Chapter

Brain-Derived Neurotrophic Factor and Stem Cell-Based Technologies in Huntington's Disease Therapy

Irina Kerkis, Joyce Macedo da Silva,
Cristiane Valverde Wenceslau,
Nicole Caroline Mambelli-Lisboa and Eduardo Osorio Frare

Abstract

Neurodegenerative disorders, such as Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD), are characterized by changes in the levels and activities of neurotrophic factors (NTFs), such as brain-derived neurotrophic factor (BDNF). Gain-of-function and loss-of-function experiments demonstrate in fact the linkage between wild-type huntingtin (HTT) and gene transcription and intracellular transport of BDNF. In the present chapter, we will analyze the involvement of BDNF in HD and other neurodegenerative diseases. We will discuss the current BDNF technologies focusing on stem cell therapies that induce BDNF upregulation, for instance, the method of autologous mesenchymal stem cell (MSC) culturing in the presence of cocktail of BDNF inducers and factors (MSC/BDNF), genetic engineering of MSC and their use as a vector for BDNF gene delivery, and combined method of establishment of embryonic stem cell (ESC)-derived BDNF-overexpressing neural progenitors, which is still at the preclinical stage. Clinical trial that uses MSC/BDNF is already in course, while genetic engineering of MSC/BDNF is in perspective to treat adult and juvenile HD. The potential application of these technologies is beyond HD. Other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases also can be further included in the list of clinical trials that use MSC/BDNF or even ESC/BDNF-overexpressing neural progenitors.

Keywords: brain-derived neurotrophic factor, stem cell technologies, Huntington's disease

1. Introduction

It is common knowledge that learning and memory depend on controlled signaling processes at synapses and include the precise synaptic communication between neurons and other cellular associates. Thus, the brain-derived neurotrophic factor (BDNF) and its partners appeared as key regulators of synaptic plasticity, which is the ability of synapses to increase or decrease their activity [1–3].

Generally, neuromodulators regulate neuronal plasticity; however, BDNF act as a mediator between synaptic plasticity and synaptic communication. In addition, BDNF can act in association with neurotransmitter signaling cascades showing immediate and helpful functions on synaptic plasticity [3]. Due to these properties, BDNF recently attracts much attention and became a leading strategy to stimulate neuronal and synaptic plasticity for potential protective and functionally restorative treatments for neurological and psychiatric disorders [4, 5].

Actions of BDNF in normal brain function and links between BDNF and neurodegenerative diseases suggest therapeutic potential of BDNF in diseases such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's diseases (PD), amyotrophic lateral sclerosis (ALS), metabolic disorders (such as obesity), spinal cord injury, stroke, ischemia, etc. [6–8].

However, delivery of BDNF to the brain is challenging. The blood–brain barrier (BBB) obstructs drug delivery to the brain for the treatment of a wide range of central nervous system (CNS) diseases [9]. BDNF, a 27-kDa protein, has minimal BBB penetrability. BDNF also has a short half-life in the blood (0.92 min) and a poor pharmacokinetic profile. Systemic intravenous deliveries of BDNF are inefficient, due to the BBB, and cause strong side effects. Direct injections of BDNF into the central nervous system are invasive and limited by diffusion restrictions. Thus, alternative strategies, such as BDNF-secreting stem cells, for delivery of neuroprotective drugs are critical for promoting their clinical potentials.

2. Brain-derived neurotrophic factor

BDNF is a member of the neurotrophin family and widely expressed in the mammalian brain [1]. Precursor BDNF (proBDNF) includes an N-terminal prodomain and a C-terminal mature domain. ProBDNF is synthesized in the endoplasmic reticulum (ER) and secreted from dense-core vesicles. After packaging into dense-core vesicles, ProBDNF is trafficked through either the regulated secretory pathway or the constitutive secretory pathway [10, 11]. ProBDNF is processed to mature BDNF by several alternative cellular mechanisms. ProBDNF can be cleaved within the endoplasmic reticulum by furin or within the trans-Golgi network in regulated secretory vesicles by proconvertase enzymes. If proBDNF reaches the extracellular milieu, it can be processed by plasmin, or become endocytosed, and then cleaved to produce mature BDNF. Mature BDNF comprises dimers of the mature domain [12, 13].

BDNF can function in a highly localized manner or at a distance [14, 15]. The fact that BDNF is expressed within the peripheral ganglia and is not restricted to neuronal target fields raises the possibility that BDNF exerts paracrine or autocrine actions on neurons and non-neuronal cells [16]. BDNF binds to tyrosine receptor kinase B (TrkB) and low-affinity nerve growth factor receptor (LNGFR), also known as CD271 and p75 (NTR) [8, 17]. BDNF has been shown to modulate the activity of various neurotransmitter receptors, such as the alpha-7 nicotinic receptor [18]. BDNF has also been shown to interact with reelin, which is a large secreted extracellular matrix glycoprotein, and it supports the processes of neuronal migration and place in the developing brain through controlling cell–cell interaction signaling chain [19].

BDNF plays an important role in neurogenesis; neuronal differentiation, polarization, and guidance; and the survival of stem cells and their progenitors. The survival and differentiation of several classes of neurons in vitro, including the neural crest neurons, placode-derived sensory neurons, dopaminergic neurons in the substantia nigra, basal forebrain cholinergic neurons, hippocampal neurons,

