Chapter

The Causative and Curative Roles of Brain-Derived Neurotrophic Factor in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is characterized by the activation of degenerative and inflammatory processes in brain circuits that control movement and, according to the degree of progression of the damage, can cause neuropsychological disorders such as cognitive dysfunction. Changes in gene expression profile or post-translational modifications in secretory proteins such as neurotrophic factors could define the disease progression. Brain-derived neurotrophic factor (BDNF) is relevant, because it not only participates in neuronal survival, neurotransmission, dendritic growth and cellular communication but also in disease progression. In this chapter, considering both experimental evidences and clinical reports, the authors will analyze the contribution of BDNF as one of the causes of neurodegeneration and neuroinflammation; discuss the participation of this neurotrophic factor in the development of cognitive dysfunction, and finally the scope of novel BDNF-based therapies for PD.

Keywords: neurodegeneration, regeneration, BDNF, therapy, cognitive dysfunction

1. Introduction

Parkinson's disease is the second most common neurodegenerative disease worldwide, with high annual costs of treatment. The death of dopaminergic neurons and inflammation are the main cellular processes associated with motor and cognitive dysfunctions in PD [1–4]; these events can be potentiated by the loss of the brain-derived neurotrophic factor (BDNF), a key neurotropic factor in degeneration and regeneration processes.

2. BDNF

2.1 Sources

BDNF, discovered in 1982, is a pleiotropic neurotrophin (NT). The gene encoding for *BDNF* is located on chromosome 11p14.1. Under normal conditions, this neurotrophic factor is synthesized as a non-covalently bound homodimer that contains a signal peptide next to the initiation codon, a pro-region containing an N-linked glycosylation site, and interacts with its receptor as a homodimer [5]. The *BDNF* gene, in rodents, consists of nine untranslated 5′ exons, each linked to individual promoter regions, and a 3′ coding exon (IX), which encodes the amino acid sequence of the BDNF pre-protein. Similarly, human *BDNF* gene also consists of multiple 5′ exons spliced to a single 3′ coding exon. The transcription of neurotrophins is finely regulated by several intracellular signaling pathways and by different transcription factors [6].

This NT is synthesized as an inactive precursor form, pre-pro-BDNF that can be cleaved to form a mature neurotrophin that is transported to the plasma membrane and then released in an unprocessed manner. The "pre" sequence is normally deleted when it translocates through the Golgi membrane, producing the pro-BDNF of 32 kDa. Small amounts of a truncated 28 kDa pro-BDNF can also be formed in the endoplasmic reticulum without interfering with the final levels of active, mature 14 kDa BDNF (m-BDNF). The N-terminal pro-domain of BDNF facilitates intracellular trafficking and regulated secretion. After cleavage of N-terminal region, the m-BDNF is released, although this does not exclude the release of the pro-BDNF form [6].

The BDNF shows affinity for two types of receptors. The first is a 75 kDa glycoprotein from the family of tumor necrosis factor receptors, represented by p75 NTR and P75 + sortilin receptors, and the second is a receptor from the protein tropomyosin receptor kinase (Trk) family, which involves the TrkA, TrkB and TrkC, whose main ligands are neuronal growth factor (NGF), BDNF/neurotrophins (NT-4 and NT-3), respectively. The p75 receptor binds to the pro-BDNF isoform and can induce apoptosis and bind non-neurotrophic ligands such as the glycoprotein of rabies virus, amyloid peptides and also other pro-neurotrophins; it can also generate neurite retraction and synaptic weakening and facilitate long-term depression [6–8]. The m-BDNF binds to TrkB receptors promoting cell survival, neurite extension and long-term synaptic potentiation and improves learning and memory; it also promotes synaptic plasticity, neurogenesis, formation of angiogenic tubes, regulation of neurotransmitter release and dendritic growth [5, 6, 9–11].

2.2 Physiological relevance

At the brain level, BDNF is produced in the hippocampus, amygdala, *stria terminalis*, septum, nuclei of the solitary tract and cortex [8, 12], where it regulates the survival and differentiation of various neuronal populations, including sensory neurons, cerebellar neurons and spinal motor neurons. However, it was observed that the brain is not the only source of BDNF, since its expression has been demonstrated in human immune cells (T or B cells and monocytes), adipose tissue cells, β-cells, vascular endothelial cells and in blood [13, 14]. Its presence in ovaries has also been described, where it participates in folliculogenesis [15]; in the heart [16] and in other organs, it participates in angiogenesis and immunomodulation process [17]. The presence of BDNF in other organs of the body raises the hypothesis that exogenous neurotrophic factors provide a symptomatic treatment during the patient's disease state rather than a cure for the nervous system disorders that cause the disease [18].

