



# Therapeutic potential of neurotrophic factors in Alzheimer's Disease

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## Abstract

**Introduction** Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia among the elderly population. AD is accompanied with the dysregulation of specific neurotrophic factors (NTFs) and their receptors, which plays a critical role in neuronal degeneration. NTFs are small proteins with therapeutic potential for human neurodegenerative diseases. These growth factors are categorized into four families: neurotrophins, neurokinins, the glial cell line-derived NTF family of ligands, and the newly discovered cerebral dopamine NTF/mesencephalic astrocyte-derived NTF family. NTFs are capable of preventing cell death in degenerative conditions and can increase the neuronal growth and function in these disorders. Nevertheless, the adverse side effects of NTFs delivery and poor diffusion of these factors in the brain restrict the efficacy of NTFs therapy in clinical situations.

**Materials and methods** In this review, we focus on the current advances in the use of NTFs to treat AD and summarize previous experimental and clinical studies for supporting the protective and therapeutic effects of these factors.

**Conclusion** Based on reports, NTFs are considered as new and promising candidates for treating AD and AD-associated cognitive impairment.

**Keywords** Alzheimer's disease · BDNF · GDNF · Neurotrophic factors · NGF

## Abbreviations

AD	Alzheimer's disease	BDNF	Brain-derived neurotrophic factor
NTF	Neurotrophic factors	NGF	Nerve growth factor
NFT	Neurofibrillary tangle	GDNF	Glial cell line-derived neurotrophic factor
SP	Extracellular senile plaque	GFL	Glial cell line-derived NTF (GDNF) family ligands
A $\beta$	$\beta$ -amyloid	NT-3	Neurotrophin 3

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NT-4/5	Neurotrophin 4/5
Trk	Tyrosine receptor kinase
p75NTR	p75 neurotrophin receptor
TNF	Tumor necrosis factor
AAV2	Adeno-associated virus serotype 2
CSF	Cerebrospinal fluid
ECB	Encapsulated cell bio-delivery
BFCNs	Basal forebrain cholinergic neurons
MCI	Mild cognitive impairment
MANF	Mesencephalic astrocyte-derived neurotrophic factor
PGC-1 $\alpha$	Peroxisome proliferators-activated receptor $\gamma$ coactivator 1 $\alpha$
FNDC5	Fibronectin type III domain-containing 5
AM-MSCs	Amniotic membrane-derived mesenchymal stem cells
BM-NSCs	Bone marrow-derived neural stem cells
hUC-MSCs	Human umbilical cord-derived mesenchymal stem cells
CNTF	Ciliary neurotrophic factor
LIF	Leukemia inhibitory factor
TAT	Transactivator of transcription
UCBMCs	Umbilical cord blood mononuclear cells
UPR	Unfolded protein response
ER	Endoplasmic reticulum

## Introduction

Alzheimer's disease (AD) is a progressive, multifarious neurodegenerative disease and the most common cause of dementia in older people. The World Alzheimer's Report informed that 46.8 million people throughout the world were living with dementia in 2015 [1]. Specific diets, physical inactivity, midlife hypertension, depression, obesity, smoking, and low educational achievements can be accounted as some of the risk factors of AD. Likewise, diabetes is a risk factor for AD and neurodegeneration, and one-third of people with AD in the world have diabetes [2]. Impaired memory, loss of directionality, language disorders, and anxiety behaviors are the main early clinical manifestations of AD. Besides declined cognition, loss of body functions, and abnormal mental activities such as emotion and behavior are considered as late-stage manifestations of AD, which eventually lead to disability and death [3]. AD is characterized by three main histopathological features: extracellular senile plaques (SPs), intracellular neurofibrillary tangles (NFTs), and degeneration of basal forebrain cholinergic neurons (BFCNs). SPs are primarily made from  $\beta$ -amyloid (A $\beta$ ) peptide aggregation, whereas NFTs are composed of hyperphosphorylation of microtubule-associated protein (MAP) tau [4].

Although this disease was under research for an extended period, available drugs such as N-methyl d-aspartate receptor antagonist (memantine) and acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) provide only symptomatic relief [5]. Pharmacological interventions for AD are severely limited and earlier approved drugs only offer symptomatic improvement, but not disease-modifying therapy. Fortunately, On June 7, 2021, aducanumab received a conditional approval from the US Food and Drug Administration (FDA) as the first new drug for the treatment of AD. Although aducanumab showed promise in clearing amyloid plaques from the brain tissue, but its efficacy in improving cognitive deficits remains to be proven [6].

Neurotrophic factors (NTFs) are small secretory proteins that play a pivotal role in the synaptic plasticity, survival, growth, differentiation, and myelination of neuronal cells [7]. It came to the limelight that altered expression of NTFs such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and glial cell-derived neurotrophic factor (GDNF) are correlated with the neurodegeneration process and cognitive impairment in AD [8, 9]. Accordingly, in this review, we attempt to explain some of the recent developments in our understanding of the NTFs dysregulation in AD and the role of these factors in treating AD.

## Limitations of neurotrophic factors application in the clinical trial and delivery methods

The earliest studies only considered the feasibility of NTFs therapy for the treatment of neurodegenerative diseases. Nevertheless, the adverse side effects of NTFs delivery in humans limit the efficacy of NTFs therapy in clinical settings. The BBB creates a primary challenge in the clinical application of NTFs, because the proteins do not pass the BBB and need to be delivered intracranially [10]. The other obstacles of clinical usage of NTFs include the short half-life [11], difficulties with administering proper dose and covering a large brain area, and stage of patients who enrolled in trials and underwent NTF therapy. Thus, a minimally invasive injection method would be optimal [12]. Furthermore, because the NTFs are proteins, chronic delivery of them can be problematic because of aggregation, misfolding, and the development of neutralizing antibodies. Moreover, they typically cannot be given orally or administered systemically because of side effects often induced by systemic exposure to organs and tissues [13]. On the other hand, in humans, some NTFs such as BDNF are present in blood platelets; thus, the levels of these factors are readily measurable in human serum [14].