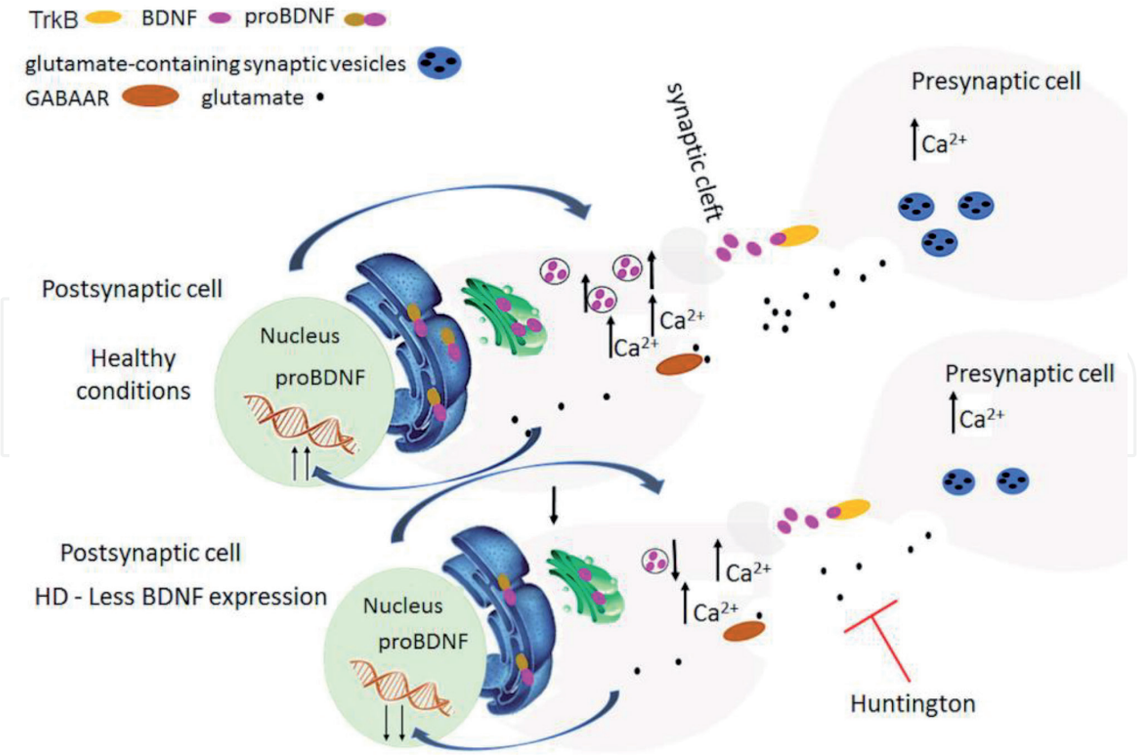

Figure 1.
The scheme of signaling involved BDNF synaptic effects and its maturation. The synthesis of BDNF from proBDNF in the endoplasmic reticulum is shown. ProBDNF binds to Golgi to enhance the proper folding of the mature domain. ProBDNF is cleaved by proteases at synapses and converted to mature BDNF. Mature BDNF binds to TrkB and glutamate released to stimulate ProBDNF transcription.

and retinal ganglia cells, are enhanced by BDNF. BDNF affects behavior by influencing the branching of differentiated neurons and the formation and maturation of spines and synapses. In the mature nervous network, amplification and enhancement of neuronal circuit structure, modulation of synaptic plasticity, and regulation of cognitive brain function (such as learning and memory) also depend on BDNF expression [4, 6–8, 20, 21].

The effects of mature BDNF are closely regulated. Even a small change in BDNF concentration may disturb the development of neural circuits and the regulation of brain function. Expression of BDNF is reduced among patients with Alzheimer's [22, 23] and Huntington's disease [7, 24]. Age-associated changes in BDNF-mediated pathways have also been shown to enhance inflammation and increase myocardial injury after myocardial infarction in the aging heart [24, 25].

The unique role of BDNF in cognitive and affective behaviors suggests their possible use to treat cognitive deficits (**Figure 1**).

3. BDNF biodistribution and serum levels in neurological and psychiatric disorders

The neocortex in the brain has morphologically stratified subdivisions into six layers: I, molecular layer; II, external granular; III, external pyramidal; IV, internal granular; V, internal pyramidal; and VI, multiform. BDNF mRNA levels vary between layers but are higher in Layer VI [26] (**Figure 2**).

The various types of afferent nerve fibers branch out in the cortex in different ways. The afferent fibers arriving from the thalamus nuclei terminate primarily in the middle layers, predominantly in the dendritic leaflets of the IV lamina.

The fibers of the other thalamic nuclei, coming from the cortical areas, ascend vertically and diffuse into different layers depending on their origin (the fibers of the thalamus intralaminal nuclei mostly terminate in Layer VI, whereas the fibers of the cortical areas terminate mainly in Layers II and III). Cortical efferent fibers, such as afferents, go to other cortical areas or to subcortical areas. Most subcortical efferences descend through the internal capsule and may or may not reach the level of the spinal cord. The blades most involved in these efferences are blade V (corticoid fibers, fibers for the brain stem and spinal cord) and lamina VI (corticothalamic fibers). Blade III is the largest source of corticocortical fibers [27].

Brain-derived neurotrophic factor is widely distributed in the central nervous system and has survival-promoting actions on a variety of CNS neurons. BDNF mRNA levels are relatively low during infancy and adolescence, peak during young adulthood, and are maintained at a constant level throughout adulthood and aging (**Figure 3**).

BDNF mRNA levels vary between layers, with Layer VI consistently higher than other layers [20, 28, 29]. The BDNF can be measured in blood samples and patients'