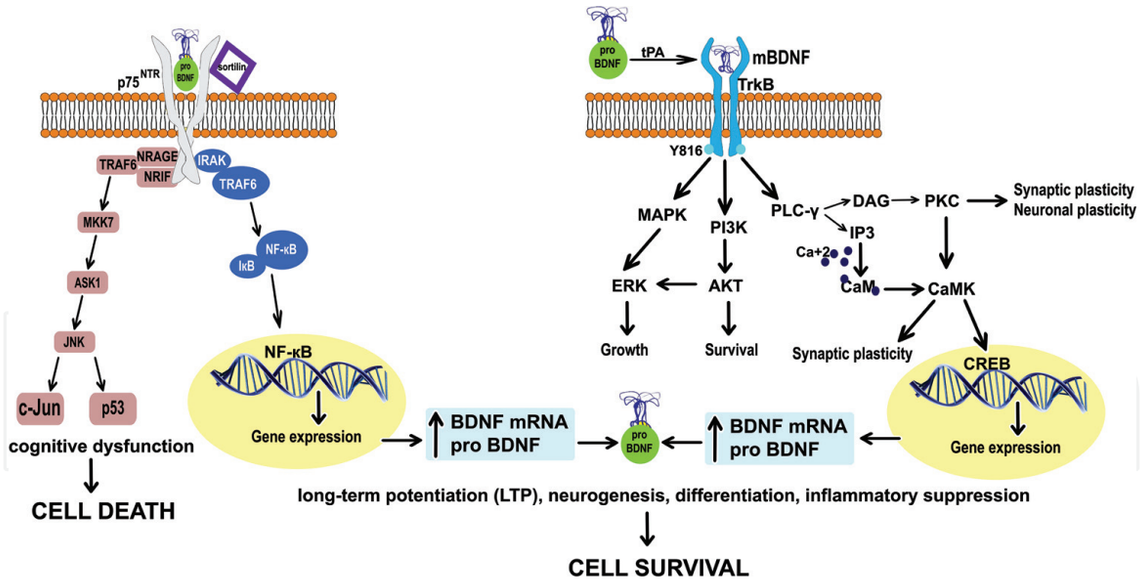

Figure 1.
Causative and curative roles of BDNF. Schematic view of cognitive dysfunction mediated by binding of pro-BDNF to p75NTR receptor leading to apoptotic cell death. Induction of BDNF gene due to the binding of pro-BDNF to p75NTR + sortilin and mBDNF to TrkB receptors leading to cell survival mediated by NF-κB and CREB, respectively. BDNF, brain-derived neurotrophic factor; mBDNF, mature BDNF; p75NTR, p75 neurotrophin receptor; NRAGE, p75NTR interacting protein; NRIF, neurotrophin receptor interacting factor; TRAF, tumor necrosis factor receptor-associated factor; MKK7, mitogen-activated protein kinase kinase 7; ASK1, apoptotic signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; IRAK, interleukin-1 receptor-associated kinase; IκB, kappa light polypeptide gene enhancer in B-cell inhibitor; NF-κB, nuclear factor kappa-light chain enhancer of B cells; TrkB, tropomyosin receptor kinase B; tPA, tissue plasminogen activator; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositol 3-kinase; AKT, protein kinase B; PLC-γ, phospholipase C gamma; DAG, diacylglycerol; PKC, protein kinase C; IP3, inositol triphosphate; CaM, calmodulin; CaMK, calmodulin-dependent protein kinase; CREB, cyclic adenosine monophosphate response element-binding protein.

Alterations of BDNF expression are implicated in the development of a variety of central nervous system (CNS) diseases, including neurodegenerative disorders, such as Alzheimer's, Parkinson's, Huntington's disease and amyotrophic lateral sclerosis, and psychiatric disorders, such as depression and schizophrenia [14, 18]. However, several studies have shown that the therapeutic application of BDNF prevents neuronal degeneration after axotomy and other forms of neuronal injury [19–22]. In addition, beneficial effects of BDNF have been reported in animal models of neurodegenerative diseases. Therefore, BDNF is now considered as a potential therapeutic agent for human neurodegenerative disease, for example, motor neuron disease and PD (**Figure 1**).

