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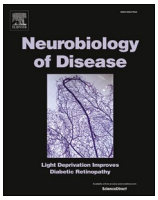

Review

Pleiotropic effects of BDNF on the cerebellum and hippocampus: Implications for neurodevelopmental disorders

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is one of the most studied neurotrophins in the mammalian brain, essential not only to the development of the central nervous system but also to synaptic plasticity. BDNF is present in various brain areas, but highest levels of expression are seen in the cerebellum and hippocampus.

After birth, BDNF acts in the cerebellum as a mitogenic and chemotactic factor, stimulating the cerebellar granule cell precursors to proliferate, migrate and maturate, while in the hippocampus BDNF plays a fundamental role in synaptic transmission and plasticity, representing a key regulator for the long-term potentiation, learning and memory. Furthermore, the expression of BDNF is highly regulated and changes of its expression are associated with both physiological and pathological conditions.

The purpose of this review is to provide an overview of the current state of knowledge on the BDNF biology and its neurotrophic role in the proper development and functioning of neurons and synapses in two important brain areas of postnatal neurogenesis, the cerebellum and hippocampus.

Dysregulation of BDNF expression and signaling, resulting in alterations in neuronal maturation and plasticity in both systems, is a common hallmark of several neurodevelopmental diseases, such as autism spectrum disorder, suggesting that neuronal malfunction present in these disorders is the result of excessive or reduced of BDNF support.

We believe that the more the relevance of the pathophysiological actions of BDNF, and its downstream signals, in early postnatal development will be highlighted, the more likely it is that new neuroprotective therapeutic strategies will be identified in the treatment of various neurodevelopmental disorders.

1. Introduction

Among the various neurotrophins, the brain-derived neurotrophic factor (BDNF) is the most studied and present in almost all brain regions (Devlin et al., 2021), although its role differs depending on the area and stage of developing and adult brain (Hofer et al., 1990; Cohen-Cory et al., 2010). BDNF plays a crucial role in the modulation of major neurodevelopmental processes—such as the survival and growth of neurons and synaptic efficiency and plasticity and, it is heavily involved in the cellular and molecular processes responsible for the formation and maintenance of memory (*e.g.*, relational, spatial, and long-term memory) by promoting synaptic consolidation (Cirulli et al., 2004; Bramham and Messaoudi, 2005; Erickson, 2010; Erickson et al., 2010). Indeed, BDNF is a key mediator of neuronal plasticity within the central nervous system, acting on both pre-synaptic and post-synaptic sites and affecting dendritic spines and adult neurogenesis at different levels (Edelmann et al., 2014; Lin et al., 2018).

The pleiotropic effects of BDNF depend on its ability to participate in a wide range of signal transduction cascades, which can be explained by the presence of variants and active isoforms interacting with two different receptors, *i.e.* the tropomyosin receptor kinase B (TrkB) and the low affinity p75 neurotrophin receptor (p75^{NTR}) (Foltran and Diaz, 2016).

Compared to the neocortex, the prolonged developmental timeline of the cerebellum and hippocampus, wherein neurogenesis and synaptogenesis occur extensively after birth (Walton, 2012), makes these brain regions highly sensitive to BDNF dysregulation and vulnerable to neurodevelopmental anomalies.

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It has become increasingly clear that changes of BDNF expression, particularly in the cerebellum and hippocampus (Ismail and Shapiro, 2019; Neeper et al., 1996) are common to several neurodevelopmental disorders (NDDs). NDDs, often named "synaptopathies" because of structural and functional synaptic plasticity abnormalities, are a broad class of disorders that share motor and cognitive deficits (Ismail and Shapiro, 2019).

A key question in this research field is: how important is the BDNF signal in cerebellar and hippocampal postnatal development and what are the direct implications of its alterations in the onset of synaptic deficits common to NDDs such as autism spectrum disorders?

To answer this question, we critically review rodent and human studies that illustrate how BDNF is essential to coordinate cellular and molecular mechanisms involved in postnatal neurogenesis and synaptogenesis under physiological conditions and how its dysregulation, in terms of expression and signaling, is commonly present in neurodevelopmental diseases.

For this reason, we have chosen to focus on: i) postnatal cerebellar development where the development of cerebellar granule cells can be accurately monitored from progenitor to mature neurons, giving the possibility to clarify the role of BDNF in coordinating the close succession of molecular events that lead to the generation, migration, differentiation of mature neurons and the development of excitatory and inhibitory synapses (Chen, 1999; Waterhouse, 2012; Chen et al., 2016); ii) the hippocampus, which due to its highly plastic and flexible nature in relation to learning and memory, represents a system of excellence for studying how BDNF controls neurogenesis, neuroprotection, synaptic plasticity and long-term potentiation (LTP), during development and in the adulthood (Leal et al., 2015; Sairanen, 2005; Leal et al., 2015).

2. BDNF synthesis and activity

The BDNF was discovered and isolated from pig brain samples by Barde and colleagues in 1982 (Barde et al., 1982). As a small dimeric protein, BDNF is structurally homologous with Nerve Grow Factor (NGF), having 50% amino acid identity with NGF, neurotrophin-3 (NT-3), and NT-4/5 (Bathina and Das, 2015).

In humans, the BDNF gene has been mapped to chromosome 11 at position 14.1 (Maisonpierre et al., 1991) in a region involved in several mental disorders and genetic syndromes (Hanson et al., 1992; Rosier et al., 1994). The human *BDNF* gene contains 11 exons in the 5′ region and nine functional promoters, which are tissue and brain-region specifically activated and give rise to alternatively spliced transcripts (Pruunsild et al., 2007). The rodent *BDNF* gene has 5′ exons with multiple tissue-specific promoters and one 3′ exon encoding the mature form of the BDNF protein (Aid, 2007; Timmusk, 1993; Aid et al., 2007).

