Modulation of Brain-Derived Neurotrophic Factor (BDNF)-Induced Trophic Signalling as an Alternative Treatment for Alzheimer’s Disease

Muthmainah
Department of Anatomy and Embryology, Faculty of Medicine, Sebelas Maret University, Surakarta

ABSTRACT
Alzheimer’s disease (AD) is a disorder of synaptic function and neuronal degeneration characterized by decline in memory and cognition as well as changes of personality. Brain-Derived Neurotrophic Factor (BDNF) is a major modulator of synaptic plasticity and is an acknowledged pharmacological target for the treatment of a range of neurological disorders including AD. Attempts to supply BDNF exogenously are limited by side effects. An alternative strategy to enhance BDNF-induced trophic signalling is through amplification of neural response to the reduced supply of endogenous BDNF found in AD.

Keywords: Alzheimer’s disease, alternative treatment, BDNF, trophic signalling

INTRODUCTION
Alzheimer’s disease (AD) is the most common form of dementia characterized by synaptic function disorder and neuronal degeneration. The symptoms include a decline in memory and cognitive performance as well as personality changes. However, the etiology of the disease is not well understood and definitive diagnosis can only be made after autopsy. The key pathological hallmark of AD is the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles composed of hyperphosphorylated tau throughout the brain.

The prevailing theory of AD states that Aβ accumulation is central to disease etiology, the brain overproduces or fails to degrade the Aβ peptide. In about 5% cases, genetic cause underlies this overproduction. However, there has been no clear answer for the remaining 95% patients. Recent finding shows that Aβ oligomeric aggregates are toxic and can inhibit synaptic activity and promote neuronal degeneration. There have been attempts to treat AD by removing Aβ plaques but failed in clinical trial. Another proposed mechanism to abolish the cognitive decline is to enable circuit rerouting by facilitating long-term potentiation (LTP) as such to enhance synaptic plasticity.

One current major hypothesis underlying cognitive impairment in AD is the reduced level of neurotrophin that are crucial for neuronal activity and survival. Therefore,

Figure 1. Pathological hallmark of Alzheimer’s disease.
Aggregation of Aβ in the extracellular compartment and neurofibrillary tangles is a common feature in AD.
neurotrophins such as brain-derived neurotrophic factor (BDNF) have been a pharmacological target for treating AD. Furthermore, BDNF is also a major mediator of synaptic and circuit plasticity.10 However, providing in vivo BDNF to treat impaired brain function is quite challenging because supplying exogenous BDNF has been shown to be ineffective.11 Thus, an alternative strategy must be developed to correct the reduced neurotrophin signalling in AD.

**The Neurotrophin Family and Their Associated Receptors**

Neurotrophins including BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) are subfamily of neurotrophic factors (NTFs) that regulate many aspects of neuronal development and function. This includes neurogenesis and differentiation, neurite outgrowth, synaptogenesis and synaptic plasticity, and circuit maintenance.12 In particular, BDNF is crucial in controlling normal adult brain function, being the major activity-dependent modulator of neuronal and synaptic activity in the brain.

There are three receptors that interact with this neurotrophin family. Each of the receptor has specificity for a particular neurotrophin but also exhibits some overlapping interaction with other neurotrophins.8 The neurotrophin-mediated signalling is mediated by tropomyosin-related kinase (Trk) receptors, p75/neurotrophin receptors (p75NTR), and the pro-neurotrophin receptor, sortilin. Neurotrophins can promote cell survival by activating Trk receptor and cause cell death by activating p75NTR. The Trk receptor family is comprised of (i) TrkA which prefers NGF as its ligand (ii) TrkB which binds to both BDNF and NT-4/5, and (iii) TrkC which prefer NT-3 as its binding partner. Recent studies showed that cholinergic basal forebrain neurons expressing TrkA receptors respond to NGF and thus promote and maintain synaptic transmission. In hippocampus, binding of BDNF via TrkB receptors at postsynaptic dendrite maintains long-term potentiation, a mechanism that underlies learning and memory formation. Thus, a reduction of either NGF or BDNF, or a change in the levels of TrkA or TrkB receptors, might lead to the impairment of memory formation and neuronal degeneration. As a result, cognitive decline which is a common symptom in AD will occur.9

**Reduced Levels of Neurotrophins are Associated with AD**

Reduced level of both NGF and BDNF are common features in AD. It is reported that the amount of NGF in serum is significantly reduced in AD patients compared to elderly controls.11 In addition, BDNF levels both in plasma and serum are also reduced in AD patients as well as subjects with mild cognitive impairments compared with controls.4 It is suggested that early memory dysfunction seen in AD is caused by decreased level of BDNF hippocampus. Evidence to support this includes substantially reduced BDNF mRNA levels in the hippocampus and parietal cortex of AD patients as well as decreased BDNF protein levels in hippocampus, temporal, frontal, and parietal cortex.12-14 In animals, loss of either BDNF or TrkB receptors impairs synaptic plasticity and gives rise to behavioural changes including cognitive deficits.15 In humans, reduced BDNF expression is also associated with cognitive impairment and neurological disorder ranging from AD to mood disorder such as depression and anxiety.16

**BDNF as a Pharmacological Target for Treating AD**

Disease severity in AD correlates well with the degree of synaptic loss in the brain. Enhancing synaptic plasticity by facilitating LTP is one of the strategies to combat the cognitive decline. As a major mediator of synaptic and circuit plasticity, BDNF is acknowledged as a pharmacological target for the treatment of a range of neurological disorders including AD (for comprehensive review see 6, 16). In animal, treatments with BDNF or its analogues can reawaken critical periods of brain organisation as well as promote cognitive function.16,17 Furthermore, in vivo and in vitro experiments show that BDNF can overcome cellular and neuritic degeneration triggered by Aβ.18,19 Thus, maintaining the level of circulating BDNF is considered a biomarker for resistance to cognitive decline.20-21

Higher serum BDNF levels may give protection against dementia and AD. Considering the fact that exercise and caloric restriction elevated BDNF level both in the brain and blood, raised BDNF level may be responsible for the positive effects of this lifestyle on the occurrence and the progression of AD.21 Thus, it is not surprising that BDNF is a potential target for the treatment of various neurological disorders including AD.20-21 The ability to provide effective concentrations of BDNF in vivo is crucial for treating impaired brain function.
However, this is quite challenging due to the fact that the permeability of neurotrophins across the blood brain barrier is minimal. Direct injection of BDNF results in poor tissue permeability while intrathecal administration induces deleterious side effects including weight loss. Another approach is through gene delivery that has been successfully performed in clinical trials. However, control of the introduced gene is a major constraint in the application of this method. Thus, further investigation should be done to find the best method to deliver exogenous BDNF effectively. Alternatively, rather than supplying exogenous BDNF, amplifying the neuronal response to limited amount of endogenous BDNF might be one of the solution.

Conclusion
Alzheimer’s disease (AD) is a disorder of synaptic function and neuronal degeneration that can increase the burden of our health care system. The disease is characterized by a decline in memory and cognitive performance as well as changes to personality. BDNF is an acknowledged pharmacological target for the treatment of a range of neurological disorders including AD. Attempts to supply BDNF exogenously are limited by the side effects. As an alternative, amplification of the neural response to limited amount of endogenous BDNF can be a focus for research.

REFERENCES
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