3. BDNF in Parkinson's disease

The cause of PD is linked with several molecular factors related to the survival and susceptibility of the dopaminergic neurons (DN) of the *substantia nigra* (SN) [23–25]. The imbalance in the levels of this neurotrophic factor can affect the motor and cognitive performance in parkinsonian patients. It has been detected that BDNF levels decrease in serum as well as in the SN and caudal-putamen nuclei of patients with PD [26, 27].

Recently, it has been proposed that the detection of a low concentration of BDNF in serum is a biomarker of the early stages of the disease [28, 29]. The low concentration of this neurotrophic factor in serum of PD patients may be due to a low transcription of the *BDNF* gene. Howells et al. [30] reported that the surviving DN located in the SN of patients with PD contained low levels of BDNF

mRNA, suggesting that this condition contribute to the death of DN and to the development of the disease. To counteract the death of DN, Salehi and Mashayekhi [31] proposed that BDNF is produced by glial cells that increase their population as a result of an active response to neurodegeneration, since they reported an increase in BDNF levels in cerebrospinal fluid of patients with PD [31].

Currently, well-known mechanisms of microRNAs (miRNAs) play a crucial role in neurotrophin gene regulation. These miRNAs are short non-coding RNAs of ~22 nucleotides that are coupled to the RNA-induced silencing complex (RISC) and regulate the degradation of the RNAs [32]. Several miRNAs regulate BDNF expression and could be directly involved in the survival of DN. It has been reported that miR-1 represses the levels of BDNF expression through regulatory sites in the 3′-UTR sequence of the gene [33–35]. In addition, miR-1 levels have been found to be decreased in patients with PD compared with healthy individuals [36]. The decrease in miR-1 in patients with PD may be due to an activated mechanism to increase the expression of BDNF and promote the survival of the remaining DN in the SN.

In this regard, it has also been reported that BDNF is negatively regulated by the damage induced with neurotoxin in a murine model of Parkinsonism using MPP+. The MPTP neurotoxin is converted to MPP+ by the enzyme monoamine oxidase (MAO-B), expressed by astrocytes. The MPP+ is then internalized into the DN specifically by the dopamine transporter and upon reaching toxic levels in the mitochondria and inhibits the complex I of the electron transport chain [37]. Zhang et al. [38] reported that the treatment with MPP+ led to an increased expression of miR-210-3p and decreased expression of BDNF. To corroborate the results, they performed the inhibition of miR-210-3p and observed that the levels of BDNF increased and the survival of the tyrosine hydroxylase-positive DN of the SN in mice injected with MPTP was also significantly improved. The regulation of BDNF expression has become a key strategy for the rescue of damaged DN in PD.

Another factor that alters the secretion of BDNF is the single nucleotide functional polymorphism Val66Met, whose effect has been widely studied in humans [39–41]. This polymorphism consists of a substitution of valine amino acid by methionine at position 66 of the precursor protein (pro-BDNF) causing a decrease in secretion induced by depolarization [42]. The distribution of alleles has been reported in several populations, with the Val/Val allele prevailing (from 59 to 72%), followed by Val/Met (from 25 to 38%) and with a lower prevalence of the Met/Met allele (from 2 to 4%) [43–45]. The effect of polymorphism has been studied with controversial results as some groups argue that there is an advantage of the carriers of the Met/Met allele, by showing a better cognitive performance than the individuals who presented the Val/Met allele [44]; other researchers conclude that the fact of carrying at least one 66Met allele has a high prevalence of having a greater cognitive deterioration when PD is present [43].

One of the main characteristics of PD is the formation of Lewy bodies that are composed mainly of α-synuclein protein [46]. Recently, it was found that this protein interacts with the neurotrophic receptor TrkB, inhibiting its internalization and its correct distribution. This interaction blocks BDNF signaling and results in increased death of DN induced by the MPTP [47]. In addition, α-synuclein has been shown to affect the retrograde axonal transport of BDNF and confirm the inhibition of the signaling pathway in a PD model [48]. The inhibition of this neurotrophic factor makes them susceptible to the DN of the SN and contributes to the symptoms observed in PD.

4. Parkinson: clinical aspects and neurological bases

Currently, PD affects the adult population (˃65 years) and even young people [49, 50]. Although PD is multifactorial, indisputable signs of the disease include the progressive degeneration of the DN of the nigrostriatal pathway due to oxido-redox imbalance, followed by neurodegeneration, neuroinflammation, Lewy bodies' deposits and the generalized damage of the neural circuits that control movement [24, 51, 52].

