Brain-derived neurotrophic factor in main neurodegenerative diseases

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Discovered in pig brains in 1982, the brain-derived neurotrophic factor (BDNF) is one of the most studied and characterized neurotrophins in the central nervous system. In recent years, BDNF has received considerable attention for its importance in the development and maintenance of normal brain function. This is because BDNF plays an important role in crucial functions of the nervous system, such as the survival, differentiation, and maturation of neurons and glial cells as well as the actions of neuroprotection in adverse conditions, such as glutamatergic overstimulation, cerebral ischemia, hypoglycemia, and neurotoxicity (Kowiarz et al., 2018).

This perspective aims to describe the role of BDNF in understanding the connection between the level of this biomarker and the management of neurodegenerative disorders, in terms of advances/perspectives in the diagnoses/prognoses of these disorders. The effort on the delivery and stability of BDNF in clinical treatment is attracting greater interest, and this is increasingly becoming a frontier topic for the prevention of numerous neurodegenerative diseases.

The human BDNF gene maps to chromosome 11 and has a highly complex structure consisting of 11 exons within the 5' region and nine functional promoters that ensure developmental stage-specific, regional, and cell type-specific expression. Through alternative splicing, each exon can generate a specific transcript/isoform characterized by the presence of a common coding region (Kowiarz et al., 2018). Like other secreted proteins, the BDNF protein is synthesized as a precursor, pro-BDNF, which undergoes proteolytic processing to release its mature form. Deposits of Aβ proteins have been observed to be associated with decreased BDNF concentration in AD, as per clinical studies conducted on the post-mortem brain of patients with this disease. BDNF is, therefore, rapidly released of calcium ions from the intracellular calcium deposit, thereby improving synaptic plasticity (Camuso et al., 2022).

Alongside a full-length TrkB, there are several transcription isoforms of this receptor that generate two truncated isoforms (TrkB-T1 and TrkB-T2), identical to TrkB in the extracellular and transmembrane regions but lacking the intracellular kinase domain. Although the biological role of TrkB-T2, receptor isoforms is not yet fully understood, it has recently been associated with important functions in neurons and glial cells, such as the activation of BDNF intracellular signaling pathways, morphological changes in neurons/glial cells, and dominant-negative inhibition of TrkB signaling. Recent studies have shown that the dysregulation of the truncated isoforms of the TrkB receptor is a common denominator of many neurodegenerative diseases. Studies conducted on mouse models of Alzheimer's disease (AD) have shown an upregulation of TrkB T1 dependent on the accumulation of amyloid-beta (Aβ) oligomers but the mechanisms of interaction between these two processes are not yet fully understood (Tessarollo and Yankappekar, 2022).

In contrast, BDNF appears to be downregulated in AD, as per clinical studies conducted on the post-mortem brain of patients with this disease. BDNF levels in several brain areas of mouse models of AD are associated with an acceleration of synaptic alterations, neuronal apoptosis, and memory deficits.

At present, based on studies on mouse models of AD and on cortical neurons in vitro cultured, it is believed that BDNF is an important protective factor against Aβ-induced neurotoxicity capable of activating the non-amyloidogenic pathway and reducing, in this way, the cytotoxic effect of Aβ oligomers. Furthermore, studies conducted on neuroblastoma cells have shown that this neuroprotective effect of BDNF was dose-dependent. In particular, treatment with 20 μM of Aβ oligomers inhibits the release of SH-SY5Y neuroblastoma cells by increasing the number of apoptotic cells, while a combination of Aβ oligomers and 10 ng/mL of BDNF increases Akt levels, which is a survival signal. In fact, it is known that in the presence of a glibenclamide, which significantly prevents neurodegeneration of these cells (Kim, 2014).

Preclinical studies on the mouse model of AD, 5xFAD, have shown the use of a potent TrkB receptor agonist known as 7,8-dihydroxyflavone, which prevents and delays the progression of the disease. In vivo studies have shown that 5xFAD mice subjected to intraperitoneal injection of 7,8-dihydroxyflavone at 12–15 months of age show an increase in the levels of TrkB expression, a reduced decrease in the number of dendrites and spines of cortical neurons and reduced deposition of Aβ-42 oligomers, preventing typical memory deficits and neurodegenerative effects related to Aβ plaque deposition (Deví and Ohno, 2012).

