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INVITED REVIEW

Neurotrophic factors in Alzheimer's and Parkinson's diseases: implications for pathogenesis and therapy

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Abstract
Neurotrophic factors comprise essential secreted proteins that have several functions in neural and non-neural tissues, mediating the development, survival and maintenance of peripheral and central nervous system. Therefore, neurotrophic factor issue has been extensively investigated into the context of neurodegenerative diseases. Alzheimer's disease and Parkinson's disease show changes in the regulation of specific neurotrophic factors and their receptors, which appear to be critical for neuronal degeneration. Indeed, neurotrophic factors prevent cell death in degenerative processes and can enhance the growth and function of affected neurons in these disorders. Based on recent reports, this review discusses the main findings related to the neurotrophic factor support – mainly brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor – in the survival, proliferation and maturation of affected neurons in Alzheimer's disease and Parkinson's disease as well as their putative application as new therapeutic approach for these diseases management.

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Introduction
Neurodegenerative disorders are debilitating conditions that have an increased incidence with the aging of population. Alzheimer's (AD) and Parkinson's diseases (PD) are the most common neurodegenerative disturbances. Several biochemical and molecular mechanisms are involved in the AD and PD pathogenesis, such as synaptic dysfunction, neurotrophic impairment, energetic deficit triggered by mitochondrial disorder, oxidative stress and neuroinflammation (O'Brien and Wong, 2011; Serrano-Pozo et al., 2011; Mack et al., 2016).

AD is characterized by a progressive cognitive decline due to a variety of pathological changes in the brain, mainly in the basal forebrain cholinergic neurons (O'Brien and Wong, 2011; Serrano-Pozo et al., 2011). On the other hand, PD is classically known as a chronic and progressive movement disorder related to dopaminergic neurodegeneration of the substantia nigra pars compacta (Gao and Wu, 2016; Hirsch et al., 2016). In both illness, neurotrophic factors play an essential role for the survival of neurons affected by degenerative processes (Bothwell, 2016; Ibanez and Andressoo, 2017).

The alterations in the regulation of specific neurotrophic factors and their receptors seem to be involved in the neurodegeneration. Neurotrophic factors prevent the cell death and support the neuronal proliferation and maturation, enhancing the growth and function of affected neurons in AD and PD (Connor and Dragunow, 1998; Sullivan and O'Keeffe, 2016).

The current therapies for AD and PD focus on managing symptoms and fail to prevent further neurodegeneration. In this way, the neurotrophic factors employment emerged as a therapeutic promise in preclinical models of these disorders. However, their effectiveness in clinical studies remains unclear (Pramanik et al., 2016; Sullivan and O'Keeffe, 2016).

Therefore, this review discusses the main findings related to the neurotrophic factor support in the survival, proliferation and maturation of affected neurons in AD and PD, such as cholinergic and dopaminergic neurons, as well as their putative employment as new therapeutic strategy for management of these diseases.

Neurotrophic Factors
Neurotrophic factors comprise essential secreted proteins that have several functions in neural and non-neural tissues, mediating the development, survival and maintenance of peripheral and central nervous system (Bothwell, 2016). These pleiotropic molecules play critical roles both in the neuronal development and neural plasticity during the adulthood (Vilar and Mira, 2016), including the establishment of appropriate contacts with specific target cells through of the axonal growth and guidance control, dendrite development and synaptic plasticity (Ledda and Paratcha, 2016).

Currently, neurotrophic factors can be grouped in three major families: neurotrophins, glial cell line-derived neurotrophic factor (GDNF) family of ligands (GFLs) and neurokines (Bothwell, 2014; Ibanez and Andressoo, 2017). Moreover, unconventional neurotrophic factors, such as cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor (MANF), have been studied (Lindahl et al., 2017).

The nerve growth factor (NGF), a protein necessary for the survival and development of peripheral nervous system, was the first discovered member of the neurotrophin family (Levi-Montalcini and Angeletti, 1963). In mammals, this family comprises four structurally-related neurotrophins: NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4, also known as NT-4/5) (Bothwell, 2014).

Neurotrophins initially are synthesized as proneurotrophins, being packaged into secretory vesicles. Proneurotrophins undergo proteolytic cleavage, releasing a N-terminal prodomain peptide and a C-terminal mature protein (Bothwell, 2016). Lee et al. (2001) demonstrated that the proneurotrophins cleavage could occur both in intracellular and extracellular medium. In contrast to neurotrophins, proneurotrophins are not inactive. They act in inducing apoptosis pathway through their interaction to the p75 neurotrophin receptor ($p75^{NTR}$) (Teng et al., 2005; Domeniconi et al., 2007). In this way, proneurotrophins mediate neuronal growth cone retraction and pro-apoptotic actions, mainly during development and pathological conditions (Lee et al., 2001; Teng et al., 2005; Deinhardt et al., 2011; Hempstead, 2014).

The neurotrophins and proneurotrophins activities are mediated by their binding to transmembrane receptor systems: tropomyosin receptor kinase (Trk) family and $p75^{NTR}$. All mature neurotrophins and proneurotrophins bind to a $p75^{NTR}$ However, $p75^{NTR}$ is more effectively activated by proneurotrophins, while the Trk receptors are only activated by mature neurotrophins (Lee et al., 2001; Hempstead, 2014). Three different Trks are described for mammals - TrkA, TrkB and TrkC, which have preferred ligands. TrkA preferentially binds to NGF, BDNF and NT-4 has more affinity to TrkB, and TrkC prefers NT-3. Besides this, NT-3 also binds to TrkA and TrkB, though with lower affinity (Hempstead et al., 1991; Squinto et al., 1991; Benedetti et al., 1993; Bibel et al., 1999; Esposito et al., 2001).

Another family of neurotrophic factors is GFLs, a family of proteins represented by GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN) (Ibanez and Andressoo, 2017). GDNF was the first discovered member of GFLs, being described as a potent neurotrophic factor for survival of midbrain dopaminergic neurons (Lin et al., 1993). The description of GDNF receptors became a target for studies soon thereafter.

Currently, it is known that the actions of GFLs are mediated by binding those to two types of receptors. In summary, each GFL selectively interacts with one of the four members of GDNF family receptor α (GFRα1 to 4). However, GFRα has no intracellular domain, being necessary glycosylphosphatidylinositol (GPI) to anchor the GFL-GFRα complex to plasma membrane (Airaksinen and Saarma, 2002). Once that GFL-GFRα complex is anchored, GFLs acquire high affinity for the canonical receptor tyrosine kinase RET or the neuronal cell adhesion molecule (NCAM). In turn, GFL-GFRα-co-receptors complex activates the downstream signaling. Additionally, GFLs can bind to NCAM directly, inducing neurite outgrowth and synapse formation (Ibanez and Andressoo, 2017).

The family of neurokines, also known as neuropoietic cytokine family, comprises the following members: ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), leukemia inhibitory factor (LIF), neuropoietin (NPN), oncostatin M (OSM), cardiotrophin-like cytokine (CLC), interleukin (IL)-6, IL-11 and IL-27 (Halvorsen and Kaur, 2006). CNTF stands out for supporting the survival of motor, dopaminergic and parasympathetic neurons (Sendtner et al., 1991; Hagg and Varon, 1993; Davey et al., 2000). Of note, LIF supports sensory neurons (Moon et al., 2009). Neurokines mediate their actions mainly through Janus tyrosine kinase-signal transducer and activator of transcription (Jak/STAT) pathway (Halvorsen and Kaur, 2006).