The degenerative process develops mainly in the DN. In humans, the early loss of dopaminergic neurons from the SN drastically reduces the striatal dopamine concentration [53, 54]. The origin of the motor and non-motor alterations can be sporadic due to genetic deregulation. Several genetic alterations have been described in *α-synuclein*, *SNCA*, *PINK 1*, *DJ-1*, *LRRK2*, *ATP13A2*, *PLA2G6*, *FBX07*, *VPS35* and *BDNF* genes [55, 56]. Independent of the etiologic origin, patients with PD develop motor and even cognitive dysfunctions.

4.1 Motor impairment

The Parkinson's motor symptoms are bradykinesia, rigidity, inclined posture and tremor at rest. Neuroimaging studies suggest that the motor signs of the disease appear when 50–70% of the DN damage is present [57]. Tremor at rest is the symptom that is present in more than 70% of the patients with PD; these idiopathic tremors are more noticeable when the patient is not performing a specific movement [58]. Electrophysiological studies suggest that tremor at rest in PD is generated by multiple oscillatory circuits that are operating at the same frequencies (4 ± 6 Hz); this tremor is improved with the administration of levodopa, while orthostatic tremor, in PD, is characterized by rapid and specific tremors that affect the legs and trunk when standing. This tremor presents a frequency of 14 ± 18 Hz, where levodopa has no effect, which indicates that the pathophysiology of orthostatic tremor in PD might be different from the tremor at rest [59].

The bradykinesia or slowness of movement is manifested by the decrease in manual dexterity or the difficulty to get up from where they are sitting. Also during the progress of the disease, patients show postural instability with increased risk of falls as they take much faster and shorter steps, and postural instability has a poor response to dopamine treatments [58]. The symptoms of PD are progressive; however, the rate of progression in motor symptoms is variable according to the period of development of the disease in which they occur [60].

Other motor imbalance is the hypomimia, which is characterized by the decrease in facial expression or in the number of eye blinks, blurred vision, altered look, speech alteration, as well as the presence of dystonia or movement disorders, which causes involuntary contractions of the muscles, stooped posture, difficulty turning, kyphosis or scoliosis, which refer to an abnormal curvature of the spine, walking with the drag of the feet, or "freezing" or inability to move in patients with advanced stage of PD [59].

In functional magnetic resonance imaging studies (fMRI) of akinetic patients, changes have been observed during the performance of a complex sequential motor task, showing a reduced functional magnetic resonance signal in the rostral part of the supplementary motor area and in the right dorsolateral prefrontal cortex. In addition, these patients also showed a significant bilateral increase in the activation of the primary sensorimotor cortex, the premotor cortex lateral, the caudal part of the supplementary motor area, the inferior parietal cortex and the anterior cingulate cortex, and in other cortical motor areas [61]. It has been mentioned that during

the earliest pathological stage of PD, neuronal degeneration occurs in motor nuclei of the brainstem, olfactory bulbs and limbic areas; as it proceeds, it continues to the temporal and paralimbic cortices, as well as to the thalamic nuclei, until reaching associative areas such as the prefrontal lobes, and to finally involve the first order and sensory motor areas [62–64].

However, Agosta et al. [65] found that the progression of the disease in patients with moderate and severe PD shows a small cortical atrophy compared with healthy individuals; this atrophy involves the thalamus and the prefrontal cortex; they also report that the loss of gray matter did not significantly worsen in later stages of the disease, with the thalamus showing this atrophy. They also observed that a microstructural damage of the white matter (WM) occurs with the increase in the severity of the disease, involving the brainstem, cerebellum, thalamocortical, interhemispheric and limbic pathways, as well as the extra motor association tracts. They correlate the damage in WM with the degree of cognitive deficit, considering that the damage in WM probably contributes to the more severe motor and non-motor dysfunctions that occur in patients in later stages.

4.2 Cognitive dysfunction

Parkinson's disease is associated with multiple cognitive deficits and an increased risk of dementia, especially in its late stage. In addition, alterations in visuospatial, attentional, executive and memory functions may occur [66]. Epidemiological studies show that cognitive impairments are present between 24 and 62% of patients with newly diagnosed PD, and in the long term about 15% of patients remain cognitively intact [67]. The incidence of dementia is approximately 100 per 100,000 patients per year among patients with PD, suggesting that people with PD have a three to six times greater risk of developing dementia than people of the same age without PD [68]. However, the pathophysiological mechanisms involved in these cognitive deficits are not yet clear.