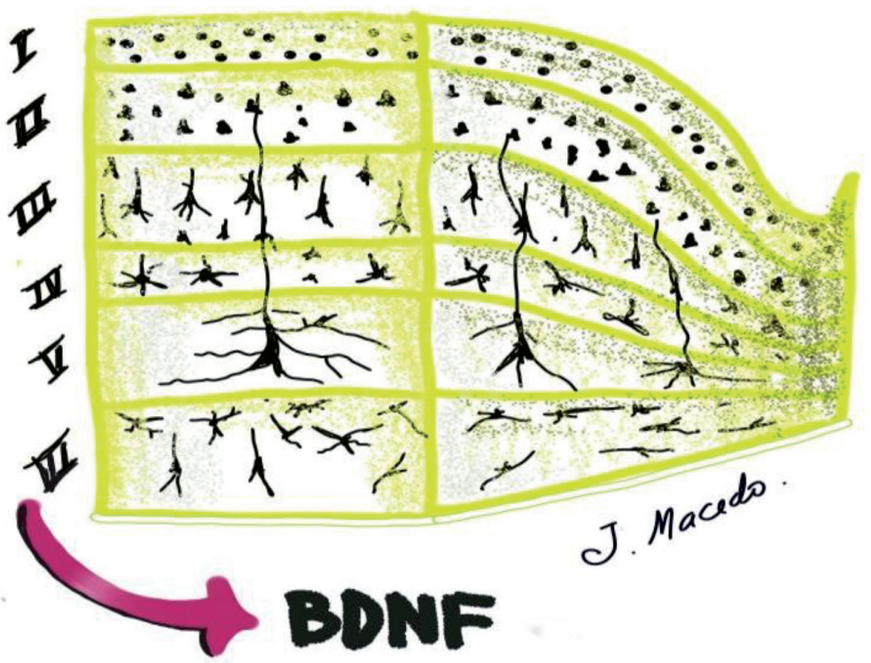

Figure 2.
Neocortex in the brain.

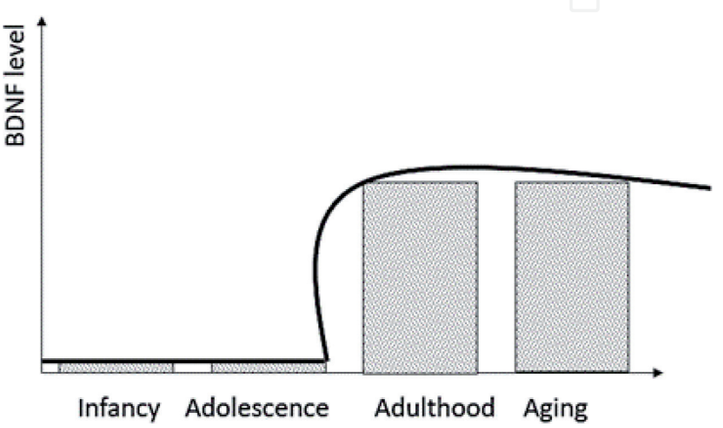

Figure 3.
BDNF throughout life.

cerebrospinal fluid. The analyses BDNF levels in CNS in neurological and psychiatric disorders showed to be different from those of normal invidious. Several studies showed a correlation between the BDNF level in serum and the clinical data for symptomatic patients [28].

Thus, the mean BDNF serum concentration was significantly lower in patients with Huntington's disease than in healthy controls ($P < 0.001$). In patients with Huntington's disease, the scale used to measure clinical parameters is Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS is a clinical evaluation including domains to assess the motor, cognitive, and behavioral functions and functional capacity (Huntington Study Group, 1996).

In patients with Huntington's disease, serum BDNF levels are lower as motor and cognitive disorders progress, as measured by the UHDRS (**Figure 4**) [30].

No significant difference in BDNF levels in serum according to the subjects' gender nor significant factor modifications related to the subjects' age or to the time of day when blood was drawn ($P > 0.05$) were found [30]. A serum BDNF deficiency in HD patients is in line with the previous works highlighting trophic factor

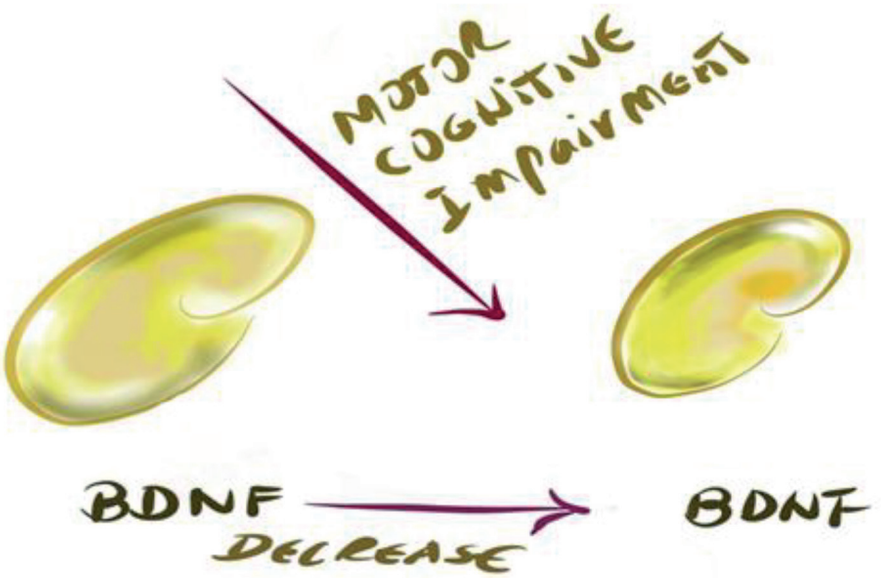

Figure 4.
BDNF decreasing with motor and cognitive impairment.

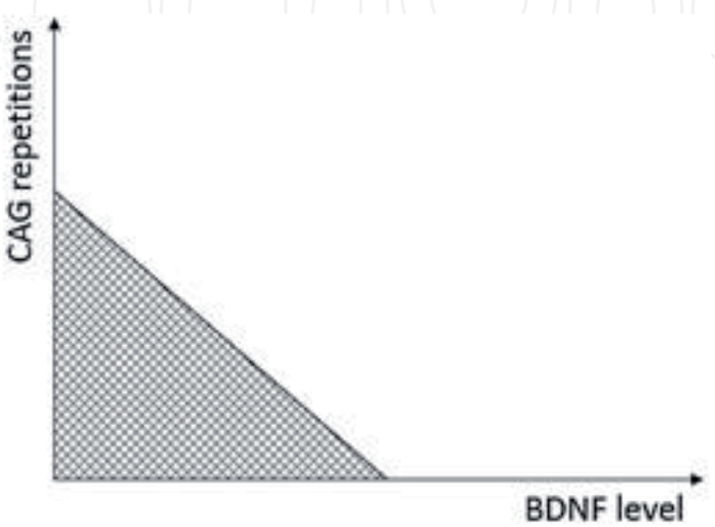

Figure 5.
Correlation between CAG repetitions and BDNF levels in patients with Huntington's disease.

dysfunction in animal models and autopsy material [31–33]. This means that BDNF levels and CAG repeats are indicators for clinical prognosis; the higher the number of CAG repeats is, the worse the prognosis, and the lower the BDNF levels are, the patient is worse clinically (**Figure 5**) [31–33].