The main constraint is the difficulty to identify a mode of administration that allows long-term delivery of NTFs in

efficient quantities to brain target areas in order to achieve clinical efficacy. Several approaches of the direct delivery of NTFs have been investigated, including direct infusion into the brain [15], intra-nasal injection [16], intra-ventricular transplantation [15], gene therapy, and stem cell-based delivery [17]. Nevertheless, in practice, it is difficult to achieve effective concentrations of NTFs, due to the substantial side-effects and rapid diffusion of a large proportion of them away from the injury site. Accordingly, it is imperative to find a better approach for delivery of NTFs into the target areas [18]. The fundamental solution to this problem is repeated injections of NTFs to the injury site so that the therapeutic concentrations can be obtained. To this end, encapsulated cell bio-delivery of NTFs leads to sustained release into the brain [19]. Another approach is the use of recombinant viral vectors to enable the long-term expression of NTFs in nerve cells [20]. As a novel solution to this issue, various biomaterials have been engineered to provide an effective, and sustained drug-delivery system. This method allows stem cells and/or small drug molecules, including NTFs to bypass the BBB and be delivered directly to the injury site [21].

## Classification of neurotrophic Factors

NTFs are growth factors that promote and regulate neuronal growth, survival, differentiation, and functions in the developing and mature nervous systems. Likewise, they are vital for the maintenance of neuronal health and function. These proteins, according to their different cellular mechanisms, are categorized into four following groups: neurotrophins, neurotrophic cytokines, glial cell line-derived NTF (GDNF) family ligands (GFLs), an evolutionary conserved cerebral dopamine neurotrophic factor- mesencephalic astrocyte-derived neurotrophic factor family (CDNF/MANF) [22].

All NTFs that are implicated in AD treatment are shown in Table 1; Fig. 1.

## Neurotrophin family

NGF, BDNF, neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5) constitute a structurally related family named neurotrophins that mediate different cellular processes, including the growth, survival, and death of neurons in the central and peripheral nervous systems [23]. These diverse biological roles are depending on their interactions with one of two receptors: tyrosine receptor kinase (Trk), one member of the tropomyosin-related tyrosine kinase receptors, or p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor (TNF) receptor superfamily. When neurotrophins interact with specific Trk receptors (NGF binds to TrkA, BDNF and NT4/5 bind to TrkB, and NT3 binds to TrkC), mediate survival and growth responses. Moreover, their interaction with P75 neurotrophic receptor (p75NTR) leads to the modulation of brain plasticity and apoptosis [24].

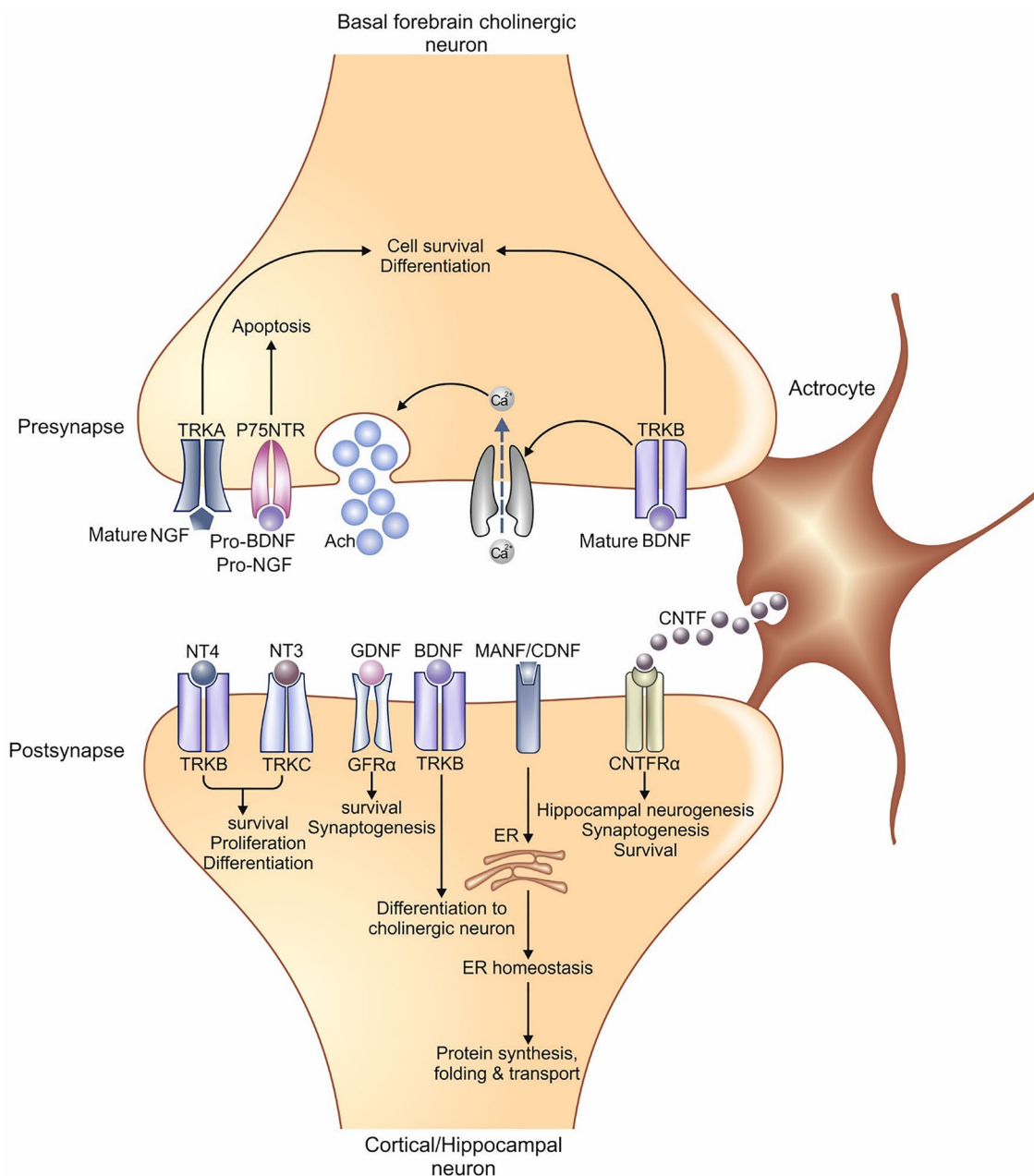
In the central nervous system (CNS), the most prominent neurotrophin is BDNF because of the wide TrkB expression in the brain, especially in the cortex, hippocampus, and basal forebrain. However, NGF provides trophic support to the BFCNs, which mainly express TrkA receptors [25].