At present, neurotrophic factors have attracted attention from both clinical and experimental levels. BDNF is one of the key molecules in the modulation of cerebral plasticity and can induce long-term potentiation (LTP) through the activation of signal transduction routes; this LTP plays a key role in the neurophysiological basis for learning and memory [69]. In experimental animal models, it has been observed that the inhibition of BDNF signaling in knockout mice can affect spatial learning and memory; on the contrary, in the general population, it has been observed that at higher levels of BDNF in the hypothalamus there is a better cognitive function, including memory [70]. Recently, it has been detected that serum levels of BDNF decrease significantly in those diseases with cognitive deficits, such as Alzheimer's disease, mild cognitive impairment and Huntington's disease [27, 71, 72].

At the clinical level, there has been an association between serum BDNF levels and cognitive impairment. For example, one study observed the association between the decreased levels of BDNF present in cerebrospinal fluid, which contributes to early cognitive deterioration in PD, in particular to executive-attentional dysfunction [20]. On the other hand, an increase in BDNF concentrations has been detected in the same sample type of individuals with this pathology with respect to non-diseased controls [31], which could be due to a glial activation to increase the synthesis of this neurotrophin in response to brain damage [19]. Some authors have reported the association between the Val66Met BDNF polymorphism and cognitive dysfunction in patients with PD [43, 44]; subjects with Met BDNF allele show decreased cognitive flexibility when compared to homozygous carriers of the Val BDNF allele [45] (**Figure 2**).

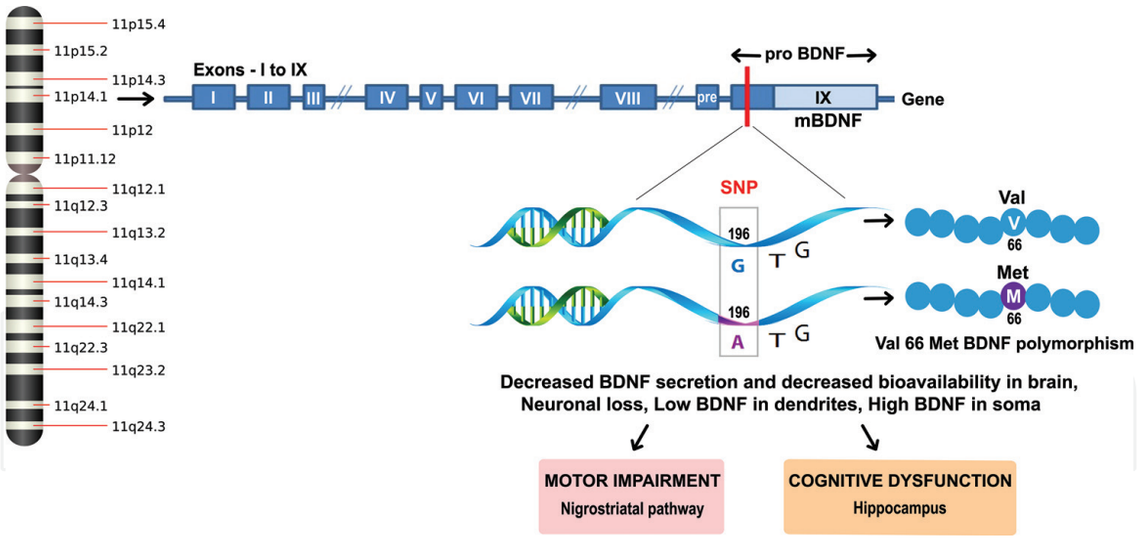

Figure 2.
Val 66 Met/G196A BDNF polymorphism in Parkinson's disease. Schematic representation showing the structure and location of BDNF gene and the location of single nucleotide polymorphism (SNP) that leads to the disease. BDNF, brain-derived neurotrophic factor.

In basic research, it has been observed that a higher concentration of hippocampal BDNF improves spatial memory in Morris's water maze [73]. The hippocampus is an important nucleus for learning and memory consolidation processes, and since BDNF plays an important role in the neuroplasticity of the hippocampus, the absence of this neurotrophin might affect the processes of learning and memory in the short and long term. Also, BDNF as well as TrKB has been shown in animal models to participate in the survival of DN in the SN [74], which is one of the main populations affected in PD. Therefore, the deficiency of BDNF, as well as its TrKB receptor, could be related to the loss of DN and the progression of the disease.

In studies of patients with dopaminergic neurodegeneration, a reduction in serum BDNF levels was observed, accompanied by a loss of striatal dopamine transporter (DAT) binding, that is, a positive correlation was found between the striatal DAT junction and BDNF levels [75]. On the other hand, there are several reports showing an increase in serum BDNF levels and also improvement in cognitive performance in PD patients, who underwent cognitive rehabilitation, when compared to a placebo group. These findings suggest that serum BDNF levels may represent a biomarker for the effects of cognitive rehabilitation in PD patients affected with mild cognitive impairment [76].

