

Poster Ref: P3-F-012

Theme: F: Nervous System Disorders

Roles of endothelin-1 in beta-amyloid-induced neurotoxicity in hippocampus: An implication for Alzheimer's pathology.

Sze Wah Tam⁽¹⁾, Sookja Kim Chung⁽²⁾ and Andrew Chi Kin Law⁽³⁾

¹The University of Hong Kong, ²Department of Anatomy, the University of Hong Kong, ³Department of Psychiatry, the University of Hong Kong

Alzheimer's disease (AD) is an incurable neurodegenerative disorder. Abnormal levels of endothelin-1 (ET-1) have been demonstrated in parietal white matter(1), cerebral cortex and vessels of the AD brain(2). Neuronal death and accumulation of beta-amyloid (A β) are prominent pathological features of AD. Significant neuronal death is found in A β -treated primary neurons and A β -overexpressing mouse models(3,4). ET-1 is a known vasoconstrictor and neuro-active peptide. ET-1 induces apoptosis in primary retinal neurons(5). In contrary, ET-receptor (ETR) type B agonist can rescue neurons from A β -induced apoptosis(6). These findings suggest ET-1 plays dual roles in neurodegeneration and neuroprotection, respectively. This study aims to investigate the effect of ET-1 on A β -induced cell death in hippocampal neurons.

Primary hippocampal neurons were pretreated with or without ETR antagonists prior to the treatment of oligomeric form of A β 1-42, ET-1 or both on 14 DIV. Cell viability was measured by MTT assay. Changes in protein expression in apoptotic and ET-1 signaling pathways were assessed by western-blot analysis. This study shed light on the roles of ET-1 in A β 1-42-neurotoxicity, building upon which the ET-1 signaling pathway as a potential therapeutic target for AD can be further investigated.

1. Barker, R., *et al.*, Pathophysiology of white matter perfusion in Alzheimer's disease and vascular dementia. *Brain*, 2014. 137(Pt 5): p. 1524-32.
2. Minami, M., *et al.*, Endothelin-1-like immunoreactivity in cerebral cortex of Alzheimer-type dementia. *Prog Neuropsychopharmacol Biol Psychiatry*, 1995. 19(3): p. 509-13.
3. Wirths, O. and T.A. Bayer, Neuron loss in transgenic mouse models of Alzheimer's disease. *Int J Alzheimers Dis*, 2010. 2010.
4. Deshpande, A., *et al.*, Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. *J Neurosci*, 2006. 26(22): p. 6011-8.
5. Oku, H., *et al.*, Endothelin-1 (ET-1) causes death of retinal neurons through activation of nitric oxide synthase and production of superoxide anion. *Exp Eye Res*, 2008. 86(1): p. 118-30.
6. Yagami, T., *et al.*, Effects of endothelin B receptor agonists on amyloid beta protein (25-35)-induced neuronal cell death. *Brain Res*, 2002. 948(1-2): p. 72-81.