REVIEW

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Neurotrophic factors in Alzheimer's disease: pathogenesis and therapy

Joachim HR Lübke[1], Faezeh Idoon[2], Mina Mohasel-Roodi[2], Fatemeh Alipour[3], Javad Hami[2], Alireza Ehteshampour[4], Hamideh Mostafaee[2] and Akram Sadeghi[1,2]*

[1] Institute of Neuroscience and Medicine (INM-10), Research Centre Jülich GmbH, Germany,
[2] Department of Anatomy and Cell Biology, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran,
[3] Department of Anatomy and Cell Biology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran,
[4] Faculty of Nursing and Midwifery, University in Qhayen, Ghayen, South Khorasan Province, Iran,
** Email: a.sadeghi@fz-juelich.de*

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; Sampaio 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 (Razavi et al., 2015; Wei, 2016), 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

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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

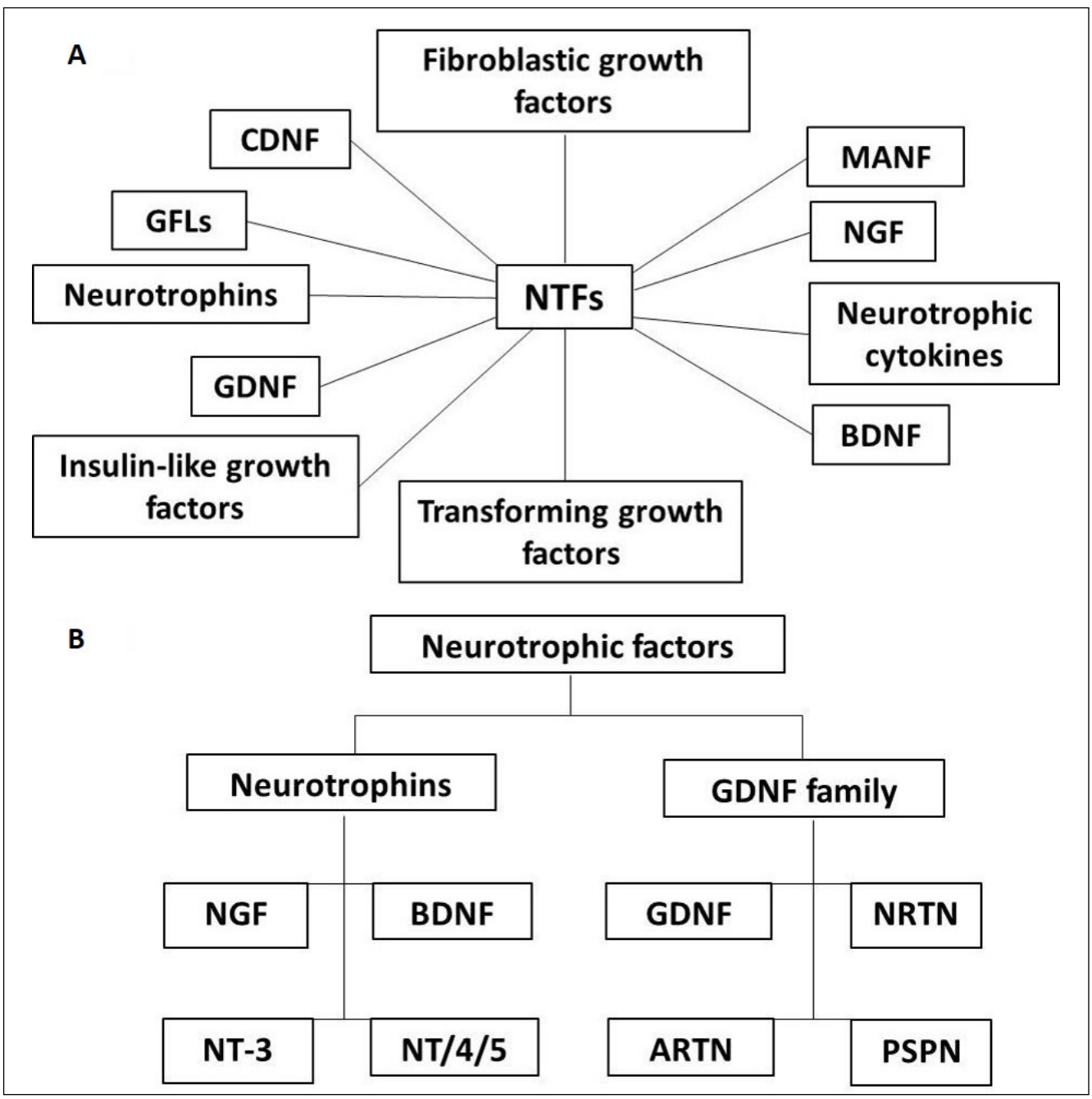

Fig. 1. Two different neurotrophic factor family classifications. (A) Neurotrophic factor (NTFs) FGF: fibroblast growth factors, CDNF: cerebral dopamine neurotrophic factor, GFLs: family ligands, IGFs: insulin-like growth factors, TGF: transforming growth factors, MANF: mesencephalic astrocyte-derived neurotrophic factor, NGF: nerve growth factor, BDNF: brain derived-neurotrophic factor. (B) NGF: nerve growth factor, BDNF: brain-derived neurotrophic factor, NT-3: neurotrophin 3, NT-4/5: neurotrophin 4/5, GDNF: glial derived neurotrophic factor family, NRTN: neurturin, artemin (ARTN), PSPN: persephin.

neurodegenerative diseases such as Alzheimer's disease (AD) (Budni et al., 2015). NTFs 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, deficiency 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 ϒ 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 $A\beta_{1-42}$ 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 $A\beta_{1-42}$ 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 (Romon 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 effector 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 (Sampaio 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)

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). Glycosil 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, PLCϒ, 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 PLCϒ, 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 Ca^{2+} ions is regulated by the PLCϒ 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 (Popsueva 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-

body, GDNF through NCAM signaling has an inhibitory effect on midbrain dopaminergic neurons (Chao et al., 2003). In some studies, an increased in wild-type PC migration has been reported with a reduction of NCAM expression (Sergaki and Ibáñez, 2017).

