Neurotrophic factors in Alzheimer’s disease: pathogenesis and therapy

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Alzheimer’s disease (AD) is a common neurodegenerative disease with a prevalence estimated to reach 115 million by 2050. It is characterized by abnormal extracellular accumulation of amyloid-beta (Aβ) peptide and intracellular neurofibrillary tangles (NFTs) that result in neuro-inflammation, synaptic dysfunction, neurotransmitter imbalance, neuronal loss, and dendritic changes. A hypothesis of neurotrophic factor (NTF) involvement in neurodegenerative diseases and their potential as a therapeutic tool has emerged. There are wide information gaps on this topic. However, consistent with this hypothesis, AD may be caused by a deficiency in neurotrophin proteins or receptors expression. In AD brains, an increase in nerve growth factor and a decrease in brain-derived neurotrophic factor in the hippocampus and certain neocortical regions, and a decrease in TrkA in the cortex and nucleus basalis has been observed. Thus, comparative data relating to recent hypotheses addressing NTF content and receptors in experimental animals and human brains, along with their potential roles in the treatment of AD, are discussed in this review.

Key words: Alzheimer’s disease, neurotrophic factors, amyloid-β, tau, oxidative stress

INTRODUCTION

Neurotrophic factors (NTFs) are considered endogenous proteins that activate neuronal repair genes in neurodegeneration (Pardridge, 2010; Géral et al., 2013). Several processes in neurons such as survival, migration, neurite outgrowth, formation of synapses, and neuronal plasticity are controlled by NTFs (Lipton, 1989; Rhee et al., 2004). Several recent reviews address which NTFs initially released by glial cells are responsible for the development of embryonic midbrain neurons (Boyd and Gordon, 2003; Tenenbaum and Humbert-Claude, 2017; Pöyhönen et al., 2019). These factors play an important role in neural regeneration, remyelination, and regulating the development and phenotypic survival of neurons of the peripheral and central nervous system (PNS and CNS, respectively) through specific receptors (Milbrandt et al., 1998; Li et al., 2012; Bothwell, 2016; Sampao et al., 2017). The NTF superfamily consists of neurotrophins, glial cell line-derived neurotrophic factor (GDNF), family ligands (GFLs), neuropoietic cytokines, the cerebral dopamine neurotrophic factor (CDNF)/mesencephalic astrocyte-derived neurotrophic factor (MANF) family, the nerve growth factor (NGF) family, brain-derived neurotrophic factor (BDNF) epidermal growth factors (EGF), fibroblast growth factors (FGF), GP130-binding growth factors such as CNTF, heparin-binding growth factors, insulin-like growth factors, and transforming growth factors (TGF) (Kolomeyer and Zarbin, 2014).

There are two classic neurotrophic factor families: neurotrophins NGF, BDNF, NT-3, and NT-4/5 belong to
the first group (Andreassen et al., 2009; Wei, 2016). NGF binds the P75NTR and the P140trk (TrkA) receptors (Deinhardt and Chao, 2014), BDNF and NT-4/5 binds the TrkB receptor, and NT-3 primarily binds the trkC receptor (Airaksinen et al., 1999; Saarma and Sariola, 1999; Kolomeyer and Zarbin, 2014). The second group is the GDNF-family, consisting of GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN) (Ibáñez and Andressoo, 2017). Currently, NTFs are categorized into four families: neurotrophins, GDNF family ligands (GFLs), neuropoietic cytokines, and the CDNF/MANF family (Fig. 1) (Airaksinen and Saarma, 2002; Lindahl et al., 2017). Recent studies have shown that NTFs play a pivotal role not only in aging but also in age-related

![Diagram](image_url)
neurodegenerative diseases such as Alzheimer’s disease (AD) (Budni et al., 2015). NFTs may serve as a potential therapeutic agent for the treatment of neurodegenerative diseases including Parkinson’s disease (PD) and AD, as well as Huntington’s disease, amyotrophic lateral sclerosis, and other neurological disorders (Gill et al., 2003; Domanskyi et al., 2015).

**Alzheimer’s disease**

AD has been regarded as the most common form of dementia and a progressive neurodegenerative disease in elderly people (Iulita and Cuello, 2014). AD affects almost 40 million people around the world, including over 5 million persons in the United States, and is estimated to steadily increase to nearly 115 million by 2050 (Bishop et al., 2010). It is worth mentioning that cognition, judgment, behavior, and memory are severely impaired in patients suffering from ongoing AD (Devi and Ohno, 2014). Firstly, AD was described by Alois Alzheimer, a German psychiatrist and neuropathologist, in 1906 (Dong et al., 2012). The disease is characterized by selective neuronal loss in the hippocampus, amygdala, basal nucleus of Meynert, locus coeruleus, and neocortex (Connor et al., 1997). Due to a decline in hippocampal functions, the most common AD symptoms include gradual loss of memory, impaired verbal memory, deficits in orientation and judgment, and behavioral and functional impairment (Alzheimer’s Association, 2016; Sajjad et al., 2018; Chiroma et al., 2019).