Although structurally and functionally distinct from the classical neurotrophic factors, CDNF and MANF also show neurotrophic properties, such as the promotion of the dopaminergic neurons survival in the midbrain and the maintenance of endoplasmic reticulum homeostasis. However, their mechanisms of action remain largely unclear (Lindahl et al., 2017).

Neurotrophic Factors in AD and PD Pathophysiology

Neurotrophic factor issue has been extensively investigated into the context of neurodegenerative diseases, particularly AD and PD, because they show alterations in their levels and in adult neurogenesis as common hallmarks (Hoglinger et al., 2004; Gakhar-Koppole et al., 2008; O'Keeffe et al., 2009; Vilar and Mira, 2016). In this way, the understanding of the neurotrophic factor roles in supporting survival, proliferation and maturation of certain neurons, such as cholinergic and dopaminergic neurons, is a focus of active research and also of this review.

Alzheimer's disease

AD is well established as a complex progressive neurodegenerative disorder that results in memory deterioration and cognitive capacity impairment. However, this illness also comprises non-cognitive symptoms, such as delusions, agitation and changes in mood and personality (Epelbaum et al., 2017). The observed symptoms are associated with cholinergic deficits, mainly those related to cognitive functions. AD patients exhibit degeneration in the basal forebrain cholinergic neurons and in their projections for the cortex and hippocampus, being the loss of neurotrophic support a likely involved mechanism (Serrano-Pozo et al., 2011).

Analyses of brains from AD patients demonstrate the presence of β-amyloid peptide aggregates in the extracellular

medium, intracellular inclusions of neurofibrillary tangles rich in microtubule-associated protein tau, and neuritic plaques, which are pathological hallmarks of this disease (Serrano-Pozo et al., 2011). Moreover, the β-amyloid toxicity may also explain pathological aspects of AD, such as neurofibrillary tangles, inflammation and oxidative damage (O'Brien and Wong, 2011).

Oxidative stress is inextricably linked with several major pathological processes in AD, including β-amyloid-induced neurotoxicity, tau pathology, mitochondrial dysfunction and metal dyshomeostasis. In addition, oxidative stress plays an important role in the initiation and progression of AD (Zhao and Zhao, 2013). In fact, amyloidosis and tau protein accumulation can induce reactive oxygen species increase that promotes a redox imbalance. In contrast, the oxidative stress could have a causal relation with the AD pathogenesis. In this way, the augment of β-amyloid production and aggregation and tau phosphorylation and polymerization induce the reactive oxygen species increase (Zhao and Zhao, 2013). Notably, the oligomeric form of β-amyloid has been considered the most neurotoxic (Allen et al., 2011).

Additionally, changes in neurotrophic factors are observed both in AD animal models and patients (Allen et al., 2011; Budni et al., 2015). In this context, the neurotrophins NGF and BDNF stand out. NGF is a key neurotrophic factor cholinergic system development, including neuronal survival and differentiation (Nilbratt et al., 2010). It is synthesized in the cortex and hippocampus and retrogradely transported to the basal forebrain cholinergic neurons (Cattaneo and Calissano, 2012). NGF also induces rapid plasticity in the barrel cortex of rats - a region of the primary somatosensory cortex – through projections to basal forebrain cholinergic system (Prakash et al., 2004). Concerning that the basal forebrain cholinergic neurons constitute the main cholinergic innervation to hippocampus and neocortex, they play an essential role in cognition and attention processes (Triaca and Calissano, 2016). Moreover, Biane et al. (2014) observed that cortical GABAergic neurons are the primary source of NGF synthesis, providing support for basal forebrain cholinergic projections in adulthood.

Regarding AD, postmortem-derived tissue show NGF levels decrease in the nucleus basalis of Meynert, a neuronal group that projects large cholinergic innervation source to widespread cortical areas and it is well known to undergo degeneration in this disorder (Scott et al., 1995). Indeed, there are *in vitro* and *in vivo* evidence suggesting that NGF levels control the amyloidogenic pathway and β-amyloid peptides production (Matrone et al., 2008a, b; Yang et al., 2014). In physiological conditions, amyloid precursor protein (APP) can bind to TrkA. However, phosphorylated APP at Thr668, presents in AD patients, does not interact with TrkA favoring the β-secretase action that, in turn, increases the β-products levels. Thus, NGF controls the amyloidogenic route through the decrease in APP phosphorylation that diminishes the APP-β-secretase interaction by reducing the β-amyloid peptides formation (Triaca et al., 2016).

NGF retrograde transport from cortex and hippocampus to the basal forebrain cholinergic neurons is TrkA dependent. Nevertheless, this transport is dysfunctional in AD (Cattaneo and Calissano, 2012). In this way, decreased TrkA gene expression may be linked to basal forebrain neurodegeneration in early AD patients and increased NGF levels in the cortex of AD postmortem brains (Fahnestock et al., 1996; Counts et al., 2004). In addition, TrkA shows pro-survival or pro-apoptotic actions that are dependent of the presence or absence of NGF. TrkA-mediated pro-death signals were demonstrated after a reduction in NGF levels and as a consequence of overactivation of NGF-TrkA signaling following NGF withdrawal (Li et al., 2010; Nikoletopoulou et al., 2010).

Furthermore, $p75^{NTR}$ expression changes also are reported in the literature. Hippocampal TrkA expression is reduced in mild cognitive impairment patients while pro-NGF is elevated, suggesting the activation of pro-apoptotic pathways by pro-NGF (Mufson et al., 2012). Current data from Crispoltoni et al. (2017) demonstrated changes in the TrkA/$p75^{NTR}$ expressions during the disease progression in monocytic cells, which perform the β-amyloid deposits clearance. Mild cognitive impairment and mild AD patients showed an elevation in TrkA expression in monocytes and in NGF levels in plasma. In contrast, a reduction in both molecules and the monocytic $p75^{NTR}$ expression increase were found in patients with severe AD (Crispoltoni et al., 2017).

Regarding BDNF, this neurotrophin is largely expressed in the central nervous system, influencing several aspects of the neuronal function. Because this, BDNF was established as the main central neurotrophic factor (Park and Poo, 2013). BNDF mediates hippocampal plasticity in adulthood, survival and integration of hippocampal new-born neurons, assists the early and late long term potentiation (LTP) phases and works as cellular substrate for learning and memory (Vilar and Mira, 2016).

Similar to NGF, imbalance in BDNF levels also has been reported in AD cases. BDNF concentrations were found elevated in plasma of patients with severe AD (Angelucci et al., 2010; Faria et al., 2014). However, studies that investigated serum BDNF levels in mild cognitive impairment subjects show conflicting results (Angelucci et al., 2010; Faria et al., 2014). On the other hand, a postmortem study revealed that hippocampal BDNF expression was not altered, while TrkB expression was increased (Kao et al., 2012). In contrast, Ferrer et al. (1999) observed that both BDNF and TrkB levels were reduced in cerebral cortex and hippocampus of AD patients. Recently, the cortical BDNF expression reduction was corroborated by Buchman et al. (2016).

Preclinical reports have described that AD transgenic mouse models show decreased cortical BDNF expression and BDNF-mediated TrkB retrograde trafficking impairment in neuronal culture submitted to β-amyloid peptides (Peng et al., 2009; Poon et al., 2011). Alterations in the anterograde and retrograde transport of BDNF-containing vesicles by extracellular products from APP also were recently demonstrated (Seifert et al., 2016). Additionally, β-amyloid at a sublethal concentration down-regulates the BDNF signaling in cultured cortical neurons (Tong et al., 2004). In contrast, both protein

and mRNA levels of BDNF were elevated in cells submitted to β-amyloid$_{(25–35)}$ treatment (Lattanzio et al., 2016).