## Nerve growth factor and Alzheimer's disease

NGF is the first identified neurotrophic factor discovered by Rita Levi-Montalcini and Cohen in the 1950s. They hypothesized that during development, the secretion of NTFs supports the innervation of a sufficient number of neurons in the target tissue. NGF is secreted in the neocortex and the hippocampus and then retrogradely transported

**Table 1** Therapeutic effects of NTFs on AD

NTFs	Effects on AD
NGF	Promotes survival and differentiation of basal forebrain cholinergic neurons, suppresses oxidative stress, and improves cognitive function.
BDNF	Induces the directional differentiation of cortical NSCs into cholinergic neurons, promotes the survival and differentiation of cholinergic neurons, stimulates the acetylcholine release, maintains cellular homeostasis, promotes neurogenesis, increases synaptic growth, induces hippocampal long-term potentiation, and improves cognitive function.
NT-3 and NT4/5	NT-4/5 promotes survival and differentiation of hippocampal, noradrenergic and dopaminergic neurons, NT-3 regulates neurogenesis and facilitates hippocampal plasticity, improves memory function.
CNTF	Induces survival and differentiation of cerebral sensory and motor neurons, parasympathetic neurons, and hippocampal neurons, enhances adult neurogenesis, improves cognitive decline.
CT-1	Delays motor neurons degeneration and improving motor function, ameliorates cognitive deficits
GDNF	Inhibits the degeneration of noradrenergic neurons of the locus coeruleus, protects dopaminergic neurons, modulates cholinergic transmission and protects against cognitive impairments in neurodegenerative disorders.
CDNF and MANF	Suppress ER stress-induced cell death, protect against A $\beta$ -induced neuronal cell death.



**Fig. 1** The schematic representation of the neurotrophic factors (NTFs) involvement in Alzheimer's disease. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) bind to two families of tyrosine kinase receptors (TRKA and TRKB). Pro-NGF mediates apoptosis via interacting with p75NTR. Mature NGF has neuroprotective effects on cholinergic neurons and promotes the survival of them. Pro-BDNF binds specifically to p75NTR and mediates cell death, while mature BDNF promotes the survival and differentiation of cholinergic neurons, stimulates the acetylcholine release in cholinergic neurons, and induces the directional differentiation of cortical neural stem cells (NSCs) into the cholinergic neurons. Neurotrophin-3 (NT-3) binds to TRKC, and neurotrophin-4/5 (NT-4/5) binds

to TRKB and promotes the survival of neural cells. Binding of glial cell line-derived neurotrophic factor (GDNF) to the GDNF $\alpha$  receptor and tyrosine kinase RET receptor leads to the cell survival and induces neuroprotective effect on nerve cells against atrophy. Ciliary neurotrophic factor (CNTF) is secreted by astrocytes and binds to CNTFR $\alpha$  and two subunits, gp130 and leukemia inhibitory factor (LIFR $\beta$ ) that are expressed by astrocytes and neurons. It has survival and differentiation-inducing effects on cerebral sensory and motor neurons and hippocampal neurons. CDNF/MANF family may exert neuroprotective effects against A $\beta$ -induced neuronal cell death by suppressing ER stress and modulating protein synthesis and folding

to the BFCNs and promotes survival and differentiation of these neurons [26] (Fig. 1). NGF is produced as large precursor proteins named pro-NGF, containing an N-terminal pro-domain and a C-terminal mature domain. Pro-NGF mediates apoptosis via interacting with p75NTR. Cleavage of pro-form and creating non-covalently linked homodimers result in mature NGF generation, which supports survival through binding to TrkA [27]. Mature NGF ultimately degraded by metalloproteases in the extracellular space. In AD brain, pro-NGF levels are increased, while NGF biosynthesis is normal, but unfortunately, the conversion of the pro-NGF molecule to its mature form is reduced in AD and the degradation of the mature form is augmented [28].

Neuropathological studies indicate that memory loss in AD patients is associated with neurodegeneration and dysfunction of the cholinergic neurons. Besides, evidence shows that decreased NGF levels is responsible for cholinergic atrophy in AD. In the AD brain, NGF receptor dysregulation has been found before phenotypic changes of BFCNs, indicating that the absence of neurotrophic support is a causative agent for basal forebrain deterioration [29]. According to these findings, NGF administration has been considered as a therapeutic approach for the regeneration of cholinergic neurons and, consequently treatment of AD.