The best strategy remains a question: positive allosteric modulation of GFLs signaling or targeting RET, NCAM, or GFRα coreceptors? The potency and other properties of available molecules should be optimized. Moreover, extensive preclinical experiments are required to evaluate their safety. However, the druggable targets of GFL receptors have been proven. Despite promising preliminary data, many questions regarding the clinical translation of compounds targeting GFL receptors remain to be answered.

Brain derived neurotrophic factor and Alzheimer's disease

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; Rossor et al., 1982). The degeneration of both the glutamatergic and cholinergic systems are characteristic neuropathological 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 overexpression 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 Fahnestock, 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 $A\beta_{1-42}$ 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 peIF2α (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 intra hippocampal 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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REFERENCES

Abrous DN, Wojtowicz JM (2015) Interaction between neurogenesis and hippocampal memory system: new vistas. Cold Spring Harb Perspect Biol 7: a018952.

Airaksinen MS, Saarma M (2002) The GDNF family: signalling, biological functions and therapeutic value. Nat Rev Neurosci 3: 383–394.

Airaksinen MS, Titievsky A, Saarma M (1999) GDNF family neurotrophic factor signaling: four masters, one servant? Mol Cell Neurosci 13: 313–325.

Albert K, Airavaara M (2019) Neuroprotective and reparative effects of endoplasmic reticulum luminal proteins–mesencephalic astrocyte-derived neurotrophic factor and cerebral dopamine neurotrophic factor. Croat Med J 60: 99–108.

Allen SJ, Watson JJ, Shoemark DK, Barua NU, Patel NK (2013) GDNF, NGF and BDNF as therapeutic options for neurodegeneration. Pharmacol Ther 138: 155–175.

Aloe L, Rocco ML, Balzamino BO, Micera A (2015) Nerve growth factor: a focus on neuroscience and therapy. Curr Neuropharmacol 13: 294–303.

Alzheimer's Association (2016) 2016 Alzheimer's disease facts and figures. Alzheimers Dement 12: 459–509.

Amor S, Puentes F, Baker D, Valk PVR (2010) Inflammation in neurodegenerative diseases. Immunology 129: 154–169.

An Y, Zhang C, Siyu H, Yaho CX, Zhang L, Zhang Q (2008) Main hypotheses, concepts and theories in the study of Alzheimer's disease. Life Sci J 5: 1–5.

Andreasen N, Hesse, C, Davidsson P, Minthon L, Wallin A, Winblad B, Blennow K (1999) Cerebrospinal fluid beta-amyloid(1–42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. Arch Neurol 56: 673–680.

Andreassen CS, Jakobsen J, Flyvbjerg A, Andersen H (2009) Expression of neurotrophic factors in diabetic muscle relation to neuropathy and muscle strength. Brain 132: 2724–2733.

Apostolou A, Shen Y, Liang Y, Luo J, Fang S (2008) Armet, a UPR-upregulated protein, inhibits cell proliferation and ER stress-induced cell death. Exp Cell Res 314: 2454–2467.

Arancibia S, Silhol M, Mouliere F, Meffre J, Höllinger I, Maurice T, Tapia-Arancibia L (2008) Protective effect of BDNF against beta-amyloid induced neurotoxicity *in vitro* and *in vivo* in rats. Neurobiol Dis 31: 316–326.

Araujo DM, Lapchak PA, Robitaille Y, Gauthier S, Quirion R (1988) Differential alteration of various cholinergic markers in cortical and subcortical regions of human brain in Alzheimer's disease. J Neurochem 50: 1914–1923.

Armstrong RA (2009) The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease. Folia Neuropathol 47: 289–299.

Bai Y, Dergham P, Nedev H, Xu J, Galan A, Rivera JC, Saragovi HU (2010) Chronic and acute models of retinal neurodegeneration TrkA activity are neuroprotective whereas p75NTR activity is neurotoxic through a paracrine mechanism. J Biol Chem 285: 39392–39400.

Baloh RH, Tansey MG, Golden JP, Creedon DJ, Heuckeroth RO, Keck CL, Zimonjic DB, Popescu NC, Johnson EM Jr, Milbrandt J (1997) TrnR2, a novel receptor that mediates neurturin and GDNF signaling through Ret. Neuron 18: 793–802.

Barnett MW, Fisher CE, Perona-Wright G, Davies JA (2002) Signalling by glial cell line-derived neurotrophic factor (GDNF) requires heparan sulphate glycosaminoglycan. J Cell Sci 115: 4495–4503.

Bartus RT (2000) On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis. Exp Neurol 163: 495–529.

Biernacki K, Antel JP, Blain M, Narayanan S, Arnold DL, Prat Al (2005) Interferon beta promotes nerve growth factor secretion early in the course of multiple sclerosis. Arch Neurol 62: 563–568.

Bishop NA, Lu T, Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. Nature 464: 529.

Blurton-Jones M, Kitazawa M, Martinez-Coria H, Castello NA, Muller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM (2009) Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci USA 106: 13594–13599.

Bondareff W, Mountjoy CQ, Roth M, Hauser DL (1989) Neurofibrillary degeneration and neuronal loss in Alzheimer's disease. Neurobiol Aging 10: 709–715.

Bothwell M (1991) Tissue localization of nerve growth factor and nerve growth factor receptors. Curr Top Microbiol Immunol 165: 55–70.

Bothwell M (2016) Recent advances in understanding neurotrophin signaling. F1000Res 5: F1000.

Boyd JG, Gordon T (2003) Neurotrophic factors and their receptors in axonal regeneration and functional recovery after peripheral nerve injury. Mol Neurobiol 27: 277–323.

Budni J, Bellettini-Santos T, Mina F, Garcez ML, Zugno AI (2015) The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. Aging Dis 6: 331–341.

Cabeza C, Figueroa A, Lazo OM, Galleguillos C, Pissani C, Klein A, Gonzalez-Billault C, Inestrosa NC, Alvarez AR, Zanlungo S, Bronfman FC (2012) Cholinergic abnormalities, endosomal alterations and up-regulation of nerve growth factor signaling in Niemann-Pick type C disease. Mol Neurodegener 7: 11.