Several lines of evidence indicate that BDNF is essential in sustaining the physiological processes of the normal, intact adult brain. BDNF has a role in modulating dendritic branching and dendritic spine morphology as well as synaptic plasticity and long-term potentiation (LTP), which is a persistent increase in synaptic strength following a high-frequency stimulation of a chemical synapse. In this manner, BDNF influences learning and memory [8, 34, 35]. BDNF also modulates hypothalamic metabolic function, further reflecting the diversity of its role in the adult brain [6].

3.1 Drugs increasing BDNF level

Some drugs may increase endogenous BDNF levels in the brain (**Figure 6**) like antidepressants, lithium, and ampakines (class of drugs that act as positive modulators of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)).

These drugs are already used for symptoms that arise in diseases concomitant with neurodegenerative diseases, such as mood swings and depression. The mechanisms of action for increasing BDNF levels are still complex and not fully understood [6, 36].

3.2 Factors affecting BDNF level

Animal studies show that exercise and a calorie-restricted diet can positively affect BDNF levels in various brain regions such as the cortex and hippocampus [6]. If this pattern can be replicated in humans, this information reinforces the importance of exercise orientation and a healthy diet throughout life, especially in the young adult phase, when humans have higher levels of BDNF production in order to have good neurological performance.

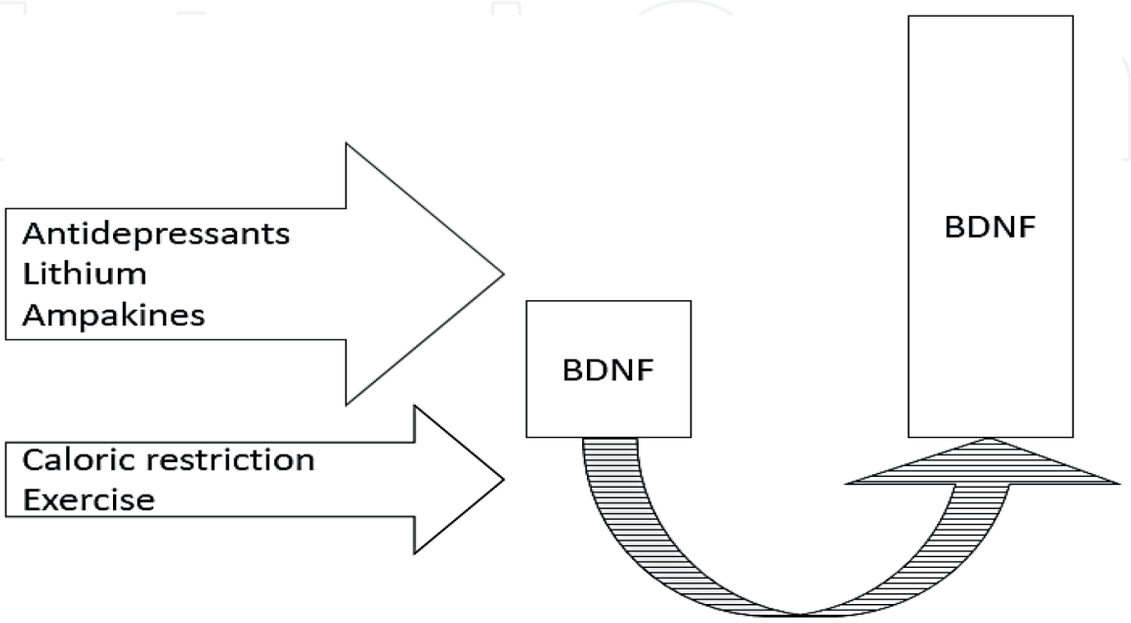

Figure 6.
Drugs and factors that increase endogenous BDNF levels.

4. BNDF therapeutic effect in neurodegenerative diseases

Neurodegenerative diseases have a continuous process of neuronal destruction and loss that can be delayed or even reversed with therapies that can improve the functional state of neurons. In theory, the earlier the diagnosis of these diseases, the greater the chance of the disease reaching a plateau and not progressing, consequently increasing the chance that the patient will preserve more functionality. Based on this therapeutic potential, growth factors have been evaluated in patients with various neurological disorders, including ALS, peripheral neuropathy, and Huntington's, Parkinson's, and Alzheimer's diseases.

4.1 Huntington's disease

Huntington's disease is a hereditary degenerative neurological disease. The most affected neurons are those that make up the extrapyramidal region but specifically the striatum (caudate and putamen nuclei). The genetic pattern of transmission is autosomal dominant, caused by the expansion of CAG triplicate repeats in the gene encoding the protein huntingtin [37].

The clinical form that expresses this lesion is evidenced by involuntary movements (chorea) in the face, trunk, and limbs, difficulty in articulating the voice, gait difficulties, and balance and cognitive decline [38–40].

In Huntington's disease, BDNF transport from the cortex to the striatum is impaired. Infusion of the BDNF protein into the striatum of HTT-mutant mice increases striatal neurons and improves motor function [39]. The use of ampakines has also been observed to increase BDNF levels in mice with beneficial results for the memory of these animals including [40].

The use of BDNF in humans would not act on the genetic cause of this disease but could slow down the progression of the disease providing a better quality of life for patients and maintaining functionality in daily activities and can be used as adjunctive therapy to currently available treatments.