Additionally, animal studies demonstrated that NGF stimulator drugs with oxidative stress suppressing activity might be a novel therapeutic option to protect and repair cellular damage in AD. For example, the aqueous extract of *A. cochinchinensis* root (AEAC) shows the NGF stimulatory activity and anti-oxidant effect in Tg2576 mice showing AD phenotypes of humans. AEAC can improve neural cell injuries by enhancing the NGF secretion and suppressing oxidative stress [30].

Based on data from animal models suggesting the neuroprotective effects of NGF on the cholinergic neurons, this NTF has been tested in patients with AD in clinical settings. Several approaches have been applied for NGF delivery in human, including intranasal administration of hNGF-61 (engineered mutein of hNGF) [31], direct injection into the cerebral lateral ventricle of the AD brain [15], gene therapy approaches [32], the cell-based delivery method by using stem-cells [17], and encapsulated cell bio delivery [33].

Intraventricular infusion of NGF in AD patients was one of the earliest neurotrophic programs. In 1992 and 1993, NGF was tested as a possible treatment for AD in two single-patient case reports. Both of these studies reported that protein infusion enhanced cholinergic activity and improved memory in these patients. No side effects were observed in either study [34, 35].

In contrast to before reports, Jönhagen et al. noted that the infusion of NGF protein showed slight improvements in a few neuropsychology tests and could not alleviate cognitive

impairments. Also, they reported side effects, including constant back pain and weight reduction during the infusion of NGF in AD patients. Eventually, these researchers suggested that a change of routes or infusion doses may eliminate the side effects [15]. The next delivery method to improve NTFs efficacy in clinical trials is gene therapy. Gene therapy has two main forms, including ex vivo and in vivo. In the ex vivo method, researchers have used bioengineered cultural cells that express therapeutic proteins such as NTFs. In contrast, direct gene delivery into the endogenous cells of the patient is considered as an in vivo form of gene therapy [36].

Tuszynski et al. performed a phase 1 trial of ex vivo gene delivery of autologous fibroblasts that expressed human NGF into the forebrain of eight patients with mild AD. This report was the first gene therapy for AD in a small open-label trial and showed that cholinergic cells extended their projections toward the implant in response to secreted NGF from transplanted cells. Also, no serious side effects were reported as a consequence of gene therapy or NGF expression [37]. Eriksdotter and coworkers performed the next ex vivo gene therapy trial several years later. Their study indicated that encapsulated cell bio-delivery of NGF to the basal forebrain of individuals with AD caused positive effects in cognition, electroencephalography, and nicotinic receptor binding. They confirmed that this delivery method is “safe, well-tolerated, and feasible” [33].

Another in vivo gene therapy trial used genetically engineered vector adeno-associated virus serotype 2 (AAV2) to deliver three ascending doses of NGF to the basal forebrain of AD patients. This open-label clinical trial indicated that AAV2-NGF was safe and well-tolerated, and also it demonstrated the initial preliminary efficacy of this method [32]. Later gene therapy described postmortem findings from 10 AD patients who enrolled in previous ex vivo and in vivo NGF gene transfer trials conducted by Tuszynski et al. and Rafii et al. This study indicated that NGF induced 10 years of persistence axonal sprouting, cell hypertrophy, and functional markers in neurons of the degenerating brain [37, 32]. NGF gene therapy appears safe over extended periods and confirms the neurotrophic effect of NGF on treating AD disease, and opens a new approach for continuing studies. Rafii et al. noted their observation of a Phase II trial of AAV2-NGF in mild to moderate AD that confirmed the feasibility and safety of this approach, but no NGF-related symptomatic improvement was detected [38]. These findings aligned with the results of the later randomized clinical trial, which reported that AAV2-NGF was safe and well-tolerated through 2 years, but no significant difference between the treatment group and placebo was measured [39]. In a recent study, AAV2-NGF was delivered into the nucleus basalis of Meynert in cases with early-to middle-stage AD. NGF could not directly reach cholinergic neurons due to restricted distribution and imprecise stereotactic targeting. Because

AAV2-NGF did not directly affect the target cholinergic neurons, it cannot be concluded that NTFs gene therapy is inefficient for AD treatment [40]. Accordingly, further studies are required to detect the efficacy of NGF gene therapy in AD treatment and the effective approach for successful gene therapy in patients.

Some researchers practiced the encapsulated cell bio-delivery (ECB) implant to deliver human NGF to the basal forebrain of AD patients in a phase I pilot study. They expected that this delivery technology allows the transplanted factor to concentrate highly at the target area, and has fewer off-target side-effects [33]. Their results demonstrated that the ECB-NGF device was safe and feasible. It also indicated decreased rates of brain atrophy, stable cognitive function, and improvement of the level of cholinergic markers in cerebrospinal fluid (CSF) of AD patients [41]. Inflammatory proteins such as IL-1 $\beta$  may have a negative effect on NGF production by ECB cells. Therefore, the combination of ECB-NGF and anti-inflammatory drugs may be a potential candidate to protect or repair cellular damage and improve behavioral performance in AD [42].

Taken together, the mentioned studies reveal that NGF can partially restore the function of cholinergic neurons and can protect them from degeneration in AD. However, it has exerted less alleviative effects on cognitive performance in AD patients. Further studies and clinical trials should be done to optimize the best delivery method of NGF in AD patients.

