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Function of leucine in excitatory neurotransmitter metabolism in the central nervous system.

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Source

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Abstract

A novel hypothesis for the role of branched-chain amino acids (BCAA) in regulating levels of the major excitatory neurotransmitter glutamate in the central nervous system is described. It is postulated that the branched-chain aminotransferase (BCAT) isoenzymes (mitochondrial BCATm and cytosolic BCATc) are localized in different cell types and operate in series to provide nitrogen for optimal rates of de novo glutamate synthesis. BCAA enter the astrocyte where transamination is catalyzed by BCATm, producing glutamate and branched-chain alpha-keto acids (BCKA). BCKA, which are poorly oxidized in astrocytes, exit and are taken up by neurons. Neuronal BCATc catalyzes transamination of the BCKA with glutamate. The products, BCAA, exit the neuron and return to the astrocyte. The alpha-ketoglutarate product in the neurons may undergo reductive amination to glutamate via neuronal glutamate dehydrogenase. Operation of the shuttle in the proposed direction provides a mechanism for efficient nitrogen transfer between astrocytes and neurons and synthesis of glutamate from astrocyte alpha-ketoglutarate. Evidence in favor of the hypothesis is: 1) The two BCAT isoenzymes appear to be localized separately in the neurons (BCATc) or in the astroglia (BCATm). 2) Inhibition of the shuttle in the direction of glutamate synthesis can be achieved by inhibiting BCATc using the neuroactive drug gabapentin. Although gabapentin does not inhibit BCATm, it does block de novo glutamate synthesis from alpha-ketoglutarate. 3) Conversely, gabapentin stimulates oxidation of glutamate. Inhibition of BCATc may allow BCKA to accumulate in the astroglia, thus facilitating conversion of glutamate to alpha-ketoglutarate.

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