UNIVERSITI TEKNOLOGI MARA

TARGETING THE BDNF/TRKB PATHWAY FOR THE TREATMENT OF AMYLOID BETA 1-40-INDUCED NEURODEGENERATION: FOCUS ON ALZHEIMER'S DISEASE AND RELATED OCULAR MANIFESTATION

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Amyloid-beta (Aβ) plays an important role in the pathophysiology of Alzheimer's disease (AD). The deposition of Aβ is associated with loss of neuronal cells in AD. Besides, it was discovered that amyloidosis-related alterations, similar to those seen in the brain of patients with AD, occur in the retina of glaucoma patients. These alterations were also identified in the retinas of AD patients. Along with neuronal cell death in AD and glaucoma, there is a significant reduction of brain-derived neurotrophic factor (BDNF) expression in the brain and retinal ganglion cells (RGCs). Therefore, a reduced level of BDNF is believed to be associated with the deposition of Aβ. However, the neuroprotective effect of BDNF against Aβ1-40-induced neurodegenerations remains unclear. In view of the potential neuroprotective effects of BDNF, we investigated its effects against RGCs and hippocampus damage induced by Aβ1-40 in *Spraque dawley* rats. In this study, rats were divided into 3 groups and substances were intravitreally and intrahippocampal administered. Group 1 (control group) and group 2 received vehicle and Aβ1-40, respectively, while group 3 received BDNF as co-treatment with Aβ1-40. Fourteen days post-injections, rats were euthanized and eyes and brain were enucleated, fixed and processed for histopathological examination of retinal and optic nerve morphology using H&E and toluidine blue staining, respectively; hippocampus morphology using Nissl staining, while retinal cells apoptosis was detected by TUNEL immunostaining. Estimation of GSH, SOD, catalase and BDNF level in retina and hippocampus were done through ELISA. It was observed that BDNF provides the prominent protection against Aβ1-40-induced retinal-injury with preservation of retinal and optic nerve morphology, lesser apoptotic cell counts, restoration of the expression of GSH, SOD, catalase and BDNF. Current study with similar experiment settings also showed that BDNF provides protection against Aβ1-40 induced hippocampal-injury with preservation of hippocampus morphology, restoration of the expression of GSH, SOD, catalase and BDNF. In the subsequent study, investigations into mechanisms underlying neuroprotective effect of BDNF showed that its neuroprotective effect against Aβ1-40 induced retinal and hippocampal injury involves suppression of the activation of pro-apoptotic signalling cascades. It was observed that BDNF treatment abolishes Aβ1-40-induced reduction in retinal expression of TrkB and ERK1/2 both in the retina and brain. Further, the association of these mechanisms with the survival of neurons in the brain and RGCs were studied. Live RGCs were retrogradely labelled using Fluoro-gold neuronal tracer and the appearances of dark neurons were counted in the hippocampus using Nissl staining. The number of live RGCs were significantly higher and the number of dark neurons were significantly lower in the BDNF-treated group as compared to the Aβ1-40 treatment group. The effect of BDNF against Aβ1-40-induced RGCs visual impairments via object recognition test using open field arena and Morris water maze. The evidence from both tests showed significant improvement in visual recognition abilities as part of the neuroprotective effects of BDNF against Aβ1-40-induced visual impairment in rats. Further studies were done to determine the hippocampal-related behaviours via activity cage meter, open field test, elevated-plus maze, avoidance tests, Morris water maze and force swimming test. These studies showed significant improvement in anxiety-related, depressive-like behaviours and memories improvement as part of the neuroprotective effects of BDNF against Aβ1-40-induced hippocampal-related behaviours impairment in rats. It was concluded that treatment with BDNF prevents Aβ1-40 induced retinal and hippocampal injury by inhibiting Aβ1-40- neuronal apoptosis via downregulation of caspase-3 and upregulation TrkB and ERK levels. The results were further corroborated with behavioural study where BDNF improved visual recognition in rats with Aβ1-40 induced retinal and optic nerve damage and abolished anxiety-related and depression-like behaviours in rats with Aβ1-40 induced hippocampal injury.

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