Cattaneo A, Calissano P (2012) Nerve growth factor and Alzheimer's disease: new facts for an old hypothesis. Mol Neurobiol 46: 588–604.

Chan JR, Watkins TA, Cosgaya JM, Zhang C, Chen L, Reichardt LF, Shooter EM, Barres BA (2004) NGF controls axonal receptivity to myelination by Schwann cells or oligodendrocytes. Neuron 43: 183–191.

Chao CC, Ma YL, Chu KY, Lee EY (2003) Integrin αv and NCAM mediate the effects of GDNF on DA neuron survival, outgrowth, DA turnover and motor activity in rats. Neurobiol Aging 24: 105–116.

Charoy C, Nawabi H, Reynaud F, Derrington E, Bozon M, Wright K, Falk J, Helmbacher F, Kindbeiter K, Castellani V (2012) gdnf activates midline repulsion by Semaphorin3B via NCAM during commissural axon guidance. Neuron 75: 1051–1066.

Chen CM, Wu CT, Chiang CK, Liao BW, Liu SH (2012) C/EBP homologous protein (CHOP) deficiency aggravates hippocampal cell apoptosis and impairs memory performance. PLoS One 7: e40801.

Chen W, Martindale JL, Holbrook NJ, Liu Y (1998) Tumor promoter arsenite activates extracellular signal-regulated kinase through a signaling pathway mediated by epidermal growth factor receptor and Shc. Mol Cell Biol 18: 5178–5188.

Chen XQ, Mobley WC (2019) Alzheimer disease pathogenesis: insights from molecular and cellular biology studies of oligomeric Aβ and tau species. Front Neurosci 13: 659.

Chen Y, Ai Y, Slevin JR, Maley BE, Gash DM (2005) Progenitor proliferation in the adult hippocampus and substantia nigra induced by glial cell line-derived neurotrophic factor. Exp Neurol 196: 87–95.

Cheng HC, Shih HM, Chern Y (2002) Essential role of cAMP-response element-binding protein activation by A2A adenosine receptors in rescuing the nerve growth factor-induced neurite outgrowth impaired by blockage of the MAPK cascade. J Biol Chem 277: 33930–33942.

Cheng YJ, Lin CH, Lane HY (2021) Involvement of cholinergic, adrenergic, and glutamatergic network modulation with cognitive dysfunction in Alzheimer's disease. Int J Mol Sci 22: 2283

Chiroma SM, Taib CNM, Moklas MAM, Baharuldin MTH, Amom Z, Jagadeesan S (2019) The use of nootropics in Alzheimer's disease: is there light at the end of the tunnel? Biom Res Ther 6: 2937–2944.

Ciaramella A, Salani F, Bizzoni F, Orfei MD, Langella R, Angelucci F, Spalletta G, Taddei AR, Caltagirone C, Bossù P (2013) The stimulation of dendritic cells by amyloid beta 1–42 reduces BDNF production in Alzheimer's disease patients. Brain Behav Immun 32: 29–32.

Colom-Cadena M, Spires-Jones T, Zetterberg H, Blennow K, Caggiano A, DeKosky ST, Fillit H, Harrison JE, Schneider LS, Scheltens P, Haan W, Grundman M, Dyck C H, Izzo N, Catalano SM (2020) The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. Alzheimers Res Ther 12: 21.

Colucci-D'Amato L, Speranza L, Volpicelli F (2020) Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci 21: 7777.

Connor B, Young D, Yan Q, Faull RLM, Synek B, Dragunow M (1997) Brain-derived neurotrophic factor is reduced in Alzheimer's disease. Brain Res Mol Brain Res 49: 71–81.

Costa RO, Ferreiro E, Oliveira CR, Pereira CMF (2013) Inhibition of mitochondrial cytochrome c oxidase potentiates Aβ-induced ER stress and cell death in cortical neurons. Mol Cell Neurosci 52: 1–8.

Cowan WM (2001) Viktor Hamburger and Rita Levi-Montalcini: the path to the discovery of nerve growth factor. Ann Rev Neurosci 24: 551–600.

Coyle JT, Price DL, Delong MR (1983) Alzheimer's disease: a disorder of cortical cholinergic innervation. Science 219: 1184–1190.

Criscuolo C, Fabiani C, Bonadonna C, Origlia N, Domenici L (2015) BDNF prevents amyloid-dependent impairment of LTP in the entorhinal cortex by attenuating p38 MAPK phosphorylation. Neurobiol Aging 36: 1303–1309.

Crowley C, Spencer SD, Nishimura MC, Chen KS, Pitts-Meek S, Armaninl MP, Ling LH, McMahon SB, Shelton DL, Levinson AD (1994) Mice lacking nerve growth factor display perinatal loss of sensory and sympathetic neurons yet develop basal forebrain cholinergic neurons. Cell 76: 1001–1011.

Berzaghi MDP, Cooper J, Castren E, Zafra F, Sofroniew M, Thoenen H, Lindholm D (1993) Cholinergic regulation of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) but not neurotrophin-3 (NT-3) mRNA levels in the developing rat hippocampus. J Neurosci 13: 3818–3826.

DaRocha-Souto B, Coma M, Pérez-Nievas BG, Scotton TC, Siao M, Sánchez-Ferrer P, Hashimoto T, Fan Z, Hudry E, Barroeta I, Serenó L, Rodríguez M, Sánchez MB, Hyman BT, Gómez-Isla T (2012) Activation of glycogen synthase kinase-3 beta mediates β-amyloid induced neuritic damage in Alzheimer's disease. Neurobiol Dis 45: 425–437.

Deinhardt K, Chao MV (2014) Trk receptors. Handb Exp Pharmacol 220: 103–19

Del Río P, Irmler M, Arango-González B, Favor J, Bobe C Bartsch, U, Vecino E, Beckers J, Hauck SM, Ueffing M (2011) GDNF-induced osteopontin from Müller glial cells promotes photoreceptor survival in the Pde6brd1 mouse model of retinal degeneration. Glia 59: 821–832.

Deponti D, Buono R, Catanzaro G, De Palma C, Longhi R, Meneveri R, Bresolin N, Bassi MT, Cossu G, Clementi E, Brunelli S (2009) The low-affinity receptor for neurotrophins p75NTR plays a key role for satellite cell function in muscle repair acting via RhoA. Mol Biol Cell 20: 3620–3627.