### Brain-derived neurotrophic factor and Alzheimer's disease

BDNF, another neurotrophin family member, mediates synaptic plasticity and has a critical role in cognitive processes, learning, and memory formation. This molecule has a vital role in the survival, maintenance, and function of neurons [43]. BDNF gene is highly expressed in the cortex, hippocampus, and basal forebrain regions, that plays a crucial role in memory, learning, and higher cognitive performances. Pro-BDNF form binds specifically to p75NTR and mediates cell death, while mature form acts via binding to TrkB [44]. BDNF promotes neurogenesis and neurotransmission across the synapses, elevates synaptic growth, and modulates synaptic plasticity. BDNF also takes part in memory formation by inducing hippocampal long-term potentiation [45]. A cohort study demonstrated that polymorphism in the gene encoding BDNF leads to the higher vulnerability of hippocampus-frontal connectivity to AD pathology and AD-related cognitive impairment [46]. It seems that the basal forebrain GABAergic neurons express NGF mRNA and can produce minor amount of NGF [47]. Besides, basal forebrain neurons rely on their cortical and hippocampal targets to generate BDNF and NGF that are transported back to cell bodies of BFCNs through retrograde

axonal transport. Therefore, retrograde axonal transport of NTFs by BFCNs has an essential role in their appropriate functioning and survival [29]. Accumulating studies declare that BDNF level is decreased during dementia and neurodegenerative diseases such as AD [48]. Recently, BDNF serum levels were decreased in dementia patients than healthy participants, concomitantly dementia cases presented a reduced hippocampal volume compared to healthy contributors [49]. In contrast, Blasko et al. did not find a significant difference in BDNF levels between AD and controls [50]. A recent meta-analysis study examined the aggregate levels of serum BDNF in patients with AD and individuals with mild cognitive impairment (MCI) compared to healthy controls. They indicated that serum BDNF levels were significantly lower in patients with AD but not MCI in comparison with healthy controls [48]. Another recent meta-analysis study evaluated the diagnostic role of peripheral BDNF concentration in AD patients affected by MCI. It revealed that although the BDNF level reduced in patients with AD or MCI, its levels are not useful markers to diagnose AD and MCI [51].

On the other hand, it has been reported that enhanced serum levels of BDNF reduced the risk of dementia and progression of AD, and acute aerobic exercise increases the plasma levels of BDNF in the elderly with AD [52]. Likewise, experimental evidence demonstrates that blood and plasma levels of BDNF reflect the brain BDNF levels [53]. The molecular mechanisms implicated in the downregulation of BDNF in AD patients are still unknown. Xia et al. disclosed that A $\beta$ 1–42 oligomers downregulate the peroxisome proliferators-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) and fibronectin type III domain-containing 5 (FNDC5) and probably by this way suppress the expression of BDNF and consequently cause a cognitive deficit in AD mice [54].

An experimental study indicated the specific and dose-response protective effect of BDNF on neural toxicity induced by A $\beta$  peptides. BDNF Val66Met polymorphism is associated with altered neuronal integrity and synaptic excitation. This process also moderates A $\beta$ -related changes in cognition and neurodegeneration, memory decline and hippocampal atrophy in AD cases [55]. Lim et al. proposed that these properties of BDNF Val66Met polymorphism are probably due to the enhanced vulnerability of brain to the toxic effects of A $\beta$  peptide [56]. Another experimental study used a transgenic mouse model overexpressing tau and showed that overexpression of wild-type tau downregulates BDNF [57].

Like NGF, BDNF promotes the survival of BFCNs and increases choline acetyl transferase activity in vitro and in vivo. BDNF also can improve the function of cholinergic neurons and increase acetylcholine release in hippocampal synapses [58]. Moreover, forebrain-specific knockout of BDNF receptor (trkB) resulted in severe impairment in

learning, indicating that increasing the level of BDNF in the forebrain could improve cognitive deficit and attenuate AD symptoms. Given this evidence, the delivery of exogenous BDNF has been considered a valuable therapeutic approach for AD [59]. However, delivery of exogenous BDNF faces different problems. As BDNF does not readily cross the BBB, the main problem is the amount of BDNF that reaches the affected neurons. The too low amounts might not be sufficient to have the desired effects, whereas too high doses might have paradoxically dangerous consequences such as neuronal excitability [60]. Similarly, Scharfman et al. reported spontaneous limbic seizures following intrahippocampal infusion of BDNF, supporting the hypothesis that BDNF injection can facilitate seizure activity [61]. To overcome such delivery problems and to get more effective results, different methods have been developed, such as ECB, gene therapy and stem cell therapy. In this context, Xuan et al. obtained neural stem cells (NSCs) from the hippocampus and transplanted them into the rat basal forebrain, followed by the transplantation of BDNF into the lateral ventricle. They revealed the differentiation of labeled NSCs into neurons and astrocytes in the basal forebrain. Besides, BDNF enhanced the therapeutic effects of transplanted NSCs after injection into the lesioned brain [62].

An *in vitro* study reveals that overexpression of BDNF has a neuroprotective effect on A $\beta$ -treated NSCs [63]. Additionally, engrafted neurons derived from BDNF-overexpressing NSCs demonstrated electrophysiological properties of mature neurons. They were capable of integrating into existing brain circuits, and eventually improved the cognitive decline in the transgenic AD mouse model. Likewise, overexpression of BDNF ameliorated the engrafted cells' viability, neurite complexity, neuronal fate, synaptic plasticity, and maturation of electrical property in AD mice [64]. In line with these findings, when BDNF was knocked down in BDNF-NSCs combination, the therapeutic efficacy of stem cell-based therapy was reduced [63]. Another study showed that BDNF modified human umbilical cord-derived mesenchymal stem cells (hUC-MSCs)-derived cholinergic-like neurons may be a promising therapeutic method for AD [58]. As another delivery method, a recent study examined the effects of ECB device-mediated long-term release of BDNF on epileptic seizures. These devices, which transplanted into the hippocampus of rats, represented a valid therapeutic effect against epilepsy and some of its comorbidities [65].