Data from Lattanzio et al. (2016) are in accordance with the putative causal role of BDNF in the AD pathogenesis. Ruiz-Leon and Pascual (2001) demonstrated that the binding of BNDF to TrkB, in a dose- and time-dependent fashion, can modulate the *in vitro* APP expression. In addition, full activation of APP gene expression by BDNF is simultaneously mediated by Ras/MAPK and PI3K/Akt signaling pathways (Ruiz-Leon and Pascual, 2001, 2004). Once that APP overexpression is an AD risk factor because it increases the β-amyloid peptide levels, BDNF could favor the formation of them. However, the most clinical and preclinical evidence indicates a BDNF reduction in the AD affected brain areas. Thus, these findings suggest a physiological role of APP in the cellular growth, which may be modulated by factors other than BDNF. Of note, these outcomes also present an open question for establishing the mechanisms undertaken by APP.

Parkinson's disease

PD is the second most common neurodegenerative disorder after AD. The PD incidence rate rises with the age, being expected a social and economic burden on the societies that prevalently have elderly population (Hirsch et al., 2016; Mack et al., 2016). PD etiology shows that although the most of patients are idiopathic or late onset PD cases (> 85 %), there is a relation between familial historic and a high PD risk. Additionally, families with inherited parkinsonism (< 10 %) had a variety of putative genes involved in PD identified individuals, showing that mitochondrial or lysosomal dysfunctions, protein aggregation, ubiquitin-proteasome system and kinase signaling pathways play a major role in the PD pathogenesis (Corti et al., 2011).

PD is clinically characterized by resting tremor, rigidity, bradykinesia and postural instability. Furthermore, nonmotor symptoms also are observed, occurring both in the late and early stages. These nonmotor symptoms comprise olfactory deficits, constipation, sleep behavior disorders, cognitive impairment and mood disturbances, such as anxiety and depression (Chaudhuri et al., 2006; Mack et al., 2016).

The disability of PD patients controlling the voluntary movements is a consequence of changes in the functional organization of the basal ganglia nuclei, which include the dopaminergic neurons loss in the substantia nigra pars compacta resulting in dopaminergic deficiency in the striatum (Gao and Wu, 2016). The major pathological hallmarks of PD comprise the presence of dystrophic neurites and Lewy bodies –intracytoplasmic inclusions in the surviving neurons composed mainly by α-synuclein and ubiquitin proteins (Wakabayashi et al., 2007).

Furthermore, neurotrophic factor alterations also are observed both in pre-clinical and clinical PD studies. In general, decreased neurotrophic factor levels have been reported in dopaminergic areas linked to PD, such as the substantia nigra (Nagatsu and Sawada, 2007). More consistent evidence suggests the major BDNF and GDNF involvement in the PD pathophysiology (Howells et al., 2000; Chauhan et al., 2001; Nagatsu and Sawada, 2007). Moreover, CDNF and MANF have emerged as new targets of study for this illness (Lindahl et al., 2017).

Accumulating data indicate the essential role and wide expression of BDNF in central motor structures, for instance basal ganglia, cerebellum and brainstem (Altar et al., 1997; He et al., 2013). So, disturbance in its homeostasis is harmful for neuronal development and survival in these areas (Li et al., 2012). Its neurotrophic functions include development and differentiation of cerebellar granule and Purkinje cells (Schwartz et al., 1997), survival support for dopaminergic neurons in the ventral tegmental area and medial substantia nigra pars compacta (Hyman et al., 1991; Baquet et al., 2005), and nigrostriatal apoptosis inhibition by BDNF/TrkB signaling (Lui et al., 2012). Moreover, the expressions of dopamine D3 receptor and tyrosine hydroxylase are mediated by BDNF (Du et al., 1995; Guillin et al., 2001).

Postmortem studies of PD patients found a reduction in the BDNF levels and in its expression in the substantia nigra pars compacta, caudate nucleus and putamen (Mogi et al., 1999; Parain et al., 1999; Howells et al., 2000; Nagatsu and Sawada, 2007). In addition, decreased BDNF levels is positively correlated to the degree of dopaminergic degeneration (Ziebell et al., 2012). Interestingly, genetic polymorphism of BDNF influences on familial PD, cognitive performance in individuals with PD and in the development of L-DOPA-induced dyskinesias (Foltynie et al., 2005; Karamohamed et al., 2005; Evans and Barker, 2008). Moreover, the α-synuclein overexpression down-regulates BDNF transcription and impairs BDNF trafficking in neurons (Yuan et al., 2010; Chu et al., 2012; Pramanik et al., 2016).

On the other hand, preclinical studies carried out in animal models show unclear results linked to BDNF levels imbalance. Hence, several factors can influence BDNF levels in PD models, for instance, the neurotoxin used, the administration protocol chosen and the degree of dopaminergic damage induced (Collier et al., 2005; Mocchetti et al., 2007; Berghauzen-Maciejewska et al., 2015; Sampaio et al., 2017).

Similar to BDNF, GDNF also assists motor and dopaminergic neurons, having an important role in their survival, differentiation, organization and maintenance (Henderson et al., 1994; Evans and Barker, 2008; Chermenina et al., 2014). Nevertheless, GDNF is five to ten times more potent than BDNF for survival promotion in injured nigrostriatal neurons of rats (Lu and Hagg, 1997). Adult mice express GDNF only in the dorsal and ventral striatum, anteroventral nucleus of the thalamus, septum and subcommissural organ (Pascual et al., 2011), whereas RET and GFRα1 are broadly expressed in the central nervous system (d'Anglemont de Tassigny et al., 2015). Curiously, there is no GDNF receptors mRNAs in the striatum, but high expression of them in the nigral cells (Trupp et al., 1997) suggesting a specific action on nigral dopaminergic neurons. Due to robust preclinical evidence of its effects, GDNF is one of the most largely investigated neurorestorative approach for PD.

Besides that, clinical reports also have related GDNF with the dopaminergic system. High expression of GDNF and RET

were found in human striatum and substantia nigra, respectively (Springer et al., 1994; Trupp et al., 1997). Furthermore, Chauhan et al. (2001) demonstrated that the nigral GDNF reduction in brain of PD patients was of two to eight times greater than those of other neurotrophic factors analyzed. Nevertheless, in another postmortem study in lysates of caudate/putamen, substantia nigra, cerebellum, frontal cortex and cerebrospinal-fluid, no significant difference was found between healthy subjects and PD patients (Mogi et al., 2001). Moreover, the detected polymorphisms in the GDNF gene did not show correlation with the disease (Wartiovaara et al., 1998).

CDNF and MANF have emerged in the PD context due to their neurotrophic effects on dopaminergic neurons. Low levels of CDNF expression have been detected in most of the brain areas of embryonic, postnatal and adult mouse, whereas CDNF levels were mainly observed in neurons of adult mouse. Nevertheless, CDNF immunocontent is not colocalized with tyrosine hydroxylase-positive cells in the substantia nigra. Indeed, few CDNF-positive neurons were stained in the substantia nigra and striatum, being more abundant in cerebellum, locus coeruleus, hippocampus and thalamus. Furthermore, CDNF expression was observed in the human brain and in central and peripheral non-neuronal tissues (Lindholm et al., 2007).

