Compartmentation of Enzymes of Glucose, Glutamate, and Branched Chain Amino Acid Metabolism in the CNS.

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Glutamate is the major excitatory neurotransmitter in mammalian brain. Detoxification and repletion of glutamate released by neurons is achieved by glutamate/glutamine cycle (GGC) and complex metabolic processes in astrocytes. Glutamate is transported into astrocytes where some is converted to glutamine; the rest is converted to pyruvate. Glutamine is transported back to the neurons completing the glutamate/lglutamine cycle (GGC). The GGC replenishes part, but not all, of the neuronal glutamate. Re-synthesis of glutamate in the glia, to make up the remaining deficit, requires de novo glutamate synthesis via pyruvate carboxylation. In the retina, increases in GGC activity resulted in increased de novo glutamate synthesis and surprisingly increased retina glycolysis but not glucose oxidation. De novo glutamate synthesis requires a nitrogen source Branched chain amino acids (BCAAs) are a major source of this nitrogen in reactions catalyzed by the branched chain aminotransferase isozymes (BCATs), mitochondrial BCATm and cytosolic BCATc. Compartmentalization of the BCAT isozymes (BCATc in neurons and BCATm in astrocytes) is thought to facilitate the GGC by providing a cyclic mechanism for shuttling of nitrogen between neurons and glia. We used immunohistochemistry to examine the distribution of BCAT isozymes and a key transporter (aspartate/glutamate carrier, AGC) of the redox shuttle required for glucose oxidation in the retina. In the retina, BCATc immunoreactivity was in the photoreceptor inner segments and in the outer plexiform layer. More diffuse labeling for BCATc was found in the inner plexiform layer. Ganglion cells were immunoreactive, as was the nerve fiber layer. The labeling pattern for BCATm was characteristic of staining of the Müller glial cells i.e., it co-localizes with vimentin. The pattern of expression of AGC was similar to the retinal localization of BCATc. We found no carrier protein in Müller cells, but abundant expression in the photoreceptor cells and inner plexiform layer. In adult rat brain, BCATc is expressed selected populations of glutamatergic and GABAergic neurons. For example in glutamatergic granule cells of the dentate gyrus in the hippocampus, BCATc was present in axons and nerve terminals whereas BCATc was concentrated in the cell bodies of GABAergic hippocampal pyramidal basket cells. There was strong expression of BCATc in the mossy fiber projection (granule cell axons) and in the zone of synaptic varicosities formed between the mossy fibers and target pyramidal cells in field CA3. BCATm was in astrocytes in the hippocampus. In brain Ramos et al. (Ramos, 2003) have shown AGC expression is neuronal. In hippocampus AGC mRNA was found in neurons that express BCATc. Our results suggest that BCATc has access to neurotransmitter pool of glu in glutamatergic neurons and metabolic pool in GABA neurons and may colocalize with AGC. Furthermore, the pattern of AGC expression provides a biochemical basis for the Magistretti hypothesis (Magistretti, 1999) and the high rate of glycolysis in Müller cells and glia.
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