Since basal forebrain cholinergic neurons (BFCN) are prominently involved in AD, utilizing neurotrophic factors for AD therapy is highly reasonable (Siegel and Chauhan, 2000). AD is a multifaceted disorder and its pathogenesis is still poorly understood. Amyloid plaques, neurofibrillary tangles (NFTs), and oxidative stress are the main neuropathological hallmarks in AD patients. Amyloid-β protein (Aβ), as extracellular plaque formations, and neurofibrillary tangles (NFTs), as intracellular formations, are two major neuropathological features of AD. NFTs consist of paired helical filaments of hyperphosphorylated tau protein (Rudelli et al., 1984; Yatin et al., 1999; Armstrong, 2009; Singh et al., 2016; Chen and Mobley, 2019), which lead to synaptic degeneration and neuronal loss (Serrano-Pozo et al., 2011; Overk and Masliah, 2014; Abrous and Wojtowicz, 2015; Colom-Cadena et al., 2020). Multiple sclerosis (MS), human immunodeficiency virus (HIV) encephalitis, brain trauma, and stroke are all characterized by an infiltration of inflammatory blood cells, though reactive microglia and astrocytes have also been observed in AD patients (Amor et al., 2010; Heneka et al., 2014). Thus, AD must be considered a neurodegenerative disease with an neuroinflammatory component (Eizirik et al., 2007). Aβ-containing plaques activate astrocytes and microglia, along with the induction of inflammatory signaling cascades (Song et al., 2015).

AD pathogenesis can be promoted by microglial-mediated inflammatory responses via two pathways (Song et al., 2015). Firstly, oxidative stress is thought to play a major role in the process of age-related neurodegeneration and cognitive decline (Kim et al., 2015). The brain is particularly vulnerable to oxidative imbalance due to its high energy demand, high consumption of oxygen, and rich in polyunsaturated fatty acids (Wang et al., 2014). Based on overwhelming evidence, oxidative stress in AD leads to protein oxidation, lipid peroxidation, DNA oxidation, and glycoxidation. It has also been observed that, in AD brains, ROS causes calcium influx via glutamate receptors and triggers an excitotoxic response leading to cell death. Moreover, oxidative stress leads to increased Aβ generation. Aβ causes lipoperoxidation of membranes and lipid peroxidation products. A close relationship has been demonstrated between lipid peroxides, antioxidant enzymes, amyloid plaques and NFTs in AD brains (Sayre et al., 2008; Zuccato and Cattaneo, 2009; Gella and Durany, 2009; Feng and Wang, 2012). It is thought that the CNS is vulnerable to damage induced by free radicals because of the high lipid content, high oxygen utilization rate, and lower of antioxidant enzymes in the brain, compared to other tissues. Thus, free radicals appear to play an important role in some neurodegenerative disease such as PD, Down’s syndrome (DS), head injury, cerebral ischemia-reperfusion, and AD (Murphy and Park, 2017; Chiroma et al., 2019; Siegel and Chauhan, 2000).

Second, up-regulation of both the levels and activity of the Aβ-generating enzymes Y-secretase complex and β secretase increase the concentration of Aβ. In AD patients, a gradual but ongoing structural alterations and thus an increasing dysfunction in the hippocampus and neocortex as the susceptible brain areas for memory and cognition, have been reported (Gralle et al., 2009; Ciaramella et al., 2013; Song et al., 2015). Based on previous studies there are numerous hypotheses regarding the causes of AD, including the Aβ hypothesis, Tau hypothesis, cholinergic hypothesis of AD, mitochondrial cascade hypothesis, calcium homeostasis hypothesis, neurovascular hypothesis, and inflammatory hypothesis (An et al., 2008; Du et al., 2018; Fan et al., 2019; Liu et al., 2019; Cheng et al., 2021). Numerous studies have shown a significant loss of cholinergic activity in AD patients’ brains (Budni et al., 2015). Meanwhile, a role for acetylcholine in cognitive functions has been demonstrated in human and animal models of AD. Moreover, it has been demonstrated that cholinergic agonists such as acetylcholinesterase inhibitors (AChEIs) can reverse...
cognitive impairments only in early phases of AD. The described studies highlight the importance of the cholinergic theory in AD as one the most plausible and reliable (Bartus, 2000; Iqbal et al., 2009; Karran et al., 2011).