In contrast to CDNF, MANF expression was found in several areas of the developing and adult brain, including striatum and midbrain (Lindholm et al., 2008; Wang et al., 2014). In addition, its immunocontent presented colocalization with dopaminergic neurons in the substantia nigra (Lindholm et al., 2008). Although no effects on dopaminergic neurons are observed when MANF is administered in naïve rodents, accumulating evidence suggests its neurorestorative role against injured neurons (Airavaara et al., 2009; Voutilainen et al., 2009). Moreover, MANF regulates the endoplasmic reticulum stress and unfolded protein response (Apostolou et al., 2008).

Although several aspects linked to physiology of CDNF and MANF, such as their cytoprotective mechanism and their ability to bind to transmembrane receptors (Lindahl et al., 2017) remain unclear, their beneficial effects against *in vitro* and *in vivo* PD experimental models justify the growing investigation about them.

Neurotrophic Factors as Therapy Strategies for AD and PD

Besides the role of neurotrophic factors in the nourishment, survival and regeneration of neurons, there is increasing evidence indicating their involvement in the survival, anti-inflammation, proliferation and differentiation of non-neuronal tissues (Bothwell, 2016). In addition, they can be found in tissue-specific adult stem cell niche, inducing tissue regeneration outside the nervous system (Matsuda et al., 1988; Meng et al., 2000; Lavasani et al., 2006). Considering these evidence and the pathophysiological features that link the neurotrophic factors to AD and PD, it is plausible the neurotrophic factors employment as therapeutic approach for neuroregeneration.

The current therapies for AD and PD are initially effective, alleviating the main symptoms of these diseases. However, disease progression is not prevented, justifying the research focus in neurorestorative approaches. In this way, pluripotent stem cells transplant, gene therapy vectors, neurotrophic factor replacement and neurotrophic factor mimetics emerge as strategies for neuronal regeneration. In contrast to current therapies, these new therapeutic strategies could provide a cure for neurodegenerative disorders.

Across the last decades, research data on the therapeutic promise of neurotrophic factors have been collected. Nevertheless, none treatment for any disease was established. Firstly, different neurotrophic factors were tested by subcutaneous route, in order to produce a systemic exposure (Group, 1999; Sorenson et al., 2008). Following serious side effects found with the subcutaneous injections, intrathecal delivery of neurotrophic factors, mainly CNTF and BDNF, was employed. Intrathecal administration avoided subcutaneous side effects, indicating the feasibility and tolerability by this delivery route. Lumbar and cervical taps analysis demonstrated the ability of neurotrophic factors to be distributed in the cerebrospinal-fluid compartment following intrathecal infusion. However, the effectiveness of these proteins to reach the spinal cord and brain was not elicited. Moreover, unexpected side effects likely dose-related were found subsequently to intrathecal administration (Aebischer et al., 1996; Penn et al., 1997; Ochs et al., 2000; Kalra et al., 2003; Beck et al., 2005).

Dosing paradigm for neurotrophic factor intrathecal administration was changed after the results obtained from intracerebral ventricular (ICV) infusion of neurotrophic factors, which suggested that cerebrospinal-fluid was not the ideal way to delivery these peptides. ICV studies using NGF and GDNF, respectively, in AD and PD patients, demonstrated significant side effects with little clinical benefit (Eriksdotter Jonhagen et al., 1998; Kordower et al., 1999; Nutt et al., 2003). In addition, dose reduction was enough to eliminate side effects observed in the ICV approach. In this way, intrathecal approach, which also reaches the cerebrospinal-fluid compartment, may yet prove useful for application of new strategies with different biological constructs, for instance, antisense oligonucleotides, some gene therapy vectors and phage-like entities (Bartus and Johnson, 2017).

Based on findings from previous trials, neurotrophic factors began to be administered directly into the target tissue. As in the pioneer study that tested NGF into the putamen of a PD patient (Olson et al., 1991), positive clinical effects have been reported using GDNF in PD subjects, without serious side effects (Gill et al., 2003; Love et al., 2005; Patel et al., 2005, 2013). Besides the enhanced performance in standardized PD scales and tests, improvement in [18F]-dopamine uptake after a year of treatment was described (Gill et al., 2003). Additionally, an autopsied brain from a study by Gill et al. (2003) showed an increase in tyrosine hydroxylase-staining at the injection area of putamen and an enhancement in L-DOPA uptake in the infused hemisphere (Love et al., 2005). However, a double-blind controlled trial

with PD patients did not replicate those clinical outcomes (Lang et al., 2006). These conflicting data were attributed to putative differences in drug delivery (Salvatore et al., 2006). Nevertheless, Morrison et al. (2007) reported that GDNF distribution and diffusion did not explain the different efficacy found.

Regarding clinical trials of AD, investigators were focused on developing effective and innovative delivery methods. Gene transfer has emerged as a technology able to provide controlled, predictable, long-term biologically active proteins, which act on specific targeted brain sites (Herzog et al., 2011). Autologous fibroblasts genetically modified to express human NGF were implanted into the basal forebrain area of AD patients. The subjects showed an improvement in the cognitive decline rate and an increase in cortical 18-fluorodeoxyglucose, indicating metabolic activity in this area (Tuszynski et al., 2005). Autopsied brain confirmed long-term, targeted, gene-mediated NGF expression and bioactivity (Rafii et al., 2014). In addition, it was observed that axons sprouted toward the local source of NGF and cell hypertrophy (Tuszynski et al., 2015).

Preclinical studies also have used innovative delivery methods to evaluate the neurotrophic factors potential against AD models. Recombinant lentiviral vectors used to overexpress hippocampal GDNF gene in astrocytes preserved cognitive functions in 3xTg-AD mice and aged rats (Pertusa et al., 2008; Revilla et al., 2014). Revilla et al. (2014) also reported that MC65 cells overexpressing GDNF presented a reduction of toxic APP content and its β-amyloid peptides-derived. Moreover, protective effect of GDNF against β-amyloid-induced neuronal death was demonstrated in rabbit hippocampus and in cultured septal neurons (Ghribi et al., 2004; Kitiyanant et al., 2012). Although these data are promising, further preclinical and clinical studies are needed to elucidate the putative application of GDNF as therapeutic strategy for AD.

Conclusion

In summary, neurotrophic factors play essential roles for survival, development and maintenance of neurons. Alterations in the neurotrophic factors levels/expression and their signaling pathways seem to be tied to the development and/or progression of neurodegenerative disorders. In this context, neurotrophic factors emerge as therapeutic promises for AD and PD. Although many data have been collected in the last decades, none neurotrophic factor treatment for any disease was established until now. However, the new drug delivery approaches, such as gene therapy vectors, search to optimize the clinical benefit in reducing the side effects observed in the tested methods. Thus, application of neurotrophic factors using new therapeutic methods should be carefully considered and evaluated for AD and PD management.

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References

Aebischer P, Schluep M, Deglon N, Joseph JM, Hirt L, Heyd B, Goddard M, Hammang JP, Zurn AD, Kato AC, Regli F, Baetge EE (1996) Intrathecal delivery of CNTF using encapsulated genetically modified xenogeneic cells in amyotrophic lateral sclerosis patients. Nat Med 2:696-699.

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

Airavaara M, Shen H, Kuo CC, Peranen J, Saarma M, Hoffer B, Wang Y (2009) Mesencephalic astrocyte-derived neurotrophic factor reduces ischemic brain injury and promotes behavioral recovery in rats. J Comp Neurol 515:116-124.

Allen SJ, Watson JJ, Dawbarn D (2011) The neurotrophins and their role in Alzheimer's disease. Curr Neuropharmacol 9:559-573.