Devi L, Ohno M (2014) PERK mediates eIF2α phosphorylation responsible for BACE1 elevation, CREB dysfunction and neurodegeneration in a mouse model of Alzheimer's disease. Neurobiol Aging 35: 2272–2281.

Domanskyi A, Saarma M, Airavaara M (2015) Prospects of neurotrophic factors for Parkinson's disease: comparison of protein and gene therapy. Hum Gene Ther 26: 550–559.

Dong S, Duan Y, Hu Y, Zhao Z (2012) Advances in the pathogenesis of Alzheimer's disease: a re-evaluation of amyloid cascade hypothesis. Transl Neurodegener 1: 18.

Du X, Wang X, Geng M (2018) Alzheimer's disease hypothesis and related therapies. Transl Neurodegener 7: 2.

Eizirik DL, Cardozo AK, Cnop M (2007) The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev 29: 42–61.

Elliott E, Atlas R, Lange A, Ginzburg I (2005) Brain-derived neurotrophic factor induces a rapid dephosphorylation of tau protein through a PI-3Kinase signalling mechanism. Eur J Neurosci 22: 1081–1089.

Fan L, Mao C, Hu X, Zhang S, Yang Z, Hu Z, Sun H, Fan Y, Dong Y, Yang J, Shi C, Xu Y (2019) New insights into the pathogenesis of Alzheimer's disease. Front Neurol 10: 1312.

Faria MC, Gonçalves GS, Rocha NP, Moraes EN, Bicalho MA, Gualberto Cintra MT, Jardim de Paula J, José Ravic de Miranda LF, Clayton de Souza Ferreira A, Teixeira AL, Gomes KB, Carvalho MG, Sousa LP (2014) Increased plasma levels of BDNF and inflammatory markers in Alzheimer's disease. J Psychiatr Res 53: 166–172.

Feng Y, Wang X (2012) Antioxidant therapies for Alzheimer's disease. Oxid Med Cell Longev 2012: 472932.

Ferreira D, Westman E, Eyjolfsdottir H, Almqvist P, Lind G, Linderoth B, Seiger A, Blennow K, Karami A, Darreh-Shori T, Wiberg M, Simmons A, Wahlund LO, Wahlberg L, Eriksdotter M (2015) Brain changes in Alzheimer's disease patients with implanted encapsulated cells releasing nerve growth factor. J Alzheimers Dis 43: 1059–1072.

Francis PT, Palmer AM, Snape M, Wilcock GK (1999) The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry 66: 137–147.

Fukuda T, Kiuchi K, Takahashi M (2002) Novel mechanism of regulation of Rac activity and lamellipodia formation by RET tyrosine kinase. J Biol Chem 277: 19114–19121.

Garcia-Alloza M, Robbins EM, Zhang-Nunes X, Purcell SM, Betensky RA, Raju S, Prada C, Greenberg SM, Bacskai BJ, Frosch MP (2006) Characterization of amyloid deposition in the APPswe/PS1dE9 mouse model of Alzheimer disease. Neurobiol Dis 24: 516–524.

Garzon DJ, Fahnestock M (2007) Oligomeric amyloid decreases basal levels of brain-derived neurotrophic factor (BDNF) mRNA via specific downregulation of BDNF transcripts IV and V in differentiated human neuroblastoma cells. J Neurosci 27: 2628–2635.

Gella A, Durany N (2009) Oxidative stress in Alzheimer disease. Cell Adh Migr 3: 88–93.

Géral C, Angelova A, Lesieur S (2013) From molecular to nanotechnology strategies for delivery of neurotrophins: emphasis on brain-derived neurotrophic factor (BDNF). Pharmaceutics 5: 127–167.

Ghemrawi R, Khair M (2020) Endoplasmic reticulum stress and unfolded protein response in neurodegenerative diseases. Int J Mol Sci 21: 6127.

Gill SS, Patel NK, Hotton GR, O'Sullivan K, McCarter R, Bunnage M, Brooks DJ, Svendsen CN, Heywood P (2003) Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 9: 589–595.

Gralle M, Botelho MG, Wouters FS (2009) Neuroprotective secreted amyloid precursor protein acts by disrupting amyloid precursor protein dimers. J Biol Chem 284: 15016–15025.

Halterman MW, Gill M, DeJesus C, Ogihara M, Schor NF, Federoff HJ (2010) The endoplasmic reticulum stress response factor CHOP-10 protects against hypoxia-induced neuronal death. J Biol Chem 285: 21329–21340.

Hamanoue M, Middleton G, Wyatt S, Jaffray E, Hay RT, Davies AM (1999) p75-mediated NF-κB activation enhances the survival response of developing sensory neurons to nerve growth factor. Mol Cell Neurosci 14: 28–40.

Harrington AW, Kim JY, Yoon Sk (2002) Activation of Rac GTPase by p75 is necessary for c-jun N-terminal kinase-mediated apoptosis. J Neurosci 22: 156–166.

Hashimoto S, Saido TC (2018) Critical review: involvement of endoplasmic reticulum stress in the aetiology of Alzheimer's disease. Open Biol 8: 180024.

Heneka MT, Kummer MP, Latz E (2014) Innate immune activation in neurodegenerative disease. Nature Rev Immunol 14: 463.

Hibbert AP, Kramer BMR, Miller FD, Kaplan DR (2006) The localization, trafficking and retrograde transport of BDNF bound to p75NTR in sympathetic neurons. Mol Cell Neurosci 32: 387–402.

Holback S, Adlerz L, Iverfeldt K (2005) Increased processing of APLP2 and APP with concomitant formation of APP intracellular domains in BDNF and retinoic acid-differentiated human neuroblastoma cells. J Neurochem 95: 1059–1068.

Hoozemans JJM, Van H, Elise S, Nijholt DAT, Rozemuller AJM, Scheper W (2012) Activation of the unfolded protein response is an early event in Alzheimer's and Parkinson's disease. Neurodegener Dis 10: 212–215.

Hsiao YH, Hung HCh, Chen ShH, Gean PW (2014) Social interaction rescues memory deficit in an animal model of Alzheimer's disease by increasing BDNF-dependent hippocampal neurogenesis. J Neurosci 34: 16207–16219.