4.3 BDNF and aging in PD

Aging is another important variable that not only leads to the slow progression of PD but also hampers the medical treatment response [77]. There is aging without PD, but there is no PD without aging [78], showing decreased dopamine levels, increased sensitivity to mitochondrial dysfunction, alterations in calcium channel activity, accumulation of iron and neuromelanin, changes in protein degradation pathways [79], striatal spine retraction [80] and loss of striatal spine density [81]. With advancing age, the loss of DA neurons is fully expressed in PD genetic models in *C. elegans* [82] and human-induced pluripotent stem cells [83]; thus, aging is the key to the pathogenesis of PD [84]. In PD patients, aging leads to severe gait disturbances including musculoskeletal rigidity, axial impairment and age-related dementia [85].

In the brain, next to nigrostriatal pathway, hippocampus is highly sensitive to aging and BDNF is critically involved in the regulation of age-related hippocampal

decline [86]. In normal striatum, BDNF maintains dendritic spine density and synapse function, whereas in aged striatum, impaired BDNF signaling is common, which is further intensified in BDNF Val66Met SNP individuals [87]. With an increase in human age, BDNF mRNA levels remained same but TrkB mRNA levels decreased in hippocampus [88], indicating that BDNF-TrkB system of hippocampus is sensitive to aging [89] and deficiency of BDNF-TrkB signaling leads to the progression of PD [74]. Recent reports in aged brain suggest a diminished capacity of aged brain to transcribe, release and/or respond to BDNF [87]. As a result, treatment with TrkB agonist activates TrkB and downstream signaling cascades in BDNF-independent manner, which is neuroprotective both *in vitro* and *in vivo* [90].

5. Anxiety and depression in PD: BDNF role

At pre-clinical level, alterations in the synthesis and presence of BDNF are related to psychiatric disorders such as anxiety and depression [91, 92]. PD patients with Val66Met BDNF and G/G-BDNF-Val66Met polymorphisms are more predisposed to develop symptoms of anxiety or depression when observed at genetic level [39]. At the protein level observation, pro-BDNF is a facilitator of hippocampal long-term depression (LTD), and Val66Met pro-BDNF impairs memory function but pro-BDNF with Met completely inhibits hippocampal LTD indicating the antagonistic activities of pro-BDNF and BDNF on hippocampal LTD [93]. A *post-mortem* study on PD patients who received antidepressant drugs reported that the treatment with antidepressants can induce BDNF expression in hippocampus [94]. However, activity-dependent secretion of BDNF and understanding the mechanism of $p75^{NTR}$-pro-BDNF pathway are crucial to completely understand the hippocampal LTD modulation [93].

In this context, murine models has led to demonstrate the presence of the Val66MetBDNF polymorphism associated with anxiety-like behavior and significant increase of corticosterone, the physiological stress hormone, in serum [95]. Similar to human findings, the decreased production of BDNF in the hippocampus, amygdala and prefrontal cortex [96, 97] can be reversed with antidepressant drugs [91]. Whereas Tuon et al. evaluated the anti-depressant effect of BDNF, in a 6-hydroxydopamine (6-OHDA) murine model, by replacing the pharmacological therapy with physical exercise and observed a decrease of depressive-like behavior, which was associated with the restoration of pro-BDNF, BDNF and TrkB receptor levels both in the hippocampus and the *striatum* of rats [98].

Despite the importance of BDNF in plasticity and cellular maintenance, the serum levels of this NT have been studied [99]. Existing evidence shows that low concentration of BDNF is a risk factor to generate depression in PD patients [100].

6. Therapy using BDNF: experimental approaches and patents in animal models

In brain, BDNF not only mediates region-specific effects on synaptic function and neuronal morphology [8] but is also involved in various functions including aging [101], anxiety [102], chronic pain [103], deafness [104], depression [105] and long-term memory storage [9]. BDNF is proven to be the best therapeutic gene for treating metabolic syndrome [106], Friedreich's ataxia [107], neuropsychiatric or neurocognitive disorders [108], brain ischemia [109], schizophrenia [110], glaucoma [111], epilepsy [112], spinocerebellar ataxia typ. 6 [113], Huntington's disease

[21], multiple sclerosis [114], amyotrophic lateral sclerosis [115], spinal cord injury [116], Alzheimer's disease [22] and PD [117].