Leyhe et al. reported that the up-regulation of BDNF might be part of a neuroprotective effect of acetylcholinesterase (AChE)-inhibitors [66]. Also, it has been revealed that donepezil, an AChE-inhibitor protects neurons, improves cognitive function, and ameliorates learning and memory impairment through regulating the cholinergic system, upregulating the expression of BDNF, increasing

the phosphorylated level of TrkB, and subsequently activation of the BDNF/TrkB signaling pathway [67]. Besides, it has been reported that lithium may exert its neuroprotective effect in AD patients through the upregulation of BDNF [68]. Alvarez et al. evaluated the synergistic action of cerebrolysin and donepezil on increasing the BDNF serum level and observed that this treatment delayed cognitive decline in AD patients [69]. Recently, the effects of BDNF-modified human amniotic membrane-derived mesenchymal stem cells (AM-MSCs) were examined on the learning and memory performance of AD rats. Human AM-MSCs transplantation improved learning and memory abilities of AD animals, and BDNF-modified cells could further ameliorate this therapeutic potential [70].

Furthermore, pharmacological mimetics or exercise, which enhance BDNF levels, may improve cognition in AD, and their application at the early stages of AD has a protective role against subsequent neuronal cell death [71]. With respect to the above-mentioned results and regarding the conflicting reports on the alteration of BDNF concentration in serum and brain tissue of AD cases, as well as limited delivery methods of BDNF, additional studies are required to achieve the best approach of BDNF delivery for exerting maximum effect on cognitive problems and treatment of AD.

### Neurotrophin 3, neurotrophin 4/5, and Alzheimer's disease

Few studies have evaluated the role of NT-3 or NT-4/5, another neurotrophin family members, in AD. NT-4/5 contributes in promoting survival and differentiation of hippocampal, noradrenergic and dopaminergic neurons [72]. NT-3 is commonly expressed in the dentate gyrus of the hippocampus, a main neurogenic microenvironment. By interacting with Trk-C, NT-3 can regulate neurogenesis and facilitate hippocampal plasticity, indicating the key role of NT-3 in memory function [73]. A study revealed that the deletion of genes for NT-3 and/or its associated receptor (TrkC) results in a loss of about 30% of striatal neurons [74]. Besides, a significant reduction of NT-3 levels in the motor cortex of post-mortem AD patients but not in the dentate gyrus and entorhinal cortex was reported in another study [75]. By contrast, Durany et al. and Hock et al. did not find altered post-mortem brain NT-3 levels in AD patients [76, 77]. Since improvements in white matter pathology are strongly correlated with the recovery of memory deficits, it was recently reported that Electroacupuncture (EA) stimulation promotes oligodendrocyte regeneration and NT4/5-TrkB signaling and the recovery of memory function following white matter injury [9]. One study has used transfected bone marrow-derived NSCs (BM-NSCs) with NT-3 to increase the delivery of NT3. The results of this study indicated that NT-3 gene transfection could promote the *in vitro* proliferation and differentiation of BM-NSCs into cholinergic

neurons by affecting the Notch signaling pathway [78]. A more recent study investigated the effects of NT-3 on the differentiation of bone marrow-derived MSCs (BM-MSCs) into neurons *in vitro* and *in vivo*. They revealed that NT-3 overexpression increased the neuronal differentiation of BM-MSCs *in vitro* and *in vivo* and improved cognitive performance in rat model of AD. While, silencing NT-3 suppressed the differentiation of BM-MSCs and reduced cognitive abilities in AD rats. They also found that NT-3 gene operated through triggering Wnt/ $\beta$ -catenin signaling pathway [73]. Based on available results, unlike BDNF and NGF, the NT-3 and NT-4/5 may not be related to the pathogenesis of AD. As well, regarding the role of these neurotrophins in the neuronal differentiation of stem cells, additional cell-based studies are needed to further evaluate the role of NT-3 and NT-4/5 in treatment of AD.

### Neurotrophic cytokine (neurotrophin) family and Alzheimer's disease

The family of neurotrophic cytokines, also known as neurotrophin, represents the small and structurally secretory proteins signaling via transmembrane gp130 receptor. This family consists of ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), leukemia inhibitory factor (LIF), neurotrophin (NPN), oncostatin M (OSM), cardiotrophin-like cytokine (CLC), interleukin 6 (IL-6), IL-11 and IL-27. Neurotrophins use either a two or three-component receptor system and play an important role in the survival of motoneurons [79]. Among neurotrophins, CNTF is the most studied neurotrophin for AD treatment and other members of this family have not yet been studied for treating AD and related cognitive decline.

#### Ciliary neurotrophic factor and Alzheimer's disease

CNTF, a neural cytokine, is expressed in the peripheral and central nervous system. In the brain, CNTF is secreted by astrocytes and binds to CNTFR $\alpha$ , which is represented by astrocytes and neurons (Fig. 1). The interaction between CNTF and its receptor activates the recruitment of two other transmembrane receptor proteins, LIFR $\beta$  and gp130, leading to their dimerization and tyrosine phosphorylation [80]. Previously, CNTF was revealed to operate synergistically with BDNF and encourage the survival of choline acetyl transferase-positive neurons in the cultured rat-derived BFCNs. BDNF alone caused a threefold enhancement in neural survival. However, CNTF along with BDNF led to an eight-fold increase in the number of survived neurons. This synergistic activity was limited only to BFCNs and not to the hippocampus, or cerebellum. CNTF showed neuronal protective activity in synergy with NT-4 but not NGF [81]. CNTF has survival and differentiation-inducing effects on cerebral sensory and motor neurons, parasympathetic neurons, and