Ibáñez CF, Andressoo JO (2017) Biology of GDNF and its receptors – Relevance for disorders of the central nervous system. Neurobiol Dis 97: 80–89.

Iqbal K, Liu F, Gong CX, Alonso Adel C, Grundke-Iqbal I (2009) Mechanisms of tau-induced neurodegeneration. Acta Neuropathol 118: 53–69.

Islam O, Loo TX, Heese K (2009) Brain-derived neurotrophic factor (BDNF) has proliferative effects on neural stem cells through the truncated TRK-B receptor, MAP kinase, AKT, and STAT-3 signaling pathways. Curr Neurovasc Res 6: 42–53.

Iulita MF, Cuello AC (2014) Nerve growth factor metabolic dysfunction in Alzheimer's disease and Down syndrome. Trends Pharmacol Sci 35: 338–348.

Iulita MF, Cuello AC (2016) The NGF metabolic pathway in the CNS and its dysregulation in Down syndrome and Alzheimer's disease. Curr Alzheimer Res 13: 53–67.

Ji Y, Lu Y, Yang F, Shen W, Tang TTT, Feng L, Duan Sh, Lu B (2010) Acute and gradual increases in BDNF concentration elicit distinct signaling and functions in neurons. Nat Neurosci 13: 302.

Jing LIU, Anning LIN (2005) Role of JNK activation in apoptosis: a double-edged sword. Cell Res 15: 36.

Karran E, Mercken M, Strooper DB (2011) The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Discov 10: 698–712.

Kemppainen Su, Lindholm P, Galli E, Lahtinen HM, Koivisto H, Hämäläinen E, Saarma M, Heikki T (2015) Cerebral dopamine neurotrophic factor improves long-term memory in APP/PS1 transgenic mice modeling Alzheimer's disease as well as in wild-type mice. Behav Brain Res 291: 1–11.

Kim GH, Kim JE, Rhie SJ, Yoon S (2015) The role of oxidative stress in neurodegenerative diseases. Exp Neurobiol 24: 325–340.

Kitiyanant N, Kitiyanant Y, Svendsen CN, Thangnipon W (2012) BDNF-, IGF-1-and GDNF-secreting human neural progenitor cells rescue amyloid β-induced toxicity in cultured rat septal neurons. Neurochem Res 37: 143–152.

Kolomeyer AM, Zarbin MA (2014) Trophic factors in the pathogenesis and therapy for retinal degenerative diseases. Surv Ophthalmol 59: 134–165.

Konishi Y, Yang LB, He P, Lindholm K, Lu B, Li R, Shen Y (2014) Deficiency of GDNF Receptor GFRα1 in Alzheimer's neurons results in neuronal death. J Neurosci 34: 13127–13138.

Kurokawa K, Iwashita T, Murakami H, Hayashi Hi, Kawai K, Takahashi M (2001) Identification of SNT/FRS2 docking site on RET receptor tyrosine kinase and its role for signal transduction. Oncogene 20: 1929.

Lanni C, Stanga S, Racchi M, Govoni S (2010) The expanding universe of neurotrophic factors: therapeutic potential in aging and age-associated disorders. Curr Pharm Des 16: 698–717.

Lattanzio F, Carboni L, Carretta D, Rimondini R, Candeletti S, Romualdi P (2014) Human apolipoprotein E4 modulates the expression of Pin1, Sirtuin 1, and Presenilin 1 in brain regions of targeted replacement apoE mice. Neuroscience 256: 360–369.

Ledda F, Paratcha G (2016) Assembly of neuronal connectivity by neurotrophic factors and leucine-rich repeat proteins. Front Cell Neurosci 10: 199.

Ledda F, Paratcha G, Ibáñez CF (2002) Target-derived GFRα1 as an attractive guidance signal for developing sensory and sympathetic axons via activation of Cdk5. Neuron 36: 387–401.

Lee KF, Davies M, Jaenisch R (1994) p75-deficient embryonic dorsal root sensory and neonatal sympathetic neurons display a decreased sensitivity to NGF. Development 120: 1027–1033.

Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294: 1945–1948.

Li Y, Yui D, Luikart BW, McKay RM, Li Y, Rubenstein John L, Parada LF (2012) Conditional ablation of brain-derived neurotrophic factor-TrkB signaling impairs striatal neuron development. Proc Natl Acad Sci USA 109: 15491–15496.

Lin LF, Doherty DH, Lile J D, Bektesh S, Collins F (1993) GDNF: a glial cell line-derived neurotrophic factor for midbrain dopaminergic neurons. Science 260: 1130–1132.

Lin Li, Yang S, Chu J, Wang L, Ning LN, Zhang T, Jiang Q, Wang JZh (2014) Region-specific expression of tau, amyloid-β protein precursor, and synaptic proteins at physiological condition or under endoplasmic reticulum stress in rats. J Alzheimers Dis 41: 1149–1163.

Lindahl M, Saarma M, Lindholm P (2017) Unconventional neurotrophic factors CDNF and MANF: Structure, physiological functions and therapeutic potential. Neurobiol Dis 97: 90–102.

Lindahl M, Danilova T, Palm E, Lindholm P, Võikar V, Hakonen E, Ustinov J, Andressoo JO, Brandon KH, Otonkoski T, Rossi J, Saarma M (2014) MANF is indispensable for the proliferation and survival of pancreatic β cells. Cell Rep 7: 366–375.

Lindahl M, Saarma M, Lindholm P (2017) Unconventional neurotrophic factors CDNF and MANF: structure, physiological functions and therapeutic potential. Neurobiol Dis 97: 90–102.

Lipton SA (1989) Growth factors for neuronal survival and process regeneration: implications in the mammalian central nervous system. Arch Neurol 46: 1241–1248.

Liu PP, Xie Y, Meng XY, Kang JS (2019) History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduct Target Ther 4: 29.

Lomb J, Desouza LA, Franklin JL, Freeman RS (2009) Prolyl hydroxylase inhibitors depend on extracellular glucose and hypoxia-inducible factor (HIF)-2α to inhibit cell death caused by nerve growth factor (NGF) deprivation: evidence that HIF-2α has a role in NGF-promoted survival of sympathetic neurons. Mol Pharmacol 75: 1198–1209.