Nerve growth factor (NGF) and Alzheimer’s disease

NGF was discovered by Rita Levi-Montalcini and Stanley Cohen in the 1950s (Cowan, 2001). It was the first member of NGF-superfamily of neurotrophins (NT), which provides neuronal survival during development and modulates neuronal functions throughout adulthood (Lanni et al., 2010). Multiple lines of evidence have indicated that the growth, differentiation, regeneration, neurotransmitter function, development, and phenotypic maintenance of neurons in the PNS are influenced and guided by NGF. NGF is found in hippocampus, cortex and olfactory bulb, and BFCN cell bodies (Lanni et al., 2010). NGF has a three-dimensional structure including α, β, and γ subunits. However, the biological activity of NGF is related to the β subunit and the γ subunit represents an EGF binding protein, whereas the role of the α subunit is still relatively unknown (Razavi et al., 2015). NGF is made by cleavage from pro-NGF, the precursor protein form of NGF (Wang et al., 2014). Treatment with pro-NGF in cervical ganglia neurons caused programmed cell death, while NGF treatment of the same neurons led to their survival and axonal growth (Lee et al., 2001). Free NGF displays multiple physiological actions in the CNS (Tucker et al., 2008; Xu et al., 2012).

Most importantly, NGF has strong anti-apoptotic and neurotrophic effects, which are critical for neurite and axonal outgrowth, survival and maintenance of neurons, and branching and extension (Lomb et al., 2009). Two specific receptors, TrkA and p75 neurotrophin receptor (NTR), mediate the biological activity of NGF. It has been demonstrated that NGF promotes the biosynthesis of myelin component sheaths in both the CNS and PNS (Chan et al., 2004). Recent in vivo and in vitro studies proposed NGF as a new potential therapeutic for the treatment of neurodegenerative disease (Chan et al., 2004; Aloe et al., 2015; Mitra et al., 2019; Wang et al., 2020). The level of NGF in the nervous system and cerebrospinal fluid (CSF) has been found to decrease in AD patients (Budni et al., 2015).

Cholinergic degeneration is reported in AD, providing a strong argument to link NGF and AD (Francis et al., 1999). Crowley and colleagues (1994) demonstrated that knockout mice lacking both NGF and TrkA showed marked reductions in ChAT immunoreactivity in the basal forebrain and loss of cholinesterase activity in both the hippocampus and neocortex. In addition, studies showed that deficits in long-term potentiation (LTP) in old cognitively impaired rats was restored by chronic intraventricular infusion of NGF (Villoslada et al., 2000; Lanni et al., 2010). To further support NGF is a crucial neurotrophin in the CNS. Several studies described that its dysregulation may be involved in various neuronal degeneration diseases such as AD and MS (Biernacki et al., 2005; Cattaneo and Calissano, 2012). Other studies also demonstrated that, in AD patients, cognitive decline and dementia are related to increasing degeneration of the basal forebrain cholinergic system that can cause NGF deficits (Iulita and Cuello, 2014; 2016). After NGF gene transfer therapy in early phase AD patients by Tuszynski et al. (2015), a trophic response to NGF included axonal extensions towards the NGF source and activation of the functional markers cAMP response element-binding protein (CREB) (as a canonical mediator of downstream neurotrophin signaling and cell activation) and c-Fos (as a canonical marker of neurotrophin-mediated activation of cell signaling) has been observed. Brain activity in an electroencephalogram, glucose metabolism, and cognition in AD patients was shown to be improved by NGF treatment (Ferreira et al., 2015). Moreover, a lower rate in brain shrinkage, a better clinical status and, increased levels of CSF Aβ1-42 were reported in these patients (Ferreira et al., 2015; Wei, 2016).