Despite encouraging and numerous researches supporting the potential therapeutic role of BDNF in non-human primate trials, no satisfactory results were found in clinical trials due to the disability to cross blood-brain barrier (BBB) and to reach degenerating neurons as such [118]. Hence, alternative methods like addition of poly ethylene glycol (PEG), either at N-terminal or at C-terminal, and vector-mediated BBB drug delivery were done to improve the BDNF distribution for use in clinical trials [119].

However, very short half-life of BDNF limits the effectiveness as a therapeutic protein, and thus, exogenous delivery methods are necessary to translate BDNF-based therapies to the clinic. In this direction, gene delivery methods through viral vectors have gained lot of attention by researchers in the beginning, but later on, it was proved that the use of viral vectors in the clinic was proven difficult due to the limited biodistribution and host immunogenicity [120]. Later on, non-viral and nanocarrier (liposome and polyplex) mediated gene delivery drew the attention as nanotechnology offers new possibilities for designing vehicles. Along with the nanotechnology, proteomics also integrated leading to the production of fusion protein vectors and mimetics (both protein and non-protein). The outline of the potential therapeutic role of BDNF in treating neurodegenerative disorders, specific focus on PD, by various researches (**Table 1**) and the patents related to BDNF (**Table 2**) are tabulated.

Animal model (toxin)	**Mode of BDNF supply**	**Result/outcome**
Mouse (MPTP) [121–123]	Intranigral	Increased cell survival
	Non-peptide mimetics of BDNF	
Rat (6-OHDA) [117, 124–127]	Intranigral transplants of human mesenchymal stem cells (hMSC) secreting the BDNF protein	Regulated neurotrophic effect and proved vehicle for the targeted neurotrophic delivery
	Intranigral injections of recombinant human BDNF in healthy rats	Chronic BDNF did not attenuate dopaminergic parameters in either striatum or SN
	Intra ventricular infusion	Adult brain parenchyma may recruit and/or generate new neurons
	Intranigral neurotensin (NTS)-polyplex nanocarrier mediated gene delivery	Neurorecovery by neuritogenesis in early stage of PD
	Intranigral recombinant adeno-associated virus (rAAV) vector-mediated gene delivery	No signs of neuroprotection
Rat (MPTP) [128]	Transplanting genetically engineered fibroblasts expressing BDNF protein	Axonal regeneration
Monkey (MPTP) [129]	Intrathecal infusion	Less neuronal loss and damage was observed in SN
Rhesus monkey [130, 131]	Stimulation of BDNF secretion by caloric restriction; physical exercise	Increased neuronal survival and locomotor activity in both SN and striatum

Table 1.
Therapeutic research works using BDNF.

Assignee/s	Inventor (date)	Title
Max-Planck Gesellschaft zur Forderung der Wissenschaften, Regeneron Pharmaceuticals Inc.	Yves-Alain Barde (1989)	Brain derived neurotrophic factor
Synergen Inc.	Frank Collins (1990)	Production of biologically active recombinant members of the NGF/BDNF family of neurotrophic proteins
Teva Pharmaceutical Industries Ltd.	Liat Hayardeny (2009)	Treatment of BDNF-related disorders using laquinimod
Center for research and advanced studies of the national polytechnic institute	Daniel Martinez-Fong (2012)	Compositions and methods for Parkinson's disease treatment by BDNF-flag gene transfer through neurotensin polyplex to nigral dopamine neurons
Curna Inc., The Scripps Research Institute	Faghini Mohammad Ali and Coito Carlos (2013)	Treatment of brain derived neurotrophic factor related diseases by inhibition of natural antisense transcript to BDNF
VDF FutureCeuticals	Zbigniew Pietrzkowski (2013)	Compositions and methods of BDNF activation
Meiji Co., Ltd.	Midori Natsume (2015)	Promoting the production for the composition of the brain-derived neurotrophic factor
Zhou Yi	Zhou Xinfu (2015)	Application of brain-derived neurotrophic factor precursor protein as target for treating affective disorders

Table 2.
Patents related to BDNF and its therapeutic role.

The experimental models of Parkinson give evidence of many recovery strategies to BDNF *in situ*, however till date exist great limitations to use these findings in novel therapies. Some pre-clinical and clinical resources have been patented (**Table 2**).