Lu, B, Nagappan G, Lu Y (2014) BDNF and synaptic plasticity, cognitive function, and dysfunction. Handb Exp Pharmacol 220: 223–50.

Lu B, Nagappan G, Guan X, Nathan PJ, Wren P (2013) BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nat Rev Neurosci 14: 401–416.

Mahata SK, Mahata M, Wu H, Parmer RJ, O'Connor DT (1999) Neurotrophin activation of catecholamine storage vesicle protein gene expression: signaling to chromogranin a biosynthesis. Neuroscience 88: 405–424.

Mann DMA (1983) The locus coeruleus and its possible role in ageing and degenerative disease of the human central nervous system. Mech Ageing Dev 23: 73–94.

Marksteiner J, Kemmler G, Weiss EM, Knaus G, Ullrich C, Mechtcheriakov S, Oberbauer H, Auffinger S, Hinterhölzl J, Hinterhuber H, Humpel Ch (2011) Five out of 16 plasma signaling proteins are enhanced in plasma of patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging 32: 539–540.

Meng Ch, He Zh, Xing D (2013) Low-level laser therapy rescues dendrite atrophy via upregulating BDNF expression: implications for Alzheimer's disease. J Neurosci 33: 13505–13517.

Michalski B, Fahnestock M (2003) Pro-brain-derived neurotrophic factor is decreased in parietal cortex in Alzheimer's disease. Mol Brain Res 111: 148–154.

Milbrandt J, de Sauvage FJ, Fahrner TJ, Baloh RH, Leitner, Melanie L, Tansey MG, Lampe PA, Heuckeroth RO, Kotzbauer PT, Simburger KS, Golden JP, Davies JA, Vejsada R, Kato AC, Hynes M, Sherman D, Nishimura M, Wang LC, Vandlen R, Moffat B, Klein RD, Poulsen K, Gray C, Garces A, Johnson Jr EM (1998) Persephin, a novel neurotrophic factor related to GDNF and neurturin. Neuron 20: 245–253.

Minichiello L (2009) TrkB signalling pathways in LTP and learning. Nat Rev Neurosci 10: 850.

Mitra S, Behbahani H, Eriksdotter M (2019) Innovative therapy for Alzheimer's disease-with focus on biodelivery of NGF. Front Neurosci 13: 38.

Mologni L (2011) Development of RET kinase inhibitors for targeted cancer therapy. Curr Med Chem 18: 162–175.

Monteggia LM, Barrot M, Powell CM, Berton Ol, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ (2004) Essential role of brain-derived neurotrophic factor in adult hippocampal function. Proc Natl Acad Sci USA 101: 10827–10832.

Muñoz-Jiménez M, Zaarkti A, García-Arnés JA, García-Casares N (2020) Antidiabetic drugs in Alzheimer's disease and mild cognitive impairment: a systematic review. Dement Geriatr Cogn Disord 49: 423–434.

Murer MG, Boissiere F, Yan Q, Hunot S, Villares J, Faucheux B, Agid Y, Hirsch E, Raisman-Vozari R (1999) An immunohistochemical study of the distribution of brain-derived neurotrophic factor in the adult human brain, with particular reference to Alzheimer's disease. Neuroscience 88: 1015–1032.

Murer MG, Yan Q, Raisman-Vozari R (2001) Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. Prog Neurobiol 63: 71–124.

Murphy KE, Park JJ (2017) Can co-activation of Nrf2 and neurotrophic signaling pathway slow Alzheimer's disease? Int J Mol Sci 18: 1168.

Murray KD, Gall CM, Jones EG, Isackson PJ (1994) Differential regulation of brain-derived neurotrophic factor and type II calcium/calmodulin-dependent protein kinase messenger RNA expression in Alzheimer's disease. Neuroscience 60: 37–48.

Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, Wang L, Blesch A, Kim A, Conner JM, Rockenstein E, Chao MV, Koo EH, Geschwind D, Masliah E, Chiba AA, Tuszynski MH (2009) Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nat Med 15: 331.

Niikura T, Tajima H, Kita Y (2006) Neuronal cell death in Alzheimer's disease and a neuroprotective factor, humanin. Curr Neuropharmacol 4: 139–147.

Oh YT, Yue P, Zhou W, Balko JM, Black EP, Owonikoko TK, Khuri FR, Sun SY (2012) Oncogenic Ras and B-Raf proteins positively regulate death receptor 5 expression through co-activation of ERK and JNK signaling. J Biol Chem 287: 257–267.

Overk CR, Masliah E (2014) Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease. Biochem Pharmacol 88: 508–516.

Palgi M, Lindstrom R, Peranen J, Piepponen TP, Saarma M, Heino TI (2009) Evidence that DmMANF is an invertebrate neurotrophic factor supporting dopaminergic neurons. Proc Natl Acad Sci USA 106: 2429–2434.

Pamphlett R (2014) Uptake of environmental toxicants by the locus ceruleus: a potential trigger for neurodegenerative, demyelinating and psychiatric disorders. Med Hypotheses 82: 97–104.

Paratcha G, Ibáñez CF (2002) Lipid rafts and the control of neurotrophic factor signaling in the nervous system: variations on a theme. Curr Opin Neurobiol 12: 542–549.

Paratcha G, Ledda F, Ibáñez CF (2003) The neural cell adhesion molecule NCAM is an alternative signaling receptor for GDNF family ligands. Cell 113: 867–879.

Pardridge WM (2010) Biopharmaceutical drug targeting to the brain. J Drug Target 18: 157–167.

Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW (1991) BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 7: 695–702.

Poon WW, Carlos AJ, Aguilar BL, Berchtold NC, Kawano CK, Zograbyan V, Yaopruke T, Shelanski M, Cotman CW (2013) β-Amyloid (Aβ) oligomers impair brain-derived neurotrophic factor retrograde trafficking by down-regulating ubiquitin C-terminal hydrolase, UCH-L1. J Biol Chem 288: 16937–16948.

