Caspase 6

Active cysteinyl protease Caspase-6 is associated with early Alzheimer and Huntington diseases.

Hippocampal atrophy is associated with cognitive impairment in AD. Here, a rare functional exonic missense CASP6 single nucleotide polymorphism (SNP), causing the substitution of asparagine with threonine at amino acid 73 in Casp6 (Casp6N73T), was associated with hippocampal subfield CA1 volume preservation. Compared to wild type Casp6 (Casp6WT), recombinant Casp6N73T altered Casp6 proteolysis of natural substrates Lamin A/C and α-Tubulin, but did not alter cleavage of the Ac-VEID-AFC Casp6 peptide substrate. Casp6N73T-transfected HEK293T cells showed elevated Casp6 mRNA levels similar to Casp6WT-transfected cells, but, in contrast to Casp6WT, did not accumulate active Casp6 subunits nor show increased Casp6 enzymatic activity. Electrophysiological and morphological assessments showed that Casp6N73T recombinant protein caused less neurofunctional damage and neurodegeneration in hippocampal CA1 pyramidal neurons than Casp6WT. Lastly, CASP6 mRNA levels were increased in several AD brain regions confirming the implication of Casp6 in AD. These studies suggest that the rare Casp6N73T variant may protect against hippocampal atrophy due to its altered catalysis of natural protein substrates and intracellular instability thus leading to less Casp6-mediated damage to neuronal structure and function [1)].

Higher entorhinal cortex and hippocampal Caspase-6 levels correlate with lower cognitive performance in aged humans. Caspase-6 induces axonal degeneration in human primary neuron cultures and causes inflammation and neurodegeneration in mouse hippocampus, and age-dependent memory impairment. To assess whether Caspase-6 causes damage to another neuronal system, a transgenic knock-in mouse overexpressing a self-activated form of Caspase-6 five-fold in the striatum, the area affected in Huntington disease, and 2.5-fold in the hippocampus and cortex, was generated. Detection of Tubulin cleaved by Caspase-6 confirmed Caspase-6 activity. The Caspase-6 expressing mice and control littermates were subjected to behavioral tests to assess Huntington disease-relevant psychiatric, motor, and cognitive deficits. Depression was excluded with the forced swim and sucrose consumption tests. Motor deficits were absent in the nesting, clasping, rotarod, vertical pole, gait, and open field analyzes. However, Caspase-6 mice developed age-dependent episodic and spatial memory deficits identified by novel object recognition, Barnes maze and Morris water maze assays. Neuron numbers were maintained in the striatum, hippocampus, and cortex. Microglia and astrocytes were increased in the hippocampal stratum lacunosum molecular and in the cortex, but not in the striatum. Synaptic mRNA profiling identified two differentially expressed genes in transgenic hippocampus, but none in striatum. Caspase-6 impaired synaptic transmission and induced neurodegeneration in hippocampal CA1 neurons, but not in striatal medium spiny neurons. These data revealed that active Caspase-6 in the striatal medium spiny neurons failed to induce inflammation, neurodegeneration or behavioral abnormalities, whereas active Caspase-6 in the cortex and hippocampus impaired episodic and spatial memories, and induced inflammation, neuronal dysfunction, and neurodegeneration. The results indicate age and neuronal subtype-dependent Caspase-6 toxicity and highlight the importance of targeting the correct neuronal subtype to identify underlying molecular mechanisms of neurodegenerative diseases [2)].

1)

Zhou L, Nho K, Haddad MG, Cherepacha N, Tubeleviciute-Aydin A, Tsai AP, Saykin AJ, Jesper Sjöström

P, LeBlanc AC. Rare CASP6N73T variant associated with hippocampal volume exhibits decreased proteolytic activity, synaptic transmission defect, and neurodegeneration. Sci Rep. 2021 Jun 16;11(1):12695. doi: 10.1038/s41598-021-91367-0. PMID: 34135352.
2)
Noël A, Zhou L, Foveau B, Sjöström PJ, LeBlanc AC. Differential susceptibility of striatal, hippocampal and cortical neurons to Caspase-6. Cell Death Differ. 2018 Jan 19. doi: 10.1038/s41418-017-0043-x. [Epub ahead of print] PubMed PMID: 29352267.

From:
https://neurosurgerywiki.com/wiki/ - **Neurosurgery Wiki**

Permanent link:
https://neurosurgerywiki.com/wiki/doku.php?id=caspase_6

Last update: **2024/06/07 02:49**