Altar CA, Cai N, Bliven T, Juhasz M, Conner JM, Acheson AL, Lindsay RM, Wiegand SJ (1997) Anterograde transport of brain-derived neurotrophic factor and its role in the brain. Nature 389:856-860.

Angelucci F, Spalletta G, di Iulio F, Ciaramella A, Salani F, Colantoni L, Varsi AE, Gianni W, Sancesario G, Caltagirone C, Bossu P (2010) Alzheimer's disease (AD) and mild cognitive impairment (MCI) patients are characterized by increased BDNF serum levels. Curr Alzheimer Res 7:15-20.

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.

Baquet ZC, Bickford PC, Jones KR (2005) Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta. J Neurosci 25:6251-6259.

Bartus RT, Johnson EM, Jr. (2017) Clinical tests of neurotrophic factors for human neurodegenerative diseases, part 1: Where have we been and what have we learned? Neurobiol Dis 97:156-168.

Beck M, Flachenecker P, Magnus T, Giess R, Reiners K, Toyka KV, Naumann M (2005) Autonomic dysfunction in ALS: A preliminary study on the effects of intrathecal BDNF. Amyotrophic Lateral Sclerosis 6:100-103.

Benedetti M, Levi A, Chao MV (1993) Differential expression of nerve growth factor receptors leads to altered binding affinity and neurotrophin responsiveness. Proc Natl Acad Sci U S A 90:7859-7863.

Berghauzen-Maciejewska K, Wardas J, Kosmowska B, Glowacka U, Kuter K, Ossowska K (2015) Alterations of BDNF and trkB mRNA expression in the 6-hydroxydopamine-induced model of preclinical stages of Parkinson's disease: an influence of chronic pramipexole in rats. PLoS One 10:e0117698.

Biane J, Conner JM, Tuszynski MH (2014) Nerve growth factor is primarily produced by GABAergic neurons of the adult rat cortex. Front Cell Neurosci 8:220.

Bibel M, Hoppe E, Barde YA (1999) Biochemical and functional interactions between the neurotrophin receptors trk and p75NTR. EMBO J 18:616-622.

Bothwell M (2014) NGF, BDNF, NT3, and NT4. Handb Exp Pharmacol 220:3-15.

Bothwell M (2016) Recent advances in understanding neurotrophin signaling. F1000Res 5:1885.

Buchman AS, Yu L, Boyle PA, Schneider JA, De Jager PL, Bennett DA (2016) Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. Neurology 86:735-741.

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.

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

Chaudhuri KR, Healy DG, Schapira AH, National Institute for Clinical E (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 5:235-245.

Chauhan NB, Siegel GJ, Lee JM (2001) Depletion of glial cell line-derived neurotrophic factor in substantia nigra neurons of Parkinson's disease brain. J Chem Neuroanat 21:277-288.

Chermenina M, Schouten P, Nevalainen N, Johansson F, Oradd G, Stromberg I (2014) GDNF is important for striatal organization and maintenance of dopamine neurons grown in the presence of the striatum. Neuroscience 270:1-11.