4.2 Other neurodegenerative diseases

For other neurodegenerative diseases, BDNF is expected to act by improving cellular function through mechanisms involving the phosphoinositide 3-kinase and AKT and protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway.

4.2.1 Amyotrophic lateral sclerosis

ALS is a neurological disease characterized by a progressive motor neuron atrophy, which leads to a generalized weakness and respiratory failure over a relatively rapid period of approximately 2 years. There was an old concept that ALS was an exclusively motor disease, but a cognitive impairment is now being observed as part of a frontal dementia.

The use of BDNF in this disease in both experimental animal models and later in human clinical studies could delay neuronal loss, improving the brain and spinal cord microenvironment [6].

4.2.2 Alzheimer's disease

Alzheimer's disease is a more common form of dementia and has an onset of insidious cognitive loss, progressive worsening of language, impaired visual–spatial

orientation, and executive functions, and the patient has no other causes of dementia in clinical research such as infectious diseases, metabolic diseases, vascular diseases, use of medicines, and use of toxic substances, among others.

BDNF levels become deficient in the entorhinal cortex and the hippocampus in Alzheimer's disease [22, 41, 42]. A series of studies was conducted in several animal models of Alzheimer's disease to assess the effect of therapeutic application of BDNF to the entorhinal cortex [6, 43].

4.2.3 Parkinson's disease

Parkinson's disease is a neurodegenerative disorder that impairs motor function and cognitive ability. The progressive degeneration of dopaminergic neurons is reflected in the motor dysfunction of the patients.

BDNF treatment can prevent the loss of dopaminergic neurons in the substantia nigra. This is true in rodent animal models and nonhuman primates [44].

Parkinson's disease is a condition where BDNF therapy is promising and may return minimal functional and perhaps even cognitive ability to patients in the future.

5. Mesenchymal stem cell-based BDNF therapy

Mesenchymal stem cells are adult stem cells capable of self-renewal and differentiation into multiple lineages including cartilage, adipose, and bone. MSCs have been isolated from a wide range of sources including bone marrow (BM), umbilical cord, adipose tissue, multiple dental tissues, etc. Taking advantage of their multipotent, regenerative, and immunosuppressive properties, as well as tropisms to inflamed, hypoxic, and cancerous sites, MSCs have been used in various therapeutic studies, and MSC-based therapies have been shown to be safe. However, when applied alone, the efficacy in some MSC-based therapies remains low. To improve therapeutic efficacy, MSCs have been genetically modified to acquire targeted delivery function, therapeutic drug incorporation, and cell surface modification. To enhance their native properties, MSCs can also be genetically modified to overexpress therapeutic proteins.

MSCs are known to promote tissue repair by expressing a variety of bioactive molecules and secreting substances such as cytokines and growth factors. MSCs naturally secrete BDNF at low levels, varying from 0 to 200 pg/mL (**Table 1**) [45–50]. Cell therapy in regenerative medicine requires MSCs that secrete high BDNF level and are safe for use in humans.

5.1 NurOwn-MSC

BrainStorm Stem Therapeutics developed the patented NurOwn® technology that uses autologous MSCs which grow in proprietary conditions (using cocktails of inducers and factors), converting them into biological factories secreting a variety of neurotrophic factors (NTFs), including BDNF. Bahat-Stroomza et al. reported that human bone marrow-derived MSCs produced an approximately 200 pg/mL and 1400 pg/mL BDNF at baseline and after BDNF induction, respectively (**Table 1**) [46, 51]. The later was tested in humans; the bone marrow-derived MSCs did not show toxicity or side effects. Finally, Gervois et al. showed BDNF value around 2–2.5 ng/mL per $1x10^5$ MSC [52]. Currently, this technology is used in Phase 2 open-label, multicenter study of repeated intrathecal administration

of autologous MSC-NTF cells in progressive multiple sclerosis. This study was designed to provide preliminary data on the safety and efficacy of these cells (**Table 2**).

5.2 MSC/BDNF and HD preclinical study

BDNF gene has been successfully introduced into MSCs using viral vectors, such as adenovirus and lentivirus (**Table 3**). Viral infections produced an 80- to 180-fold increase in BDNF production, although the absolute BDNF concentration varied significantly among the different studies (**Table 1**) [48, 53, 54] and toxicity and side effects remain unknown. More recently, preclinical double-blinded study transplanted human MSC/BDNF intrastriatal (within the corpus striatum) in two strains of immune-suppressed HD transgenic mice: YAC128 and R6/2. Following MSC/BDNF transplantation, atrophy in YAC128 mice decreased. This treatment reduced mice's anxiety that was measured in the open-field assay and increased the mean life span of the R6/2 mice. It is interesting that both MSC and MSC/BDNF transplantations induced a significant increase in neurogenesis-like activity in R6/2 mice [54]. These cells provide a platform delivery system for future studies involving corrective gene-editing strategies. Researches plan to submit an investigational new drug application to the Food and Drug Administration in order to develop Phase 1 safety and tolerability trial of MSC/BDNF in patients with Huntington's disease [55].

Cell type	Cell passage	Time of measuring (hrs)	Amount	Measure	Measure/ cell number	References
hBM-MSC	3	24	190.5	pg	5×10^5 serum free	[45]
hBM-MSC (NurOwn®)	n/if	n/if	200	pg	10^6	[46]
hBM-MSC	7–9	n/if	20–188	pg	n/if	[47]
heMSC			74–196			
hAD-MSC			35			
hBM-MSC	n/if	48	72.2	pg	—	[48]
hUC-MSC	n/if	24	50	pg	—	[49]
hWJ-MSC	n/if		37	pg	n/if	[50]

hBM-MSC, human bone marrow MSC; heMSC, human endometrial MSC; hAD-MSC, human adipose tissue-derived MSC; hUC-MSC, human umbilical cord blood MSC; hWJ-MSC, human Wharton jelly MSC; n/if, not informed.

