HEMICHANNEL-MEDIATED RELEASE OF LACTATE IN HEALTH AND DISEASE

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Background and Aims: Astrocytes, the most numerous glial cells, are hypothesized to play a role in the pathological mechanisms underlying hepatic encephalopathy (HE), although the clinical manifestations are mainly neuronal. Astrocytes are extensively connected by gap junctions formed of connexins, which may also exist as functional hemichannels allowing the exchange of molecules between the cytoplasm and the extracellular milieu. The astrocyte-neuron lactate shuttle hypothesis is a highly debated yet valuable concept suggesting that neuronal activity is fueled by lactate provided by neighboring astrocyte during periods of high demand. In pathological conditions, including HE, significant changes in astroglial anatomy and function are known to occur which could be impairing the astrocyte-neuron communication. In this study, we investigated changes in the hemichannel function and lactate release in the cerebral cortex and the role of ammonia in animal (rat) models of HE (bile duct ligation [BDL] and hyperammonemia) and the effect of ammonia lowering treatment, ornithine phenylacetate (OP).
Methods: Microelectrode biosensors were used for real time measurements of lactate release by cortical slices prepared from the brains of SHAM-operated (n=18), SHAM + high ammonia diet (HA, n=16), BDL (n=18) and BDL animals treated with OP (BDL+OP, n=14). Fluorescent dye loading on cortical slices of the same animal models was also performed. The involvement of hemichannels was validated using hemichannel blockers, carbenoxolone and 5-Nitro-2-(3-phenylpropylamino)benzoic Acid.
Results: Both HA and BDL were hyperammonemic but the ammonia levels in the BDL+OP animals were significantly lower. Biosensors showed a significant reduction ($p<0.05$) in both tonic and hypoxia induced lactate release in the cortex of HA and BDL rats, which recovered with OP treatment. Cortical dye loading indicated a decrease in hemichannel-mediated loading ($p<0.05$) in BDL compared to SHAM-operated rats.
Conclusions: The results of the present study suggest for the first time that HE is associated with significant changes in the hemichannel functionality in the CNS under normal and hypoxic conditions, with ammonia playing an important role in mediating this dysfunction. These changes may play a role in the distinct neurochemical phenotype and is therefore hypothesized to play a significant role in the pathogenesis of HE.