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Novel Mechanism of Glutamine Formation From Branched-Chain Amino Acids in Brain Areas of Astroglial Glutamine Synthetase Deficiency

Abstract

Elevations in extracellular glutamate in the brain are implicated in the pathogenesis of several neurological conditions. The underlying mechanisms of this elevation are not completely understood, however, and there are no effective methods that reduce the elevation or limit its neurotoxic effects. Furthermore, the actions of glutamate and gamma-aminobutryic acid (GABA) have been implicated in both the toxic and therapeutic effects of many general anesthetics. Astroglial glutamine synthetase plays a critical role in the metabolism and clearance of synaptic glutamate and conversion to glutamine. Glutamine synthetase is the only known enzyme to synthesize glutamine from glutamate in humans and other vertebrates, and its function is critically important for several physiological processes. Our laboratory has produced strong preliminary evidence to suggest that glutamine can be produced through a previously unrecognized, glutamine synthetase-independent pathway that involves branched-chain amino acids. The specific aim of the proposed study is to examine the role of branched-chain amino acids in the formation of brain glutamine in wild type and glutamine synthetase knockout mice, using in vivo methods of isotope labeling, microdialysis, mass spectrometry and glutamine synthetase assay. The discovery of a new pathway of brain glutamine synthesis will be paradigm changing, and is likely to have profound consequences for our understanding of how glutamate, glutamine and GABA are made in the brain. This project is expected to have broad applications to many conditions with glutamate dysregulation, and will likely facilitate the development of novel treatments and anesthetics.