Popsueva A, Poteryaev D, Arighi E, Meng X, Angers-Loustau A, Kaplan D, Saarma M, Sariola H (2003) GDNF promotes tubulogenesis of GFRα1-expressing MDCK cells by Src-mediated phosphorylation of Met receptor tyrosine kinase. J Cell Biol 161: 119–129.

Pöyhönen S, Er S, Domanskyi A, Airavaara M (2019) Effects of neurotrophic factors in glial cells in the central nervous system: expression and properties in neurodegeneration and injury. Front Physiol 10: 486.

Ramser EM, Gan KJ, Decker H, Fan EY, Suzuki MM, Ferreira ST, Silverman MA (2013) Amyloid-β oligomers induce tau-independent disruption of BDNF axonal transport via calcineurin activation in cultured hippocampal neurons. Mol Biol Cell 24: 2494–2505.

Razavi S, Ghasemi N, Mardani M, Esfandiari E, Salehi H, Zarkesh Esfahani SH (2015) Neurotrophic factors and their effects in the treatment of multiple sclerosis. Adv Biomed Res 4: 53.

Revilla S, Ursulet S, Álvarez-López MJ, Castro-Freire M, Perpiñá U, García-Mesa Y, Bortolozzi A, Giménez-Llort L, Kaliman P, Cristòfol R, Sarkis Ch, Sanfeliu C (2014) Lenti-GDNF gene therapy protects against Alzheimer's disease-like neuropathology in 3xTg-AD mice and MC65 cells. CNS Neurosci Ther 20: 961–972.

Rhee KD, Goureau O, Chen S, Yang XJ (2004) Cytokine-induced activation of signal transducer and activator of transcription in photoreceptor precursors regulates rod differentiation in the developing mouse retina. J Neuroscience 24: 9779–9788.

Rohe M, Synowitz M, Glass R, Paul SM, Nykjaer A, Willnow TE (2009) Brain-derived neurotrophic factor reduces amyloidogenic processing through control of SORLA gene expression. J Neurosci 29: 15472–15478.

Romon R, Adriaenssens E, Lagadec Ch, Germain E, Hondermarck H, Bourhis XL (2010) Nerve growth factor promotes breast cancer angiogenesis by activating multiple pathways. Mol Cancer 9: 157.

Rosa E, Fahnestock M (2015) CREB expression mediates amyloid β-induced basal BDNF downregulation. Neurobiol Aging 36: 2406–2413.

Rösch H, Schweigreiter R, Bonhoeffer T, Barde YA, Korte Martin (2005) The neurotrophin receptor p75NTR modulates long-term depression and regulates the expression of AMPA receptor subunits in the hippocampus. Proc Natl Acad Sci 102: 7362–7367.

Rossor MN, Garrett NJ, Johnson AL, Mountjoy CQ, Roth M, Iversen LL (1982) A post-mortem study of the cholinergic and GABA systems in senile dementia. Brain 105: 313–330.

Rudelli RD, Ambler MW, Wisniewski HM (1984) Morphology and distribution of Alzheimer neuritic (senile) and amyloid plaques in striatum and diencephalon. Acta Neuropathol 64: 273–281.

Saarma M, Sariola H (1999) Other neurotrophic factors: Glial cell line-derived neurotrophic factor (GDNF). Microsc Res Tech 45: 292–302.

Sajjad R, Arif R, Shah AA, Manzoor I, Mustafa G (2018) Pathogenesis of Alzheimer's disease: role of amyloid-beta and hyperphosphorylated tau protein. Indian J Pharm Sci 80: 581–591.

Sampaio TB, Savall AS, Gutierrez MEZ, Pinton S (2017) Neurotrophic factors in Alzheimer's and Parkinson's diseases: implications for pathogenesis and therapy. Neural Regen Res 12: 549–557.

Sandhya VK, Raju R, Verma R, Advani J, Sharma R, Radhakrishnan A, Nanjappa V, Narayana J, Somani BL, Mukherjee KK, Pandey A, Christopher, Keshava Prasad TS (2013) A network map of BDNF/TRKB and BDNF/p75NTR signaling system. J Cell Commun Signal 7: 301–307.

Santoro M, Melillo RM, Carlomagno F, Vecchio G, Fusco A (2004) Minireview: RET: normal and abnormal functions. Endocrinology 145: 5448–5451.

Sariola H, Saarma M (2003) Novel functions and signalling pathways for GDNF. J Cell Sci 116: 3855–3862.

Sayre LM, Perry G, Smith MA (2008) Oxidative stress and neurotoxicity. Chem Res Toxicol 21: 172–188.

Sergaki MC, Ibáñez CF (2017) GFRα1 regulates Purkinje cell migration by counteracting NCAM function. Cell Rep 18: 367–379.

Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1: a006189.

Shacham T, Patel C, Lederkremer GZ (2021) PERK pathway and neurodegenerative disease: to inhibit or to activate? Biomolecules 11: 354.

Shieh JC, Huang PT, Lin YF (2020) Alzheimer's Disease and diabetes: insulin signaling as the bridge linking two pathologies. Mol Neurobiol 57: 1966–1977.

Sidorova YA, Saarma M (2016) Glial cell line-derived neurotrophic factor family ligands and their therapeutic potential. Mol Biol 50: 521–531.

Siegel GJ, Chauhan NB (2000) Neurotrophic factors in Alzheimer's and Parkinson's disease brain. Brain Res Rev 33: 199–227.

Singh SK, Srivastav S, Yadav AK, Srikrishna S, Perry G (2016) Overview of Alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic and herbal compounds. Oxid Med Cell Longev 2016: 7361613.

Song JH, Yu JT, Tan L (2015) Brain-derived neurotrophic factor in Alzheimer's disease: risk, mechanisms, and therapy. Mol Neurobiol 52: 1477–1493.

Southwood CM, Garbern J, Jiang W, Gow A (2002) The unfolded protein response modulates disease severity in Pelizaeus-Merzbacher disease. Neuron 36: 585–596.

Tanila H (2017) The role of BDNF in Alzheimer's disease. Neurobiol Dis 97: 114–118.

Tansey MG, Baloh RH, Milbrandt J, Johnson Jr, Eugene M (2000) GFRα-mediated localization of RET to lipid rafts is required for effective downstream signaling, differentiation, and neuronal survival. Neuron 25: 611–623.