Table 1.
BDNF secretions observed in different MSCs that naturally secrete BDNF.

Cell type	BDNF-expressing cells	Cell passage	Time of measuring (h)	Amount	Measure	Measure/ cell number	References
hBM-MSC (NurOwn®)	Wild type	n/if	n/if	200	pg	10^6	[46]
	Induced to express			1400			

Table 2.
BDNF secretions observed in BM-MSCs that naturally secrete BDNF in comparison with NurOwn BM-MSC.

Cell type	BDNF-expressing cells	Cell passage	Time of measuring (h)	Amount	Measure	Measure/ cell number	References
hBM-MSC	Adenovirus	—	48	4.73	ng	10^5	[53]
hBM-MSC	Adenovirus	—	48	643.63–13229.09 Control cells: 72.72	pg	n/if	[48]
hBM-MSC	Lentivirus	—	24	10.9–18.1	ng	2×10^5	[54]

Table 3.
BDNF secretion in BM-MSC transduced with BDNF.

6. Embryonic stem cell-derived neural progenitors/BDNF

Embryonic stem cells are pluripotent stem cells that propagated indefinitely. These cells can differentiate into cells of all three germ layers (endoderm, mesoderm, and ectoderm). ESC from teratoma and embryoid body (EB) that mimics early embryonic development. These cells differentiate efficiently into neural progenitor and functional neurons. Therefore, they can be used to differentiate into striatal medium spiny neurons (MSNs) that are lost in HD. MSNs depend on BDNF activity, and different studies try to use exogenous BDNF for striatal neuroprotection in rodent striatum HD models. Therefore, ESC and induced pluripotent stem cells (iPSC) seem to be an appropriate cell source for HD and other neurodegenerative diseases. Accordingly, ESC-derived neural progenitors overexpressing BDNF were transplanted into quinolinic acid (QA) chemical and two genetic HD mouse models (R6/2 and N171-82Q). Thus, this study combined cell replacement and BDNF supply as a potential HD therapy approach. QA-lesioned mice demonstrate the rescue of motor function by BDNF neural progenitors, while genetic mouse models showed fewer improvements. It is important to note that tumor formation was absent. The study also showed that adult neurogenesis was preserved in a BDNF-dependent manner. It was concluded that ESC-derived neural progenitors and BDNF are potential therapeutic strategies for HD to ameliorate neurodegenerative symptoms [55, 56].

7. Conclusions

It is possible to conclude that BDNF is essential for the survival, phenotypic features, and function of mature, fully developed neurons. In turn, changes in BDNF level or distribution seem to be important in the pathogenesis of neurodegenerative conditions in humans and especially in HD.

Preclinical studies over the past 20 years tested a possible neuroprotective role of BDNF in HD, which is a potent pro-survival and pro-differentiation factor for developing and adult neurons. Robust preclinical data in animals suggest that the neurotrophic action of BDNF alleviates both neuropathological and motor function deficits in the brain of patients with HD.

The intention of BDNF administration is suggested as a possible therapeutic strategy for patients with HD. However, clinical studies that used recombinant BDNF demonstrated a series of technical problems and the limited neuroprotective effects, which led to an interruption of trials with BDNF.

Based on the evidence described above, other approaches, such as stem cell-based technologies, of BDNF delivery to the brain have been developed and are currently under investigation providing promising results.

Acknowledgements

This work was supported from Cellavita Ltd., Valinhos, SP, Brazil, and Butantan Foundation, São Paulo, SP, Brazil. The funder had no role in the study design, data analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

Dr. Kerkis I. received research support from Cellavita Ltd.

Author details

Irina Kerkis[1*], Joyce Macedo da Silva[2], Cristiane Valverde Wenceslau[3], Nicole Caroline Mambelli-Lisboa[3] and Eduardo Osorio Frare[1]

1 Laboratory of Genetics, Butantan Institute, São Paulo, Brasil

2 Azidus Brasil, Valinhos, São Paulo, Brasil

3 CellAvita Ltd., Valinhos, São Paulo, Brasil

*Address all correspondence to: irina.kerkis@butantan.gov.br

References

[1] Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors. 2004;**22**:123-131. DOI: 10.1080/08977190410001723308

[2] Chao MV. Neurotrophins and their receptors: A convergence point for many signalling pathways. Nature Reviews. Neuroscience. 2003;**4**:299-309. DOI: 10.1038/nrn1078

[3] Park H, Poo MM. Neurotrophin regulation of neural circuit development and function. Nature Reviews. Neuroscience. 2013;**14**:7-23. DOI: 10.1038/nrn3379

[4] Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nature Reviews. Neuroscience. 2013;**14**:401-416. DOI: 10.1038/nrn3505

[5] Leal G, Comprido D, Duarte CB. BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology. 2014;**76**:639-656. DOI: 10.1016/j.neuropharm.2013.04.005

[6] Nagahara AH, Tuszynski MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nature Reviews. Drug Discovery. 2011;**10**:209-219. DOI: 10.1038/nrd3366

[7] Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nature Reviews. Neurology. 2009;**5**:311-322. DOI: 10.1038/nrneurol.2009.54

[8] Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Archives of Medical Science. 2015;**11**:1164-1178. DOI: 10.5114/aoms.2015.56342

[9] Pardridge WM. Blood-brain barrier delivery. Drug Discovery Today. 2007;**12**:54-61. DOI: 10.1016/j.drudis.2006.10.013

[10] Aid T, Kazantseva A, Piirsoo M, Palm K, Timmusk T. Mouse and rat BDNF gene structure and expression revisited. Journal of Neuroscience Research. 2007;**85**:525-535. DOI: 10.1002/jnr.21139

[11] Al-Qudah MA, Al-Dwairi A. Mechanisms and regulation of neurotrophin synthesis and secretion. Neurosciences (Riyadh). 2016;**21**:306-313. DOI: 10.17712/nsj.2016.4.20160080