Chu Y, Morfini GA, Langhamer LB, He Y, Brady ST, Kordower JH (2012) Alterations in axonal transport motor proteins in sporadic and experimental Parkinson's disease. Brain 135:2058-2073.
Collier TJ, Dung Ling Z, Carvey PM, Fletcher-Turner A, Yurek DM, Sladek JR, Jr., Kordower JH (2005) Striatal trophic factor activity in aging monkeys with unilateral MPTP-induced parkinsonism. Exp Neurol 191 Suppl 1:S60-67.
Connor B, Dragunow M (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res Brain Res Rev 27:1-39.
Corti O, Lesage S, Brice A (2011) What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev 91:1161-1218.
Counts SE, Nadeem M, Wuu J, Ginsberg SD, Saragovi HU, Mufson EJ (2004) Reduction of cortical TrkA but not p75(NTR) protein in early-stage Alzheimer's disease. Ann Neurol 56:520-531.
Crispoltoni L, Stabile AM, Pistilli A, Venturelli M, Cerulli G, Fonte C, Smania N, Schena F, Rende M (2017) Changes in plasma beta-NGF and its receptors expression on peripheral blood monocytes during Alzheimer's disease progression. J Alzheimers Dis 55:1005-1017.
d'Anglemont de Tassigny X, Pascual A, Lopez-Barneo J (2015) GDNF-based therapies, GDNF-producing interneurons, and trophic support of the dopaminergic nigrostriatal pathway. Implications for Parkinson's disease. Front Neuroanat 9:10.
Davey F, Hilton M, Davies AM (2000) Cooperation between HGF and CNTF in promoting the survival and growth of sensory and parasympathetic neurons. Mol Cell Neurosci 15:79-87.
Deinhardt K, Kim T, Spellman DS, Mains RE, Eipper BA, Neubert TA, Chao MV, Hempstead BL (2011) Neuronal growth cone retraction relies on proneurotrophin receptor signaling through Rac. Sci Signal 4:ra82.
Domeniconi M, Hempstead BL, Chao MV (2007) Pro-NGF secreted by astrocytes promotes motor neuron cell death. Mol Cell Neurosci 34:271-279.
Du X, Stull ND, Iacovitti L (1995) Brain-derived neurotrophic factor works coordinately with partner molecules to initiate tyrosine hydroxylase expression in striatal neurons. Brain Res 680:229-233.
Epelbaum S, Genthon R, Cavedo E, Habert MO, Lamari F, Gagliardi G, Lista S, Teichmann M, Bakardjian H, Hampel H, Dubois B (2017) Preclinical Alzheimer's disease: A systematic review of the cohorts underlying the concept. Alzheimers Dement doi:10.1016/j.jalz.2016.12.003.
Eriksdotter Jonhagen M, Nordberg A, Amberla K, Backman L, Ebendal T, Meyerson B, Olson L, Seiger, Shigeta M, Theodorsson E, Viitanen M, Winblad B, Wahlund LO (1998) Intracerebroventricular infusion of nerve growth factor in three patients with Alzheimer's disease. Dement Geriatr Cogn Disord 9:246-257.
Esposito D, Patel P, Stephens RM, Perez P, Chao MV, Kaplan DR, Hempstead BL (2001) The cytoplasmic and transmembrane domains of the p75 and Trk A receptors regulate high affinity binding to nerve growth factor. J Biol Chem 276:32687-32695.
Evans JR, Barker RA (2008) Neurotrophic factors as a therapeutic target for Parkinson's disease. Expert Opin Ther Targets 12:437-447.
Fahnestock M, Scott SA, Jette N, Weingartner JA, Crutcher KA (1996) Nerve growth factor mRNA and protein levels measured in the same tissue from normal and Alzheimer's disease parietal cortex. Brain Res Mol Brain Res 42:175-178.
Faria MC, Goncalves GS, Rocha NP, Moraes EN, Bicalho MA, Gualberto Cintra MT, Jardim de Paula J, Jose Ravic de Miranda LF, Clayton de Souza Ferreira A, Teixeira AL, Gomes KB, Carvalho M, Sousa LP (2014) Increased plasma levels of BDNF and inflammatory markers in Alzheimer's disease. J Psychiatr Res 53:166-172.
Ferrer I, Marin C, Rey MJ, Ribalta T, Goutan E, Blanco R, Tolosa E, Marti E (1999) BDNF and full-length and truncated TrkB expression in Alzheimer disease. Implications in therapeutic strategies. J Neuropathol Exp Neurol 58:729-739.
Foltynie T, Lewis SG, Goldberg TE, Blackwell AD, Kolachana BS, Weinberger DR, Robbins TW, Barker RA (2005) The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. J Neurol 252:833-838.
Gakhar-Koppole N, Hundeshagen P, Mandl C, Weyer SW, Allinquant B, Muller U, Ciccolini F (2008) Activity requires soluble amyloid precursor protein alpha to promote neurite outgrowth in neural stem cell-derived neurons via activation of the MAPK pathway. Eur J Neurosci 28:871-882.
Gao LL, Wu T (2016) The study of brain functional connectivity in Parkinson's disease. Transl Neurodegener 5:18.
Ghribi O, Herman MM, Pramoonjago P, Spaulding NK, Savory J (2004) GDNF regulates the A beta-induced endoplasmic reticulum stress response in rabbit hippocampus by inhibiting the activation of gadd 153 and the JNK and ERK kinases. Neurobiol Dis 16:417-427.
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.
Group TBS (1999) A controlled trial of recombinant methionyl human BDNF in ALS. Neurology 52:1427.
Guillin O, Diaz J, Carroll P, Griffon N, Schwartz JC, Sokoloff P (2001) BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature 411:86-89.
Hagg T, Varon S (1993) Ciliary neurotrophic factor prevents degeneration of adult rat substantia nigra dopaminergic neurons in vivo. Proc Natl Acad Sci U S A 90:6315-6319.
Halvorsen SW, Kaur N (2006) CNTF and related neurokines. In: Handbook of Neurochemistry and Molecular Neurobiology: Neuroactive Proteins and Peptides (Lajtha A, Lim R, eds), pp 43-68. Boston, MA: Springer US.
He YY, Zhang XY, Yung WH, Zhu JN, Wang JJ (2013) Role of BDNF in central motor structures and motor diseases. Mol Neurobiol 48:783-793.
Hempstead BL (2014) Deciphering proneurotrophin actions. Handb Exp Pharmacol 220:17-32.
Hempstead BL, Martin-Zanca D, Kaplan DR, Parada LF, Chao MV (1991) High-affinity NGF binding requires coexpression of the trk proto-oncogene and the low-affinity NGF receptor. Nature 350:678-683.
Henderson CE, Phillips HS, Pollock RA, Davies AM, Lemeulle C, Armanini M, Simmons L, Moffet B, Vandlen RA, Simpson LCctSL, Koliatsos VE, Rosenthal A (1994) GDNF: a potent survival factor for motoneurons present in peripheral nerve and muscle. Science 266:1062-1064.
Herzog CD, Bishop KM, Brown L, Wilson A, Kordower JH, Bartus RT (2011) Gene transfer provides a practical means for safe, long-term, targeted delivery of biologically active neurotrophic factor proteins for neurodegenerative diseases. Drug Deliv Transl Res 1:361-382.
Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T (2016) The incidence of Parkinson's disease: a systematic review and meta-analysis. Neuroepidemiology 46:292-300.
Hoglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC (2004) Dopamine depletion impairs precursor cell proliferation in Parkinson disease. Nat Neurosci 7:726-735.
Howells DW, Porritt MJ, Wong JYF, Batchelor PE, Kalnins R, Hughes AJ, Donnan GA (2000) Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol 166:127-135.
Hyman C, Hofer M, Barde YA, Juhasz M, Yancopoulos GD, Squinto SP, Lindsay RM (1991) Bdnf is a neurotrophic factor for dopaminergic-neurons of the substantia-nigra. Nature 350:230-232.
Ibanez CF, Andressoo JO (2017) Biology of GDNF and its receptors - Relevance for disorders of the central nervous system. Neurobiol Dis 97:80-89.
Kalra S, Genge A, Arnold DL (2003) A prospective, randomized, placebo-controlled evaluation of corticoneuronal response to intrathecal BDNF therapy in ALS using magnetic resonance spectroscopy: feasibility and results. Amyotroph Lateral Scler Other Motor Neuron Disord 4:22-26.
Kao PF, Banigan MG, Vanderburg CR, McKee AC, Polgar PR, Seshadri S, Delalle I (2012) Increased expression of TrkB and Capzb2 accompanies preserved cognitive status in early Alzheimer disease pathology. J Neuropathol Exp Neurol 71:654-664.
Karamohamed S, Latourelle JC, Racette BA, Perlmutter JS, Wooten GF, Lew M, Klein C, Shill H, Golbe LI, Mark MH, Guttman M, Nicholson G, Wilk JB, Saint-Hilaire M, DeStefano AL, Prakash R, Tobin S, Williamson J, Suchowersky O, Labell N, et al. (2005) BDNF genetic variants are associated with onset age of familial Parkinson disease: GenePD Study. Neurology 65:1823-1825.
Kitiyanant N, Kitiyanant Y, Svendsen CN, Thangnipon W (2012) BDNF-, IGF-1- and GDNF-secreting human neural progenitor cells rescue amyloid beta-induced toxicity in cultured rat septal neurons. Neurochem Res 37:143-152.

Kordower JH, Palfi S, Chen EY, Ma SY, Sendera T, Cochran EJ, Cochran EJ, Mufson EJ, Penn R, Goetz CG, Comella CD (1999) Clinicopathological findings following intraventricular glial-derived neurotrophic factor treatment in a patient with Parkinson's disease. Ann Neurol 46:419-424.

Lang AE, Gill S, Patel NK, Lozano A, Nutt JG, Penn R, Brooks DJ, Hotton G, Moro E, Heywood P, Brodsky MA, Burchiel K, Kelly P, Dalvi A, Scott B, Stacy M, Turner D, Wooten VG, Elias WJ, Laws ER, et al. (2006) Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. Ann Neurol 59:459-466.

Lattanzio F, Carboni L, Carretta D, Candeletti S, Romualdi P (2016) Treatment with the neurotoxic Abeta (25-35) peptide modulates the expression of neuroprotective factors Pin1, Sirtuin 1, and brain-derived neurotrophic factor in SH-SY5Y human neuroblastoma cells. Exp Toxicol Pathol 68:271-276.

Lavasani M, Lu A, Peng H, Cummins J, Huard J (2006) Nerve growth factor improves the muscle regeneration capacity of muscle stem cells in dystrophic muscle. Hum Gene Ther 17:180-192.

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

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

Levi-Montalcini R, Angeletti PU (1963) Essential role of the nerve growth factor in the survival and maintenance of dissociated sensory and sympathetic embryonic nerve cells in vitro. Dev Biol 6:653-659.

Li C, Macdonald JI, Hryciw T, Meakin SO (2010) Nerve growth factor activation of the TrkA receptor induces cell death, by macropinocytosis, in medulloblastoma Daoy cells. J Neurochem 112:882-899.

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

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

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

Lindholm P, Peranen J, Andressoo JO, Kalkkinen N, Kokaia Z, Lindvall O, Timmusk T, Saarma M (2008) MANF is widely expressed in mammalian tissues and differently regulated after ischemic and epileptic insults in rodent brain. Mol Cell Neurosci 39:356-371.

Lindholm P, Voutilainen MH, Lauren J, Peranen J, Leppanen VM, Andressoo JO, Lindahl M, Janhunen S, Kalkkinen N, Timmusk T, Tuominen RK, Saarma M (2007) Novel neurotrophic factor CDNF protects and rescues midbrain dopamine neurons in vivo. Nature 448:73-77.

Love S, Plaha P, Patel NK, Hotton GR, Brooks DJ, Gill SS (2005) Glial cell line-derived neurotrophic factor induces neuronal sprouting in human brain. Nat Med 11:703-704.