7. Clinical perspectives of BDNF-related therapy

The main objectives of experimental and clinical research include better understanding and proper diagnosis, developing new treatments and preventing them to the maximum extent. Currently, there are innumerable experimental pathology studies dedicated to solve the pathophysiology and possible treatment of PD. Based on this, clinical trials offer an excellent opportunity to help doctors and researchers to find better ways in detection, treatment or prevention in a safe way and, therefore, offer hope to people suffering from PD. Current studies include genetics, diagnostic imaging, studies that allow the identification of biomarkers of this disease, pharmacological treatment methods and various proposals for experimental therapies [132, 133]. Development and application of deep brain stimulation through implanting electrodes at specific sites to recover neuronal function is now a treatment option for some people with advanced PD when patients no longer respond to medications [134].

Having PD during aging involves rapid progression of motor impairment, altered mood and cognitive dysfunction. At the cellular level, there is a rapid loss of function and neuronal survival due to the absence of production of neurotrophic

factors such as BDNF. In the preclinical phase, some experimental approaches evaluated in animal models have partially prevented the DN degeneration and neuroinflammation. However, these approaches have great challenges; the therapies should be specific to one cell population, guarantee biosafety for human use, low cost and induce a sustained therapeutic effect.

Although BDNF was found to be promising in animal models of PD, no significant results from clinical trials are reported [135], and thus, therapeutic usage of BDNF for PD in humans is not yet reported. However, as BDNF cannot pass through the BBB, intracranial administration is must and this may be overcome by delivering BDNF bound to certain molecular carriers that can cross BBB to avoid intracranial surgery-related complications and long-term effects on behavioral disorders [136]. In this aspect, researchers from University of California have combined BDNF with mesenchymal stem cells (MSC) for treating neurodegenerative diseases, but no published scientific reports exist on preclinical and clinical trials of MSC/BDNF stem cell product [137].

8. Conclusion

Brain-derived neurotropic factor is relevant to neuronal maintenance and participates in the survival of dopaminergic neurons. The deficit of this neurotrophin is the key for the pathophysiology of PD because it limits the regeneration of motor and cognitive circuits. The absence of BDNF could promote the cognitive dysfunction in vulnerable subjects. The knowledge of the synthesis and delivery routes of this neurotrophin will allow the search for better therapies focused in patients with neurodegenerative diseases.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Glossary

6-OHDA (6-hydroxydopamine) is an analogue of dopamine that produces high neurotoxicity into catecholaminergic neurons. The intracerebral 6-OHDA model is widely used to evaluate some Parkinson's symptoms in rodents.

Cognitive dysfunction is characterized by damage in neuronal circuits that regulate intellectual function, memory and concentration in humans.

Functional magnetic resonance imaging (fMRI) is a clinical technique to evaluate function and systems-level structure in living brain.

Gene delivery is referred as inserting or silencing foreign material into host cells for eliciting a therapeutic benefit. This can be achieved by vectors which include viral/non-viral, liposome, nanoparticles and peptides.

Levodopa (L-3, 4-dihydroxyphenylalanine) is a molecule derived from tyrosine (Y) amino acid, a catecholamine precursor. Levodopa is the drug more widely used to treat early stage of PD.

Lewy bodies are intracytoplasmic inclusions comprising mainly aggregates of α-synuclein protein.

Long-term depression (LTD) is lasting of neuronal synapses for a long time followed by a long patterned stimulus.

Long-term potentiation (LTP) is a result of increased levels of signal transmission of neurons in learning and memory processes.

MicroRNAs are short sequences of ribonucleotides. These molecules show complementarity and thus with messenger RNAs (mRNAs), thereby degrading their mRNA targets or preventing their translation into proteins.

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a pro-drug to MPP+ neurotoxin that induces loss of catecholaminergic and GABAergic neurons. The systemic administration of MPTP is referred as classic model of PD in mouse and monkeys.

Neurodegeneration means progressive loss of structure and/or function of neurons and finally leading to death.

Neuroinflammation is a highly regulated process that makes the host organism to deal and eradicate the infection by means of innate and adaptive immune systems. This includes the activation of immune cells and release of pro or anti-inflammatory cytokines, thus protecting the nervous tissue.

Neurotrophins are growth factors that regulate the survival and cell differentiation in several processes such as motor control, learning, memory and cognition.

Mitochondrial dysfunction is characterized by the loss of electron transport chain efficiency leading to reduced synthesis of adenosine-5′-triphosphate (ATP) and increased synthesis of free radicles. This is the characteristic feature of aging and chronic disorders.

Polymorphism is referred as diverse forms of a gene, formed due to the result of mutations or epigenetic changes.

Trk (tropomyosin receptor kinase) receptors correspond to membrane receptor proteins that regulate several biological processes including synaptic strength and plasticity in nervous system. Till date, TrkA, TrkB and TrkC are recognized as members of this family.

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