Dynamin-like protein 1 cleavage by calpain in Alzheimer's disease

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Abnormal mitochondrial dynamics contributes to mitochondrial dysfunction in Alzheimer's disease (AD), yet the underlying mechanism remains elusive. In the current study, we reported that DLP1, the key mitochondrial fission GTPase, is a substrate of calpain which produced specific N-terminal DLP1 cleavage fragments around 50kDa. In addition, various AD-related insults such as exposure to glutamate, soluble amyloid-β oligomers, or reagents inducing tau hyperphosphorylation (i.e., okadaic acid) led to calpain-dependent cleavage of DLP1 in primary cortical neurons. DLP1 cleavage fragments were found in cortical neurons of CRND8 APP transgenic mice which can be inhibited by calpeptin, a potent small molecule inhibitor of calpain. Importantly, these N-terminal DLP1 fragments were also present in the human brains, and the levels of both full-length and N-terminal fragments of DLP1 and the full-length and calpain-specific cleavage product of spectrin were significantly reduced in AD brains along with significantly increased calpain. The cleavage of DLP1 by calpain was further analyzed by bioinformatic and mutagenesis studies that demonstrated the cleavage site at DLP1(511-521) in the VD domain by calpain. Synthesized peptides of the sequence flanking the DLP1 cleavage sites could effectively block calpain cleavage in AD models. Taken together, our study suggests that calpain-dependent cleavage is at least one of the posttranscriptional mechanisms that contribute to the dysregulation ofmitochondrial dynamics and provide novel target to rescue related mitochondrial dysfunction in AD.