Intriguingly, genetic studies on mouse models of AD have demonstrated how the Val66Met polymorphism associated with codon 663 of the BDNF gene is related to hippocampal volume reduction, memory impairment, depression behaviors, and the pathogenesis of AD. For AD, the Val/Val genotype induces an increase in phosphorylation of the tau protein, contributing to cognitive decline; furthermore, considering the gender effect on AD susceptibility, the presence of the Met allele in women, but not in men, increases the risk of developing AD (Lim et al., 2022).

Beyond BDNF, clinical reports have demonstrated the involvement of BDNF precursors in AD pathogenesis. Anomalies in the pro-BDNF cleavage have been found in a mouse model of AD resulting in an increase in pro-BDNF levels and a consequent decrease in BDNF mature protein. Conversely, several studies have also highlighted the role of pro-BDNF and mature protein in several regions of AD patients, especially in the parietal cortex, compared to controls (Geren et al., 2017).

Collectively, this evidence suggests a potentially critical role of pro-BDNF in the pathogenesis of AD to support the use of BDNF and its precursor as a novel therapeutic approach to treat AD; it is not surprising that deficiencies in BDNF signaling contribute to the pathogenesis of other important pathological conditions such as Parkinson's disease (PD), where the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta leads to dysfunction of the motor/cognitive system. Several studies have shown that in PD the misfolding of α-synuclein, the main feature of the disorder, could be associated with a reduction in both transcript and protein levels of BDNF in the substantia nigra of PD patients, contributing to the death of nigral dopaminergic neurons. In particular, it was found that the reduction in BDNF levels is accompanied by overexpression of α-synuclein which can interact with the TrkB receptor, preventing its internalization and contributing to the degeneration of dopaminergic neurons. Recent studies have also found upregulated in striatal neurons and the substantia nigra of mouse models of PD, suggesting that this truncated form of the receptor could also represent, along with upregulation of BDNF, a valid therapeutic strategy for slowing or preventing the degeneration of dopaminergic neurons during the progression of the disease (Zuccato and Cattaneo, 2009).

As already known, among the neurotrophins, BDNF plays a key role during the postnatal development of the cerebellar cortex and in the regulation of the survival of granular cells and Purkinje cells. However, beyond its trophic action on cerebellar neuroblasts/TrkB signaling, BDNF has an important role in organizing cytoarchitecture and connectivity within the cerebellar cortex and is considered a critical determinant of cerebellar functions (Camuso et al., 2022). BDNF is, therefore, rapidly emerging as a powerful therapeutic strategy for a cerebellar disease known as spinocerebellar ataxia type 1 (SCA1). SCA1 is a neurodegenerative disease caused by mutations in the Ataxin-1 gene, which progressively leads to cerebellar ataxia, motor dysfunction, and loss of balance.
Several studies conducted on SCA1 mouse models have shown an increase in cerebellar BDNF levels in the early stages of SCA1 and a decrease during the later stages of the disease, mainly in Purkinje cells. Using Ataxin-1 gene (82 Q) mice, a neuron-specific transgenic mouse model of SCA1, Mellesmoen et al. (2019) demonstrated that if BDNF is given early in the brain, it is possible to delay the progression and pathogenesis of this disease in terms of reducing deficit motors and Purkinje cell atrophy.

Although BDNF is widely distributed in the central nervous system, as seen in the cerebellum, the highest level of expression was found in the striatum, where it supports the survival, maturation, and differentiation of striatal neurons, influencing the final size of this brain region. The striatum is an area of the brain involved in Huntington’s disease, an inherited neurodegenerative disease caused by mutations in the gene encoding the huntingtin protein and characterized by impaired involuntary movements involving different parts of the body, progressively leading to motor and cognitive dysfunctions (Zuccato and Cattaneo, 2009). One of the roles of huntingtin is to regulate the transcription and trafficking of BDNF, favoring its interaction with its TrkB receptor. Under physiological conditions, the huntingtin protein promotes the anterograde transport of BDNF from the cortex to the striatum, to support the survival and maturation of striatal neurons. Growing evidence shows that huntingtin mutation inhibits this anterograde trafficking, reducing striatal BDNF levels and thus contributing to striatal BDNF dyshomeostasis (Gauthier et al., 2004).

