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The role of AMP-activated protein kinase as a novel therapeutic target for alzheimer's disease

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Alzheimer 's Disease (AD) is an aging-associated neurodegenerative disease. AD patients suffer from behavioral deficits, mental distress and progressive memory impairments. Currently existing AD drugs are merely symptomatic treatments. Therefore, we need to find a novel therapeutic strategy for AD. Amyloid beta (Aβ), known as a marker of AD, is generated by cleaving Amyloid-Precursor Protein (APP) with β-secretase (BACE1) and γ-secretase. Identifying effective methods to suppress the Aβ accumulation has long been of great interest. Recently, AMP-Activated Protein Kinase (AMPK), a serine/threonine protein kinase, began to be focused as a novel therapeutic target since it has been reported to regulate formation of Aβ. Thus, in this study, 100 compounds were selected from screening a chemical library containing one million compounds by in silico study. We finally found YE-06 through chemical modifications and various bioassays. In accordance with the docking study, YE-06 potentially bound to the AMP binding site of AMPK. Compared to Metformin, which is a well-known AMPK activator, YE-06 significantly activated AMPK and consequently down-regulated the protein level of BACE1. The mRNA level of BACE1 was significantly reduced. We showed improvements in the cognition and movement coordination of AD rat model in YE-06 treated group through water maze test, probe test, passive avoidance test, rotarod test and vertical pole test. YE-06 efficiently increased ACh and decreased the AChE activity. Also, YE-06 significantly reduced neuronal cell death of AD rat models. Therefore, our results suggest that YE-06 is a potential compound for AD treatment.

Biography

Hyunji Jo has graduated from Konyang University in 2016. She is currently pursuing Doctoral studies in Pharmacy at Ewha Womans University. Her research focuses on studying the role of AMPK as a novel therapeutic target for Alzheimer's disease.

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