[12] Greenberg ME, Xu B, Lu B, Hempstead BL. New insights in the biology of BDNF synthesis and release: Implications in CNS function. Journal of Neuroscience. 2009;**29**:12764-12767. DOI: 10.1523/JNEUROSCI.3566-09.2009

[13] Kuczewski N, Porcher C, Lessmann V, Medina I, Gaiarsa JL. Activity-dependent dendritic release of BDNF and biological consequences. Molecular Neurobiology. 2009;**39**:37-49. DOI: 10.1007/s12035-009-8050-7

[14] Ammar MR, Thahouly T, Hanauer A, Stegner D, Nieswandt B, Vitale N. PLD1 participates in BDNF-induced signalling in cortical neurons. Science Reports. 2015;**5**:14778. DOI: 10.1038/srep14778

[15] Dechant G, Barde YA. The neurotrophin receptor p75(NTR): Novel functions and implications for diseases of the nervous system. Nature Neuroscience. 2002;**5**:1131-1136. DOI: 10.1038/nn1102-1131

[16] Gibon J, Buckley SM, Unsain N, Kaartinen V, Seguela P, Barker PA. proBDNF and p75NTR control excitability and persistent firing of cortical pyramidal neurons. The Journal of Neuroscience.

2015;**35**:9741-9753. DOI: 10.1523/JNEUROSCI.4655-14

[17] Lima Giacobbo B, Doorduin J, Klein HC, Dierckx RAJO, Bromberg E, de Vries EFJ. Brain-derived neurotrophic factor in brain disorders: Focus on Neuroinflammation. Molecular Neurobiology. 2019;**56**:3295-3312. DOI: 10.1007/s12035-018-1283-6

[18] Massey KA, Zago WM, Berg DK. BDNF up-regulates alpha7 nicotinic acetylcholine receptor levels on subpopulations of hippocampal interneurons. Molecular and Cellular Neurosciences. 2006;**33**:381-388. DOI: 10.1016/j.mcn.2006.08.011

[19] Ringstedt TA. Tale of two genes: Reelin and BDNF. In: Fatemi SH, editor. Reelin Glycoprotein: Structure, Biology and Roles in Health and Disease. New York, USA: Springer; 2008. pp. 237-238. DOI: 10.1007/978-0-387-76761-1_16

[20] Cohen-Cory S, Kidane AH, Shirkey NJ, Marshak S. Brain-derived neurotrophic factor and the development of structural neuronal connectivity. Developmental Neurobiology. 2010;**70**:271-288. DOI: 10.1002/dneu.20774

[21] Ninan I. Synaptic regulation of affective behaviors; role of BDNF. Neuropharmacology. 2014;**76**(Pt C):684-695. DOI: 10.1016/j.neuropharm.2013.04.011

[22] Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RC. Decreased serum brain-derived Neurotrophic factor (BDNF) levels in patients with Alzheimer's disease (AD): A systematic review and meta-analysis. International Journal of Molecular Sciences. 2019;**20**:257. DOI: 10.3390/ijms20020257

[23] Jiao S-S, Shen L-L, C Zhu X-LB, Liu Y-H, Liu C-H, Yao X-Q, et al. Brain-derived neurotrophic factor protects against tau-related neurodegeneration of Alzheimer's disease. Translational Psychiatry. 2016;**6**:e907. DOI: 10.1038/tp.2016.186

[24] Zuccato C, Marullo M, Vitali B, Tarditi A, Mariotti C, Valenza M, et al. Brain-derived neurotrophic factor in patients with Huntington's disease. PLoS One. 2011;**6**:e22966. DOI: 10.1371/journal.pone.0022966

[25] Kermani P, Hempstead BBDNF. Actions in the cardiovascular system: Roles in development, adulthood and response to injury. Frontiers in Physiology. 2019;**10**:455. DOI: 10.3389/fphys.2019.00455

[26] Hevner RF. Layer-specific markers as probes for neuron type identity in human neocortex and malformations of cortical development. Journal of Neuropathology and Experimental Neurology. 2007;**66**:101-109. DOI: 10.1097/nen.0b013e3180301c06

[27] Standring S. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 40th ed. London, UK: Churchill Livingstone, Elsevier; 2008. p. 1584

[28] Webster MJ, Weickertb CS, Hermanb MM, Kleinmanb JE. BDNF mRNA expression during postnatal development, maturation and aging of the human prefrontal cortex. Brain Research. Developmental Brain Research. 2002;**139**:139-150. DOI: 10.1016/S0165-3806(02)00540-0

[29] Fukumitsu H, Ohtsuka M, Murai R, Nakamura H, Itoh K, Furukawa S. Brain-derived neurotrophic factor participates in determination of neuronal laminar fate in the developing mouse cerebral cortex. The Journal of Neuroscience. 2006;**26**:13218-13230. DOI: 10.1523/JNEUROSCI.4251-06.2006

[30] Ciammola A, Sassone J, Cannella M, Calza S, Poletti B, Frati L,

et al. Low brain-derived neurotrophic factor (BDNF) levels in serum of Huntington's disease patients. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics. 2007;**144b**:574-577. DOI: 10.1002/ajmg.b.30501

[31] Ferrer I, Goutan E, Marín C, Rey MJ, Ribalta T. Brain-derived neurotrophic factor in Huntington disease. Brain Research. 2000;**866**:257-261. DOI: 10.1016/s0006-8993(00)02237-x

[32] Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science. 2001;**293**:493-498. DOI: 10.1126/science.1059581

[33] Baydyuk M, Xu B. BDNF signaling and survival of striatal neurons. Frontiers in Cellular Neuroscience. 2014;**8**:254. DOI: 10.3389/fncel.2014.00254

[34] Yamada K, Mizuno M, Nabeshima T. Role for brain-derived neurotrophic factor in learning and memory. Life Sciences. 2002;**70**:735-744. DOI: 10.1016/s0024-3205(01)01461-8