Numerous studies have indicated that NGFs enriched amyloid precursor protein (APP), the non-amyloidogenic cleavage pathway, and reduced Aβ generation in the brain of investigated mice (Yang et al., 2014). There is also evidence that NGF levels in the CSF and dentate gyrus of AD patients were higher as compared to a control group (Budni et al., 2015; Faria et al., 2014). Some interesting studies have revealed positive results showing lower levels of Aβ1-42 in CSF with NGF treatment in patients with AD (Andreasen et al., 1999; Ferreira et al., 2015). Receptors for NGF located at the surface membrane of cells and TrkA are considered high affinity catalytic active receptors for NGF (Romani et al., 2010). After the binding of NGF to TrkA, phosphorylation of TrkA occurs and then protein kinase B (Akt) is activated or extracellular signals will regulate protein kinase 1/2 (ERK1/2), then docking sites for effect molecules such as Shc will be provided, which in turn induces the recruitment of a Shc/Grb2 complex (Mahata et al., 1999). After phosphorylation of the TrkA receptor, TrkA interacts with phosphatidylinositol 3-kinase (PI3K) (Xia et al., 2012; Xu et al., 2012). Activated PI3K leads to the production of phosphoinositide 3,4,5-trisphosphate and membrane translocation of the serine/threonine-protein kinases Akt and Akt activation (Wang et al., 2014).
It should be noted that the PI3K/Akt signaling pathway is particularly important for neuronal survival and the synthesis of many new cellular proteins and eventually causes neural differentiation and prevention of apoptosis. For example, head box-O transcription factors (FoxO) and B-cell lymphoma 2 family members inhibit neuronal apoptosis (Wang et al., 2013). The low affinity receptor p75NTR is another NGF receptor (Deponti et al., 2009). However, the role of p75NTR is highly complex, for example it appears to promote cell survival, cell death, or growth inhibition (Bai et al., 2010). Even though the affinity of NGF binding to p75NTR receptor is weaker than NGF binding to TrkA, the cell type distribution of p75NTR is broader than that of TrkA; the TrkA receptor is mainly expressed in neurons responsive to NGF such as peripheral sensory, sympathetic, and BFCNs, while the p75NTR receptor displays a more broad distribution in motor neurons (Lee et al., 1994). In addition, Schwann cells and cerebellar Purkinje cells (PCs) also express the TrkA receptor (Bothwell, 1991). Rac GTPase and activated c-jun N-terminal kinase (JNK) are activated by p75NTR, and JNK3 is an injury-specific isoform JNK (Harrington et al., 2002). The expression of proapoptotic genes through the transactivation of specific transcription factors is stimulated by JNKs, consequently p75NTR can promote cell death (Jing and Anning, 2005). Nevertheless, it also increases cell survival; NGF treatment activates nuclear transcription factor κB (NF-κB) through p75NTR and, during this process, p75NTR-mediated NF-κB activation enhances the survival response of developing sensory neurons to nerve growth factor (Hamanoue et al., 1999).

Ras, a membrane-associated G-protein mediates activation of the mitogen-activated protein kinase (MAPK) pathway, which is another NGF-activated signaling pathway activated by recruitment and phosphorylation of Shc (Chen et al., 1998). The active Ras protein binds to and phosphorylates several proteins, including the proto-oncogene Raf. Then, MAPK kinase (MEK) is activated by Raf and subsequently ERK1/2 is activated by phosphorylated MEK (Wang et al., 2013). The activity of many transcription factors, including ETS domain-containing protein ELK1, is regulated by phosphorylated ERK1/2 when it enters into the nucleus (Oh et al., 2012). Furthermore, if ERK1/2 phosphorylates ribosomal S6 kinase (S6K), it can lead to the phosphorylation of cyclic adenosine monophosphate response element binding protein, affect the regulation of the expression of NGF-inducible genes, and, taken together, contribute to neuronal differentiation or neurite outgrowth (Cheng et al., 2002). Apart from the two pathways mentioned previously, TrkA activation through phospholipase C gamma1 (PLCγ1) is also involved in the survival and growth of neuronal cells (Wang et al., 2014). As a matter of fact, PLCγ1 supports the activation of the PKC signaling pathway and is thus involved in antimitogenic/mitogenic signaling (Cabeza et al., 2012).

Glial cell line derived neurotrophic factor and Alzheimer’s disease

GDNF is a well-known member of the neurotrophin family, which was characterized in 1993 as the first member of the GFLs in the CNS (Lin et al., 1993; Sariola and Saarma, 2003; Sidorova and Saarma, 2016). GDNF is produced by dopaminergic neurons of the substantia nigra, BFCNs, brainstem noradrenergic neurons, and PCs. GDNF and its receptors are also widely expressed in hippocampus from early embryonic ages to adulthood (Lanni et al., 2010). Furthermore, apoptosis in motor neurons and regeneration of sensory axons after spinal cord injury is promoted by GDNF (Razavi et al., 2015). It is known that GFL binds to one of the four members of GDNF family receptor α (GFRα1 to α4). After anchoring the GFL-GFRα complex, GFLs connect to receptor tyrosine kinase RET or the neuronal cell adhesion molecule (NCAM). RET is widely expressed and is activated by GDNF, NRTN, or ARTN stimulation. The development of sympathetic, parasympathetic, motor, and sensory neurons is regulated by RET, which is also required for the postnatal survival of dopaminergic neurons (Sam-piao et al., 2017; Tansey et al., 2000).

