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Modulating ADAM10 and BACE1 activities by carboxylated DHED reduce brain beta-amyloid accumulation and memory deficit in Alzheimer's disease mouse model

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We have recently demonstrated that DHED can reduce the generation of amyloid beta peptide by inhibiting beta-secretase (BACE-1) activity. In this study, carboxylated DHED (cx-DHED), soluble analogue of DHED was developed and its mechanism was investigated. Administration of cx-DHED (1 mg/kg) for four months resulted in more significantly lowering of brain amyloid beta peptide than that of DHED in Tg2576 mice. Moreover, cx-DHED ameliorates memory impairments and hippocampal cell death in Tg2576 mice. Treatment of 10 μM cx-DHED impedes amyloid beta peptide production in Tg2576 primary neuronal cell. Furthermore, cx-DHED significantly reduced beta-secretase activity and increased alpha-secretase activity in an enzymatic activity test. 3D-QSAR study was shown that cx-DHED strongly binds substrate recognition domain of ADAM10 as well as BACE1. These results strongly suggest that cx-DHED may reduce the biosynthesis of amyloid beta peptide by inhibiting BACE1 and activating alpha-secretase concurrently. Combined with previous findings of direct inhibition of BACE-1 by DHED, this work indicates that carboxylating strategy on beta-secretase inhibitor may have potential to provide new insights into designing novel drugs that target multiple steps of aberrant amyloid precursor protein (APP) processing to treat Alzheimer's disease.

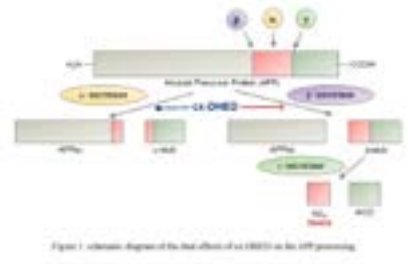

Figure1: Schematic diagram of the dual effects of cx–DHED on the APP processing.

Recent Publications

1. Shin K Y, Noh S J, Park C H, Jeong Y H, Chang K A, Yoo J, Kim H J, Ha S, Kim H S, Park H J, Lee H J, Moon C and Suh Y H (2016) Dehydroevodiamine HCl protects against memory impairment and cerebral amyloid-beta production in Tg2576 mice by acting as a beta-secretase inhibitor. CNS & Neurological Disorders - Drug Targets 15(8):935-944.
2. Ryu J, Zhang R, Hong B H, Yang E J, Kang K A, Choi M, Kin K C, Noh S J, Kim H S, Lee N H, Hyun J W and Kim H S (2013) Phloroglucinol attenuates motor functional deficits in an animal model of Parkinson's disease by enhancing Nrf2 activity. PLOS One 8(8):e71178.
3. Kopalli S R, Noh S J, Koppula S and Suh Y H (2013) Methylparaben protects 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y cells and improved behavioral impairments in mouse model of Parkinson's disease. NeuroToxicology 34:25-32.

4. Kopalli S R, Koppula S, Shin K Y, Noh S J, Jin Q, Hwang B Y and Suh Y H (2012) SF-6 attenuates 6-hydroxydopamine-induced neurotoxicity: An *in vitro* and *in vivo* investigation in an experimental models of Parkinson's disease. Journal of Ethnopharmacology 143(2):686-94.
5. Noh S J, Lee J M, Lee K S, Hong H S, Lee C K, Cho I H, Kim H S and Suh Y H (2011) SP-8203 shows neuroprotective effects and improves cognitive impairment in ischemic brain injury through NMDA receptor. Pharmacology Biochemistry and Behavior 100(1):73-80.

Biography

Su Jin Noh has her expertise in drug development and evaluation in neurological disorders. She studied potential drug development by mechanism based targeting for curing neurodegenerative disease such as Alzheimer's disease, Parkinson's disease and stroke during her PhD program. Now she focuses on discovery of pathology of neuropsychiatric disease including schizophrenia or addiction.

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