In the mouse model of Huntington’s disease, it has been shown that overexpression of the BDNF gene in the forebrain allows the recovery of motor defects and reduces brain weight loss; also the upregulation of BDNF induced by a pharmacological approach through amapakine, a positive modulator of AMPA receptors, resulted in an improvement in both synaptic plasticity and memory performance, in accordance with the role of BDNF in the modulation of synaptic transmission and the growth of dendrites and axons. Based on this evidence, manipulation of BDNF expression has been proposed to represent a promising strategy for the treatment of Huntington’s disease (Fumagalli et al., 2006).

Unlike neuronal loss, which is irreversible, the common synaptic defects present in all of these disorders could be recovered through the growth of new terminals and/or dendritic spines. In this context, BDNF plays a key role in the protection and repair of synapses against various toxic insults, as seen in many mouse models of neurodegenerative diseases (Figure 1), representing a powerful and valid molecule recovery of neuronal and synaptic homeostasis.

Newly developed therapeutic interventions and drugs clinically used to counter AD share the same property of positively interfering with BDNF biosynthesis in key brain regions directly involved in the pathophysiology of the disease, such as the prefrontal cortex, hippocampus, striatum, and cerebellum (Fumagalli et al., 2006). In fact, we believe that the reversal of BDNF deficiency in the forebrain regions can contribute to the improvement of AD symptoms.

In conclusion, we underline that the possibility of refining the expression of BDNF in specific brain sites affected by trophic exhaustion could allow a general advancement of strategies to combat neurodegenerative disorders. It must necessarily be considered that the possibility of interfering with endogenous BDNF, for example through lifestyle changes such as an enriched environment, could greatly promote the future therapeutic uses of BDNF in diseases of the nervous system.

This work was supported by “Sapienza” University (Ateneo 2021, RP1211748875C585 to SC).

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References
Camuso S, La Rosa F, Fiorenza MT, Canterini S (2022) Pleiotropic effects of BDNF on the cerebellum and hippocampus: Implications for neurodevelopmental disorders. Neurobiol Dis 163:105606.
Chao MV, Bothwell M (2002) Neurotrophins: to cleave or not to cleave. Neuron 33:3-15.
Devi L, Ohno M (2012) 7,8-dihydroxyflavone, a small-molecule TrkB agonist, rescues memory deficits and BACE1 elevation in a mouse model of Alzheimer’s disease. Neuropsychopharmacology 37:434-444.
Fumagalli F, Racagni G, Riva MA (2006) The expanding role of BDNF: a key factor with multipotent neuroprotective actions against amyloid β-induced apoptosis in neuroblastoma cells. Exp Ther Med 8:1891-1895.
Kowalski P, Pietzau G, Zubia E, Waisk M, Steliga A, Morys J (2018) BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity. Cell Mol Neurobiol 38:579-593.
Lim Y, Maruff P, Barthelemy NR, Goate A, Hassenstab J, Sato C, Fagan AM, Benzinger TLS, Xiong C, Cruchaga C, Levin I, Farlow MR, Graff-Radford NR, Lasker C, Masters CL, Salloway S, Schofield PR, Morris JC, Bateman RJ, McDade E, et al. (2022) Association of BDNF Val66Met with tau hyperphosphorylation and cognition in dominantly inherited Alzheimer disease. JAMA Neurology 79:261-270.
Mellesmoen A, Sheeler C, Ferro A, Rainwater O, Cvetanovic M (2019) Brain-derived neurotrophic factor (BDNF) delays onset of pathogenesis in transgenic mouse model of spinocerebellar ataxia type 1 (SCA1). Front Cell Neurosci 13:509.
Tessarollo I, Yapapaliew S (2022) TrkB truncated isoform receptors as transducers and determinants of BDNF functions. Front Neurosci 16:847572.
Zuccato C, Cattaneo E (2005) Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol 5:311-322.

Figure 1 | Schematic illustration of BDNF expression in different brain regions (color coded) associated with neurodegenerative diseases.

AD: Alzheimer’s disease; BDNF: brain-derived neurotrophic factor; HD: Huntington’s disease; PD: Parkinson’s disease; SCA1: spinocerebellar ataxia type 1. Created with BioRender.com.