Role of mu-calpain in proteolytic cleavage of brain l-glutamic acid decarboxylase

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摘要

Abstract

Glutamic acid decarboxylase (GAD) is the rate-limiting enzyme for gamma-aminobutyric acid (GABA) biosynthesis. Previously, we reported the presence of truncated forms of GAD in vivo and in vitro. In addition, an unidentified endogenous protease responsible for proteolytic cleavage of full-length GAD (fGAD) to its truncated form (tGAD) was also observed. In this communication, we report that mu-calpain is a good candidate for conversion of fGAD(67) to tGAD(67). This conclusion is based on the following observations: 1. purified recombinant GAD(67) is cleaved by mu-calpain at specific sites; 2. in brain synaptosomal preparation, GAD(67) is cleaved to its truncated form by an endogenous protease which is inhibited by specific calpain inhibitors; 3. in mu-calpain knockout mice, the level of tGAD in the brain is greatly reduced compared with the wild type; 4. when mu-calpain gene is silenced by siRNA, the level of tGAD is also markedly reduced compared to the control group; and 5. mu-calpain is activated by neuronal stimulation and Ca(2+)-influx. The physiological significance of calpain in regulation of GABA synthesis and GABAergic neurotransmission is also discussed