Lu X, Hagg T (1997) Glial cell line-derived neurotrophic factor prevents death, but not reductions in tyrosine hydroxylase, of injured nigrostriatal neurons in adult rats. J Comp Neurol 388:484-494.

Lui NP, Chen LW, Yung WH, Chan YS, Yung KK (2012) Endogenous repair by the activation of cell survival signalling cascades during the early stages of rat Parkinsonism. PLos One 7:e51294.

Mack JM, Schamne MG, Sampaio TB, Pertile RA, Fernandes PA, Markus RP, Prediger RD (2016) Melatoninergic system in Parkinson's disease: from neuroprotection to the management of motor and nonmotor symptoms. Oxid Med Cell Longev 2016:3472032.

Matrone C, Ciotti MT, Mercanti D, Marolda R, Calissano P (2008a) NGF and BDNF signaling control amyloidogenic route and Abeta production in hippocampal neurons. Proc Natl Acad Sci U S A 105:13139-13144.

Matrone C, Di Luzio A, Meli G, D'Aguanno S, Severini C, Ciotti MT, Cattaneo A, Calissano P (2008b) Activation of the amyloidogenic route by NGF deprivation induces apoptotic death in PC12 cells. J Alzheimers Dis 13:81-96.

Matsuda H, Coughlin MD, Bienenstock J, Denburg JA (1988) Nerve growth factor promotes human hemopoietic colony growth and differentiation. Proc Natl Acad Sci U S A 85:6508-6512.

Meng X, Lindahl M, Hyvonen ME, Parvinen M, de Rooij DG, Hess MW, Raatikainen-Ahokas A, Sainio K, Rauvala H, Lakso M, Pichel JG, Westphal H, Saarma M, Sariola H (2000) Regulation of cell fate decision of undifferentiated spermatogonia by GDNF. Science 287:1489-1493.

Mocchetti I, Bachis A, Nosheny RL, Tanda G (2007) Brain-derived neurotrophic factor expression in the substantia nigra does not change after lesions of dopaminergic neurons. Neurotox Res 12:135-143.

Mogi M, Togari A, Kondo T, Mizuno Y, Komure O, Kuno S, Ichinose H, Nagatsu T (1999) Brain-derived growth factor and nerve growth factor concentrations are decreased in the substantia nigra in Parkinson's disease. Neurosci Lett 270:45-48.

Mogi M, Togari A, Kondo T, Mizuno Y, Kogure O, Kuno S, Ichinose H, Nagatsu T (2001) Glial cell line-derived neurotrophic factor in the substantia nigra from control and parkinsonian brains. Neurosci Lett 300:179-181.

Moon C, Liu BQ, Kim SY, Kim EJ, Park YJ, Yoo JY, Han HS, Bae YC, Ronnett GV (2009) Leukemia inhibitory factor promotes olfactory sensory neuronal survival via phosphoinositide 3-kinase pathway activation and Bcl-2. J Neurosci Res 87:1098-1106.

Morrison PF, Lonser RR, Oldfield EH (2007) Convective delivery of glial cell line-derived neurotrophic factor in the human putamen. J Neurosurg 107:74-83.

Mufson EJ, He B, Nadeem M, Perez SE, Counts SE, Leurgans S, Fritz J, Lah J, Ginsberg SD, Wuu J, Scheff SW (2012) Hippocampal proNGF signaling pathways and beta-amyloid levels in mild cognitive impairment and Alzheimer disease. J Neuropathol Exp Neurol 71:1018-1029.

Nagatsu T, Sawada M (2007) Biochemistry of postmortem brains in Parkinson's disease: historical overview and future prospects. J Neural Transm Suppl:113-120.

Nikoletopoulou V, Lickert H, Frade JM, Rencurel C, Giallonardo P, Zhang L, Bibel M, Barde YA (2010) Neurotrophin receptors TrkA and TrkC cause neuronal death whereas TrkB does not. Nature 467:59-63.

Nilbratt M, Porras O, Marutle A, Hovatta O, Nordberg A (2010) Neurotrophic factors promote cholinergic differentiation in human embryonic stem cell-derived neurons. J Cell Mol Med 14:1476-1484.

Nutt JG, Burchiel KJ, Comella CL, Jankovic J, Lang AE, Laws ER, Jr., Lozano AM, Penn RD, Simpson RK, Jr., Stacy M, Wooten GF, factor IGSGIiGcl-dn (2003) Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 60:69-73.

O'Brien RJ, Wong PC (2011) Amyloid precursor protein processing and Alzheimer's disease. Annu Rev Neurosci 34:185-204.

O'Keeffe GC, Tyers P, Aarsland D, Dalley JW, Barker RA, Caldwell MA (2009) Dopamine-induced proliferation of adult neural precursor cells in the mammalian subventricular zone is mediated through EGF. Proc Natl Acad Sci U S A 106:8754-8759.

Ochs G, Penn RD, York M, Giess R, Beck M, Tonn J, Haigh J, Malta E, Traub M, Sendtner M, Toyka KV (2000) A phase I/II trial of recombinant methionyl human brain derived neurotrophic factor administered by intrathecal infusion to patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:201-206.

Olson L, Backlund EO, Ebendal T, Freedman R, Hamberger B, Hansson P, Hoffer B, Lindblom U, Meyerson B, Stromberg I, Sydow O, Seiger A (1991) Intraputaminal infusion of nerve growth factor to support adrenal medullary autografts in Parkinson's disease. One-year follow-up of first clinical trial. Arch Neurol 48:373-381.

Parain K, Murer MG, Yan Q, Faucheux B, Agid Y, Hirsch E, Raisman-Vozari R (1999) Reduced expression of brain-derived neurotrophic factor protein in Parkinson's disease substantia nigra. Neuroreport 10:557-561.

Park H, Poo MM (2013) Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci 14:7-23.

Pascual A, Hidalgo-Figueroa M, Gomez-Diaz R, Lopez-Barneo J (2011) GDNF and protection of adult central catecholaminergic neurons. J Mol Endocrinol 46:R83-92.

Patel NK, Bunnage M, Plaha P, Svendsen CN, Heywood P, Gill SS (2005) Intraputamenal infusion of glial cell line-derived neurotrophic factor in PD: a two-year outcome study. Ann Neurol 57:298-302.

Patel NK, Pavese N, Javed S, Hotton GR, Brooks DJ, Gill SS (2013) Benefits of putaminal GDNF infusion in Parkinson disease are maintained after GDNF cessation. Neurology 81:1176-1178.

Peng S, Garzon DJ, Marchese M, Klein W, Ginsberg SD, Francis BM, Mount HT, Mufson EJ, Salehi A, Fahnestock M (2009) Decreased brain-derived neurotrophic factor depends on amyloid aggregation state in transgenic mouse models of Alzheimer's disease. J Neurosci 29:9321-9329.

Penn RD, Kroin JS, York MM, Cedarbaum JM (1997) Intrathecal ciliary neurotrophic factor delivery for treatment of amyotrophic lateral sclerosis (phase I trial). Neurosurgery 40:94-99; discussion 99-100.

Pertusa M, Garcia-Matas S, Mammeri H, Adell A, Rodrigo T, Mallet J, Cristofol R, Sarkis C, Sanfeliu C (2008) Expression of GDNF transgene in astrocytes improves cognitive deficits in aged rats. Neurobiol Aging 29:1366-1379.

Poon WW, Blurton-Jones M, Tu CH, Feinberg LM, Chabrier MA, Harris JW, Jeon NL, Cotman CW (2011) beta-Amyloid impairs axonal BDNF retrograde trafficking. Neurobiol Aging 32:821-833.