[35] Cunha C, Brambilla R, Thomas KL. A simple role for BDNF in learning and memory? Frontiers in Molecular Neuroscience. 2010;**3**:1. DOI: 10.3389/neuro.02.001.2010

[36] Lynch G. Glutamate-based therapeutic approaches: Ampakines. Current Opinion in Pharmacology. 2006;**6**:82-88. DOI: 10.1016/j.coph.2005.09.005

[37] Saudou F, Humbert S. The biology of Huntingtin. Neuron. 2016;**89**:910-926. DOI: 10.1016/j.neuron.2016.02.003

[38] Zuccato C, Cattaneo E. Huntington's disease. Handbook of Experimental Pharmacology. 2014;**220**:357-409. DOI: 10.1007/978-3-642-45106-5_14

[39] Bissonnette S, Vaillancourt M, Hébert SS, Drolet G, Samadi P. Striatal pre-enkephalin overexpression improves Huntington's disease symptoms in the R6/2 mouse model of Huntington's disease. PLoS One. 2013;**8**:e75099. DOI: 10.1371/journal.pone.0075099

[40] Simmons DA, Rex CS, Palmer L, Pandyarajan V, Fedulov V, Gall CM, et al. Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**:4906-4911. DOI: 10.1073/pnas.0811228106

[41] Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, et al. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nature Medicine. 2009;**15**:331-337. DOI: 10.1038/nm.1912

[42] Giuffrida ML, Copani A, Rizzarelli E. A promising connection between BDNF and Alzheimer's disease. Aging. 2018;**10**:1791-1792. DOI: 10.18632/aging.101518

[43] Peng S, Garzon DJ, Marchese M, et al. Decreased brain-derived neurotrophic factor depends on amyloid aggregation state in transgenic mouse models of Alzheimer's disease. The Journal of Neuroscience. 2009;**29**:9321-9329. DOI: 10.1523/JNEUROSCI.4736-08.2009

[44] Mercado NM, Collier TJ, Sortwell CE, Steece-Collier K. BDNF in the aged brain: Translational implications for Parkinson's disease. Austin Neurology & Neuroscience. 2017;**2**:1021. PMID: 29726549

[45] Wilkins A, Kemp K, Ginty M, Hares K, Mallam E, Scolding N. Human

bone marrow-derived mesenchymal stem cells secrete brain-derived neurotrophic factor which promotes neuronal survival *in vitro*. Stem Cell Research. 2009;**3**:63-70. DOI: 10.1016/j.scr.2009.02.006

[46] Bahat-Stroomza M, Barhum Y, Levy YS, Karpov O, Bulvik S, Melamed E, et al. Induction of adult human bone marrow mesenchymal stromal cells into functional astrocyte-like cells: Potential for restorative treatment in Parkinson's disease. Journal of Molecular Neuroscience. 2009;**39**:199-210. DOI: 10.1007/s12031-008-9166-3

[47] Zemel'ko VI, Kozhukharova IV, Kovaleva ZV, Domnina AP, Pugovkina NA, Fridlianskaia II, et al. BDNF secretion in human mesenchymal stem cells isolated from bone marrow, endometrium and adipose tissue. Tsitologiia. 2014;**56**:204-211. PMID: 25509416

[48] Jeong CH, Kim SM, Lim JY, Ryu CH, Jun JA, Jeun SS. Mesenchymal stem cells expressing brain-derived neurotrophic factor enhance endogenous neurogenesis in an ischemic stroke model. Biomed Research International. 2014;**2014**:129145. DOI: 10.1155/2014/129145

[49] Ahn SY, Chang YS, Sung DK, Sung SI, Ahn JY, Park WS. Pivotal role of brain-derived neurotrophic factor secreted by mesenchymal stem cells in severe intraventricular hemorrhage in newborn rats. Cell Transplantation. 2017;**26**:145-156. DOI: 10.3727/096368916X692861

[50] Martins LF, Costa RO, Pedro JR, Aguiar P, Serra SC, Teixeira FG, et al. Mesenchymal stem cells secretome-induced axonal outgrowth is mediated by BDNF. Scientific Reports. 2017;**7**:4153. DOI: 10.1038/s41598-017-03592-1

[51] Sadan O, Shemesh N, Barzilay R, Bahat-Stromza M, Melamed E, Cohen Y, et al. Migration of neurotrophic factors secreting mesenchymal stem cells towards a quinolinic acid lesion as viewed by magnetic resonance imaging. Stem Cells. 2008;**26**:2542-2551. DOI: 10.1634/stemcells.2008-0240

[52] Gervois P, Struys T, Hilkens P, Bronckaers A, Ratajczak J, Politis C, et al. Neurogenic maturation of human dental pulp stem cells following neurosphere generation induces morphological and electrophysiological characteristics of functional neurons. Stem Cells and Development. 2015;**24**:296-311. DOI: 10.1089/scd.2014.0117

[53] Nomura T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis JD. I.V. infusion of brain-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Neuroscience. 2005;**136**:161-169. DOI: 10.1016/j.neuroscience.2005.06.062

[54] Pollock K, Dahlenburg H, Nelson H, Fink KD, Cary W, Hendrix K, et al. Human mesenchymal stem cells genetically engineered to overexpress brain-derived neurotrophic factor improve outcomes in Huntington's disease mouse models. Molecular Therapy. 2016;**24**:965-977. DOI: 10.1038/mt.2016.12

[55] Zimmermann T, Remmers F, Lutz B, Leschik J. ESC-derived BDNF-overexpressing neural progenitors differentially promote recovery in Huntington's disease models by enhanced striatal differentiation. Stem Cell Reports. 2016;**7**:693-706. DOI: 10.1016/j.stemcr.2016.08.018

[56] Reidling JC, Relaño-Ginés A, Holley SM, Ochaba J, Moore C, Fury B, et al. Human neural stem cell transplantation rescues functional deficits in R6/2 and Q140 Huntington's disease mice. Stem Cell Reports. 2018;**10**:58-72. DOI: 10.1016/j.stemcr.2017.11.005