Although the importance of GDNF in AD brains is poorly documented, it was found to be decreased in plasma but increased in CSF from patients with mild cognitive impairment and AD (Marksteiner et al., 2011). Due to the fact that overexpression of GDNF (recombinant lentiviral vectors) led to improvement in learning and memory (Allen et al., 2013; Revilla et al., 2014), it was proposed that it GDNF may be important to protect neurons from both atrophy and degeneration (Allen et al., 2013). Recent studies revealed that gene therapy provides a safe and effective treatment for AD. Revilla et al. (2014) used recombinant lentiviral vectors to overexpress GDNF gene in hippocampal astrocytes of 3xTg-AD mice in vivo; they concluded that the overexpression of GDNF protected against cognitive loss and memory impairment and this behavior represented a cross-talk between astrocytes and neurons in the injured brain.

Numerous studies have demonstrated that, in normal neurons, GDNF is responsible for expression of GFRα1, whereas it induced neuronal death in AD brains because it failed to induce GFRα1 expression in cortical neurons (Konishi et al., 2014). RET is known as a proto-oncogene encoding a receptor tyrosine kinase (RTK)
Neurotrophic factors and Alzheimer's disease


Neurotrophic factors and Alzheimer's disease

that forms a transmembrane receptor complex with the glial GDNF. Unlike most receptor tyrosine kinases, since RET cannot bind its ligands directly and requires a co-receptor (GFRα), GFLs are essential for activation of RET. GFRα1-GFRα4 represent a novel family of glycosyl-phosphatidylinositol (GPI)-anchored proteins that bind GFLs with high affinity. The GFL-GFR complex triggers auto-phosphorylation and intracellular signaling (Mologni, 2011; Santoro et al., 2004; Tansey et al., 2000). For activation of RET, GFLs form a complex with glycosyl phosphatidylinositol (GPI)-anchored co-receptors. The co-receptors themselves are characterized as members of the GFRα protein family. The unique binding affinity feature for each GFL is determined by GFRα proteins such that GFRα1, GFRα2, GFRα3, and GFRα4 specifically bind to GDNF, NRTN, ARTN, and PSPN, respectively (Airaksinen and Saarma, 2002). After binding to the GFRα1–4, a high-affinity complex is formed and promotes the binding two RET molecules, triggering transphosphorylation of specific tyrosine residues in their tyrosine kinase domains and intracellular signaling (Airaksinen et al., 1999; Saarma and Sariola, 1999; Kolomeyer and Zarbin, 2014).

Several intracellular signaling cascades are activated by RET, which regulate cell survival, differentiation, proliferation, migration, chemotaxis, branching morphogenesis, neurite outgrowth, and synaptic plasticity (Chen et al., 2005). For both neuronal survival and neurite outgrowth, the PI3K pathway is essential (Del Río et al., 2011). Different targets inside and outside lipid rafts are affected after RET activation and lipid rafts are essential signaling compartments in the cell membrane, proposed to serve an important role in cell adhesion, axon guidance, and synaptic transmission (Sariola and Saarma, 2003). Glicosyl phosphatidyl inositol (GPI)-anchored transmembrane, double acylated proteins, and cholesterol-linked and palmitylated proteins are enriched in the lipid rafts (Paratcha and Ibáñez, 2002; Tsui-Pierchala et al., 2002). Inactive RET is situated outside rafts and, through GDNF stimulation, GFRα1 recruits RET into lipid rafts; however, the exact mechanism is not completely understood (Paratcha and Ibáñez, 2002; Sariola and Saarma, 2003). Soluble GFRα1 also targets RET to lipid rafts. Additionally, Ledda et al. (2002) demonstrated that prolonged GDNF-mediated activation of cyclin-dependent kinase 5 (CDK5) acts as an attractive guidance signal for axons. Activated RET is preferentially associated with the adaptor SHC outside rafts, and with FGF receptor substrate 2 (FRS2) within rafts (Paratcha and Ibáñez, 2002). These data suggest that differences in GDNF signaling through RET within and outside the rafts could lead to dramatically different cellular responses (Sariola and Saarma, 2003). GDNF can also signal RET independently through GFRα1 (Baloh et al., 1997; Trupp et al., 1996). Upon ligand binding, GDNF, together with GFRα1, may interact with heparan sulphate glycosaminoglycans to activate the Met receptor tyrosine kinase through cytoplasmic Src-family kinases that cause neurite outgrowth, neuronal survival, and ureteric branching (Airaksinen and Saarma, 2002; Barnett et al., 2002; Sariola and Saarma, 2003). In several studies, four of these residues have been identified as the docking sites for various cytoplasmic adaptor proteins that include: Grb7r10, Tyr905, PLCγ, Tyr1015, Shc, ENIGMA, Tyr1062, Grb2, and Tyr1096. They are phosphorylated and, after the elevation of cyclic AMP levels, Ser696 is also phosphorylated (Fukuda et al., 2002). In numerous studies PLCγ, JNK, PI3K, and Ras-MAP kinase pathways are considered second messenger pathways that are activated by RET (Kurokawa et al., 2001). The intracellular level of Ca2+ ions is regulated by the PLCγ pathway by increasing the level of inositol (1,4,5)-trisphosphate (Airaksinen and Saarma, 2002). Rac activation (Rac as Ras-related C3 botulinum toxin substrate) in neurons plays a pivotal role in lamellipodia formation that is critical for neuritogenesis (Fukuda et al., 2002). Hence, Rac activity is controlled via activation of PI3K by a variety of receptor tyrosine kinases. For GDNF-induced Rac activation, protein kinase A (PKA)-dependent Ser696 phosphorylation is essential (Fukuda et al., 2002). RET contains additional tyrosine residues that are phosphorylated upon GFL binding (Tyr687, Tyr826, and Tyr1029), but the role of these proteins in GFL signaling is not been fully understood (Sariola and Saarma, 2003).

