Neurotrophin analog BNN27 exerts neuroprotective and neurogenic effects in mouse model of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD), the most common cause of dementia, is a fatal age-associated neurodegenerative disorder that impairs memory and cognitive judgment, and is often accompanied by mood swings, disorientation and eventually delirium. AD pathogenesis is complex, involving neuronal loss, abnormal amyloid-β (Aβ) metabolism, myelin and axonal failure, degeneration of the cholinergic neurons in the basal forebrain and other pathological events. The hippocampus - a structure hosting one of the most unique phenomena of the adult mammalian brain, namely, the addition of new neurons throughout life, called adult hippocampal neurogenesis (AHN) – is one of the most affected areas in AD. The nerve growth factor (NGF) was the first neurotrophin discovered for its stimulatory effect on survival, differentiation and growth of neurons in peripheral and central nervous system, while its expression is noticeably decreased on AD. BNN27 is a newly developed 17–spiro-steroid analog of the endogenous neurosteroid Dehydroepiandrosterone that mimics the neuroprotective effects of NGF, acting as selective activator of its receptors, TrkA and p75NTR, promoting neuronal survival. Thus, determining whether BNN27 is able to alleviate the AD–related pathology, the cognitive impairment as well as the reciprocal protection against neuronal loss and/or promotion of neurogenesis is a crucial question with outstanding therapeutic potential.

Microneurotrophin BNN27 capsules were subdermally applied and steadily released over 60 days (10mg/kg/day) in 1.5 months old 5xFAD mice and their wild type littermates. Spontaneous alternation test was used to justify possible working memory amelioration, which indeed was the case. BNN27 was able to improve cognitive performance in the 5xFAD mouse model. Furthermore, BNN27 treatment considerably decreased the formation of Aβ plaques within the hippocampus. We further successfully detected improvement of AHN in the BNN27-treated mice compared to their WT littermates via promotion of new neurons generation and induction of proliferation of newborn cells in the dentate gyrus neurogenic niche of the 5xFAD animals. BNN27 exerted cholinergic atrophy rescue in the basal forebrain by amelioration of the AD pathology at the soma size in TrkA (+) cells. Nonetheless, no significant improvement of further AD pathological hallmarks, for instance impaired synaptic communication, myelin and axonal disruption was observed in the hippocampus after treatment of 5xFAD mice with BNN27.

The aforementioned results demonstrate that BNN27 significantly reduces the Aβ plaque load and stimulates the hippocampal generation of newly formed neurons in the dentate gyrus of the 5xFAD mouse model. The downstream pathways – through which these procedures are manifested - are currently a subject of intense interest.