hippocampal neurons [82]. It additionally enhances neurite outgrowth in the hippocampus and hypothalamus, that are implicated in stress and anxiety responses. Furthermore, CNTF enhances adult neurogenesis, and cognitive performance in rodent models. CNTF levels are also enhanced following brain injury and promote neuronal survival after injury [80]. Given the role of CNTF in cell survival, neurite outgrowth, and hippocampal neurogenesis, its over-expressing in the AD brain may be a promising approach to improve AD-induced cognitive decline. However, its clinical usage is limited because of its inability to automatically cross the bio-membranes and spread in the target region. Accordingly, some novel approaches have been utilized to solve this problem [83]. In a previous study, continuous direct CNTF implantation to the brain of A $\beta$ -received mice had neuroprotective effects against neuronal and behavioral impairments [84]. In the other study, the researchers used P11 linked to CNTF to solve this problem and help fast and efficient delivery of CNTF to the brain in a non-invasive way. P11-CNTF treatment in the AD model of mice significantly shortened the mean latency in the Morris water maze test. The outstanding characteristics of P11-CNTF as a non-invasive way make it a novel efficient therapeutic method for AD [82]. Recently, treatment with P021, a small peptidergic compound derived from CNTF that is the BBB permeable, successfully prevented synaptic and neurogenesis deficits, neurodegeneration, A $\beta$  and tau pathologies, and subsequently cognitive impairment in the transgenic model of mice. These results confirm the potential therapeutic outcome of P021 on several main features of AD [85]. In the other work, the trans activator of transcription (TAT) was connected to truncate CNTF (tCNTF) and generated TAT-tCNTF, to overcome the inability of CNTF to access the brain. TAT-tCNTF could transport automatically through bio-membranes and enter into the cells generally by macro-pinocytosis. TAT-tCNTF promoted cell viability in hippocampal neurons treated with A $\beta$  by interacting with its receptor, CNTFR $\alpha$ , and activating the extracellular regulated protein kinases (Erk) and Protein kinase B/Akt pathways [86]. Overall, according to evidence, CNTF is potentially able to promote neurogenesis and neuronal survival as well as has neuroprotective effects against neuronal and neurobehavioral impairments following AD. However, its clinical application is restricted due to its inability to cross bio-membranes and reach the target region. Despite the findings as mentioned earlier to overcome this problem, additional investigations should be done to provide the supreme solution for this obstacle.

#### Cardiotrophin-1 and Alzheimer's disease

This trophic factor displays remarkable neuroprotective effects and delays motor neurons degeneration via promoting neuronal regeneration, extending the neuronal survival,



and improving motor function [87]. CT-1 is capable of alleviating high fat diet-induced cognitive impairment by suppressing proinflammatory cytokines in the brain, improving mitochondrial/synaptic dysfunction, and increasing insulin signaling sensibility by AMPK activation [88, 89]. Another study by Wang et al. examined the involvement of CT-1 in AD-related cognitive decline. They indicated the down-regulation of CT-1 in the brain of the APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic mice. The APP<sup>swe</sup>/PS1<sup>dE9</sup> transgenic mouse model of AD shows generation of senile plaque and amyloid neuropathy. Moreover, in their study, induced expression of CT-1 ameliorated cognitive deficits through GSK-3 $\beta$  inhibition [87].

### Glial cell line-derived neurotrophic factor family ligands and Alzheimer's disease

GFLs are a distinct family within the TGF- $\beta$  superfamily, which consists of four members including, GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN). Complex signaling made of the receptor tyrosine kinase Ret and one of the four members of the glycosylphosphatidylinositol-linked GDNF family receptor  $\alpha$  (GFR $\alpha$ 1, GFR $\alpha$ 2, GFR $\alpha$ 3, and GFR $\alpha$ 4) network mediates the biological functions of these proteins. Supportive and neurorestorative effects of these molecules on various neuronal populations such as basal forebrain, hippocampal, dopaminergic, motor, sensory, enteric, sympathetic, and parasympathetic neurons have attracted significant attention as a potential treatment for degenerative diseases [90]. Based on the evidence, GDNF is the best understood and most commonly used GFL for AD treatment and other members of this family have not yet been studied for treating AD and associated cognitive deficits.

### Glial cell line-derived neurotrophic factor and Alzheimer's disease

GDNF, a potent NTF and a member of GFLs, protects and repairs midbrain dopamine neurons. Besides, GDNF can inhibit the degeneration of noradrenergic neurons of the locus coeruleus, which diminished during AD progression. It has shown that a decreased concentration of GDNF leads to excessive glutamate release and excitotoxicity in the CNS, resulting in dopaminergic degeneration [91]. Degeneration of dopaminergic neurons takes part in AD pathogenesis and, therefore, pharmacological approaches focusing on enhancing the cortical and hippocampal dopamine transmission may promote synaptic functions and improve memory impairment in AD patients [92]. A recent study revealed that endogenous GDNF acts as a potential modulator of cholinergic transmission and protects against cognitive impairments in neurodegenerative disorders [93]. Additionally, data of a postmortem investigation displayed GDNF downregulation

in the middle temporal gyrus of AD subjects [94]. In the context of altered expression of GDNF in AD serum, a recent study reported the decreased serum GDNF levels in AD patients compared to the control group, indicating the involvement of GDNF in disease pathology [95]. However, an increased concentration of GDNF was detected in the serum and CSF of patients with early stages AD to compensate for the neurotrophic loss in the impaired brain [96]. Moreover, this protein promotes neuronal plasticity, and age-related cognitive deficits. Furthermore, GDNF signaling is mainly affected during both the aging process and AD, leading to cognitive impairment [91]. In hippocampal neuron culture, GDNF seems to enhance the number of synapses. Also, mutant mice with decreased levels of GDNF showed reduced presynaptic maturation during hippocampal synaptogenesis [97]. Only a handful of literature examined the therapeutic potential of GDNF for AD. A study performed by Ghribi et al. showed that the GDNF administration has a protective role against AD-like changes induced by the injection of aluminum complexes in rabbits [98]. Moreover, Revilla et al. have unveiled that GDNF was down-regulated in transgenic 3xTgAD mice and voluntary exercise for 6 months reversed this effect [99]. Besides, 6 months of over-expressing GDNF and BDNF by using engineered-lentiviral vectors in 10-month-old 3xTg-AD mice may protect neurons from atrophy and degeneration and by this way protect against AD neuropathology such as learning and memory impairment [100].

