other conditions, attenuated the neurobehavioral abnormalities observed in CHE. Our findings suggest that increasing brain levels of MCPs may represent a useful therapeutic approach for patients with chronic hepatic encephalopathy.

CONFLICTS OF INTEREST

The authors have none to declare.

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SESSION 4: WORKSHOP 1 (CLINICAL): MINIMAL/COVERT HEPATIC ENCEPHALOPATHY

7

THE BRAIN-MUSCLE AXIS IN MINIMAL HEPATIC ENCEPHALOPATHY (MHE): A PLACEBO-CONTROLLED, LONGITUDINAL DOUBLE-BLIND TRIAL WITH L-ORNITHINE L-ASPARTATE (LOLA) – PRELIMINARY RESULTS

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ORAL PRESENTATION

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Background and Aim: LOLA promotes nitrogen elimination and experimentally, has been shown to reduce sarcopenia. We investigated effects of 12 weeks of oral LOLA in an outpatient series with compensated cirrhosis and mHE. Patients were pre-screened with PHES tests and included if they scored −4 or worse.

Methods: 34 English-speakers were included; twelve randomised to 12 weeks of oral LOLA at 6 g tds, 22 randomised to an identical-looking placebo. At baseline, 4 and 12 weeks, subjects underwent psychometric testing using PHES and a multi-domain, computerised battery, CogstateTM, serial Stroop, WTAR and Short Form-36 health questionnaires. Markers of muscle function were recorded including handgrip strength, calliper-measured thickness of biceps, triceps and subscapular skin folds, and 6-minute-walk-test. Subjects underwent magnetic resonance imaging on a Siemens 3T magnet including standard T1 and T2 sequences, functional MRI (fMRI) sequences (tasks and resting states) and proton MR spectroscopy of anterior cingulate cortex (ACC). LC Model software was used for metabolite identification.

Results: At baseline both groups of patients were matched for drug compliance, age, years of education, PHES, WTAR, Stroop tests and SF-36. 57% of subjects in LOLA arm reported better energy levels than placebo group 0.04% (P-value < 0.001). Better concentration was reported by 21% of subjects in treatment arm, compared with none (P = 0.05). 28% reported improved memory in the treatment group vs 0.04% with placebo. Sleep improvements were reported by 35% in treatment arm, compared to 0.09% of placebo (P = 0.05). In both groups, changes in PHES totals, based on English normative data, between baseline and visit3 and on Cogstate testing were non-significant. Sub-analysis of the Digit-Symbol revealed significant improvement in performance within the LOLA-treated group (P = 0.05). WTAR and Stroop test performance did not show group differences. Change-in-biceps skinfold thickness showed a mean gain of 1.5 mm in the LOLA group with a mean loss of 1.0 mm (P = 0.05) with placebo. No differences were found in other skinfolds, or hand-grip or 6-minute-walk-tests. Significant volume reduction was seen in several regions (see Table 1) fMRI tasks did not vary significantly between groups. Spectroscopy of ACC showed significant changes in glutamate concentration (rm P = 0.03), after LOLA treatment.

Table 1 Subcortical Regions Showing Significant Volume Reduction (mm^3) With LOLA Treatment at 12 Weeks on Co-registered MRI.

Subcortical brain volume region	*P*-value
Left-lateral-ventricle	0.014
Right-cerebellum-cortex	0.050
right-pallidum	0.021
CC_Mid_Anterior	0.049

Conclusion: After 12 weeks of LOLA, patients reported a highly significant improvement in energy levels, and significant improvements in concentration. A significant treatment-related improvement in digit-symbol PHES-subtest in those receiving LOLA was seen. Comparable to LOLA-animal studies, an increase was noted in biceps skin fold thickness, which may indicate improved nutrition. Certain areas demonstrated significant volume-reduction with treatment, an observation that has not previously been noted in imaging studies of patients receiving this drug. Unlike previous studies, no functional changes were seen, but significant changes were found on MR spectroscopy of the ACC, a region (part of the default mode network) known to be metabolically active in mHE.

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CONFLICTS OF INTEREST

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8

COMPARATIVE EFFECTIVENESS OF DIFFERENT PHARMACOLOGICAL INTERVENTIONS FOR THE TREATMENT OF MINIMAL HEPATIC ENCEPHALOPATHY: A SYSTEMATIC REVIEW WITH NETWORK META-ANALYSIS

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Background and Aims: Minimal hepatic encephalopathy (MHE) is the mildest presentation of hepatic encephalopathy (HE), which includes a spectrum of neuropsychiatric manifestations ranging from subtle cognitive decline to deep coma. MHE has been shown to impair quality of life, predict overt HE (OHE), and even death. Various treatment