Tenenbaum L, Humbert-Claude M (2017) Glial cell line-derived neurotrophic factor gene delivery in Parkinson's disease: a delicate balance between neuroprotection, trophic effects, and unwanted compensatory mechanisms. Fron Neuroant 11: 29.

Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25: 5455–5463.

Traver S, Marien M, Martin E, Hirsch EC, Michel PP (2006) The phenotypic differentiation of locus ceruleus noradrenergic neurons mediated by brain-derived neurotrophic factor is enhanced by corticotropin releasing factor through the activation of a cAMP-dependent signaling pathway. Mol Pharmacol 70: 30–40.

Trupp M, Arenas E, Fainzilber M, Nilsson AS, Sieber BA, Grigoriou M, Kilkenny C, Salazar-Grueso E, Pachnis V, Arumäe U, Sariola H, Saarma M, Ibáñez CF (1996) Functional receptor for GDNF encoded by the c-ret proto-oncogene. Nature 381: 785–789.

Tsui-Pierchala BA, Encinas M, Milbrandt J, Johnson Jr, Eugene M (2002) Lipid rafts in neuronal signaling and function. Trends Neurosci 25: 412–417.

Tucker BA, Rahimtula M, Mearow KM (2008) Src and FAK are key early signalling intermediates required for neurite growth in NGF-responsive adult DRG neurons. Cell Signal 20: 241–257.

Tuszynski MH, Yang JH, Barba D, Hoi-Sang U, Bakay RAE, Pay MM, Masliah E, Conner JM, Kobalka P, Roy, Nagahara AH (2015) Nerve growth factor gene therapy: activation of neuronal responses in Alzheimer disease. JAMA Neurol 72: 1139–1147.

Van der Harg JM, Nolle A, Zwart R, Boerema AS, van Haastert ES, Strijkstra AM, Hoozemans JJM, Scheper W (2014) The unfolded protein response mediates reversible tau phosphorylation induced by metabolic stress. Cell Death Dis 5: e1393.

Villoslada P, Hauser SL, Bartke I, Unger J, Heald N, Rosenberg D, Cheung SW, Mobley WC, Fisher S, Genain CP (2000) Human nerve growth factor protects common marmosets against autoimmune encephalomyelitis by switching the balance of T helper cell type 1 and 2 cytokines within the central nervous system. J Exp Med 191: 1799–1806.

Wan G, Gómez-Casati ME, Gigliello AR, Liberman MC, Corfas G (2014) Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma. Elife 3: e03564.

Wang H, Wang R, Thrimawithana T, Little PJ, Xu J, Feng ZP, Zheng W (2014) The nerve growth factor signaling and its potential as therapeutic target for glaucoma. Biomed Res Int 2014: 759473.

Wang H, Zhou X, Huang J, MU N, Guo Z, Wen Q, Wang R, Chen S, Feng ZP, Zheng W (2013) The role of Akt/FoxO3a in the protective effect of venlafaxine against corticosterone-induced cell death in PC12 cells. Psychopharmacology 228: 129–141.

Wang J, Hu WW, Jiang Z, Feng MJ (2020) Advances in treatment of neurodegenerative diseases: Perspectives for combination of stem cells with neurotrophic factors. World J Stem Cells 12: 323–338.

Wang L, Wang Z, Zhu R, Bi J, Feng X, Liu W, Wu J, Zhang H, Wu H, Kong W, Yu B, Yu X (2017) Therapeutic efficacy of AAV8-mediated intrastriatal delivery of human cerebral dopamine neurotrophic factor in 6-OHDA-induced parkinsonian rat models with different disease progression. PloS One 12: e0179476.

Wang X, Wang W, Li L, Perry G, Lee HG, Zhu X (2014) Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. Biochim Biophys Acta 1842: 1240–1247.

Wang Zh, Liu Y, Takahashi M, Van Hook K, Sheppard KM, Sheppard BC, Sears RC, Stork Ph, Lopez Ch (2013) N terminus of ASPP2 binds to Ras and enhances Ras/Raf/MEK/ERK activation to promote oncogene-induced senescence. Proc Natl Acad Sci USA 110: 312–317.

Wei S (2016) Potential therapeutic action of natural products from traditional Chinese medicine on Alzheimer's disease animal models targeting neurotrophic factors. Fundam Clin Pharmacol 30: 490–501.

Xia YP, Dai RL, Li YN, Mao L, Xue YM, He QW, Hung M, Hu B (2012) The protective effect of sonic hedgehog is mediated by the phosphoinositide [corrected] 3-kinase/AKT/Bcl-2 pathway in cultured rat astrocytes under oxidative stress. Neuroscience 209: 1–11.

Xu L, Zhou S, Feng GY, Zhang LP, Zhao DM, Sun Y, Lio Q, Huang F (2012) Neural stem cells enhance nerve regeneration after sciatic nerve injury in rats. Mol Neurobiol 46: 265–274.

Yang C, Liu Y, Ni X, Li N, Zhang B, Fang X (2014) Enhancement of the nonamyloidogenic pathway by exogenous NGF in an Alzheimer transgenic mouse model. Neuropeptides 48: 233–238.

Yatin SM, Varadarajan S, Link CD, Butterfield DA (1999) *In vitro* and *in vivo* oxidative stress associated with Alzheimer's amyloid beta-peptide (1–42) Neurobiol Aging 20: 325–330.

Zarow C, Lyness SA, Mortimer JA, Chui HC (2003) Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol 60: 337–341.

Zheng Z, Sabirzhanov B, Keifer J (2010) Oligomeric amyloid-β inhibits the proteolytic conversion of brain-derived neurotrophic factor (BDNF), AMPA receptor trafficking, and classical conditioning. J Biol Chem 285: 34708–34717.

Zhou W, Chang L, Fang Y, Du Z, Li Y, Song Y, Hao F, Wu Y (2016) Cerebral dopamine neurotrophic factor alleviates Aβ25–35-induced endoplasmic reticulum stress and early synaptotoxicity in rat hippocampal cells. Neurosci Lett 633: 40–46.

Zuccato C, Cattaneo E (2009) Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol 5: 311–322.