In a more recent study, GDNF-overexpressing umbilical cord blood mononuclear cells (UCBMCs) were administered to AD transgenic mice and this gene-cell therapy method stimulated synaptogenesis and promoted long-lasting neuroprotection [101]. A considerable number of preclinical and clinical studies demonstrated the beneficial effects of lithium on cognitive performance in subjects with AD. According to Straten et al. study, GDNF is the main target of lithium in AD patients, especially in early steps. They found a significant negative correlation between lithium concentration in serum and GDNF concentration in serum and CSF. These findings indicate that lithium treatment might reduce the necessity of enhanced GDNF expression in the CNS in early AD [102]. A recent work reported that GDNF-overexpressing UCBMCs transplantation significantly improved spatial memory in transgenic AD model in mice (APP/PS1 mice), which has confirmed by the existence of implanted cells and their GDNF expression in the hippocampus and cortex for several weeks after transplantation [103]. Another recent study indicated the contribution of the Hippo/YAP signaling pathway in the action of GDNF against A $\beta$ -induced inflammatory response in microglia. Accordingly, targeting GDNF or the Hippo/YAP signaling may be a promising treatment for AD [104]. Therefore, based on these results, it can be concluded that the GDNF administration or over-expression

can be a therapeutic approach for the treatment of AD and subsequent cognitive impairment.

### **Cerebral dopamine neurotrophic factor: mesencephalic astrocyte—derived neurotrophic factor family and Alzheimer’s disease**

CDNF and MANF proteins are two members of the evolutionary conserved CDFN/MANF family and have varied critical roles in the brain. These proteins are widely expressed in different areas in the mammalian brain, such as the hippocampus, thalamus, cerebral cortex, cerebellum, and striatum [7]. Some neuropathological studies provided evidence that misfolded proteins’ aggregation leads to endoplasmic reticulum (ER) stress, which is a primary feature of AD. The accumulation of misfolded proteins in the ER disrupts its homeostasis and activates a cellular stress response named the unfolded protein response (UPR) [88]. Whereas UPR protects the cell against the formation of toxic misfolded proteins, its long-term activation can induce cell death [105]. Numerous studies have revealed that UPR is activated in the AD brain [106]. MANF and CDFN are two ER stress response proteins that diminish ER stress-induced cell death via interaction with the UPR [107]. A study conducted by Kempainen and coworkers showed that intrahippocampal CDFN protein or gene-therapy improved long-term memory in both mice models of AD and wild-type controls, but did not influence spontaneous activity, short-term memory, or object neophobia [108]. Synaptic dysfunction is one of the main characterizations of early-stage AD related to soluble oligomers of A $\beta$ . CDFN shows a protective effect on A $\beta$ -induced synaptotoxicity in hippocampal cells, suggesting that CDFN may protect against A $\beta$ -induced synaptotoxicity through decreased the expression of ER stress-related proteins and attenuating ER stress [109]. Similarly, MANF may exert neuroprotective effects against A $\beta$ -induced neuronal cell death by suppressing ER stress [107]. These findings are proposing CDFN and MANF as a therapeutic candidate for the treatment of AD that needs further investigations before application of them in clinical settings.

### **Neurotrophic factors and other neurodegenerative conditions**

NTFs have been revealed to be effective in the protection of neurons and prevention of progressive cell loss in a range of other neurodegenerative disorders. The bulk of these results were obtained from animal studies. In animal models of Parkinson’s disease, many researchers have reported improved motor function and plasticity, and also observed reduced Lewy neurites/bodies accumulation, inflammation, as well

as oxidative stress. Some of these NTFs promote the survival of dopaminergic neurons and prevent their degeneration and exert neuroprotective and neurorestorative effects on these cells; in contrast to their robust effects in animal models, NTFs have shown relatively weak results in human clinical trials [107].

In the case of amyotrophic lateral sclerosis (ALS), administration of NTFs in experimental animal models of ALS revealed significant improvement in the survival of degenerating motoneuron and rescue of the axotomized motoneuron. Likewise, several NTFs such as BDNF, CNTF and, GDNT have been tested in clinical settings to treat ALS patients. However, dose-limited side effects, particularly weight loss, anorexia, and inappropriate administration methods cause poor outcomes [110].

Furthermore, several delivery approaches like gene therapy have since been used to distribute NTFs in many different animal models of other neurodegenerative diseases, including Huntington’s disease [111] and stroke [112]; still, these programs have not advanced into clinical trials.

### **Concluding remarks and future directions**

As mentioned above, although aducanumab is efficient in removing amyloid plaques from the brain, but its efficacy in treating AD-related cognitive deficits has not confirmed. Accordingly, another approach may be more applicable in treatment of cognitive decline following AD. In this context, NTFs as new and promising candidates for treating AD and AD-associated cognitive impairment are currently under investigation. Mounting evidence shows that NTFs have varied biological effects such as survival, development, and neurons’ maintenance. Changes in the levels or expression of NTFs may have a critical role in the progression of AD and concomitant cognitive decline. Nevertheless, mounting shreds of evidence have been collected in the last decades; more studies are needed before the application of NTFs as therapeutic promises for AD management. In this context, some limitations for clinical application of NTFs such as their delivery across the BBB, having short half-lives, difficulties with the injection of proper dose, and side effects on organs and tissues should be resolved in the future. However, emergent delivery approaches, such as gene therapy vectors and biomaterial-based drug-delivery system, seem to improve NTF therapy outcomes, decreased side effects, and increased clinical benefit.

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