Neural cell adhesion molecule (NCAM) has also been demonstrated to be a ligand for the GDNF family (Pop-sueva et al., 2003). In neurons, in the absence of the RET proteins, GDNF has a high affinity for binding to NCAM and GFRα1 complex (Chao et al., 2003), which activates the Src-like kinase Fyn and focal adhesion kinase (FAK) in the cytoplasm. In some studies, NCAM is considered to function as an alternative or second signaling receptor for GFLs (Paratcha et al., 2003). Paratcha and colleagues (2003) noticed that if GDNF is absent, GFRα1 downregulates NCAM-mediated cell adhesion. Schwann cell migration and axonal growth in hippocampal and cortical neurons are stimulated by the binding of NCAM to GDNF in a RET-independent fashion (Chao et al., 2003). Accordingly, by using different signaling pathways it modulates both short and long-range intercellular communication. Interestingly, many studies demonstrated that NCAM is co-expressed and directly interacts with GFRα1 in embryonic PCs (Charoy et al., 2012; Paratcha et al., 2003; Sariola and Saarma, 2003; Sergaki and Ibáñez, 2017). In vitro and in vivo studies demonstrated that, by using an NCAM blocking anti-
BDNF is highly expressed and widely distributed in the CNS in both neurons and glia, especially in the hippocampus, cerebral cortex, hypothalamus, claustrum, and amygdala, which are brain regions involved in learning and memory processes and vegetative functions in the adult brain (Murer et al., 1999; 2001). As BDNF regulates LTD (long-term depression) and LTP, synaptic plasticity, axonal sprouting, dendritic proliferation, and neuronal differentiation, it is a critical factor in learning and memory processes (Minichiello, 2009; Rösch et al., 2005). It should be noted that such mechanisms in the CNS are activated through BDNF’s interaction with tyrosine receptor kinase B (TrkB) receptors (Islam et al., 2009). Pro-BDNF (an inactive precursor) binds to p75NTR and then apoptotic pathways are activated in peripheral neurons and glia (Hibbert et al., 2006; Teng et al., 2005). As the TrkB receptor is activated by mature BDNF (Lu et al., 2014; Lu et al., 2013) and auto-phosphorylation of tyrosine residues, activation of PI3K begins (Ledda and Paratcha, 2016). Accordingly, it provides trophic support to neurons and induces neuronal growth (Sandhya et al., 2013). The BDNF-TrkB pathway can be regarded as a crucial signaling pathway in the biological activity of BDNF, and a loss of the signal may be particularly involved in several neurodegenerative diseases, such as AD and PD (Song et al., 2015).

The development of sympathetic, parasympathetic, motor, and sensory neurons, and the postnatal maintenance of dopaminergic neurons are regulated by RET (Mologni, 2011). A reduction of BDNF mRNA levels in the hippocampus was reported after blockade by administration of scopolamine to glutamatergic neurons and/or stimulation of the GABAergic system (Connor et al., 1997; Berzaghi et al., 1993). Additionally, involvement of the cholinergic neuronal system in regulating BDNF mRNA levels within the hippocampus has been observed (Phillips et al., 1991; Rosser et al., 1982). The degeneration of both the glutamatergic and cholinergic systems are characteristic neuro-pathological features of AD (Araujo et al., 1988; Coyle et al., 1983). Thus, it is hypothesized that BDNF might be involved in the etiology of cognitive impairment (Connor et al., 1997). Since BDNF provides trophic support to the basal forebrain cholinergic system it is most likely that a decrease in BDNF may contribute to the progressive atrophy of BFCNs associated with AD (Phillips et al., 1991). As Phillips et al. (1991) found that BDNF mRNA decreased in the hippocampus of individuals with AD, it was suggested that BDNF may contribute to the progression of cell loss (apoptosis) in AD.