Prakash N, Cohen-Cory S, Penschuck S, Frostig RD (2004) Basal forebrain cholinergic system is involved in rapid nerve growth factor (NGF)-induced plasticity in the barrel cortex of adult rats. J Neurophysiol 91:424-437.

Pramanik S, Sulistio YA, Heese K (2016) Neurotrophin signaling and stem cells-implications for neurodegenerative diseases and stem cell therapy. Mol Neurobiol doi:10.1007/s12035-016-0214-7.

Rafii MS, Baumann TL, Bakay RA, Ostrove JM, Siffert J, Fleisher AS, Herzog CD, Barba D, Pay M, Salmon DP, Chu Y, Kordower JH, Bishop K, Keator D, Potkin S, Bartus RT (2014) A phase1 study of stereotactic gene delivery of AAV2-NGF for Alzheimer's disease. Alzheimers Dement 10:571-581.

Revilla S, Ursulet S, Alvarez-Lopez MJ, Castro-Freire M, Perpina U, Garcia-Mesa Y, Bortolozzi A, Gimenez-Llort L, Kaliman P, Cristofol R, Sarkis C, 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.

Ruiz-Leon Y, Pascual A (2001) Brain-derived neurotrophic factor stimulates beta-amyloid gene promoter activity by a Ras-dependent/AP-1-independent mechanism in SH-SY5Y neuroblastoma cells. J Neurochem 79:278-285.

Ruiz-Leon Y, Pascual A (2004) Regulation of beta-amyloid precursor protein expression by brain-derived neurotrophic factor involves activation of both the Ras and phosphatidylinositide 3-kinase signalling pathways. J Neurochem 88:1010-1018.

Salvatore MF, Ai Y, Fischer B, Zhang AM, Grondin RC, Zhang Z, Gerhardt GA, Gash DM (2006) Point source concentration of GDNF may explain failure of phase II clinical trial. Exp Neurol 202:497-505.

Sampaio TB, Pinton S, da Rocha JT, Gai BM, Nogueira CW (2017) Involvement of BDNF/TrkB signaling in the effect of diphenyl diselenide on motor function in a Parkinson's disease rat model. Eur J Pharmacol 795:28-35.

Schwartz PM, Borghesani PR, Levy RL, Pomeroy SL, Segal RA (1997) Abnormal cerebellar development and foliation in BDNF-/- mice reveals a role for neurotrophins in CNS patterning. Neuron 19:269-281.

Scott SA, Mufson EJ, Weingartner JA, Skau KA, Crutcher KA (1995) Nerve growth factor in Alzheimer's disease: increased levels throughout the brain coupled with declines in nucleus basalis. J Neurosci 15:6213-6221.

Seifert B, Eckenstaler R, Ronicke R, Leschik J, Lutz B, Reymann K, Lessmann V, Brigadski T (2016) Amyloid-beta induced changes in vesicular transport of BDNF in hippocampal neurons. Neural Plast 2016:4145708.

Sendtner M, Arakawa Y, Stockli KA, Kreutzberg GW, Thoenen H (1991) Effect of ciliary neurotrophic factor (CNTF) on motoneuron survival. J Cell Sci Suppl 15:103-109.

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

Sorenson EJ, Windbank AJ, Mandrekar JN, Bamlet WR, Appel SH, Armon C, Barkhaus PE, Bosch P, Boylan K, David WS, Feldman E, Glass J, Gutmann L, Katz J, King W, Luciano CA, McCluskey LF, Nash S, Newman DS, Pascuzzi RM, et al. (2008) Subcutaneous IGF-1 is not beneficial in 2-year ALS trial. Neurology 71:1770-1775.

Springer JE, Mu X, Bergmann LW, Trojanowski JQ (1994) Expression of GDNF mRNA in rat and human nervous tissue. Exp Neurol 127:167-170.

Squinto SP, Stitt TN, Aldrich TH, Davis S, Bianco SM, Radziejewski C, Glass DJ, Masiakowski P, Furth ME, Valenzuela DM, Distefano PS, Yancopoulos GD (1991) trkB encodes a functional receptor for brain-derived neurotrophic factor and neurotrophin-3 but not nerve growth factor. Cell 65:885-893.

Sullivan AM, O'Keeffe GW (2016) Neurotrophic factor therapy for Parkinson's disease: past, present and future. Neural Regen Res 11:205-207.

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.

Tong L, Balazs R, Thornton PL, Cotman CW (2004) Beta-amyloid peptide at sublethal concentrations downregulates brain-derived neurotrophic factor functions in cultured cortical neurons. J Neurosci 24:6799-6809.

Triaca V, Calissano P (2016) Impairment of the nerve growth factor pathway driving amyloid accumulation in cholinergic neurons: the incipit of the Alzheimer's disease story? Neural Regen Res 11:1553-1556.

Triaca V, Sposato V, Bolasco G, Ciotti MT, Pelicci P, Bruni AC, Cupidi C, Maletta R, Feligioni M, Nistico R, Canu N, Calissano P (2016) NGF controls APP cleavage by downregulating APP phosphorylation at Thr668: relevance for Alzheimer's disease. Aging Cell 15:661-672.

Trupp M, Belluardo N, Funakoshi H, Ibanez CF (1997) Complementary and overlapping expression of glial cell line-derived neurotrophic factor (GDNF), c-ret proto-oncogene, and GDNF receptor-alpha indicates multiple mechanisms of trophic actions in the adult rat CNS. J Neurosci 17:3554-3567.

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

Tuszynski MH, Thal L, Pay M, Salmon DP, U HS, Bakay R, Patel P, Blesch A, Vahlsing HL, Ho G, Tong G, Potkin SG, Fallon J, Hansen L, Mufson EJ, Kordower JH, Gall C, Conner J (2005) A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat Med 11:551-555.

Vilar M, Mira H (2016) Regulation of neurogenesis by neurotrophins during adulthood: expected and unexpected roles. Front Neurosci 10:26.

Voutilainen MH, Back S, Porsti E, Toppinen L, Lindgren L, Lindholm P, Peranen J, Saarma M, Tuominen RK (2009) Mesencephalic astrocyte-derived neurotrophic factor is neurorestorative in rat model of Parkinson's disease. J Neurosci 29:9651-9659.

Wakabayashi K, Tanji K, Mori F, Takahashi H (2007) The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of alpha-synuclein aggregates. Neuropathology 27:494-506.

Wang H, Ke Z, Alimov A, Xu M, Frank JA, Fang S, Luo J (2014) Spatiotemporal expression of MANF in the developing rat brain. PLoS One 9:e90433.

Wartiovaara K, Hytonen M, Vuori M, Paulin L, Rinne J, Sariola H (1998) Mutation analysis of the glial cell line-derived neurotrophic factor gene in Parkinson's disease. Exp Neurol 152:307-309.

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.

Yuan Y, Sun J, Zhao M, Hu J, Wang X, Du G, Chen NH (2010) Overexpression of alpha-synuclein down-regulates BDNF expression. Cell Mol Neurobiol 30:939-946.

Zhao Y, Zhao B (2013) Oxidative stress and the pathogenesis of Alzheimer's disease. Oxid Med Cell Longev 2013:316523.

Ziebell M, Khalid U, Klein AB, Aznar S, Thomsen G, Jensen P, Knudsen GM (2012) Striatal dopamine transporter binding correlates with serum BDNF levels in patients with striatal dopaminergic neurodegeneration. Neurobiol Aging 33:428 e421-425.