Several lines of evidence further demonstrate that BDNF treatment may decrease abnormal Aβ production and repair Aβ-induced damage, mediate cell death, ameliorate cognitive dysfunction and loss of synapses, and even retard cognitive decline (Li et al., 2012; Rohe et al., 2009). Reduced BDNF signaling through TrkB leads to impaired spatial memory, whereas over-expression of TrkB enhances memory. In addition, signaling through TrkB and BDNF improved LTP at hippocampal synapses. Consequently, these properties of BDNF led to speculations about its role in AD (Ji et al., 2010; Monteggia et al., 2004; Wan et al., 2014). Some studies reported that BDNF mRNA and protein levels were reduced in postmortem brains of AD patients (Meng et al., 2013; Michalski and Fahnstock, 2003). Gene transfer of BDNF into the entorhinal cortex led to increased BDNF protein levels in the hippocampus and improved hippocampal-dependent memory in APP transgenic mice and aged rats, and spatial learning improved after transplantation of neuronal stem cells into the hippocampi of aged APP/PS1/tau transgenic mice (Lattanzio et al., 2014; Nagahara et al., 2009; Blurton-Jones et al., 2009).

In addition to increased hippocampal neurogenesis and spatial memory in APP/PS1 mice, other studies demonstrated an increased level of hippocampal BDNF mRNA (Hsiao et al., 2014). While there is little experimental evidence supporting this view, a reduction in BDNF mRNA expression has been observed in human post-mortem AD hippocampi when compared to normal hippocampal levels. While the level of BDNF mRNA expression in human post-mortem AD hippocampus has been reported, it is unknown whether this observed alteration in BDNF expression also occurs at the protein level. Using a polyclonal antibody directed against the BDNF polypeptide, we compared the
level of BDNF protein in human post-mortem AD and neurologically normal hippocampal and temporal cortex sections using immunohistochemistry techniques (Murray et al., 1994). The locus coeruleus (LC), as a noradrenergic (NAergic) area in the brainstem, plays important roles in the regulation of behaviors such as anxiety, depression, and attention (Mann, 1983). In several studies neuronal damage was reported in neurodegenerative diseases and in up to 70% of AD (Bondareff et al., 1989; Niikura et al., 2006; Pamphlett, 2014; Zarow et al., 2003).

Despite many efforts to reduce LC damage and data revealing that BDNF is one of the factors essential to LC survival, the role of the factors responsible are not fully understood (Traver et al., 2006). Zheng provided evidence that proteolytic conversion to BDNF from pro-BDNF can be inhibited by Aβ protein (Zheng et al., 2010). Additionally, BDNF levels can be affected by Aβ indirectly at synapses via hyperphosphorylation of the microtubule-associated protein tau through calcineurin activation (Ramser et al., 2013). Moreover, Aβ, via a mechanism involving the deubiquitinating enzyme ubiquitin C-terminal hydrolase L1, can inhibit retrograde axonal transport of the BDNF-TrkB complex (Poon et al., 2013). In vitro experiments further confirmed that administration of oligomeric Aβ significantly down-regulated BDNF expression (DaRocha-Souto et al., 2012; Garzon and Fahnestock, 2007; Rosa and Fahnestock, 2015). Thus, it was suggested that the interaction of Aβ with PKA activation can downregulate CREB phosphorylation, which may be a new mechanism for Aβ-induced BDNF downregulation (Colucci-D’Amato et al., 2020; Rosa and Fahnestock, 2015).

Holback et al. (2005) suggested that BDNF could shift APP processing towards the α-secretase pathway in a neuronal cell line, however, reports on the effects of BDNF on APP processing in primary neurons are, currently, non-existent. Moreover, interactions between BDNF and tau protein are not completely understood (Tanila, 2017). Hypothetically, the activity of the most important tau kinase, glycogen synthase kinase-3 beta (GSK3β), should be reduced by BDNF signaling via the TrkB receptor and also activation of the PI3K-Akt pathway via its inhibitory phosphorylation (Elliott et al., 2005). One study reported that, after BDNF stimulation, tau de-phosphorylation could be distinguished in the common AD-associated AT8 site in neuronal cells (Tanila, 2017). Although less is known about possible effects of BDNF on Aβ production, BDNF co-incubation in hippocampal or entorhinal cortical slices also prevented Aβ1-42 induced impairment in LTP induction (Arancibia et al., 2008; Criscuolo et al., 2015; Kitiyanant et al., 2012; Tanila, 2017).

Cerebral dopamine neurotrophic factor and Alzheimer’s disease

Cerebral dopamine neurotrophic factor (CDNF) is a new class of the NTF family located in the endoplasmic reticulum (ER) (Lindahl et al., 2014). It has been shown that CDNF has a strong protective and restorative effect in dopaminergic neurons (Garcia-Alloza et al., 2006). Previous studies using overexpression of CDNF provided further evidence that cell damage could be alleviated and nerve regeneration could be promoted (Kemppainen et al., 2015). Since CDNF and a related protein, mesencephalic astrocyte-derived neurotrophic factor (MANF), are involved in ER stress and unfolded protein response (UPR) and since protein aggregation triggers ER stress and neuronal death in AD, it can be speculated that CDNF may reduce ER stress, block neuronal cell death, partially regenerate hippocampal neurons, and thus improve cognitive function in a mouse model of AD (Lindahl et al., 2014; Albert and Airavaara, 2019; Garcia-Alloza et al., 2006; Kemppainen et al., 2015; Wang et al., 2017).

As several studies have proposed that UPR is activated in AD brain (Costa et al., 2013; Hoozemans et al., 2012; Kemppainen et al., 2015), Wei et al. (2016) hypothesized that UPR activation occurs in Aβ-induced early synaptic dysfunction, an effect that can be rescued by CDNF. They showed that Aβ induced an increase in Bip/GRP78 and p-eIF2α (two known ER stress markers), pJNK (phosphorylated JNK), CHOP, and cleaved caspase-3 (another three ER stress related proteins) indicating that UPR could be triggered by Aβ treatment at an early stage (Zhou et al., 2016). Surprisingly, they confirmed that the increase in Bip, p-eIF2α, and p-JNK could be suppressed by pre-treatment with CDNF, suggesting that CDNF could alleviate UPR in ER stress and facilitate restoration of ER homeostasis (Apostolou et al., 2008; Palgi et al., 2009). Interestingly, they found that by pre-treatment with CDNF before Aβ exposure, CHOP (a well-known proapoptotic factor) was significantly upregulated (Zhou et al., 2016). This was further substantiated by other studies demonstrating that CHOP can prevent cell death and promote demyelination (Chen et al., 2012; Halterman et al., 2010; Southwood et al., 2002). In summary, CHOP should be regarded more broadly as a mediator of responses to stress rather than only a proapoptotic factor during different time windows (Zhou et al., 2016).

Since, it was demonstrated that synaptic proteins such as PSD95 or synapsin I decreased in hippocampus with tunicamycin-induced ER stress, it was hypothesized that ER stress is linked to synaptic dysfunction (Lin et al., 2014). All these results indicate that CDNF may play a protective role through distinct mecha-
nisms that has to be further investigated (Zhou et al., 2016). Revilla and colleagues (2014) reported a decline in spatial memory by using intra hippocampal protein CDNF in APP/PS1 mice modeling AD. Moreover, Wei et al. (2016) showed that CDNF could cause an Aβ-induced decrease in synaptic proteins such as PSD95 and synaptophysin. Thus, it has been suggested that CDNF may have a synapto-protective role during early Aβ treatment. In addition, gene therapy with CDNF showed the potential to improve long-term memory in APP/PS1 transgenic animals (Kemppainen et al., 2015). Kemppainen et al. (2015) reported that although long-term memory is improved by CDNF-therapy in one-year-old APP/PS1 mice, it was without evidence of a decline in amyloid load or hippocampal neurogenesis. In other words, spontaneous exploration, object neophobia, or early stages of spatial learning were not affected by intrahippocampal CDNF treatment (Lindahl et al., 2017; Zhou et al., 2016). Even though long-term memory is improved by intracranial CDNF treatment, the underlying mechanism still remains unknown and requires further attention (van der Harg et al., 2014; Zhou et al., 2016).

However, a number of studies demonstrated that in AD animal models, PERK (pancreatic ER kinase [PKR]-like ER kinase) phosphorylation can lead to activation of Aβ-producing β-secretase (BACE1), tau hyperphosphorylation, and, as a result, to memory impairment and neuronal loss (Ghemrawi and Khair, 2020; Hashimoto and Saido, 2018; Shacham et al., 2021). In animal studies, the connection between diabetes and AD has been demonstrated, while the rate of cognitive decline and age-related memory impairment in humans increased with decreased insulin-signaling (type 1 diabetes [T1D]) and insulin-resistance (type 2 diabetes [T2D]) (Muñoz-Jiménez et al., 2020; Shieh et al., 2020).

CONCLUSION

A direct link between impairments in NTFs generation and neurodegenerative pathogenesis has been demonstrated. Thus, in light of the above-mentioned data, NTF treatment may be a good candidate for delaying several neurodegenerative diseases such as AD. This review aimed to provide the pharmacological basis for clinical usage of NTFs in the prevention and treatment of AD.

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Neurotrophic factors and Alzheimer’s disease