BDNF expression levels are low during fetal development, increase significantly after birth, and then decrease during adulthood (Bathina and Das, 2015; Hohn et al., 1990). BDNF is expressed throughout the brain (Hohn et al., 1990; Chen et al., 2017), but its highest level of expression is found within hippocampal and cerebellar neurons (Wetmore et al., 1990; Miranda et al., 2019).

Like other secreted proteins, BDNF is synthesized in the endoplasmic reticulum (ER) as pre-pro-BDNF (Greenberg et al., 2009), which is cleaved in the Golgi apparatus to form a ~ 32 kDa protein called pro-BDNF (Mowla et al., 2001). The resulting precursor can be further processed by specific intracellular and/or extracellular proteases, generating the mature form of ~13 kDa, although pro-BDNF itself can act as an active ligand upon its release into the extracellular space (Mowla et al., 2001; Kolarow et al., 2007; Yang et al., 2014). Upon synthesis, BDNF is stored in secretory granules and, depending on the cell type, it is: i) delivered to dendrites, to modulate the architecture of spines and thus synaptic plasticity (Kellner et al., 2014); or, ii) transported along the axons in an antegrade manner (Altar et al., 1997) to coordinate the stabilization of the presynaptic site and the growth/branching of the axon terminals (Hu et al., 2005; Cohen-Cory et al., 2010).

The opposite effects on cell survival of pro-BDNF and mature BDNF were clarified when these forms were shown to bind two different receptors (Je et al., 2013) (Fig. 1).

The pro-BDNF preferentially interacts with a member of the tumor necrosis factor receptor family, known as the low-affinity neurotrophin receptor p75 ($p75^{NTR}$) (Teng et al., 2005), while BDNF binds with high affinity to tropomyosin kinase receptor B (TrkB), favoring cell survival (Chao and Hempstead, 1995; Zaccaro et al., 2001). Nevertheless, pro-BDNF can also bind with low affinity to TrkB receptor, activating a cell survival signaling, named "extracellular signal-regulated kinases (ERKs)- related pathway" (Fayard et al., 2005).

Mature BDNF binding to TrkB receptor leads to receptor dimerization and autophosphorylation of its intracellular tyrosine residues (Chao, 2003; Philippidou et al., 2011). Phosphorylated receptor (pTrkB) and its ligand are then internalized *via* endosomes, activating three principal cytoplasmic signaling cascades, which are important for cell survival (Huang and Reichardt, 2003; Chen et al., 2005). This is unusual because the internalization of other growth factor receptors is necessary to inactivate the signaling processes (Sorkin and Waters, 1993). The internalized TrkB receptor remains phosphorylated and closely associated with a number of signaling molecules such as PI3 kinase, MAP kinase and PLC-γ (Huang and Reichardt, 2003).

The first pathway is the phosphatidylinositol 3-kinase (PI3K)–serine/threonine kinase 1 (AKT), which suppresses cell death by inhibiting the activities of two forkhead transcription factors, Bax and BAD (the BCL2-associated agonist of cell death) (Cantley, 2002; Tsuruta et al., 2002; Huang and Reichardt, 2003). The second pathway is the Ras mitogen activated protein kinase (MAPK) signaling cascade (Skaper, 2008). Ras is a small protein that binds to GTP, a molecule upstream of several signaling pathways, including Raf/MEK/ERK (extracellular signal-regulated kinases), stimulating the expression of anti-apoptotic proteins such as BCL2 and CREB (a cAMP-response element binding protein) (McCubrey et al., 2007). Thirdly, the phospholipase C-gamma (PLC-γ) pathway, with the activation of the inositol triphosphate receptor (IP3R), leads to the release of intracellular calcium deposits that start the activation of calmodulin kinase (CamK) and protein kinase C (PKC) and, consequently, the synaptic plasticity by the transcription factor CREB (Minichiello et al., 2002; Chao, 2003). It is important to point out that, the PLCγ-mediated response is responsible for fast, short-term effects and favors cell growth and differentiation, while MAPK and PI3K pathways generate long-term transcriptional effects (Yoshii and Constantine-Paton, 2010).

In the developing and adult brain, the TrkB receptor can perform its functions even in the absence of the BDNF ligand, a mechanism known as "transactivation," due to the activation of G protein-coupled receptors (GPRs) (Lee and Chao, 2001). Adenosine and pituitary adenylate cyclase-activating polypeptide (PACAP), two GPR ligands, can activate the TrkB receptor even without BDNF and improve neural cell survival *via* Akt signaling (Rajagopal et al., 2004).

In contrast to TrkB receptor, which has a well-characterized trophic role, $p75^{NTR}$ functions are sometimes opposite. Indeed, by interacting with the TrkB receptor, $p75^{NTR}$ can potentiate and/or reduce TrkB receptor activity, otherwise, it can act with pro-BDNF triggering apoptotic cascades (MacPhee and Barker, 1997; Roux and Barker, 2002; Teng et al., 2005). This binding requires the formation of a complex with adaptor proteins, including sortilin (Nykjaer et al., 2004; Teng et al., 2005). The $p75^{NTR}$ /sortilin receptor complex leads to various activators of apoptotic signaling pathways, such as the c-Jun N-terminal kinase (JNK) and caspase 3–9; while the Ras homolog gene family member A (RhoA), and the nuclear factor kappa B (NF-κB) can also trigger neuronal survival and growth cone development (Teng et al., 2005; Eggert et al., 2021). Although the $p75^{NTR}$ receptor was discovered in 1986 (Johnson et al., 1986), and despite numerous structural and functional aspects studied in depth, its complex activation mechanisms remain elusive.

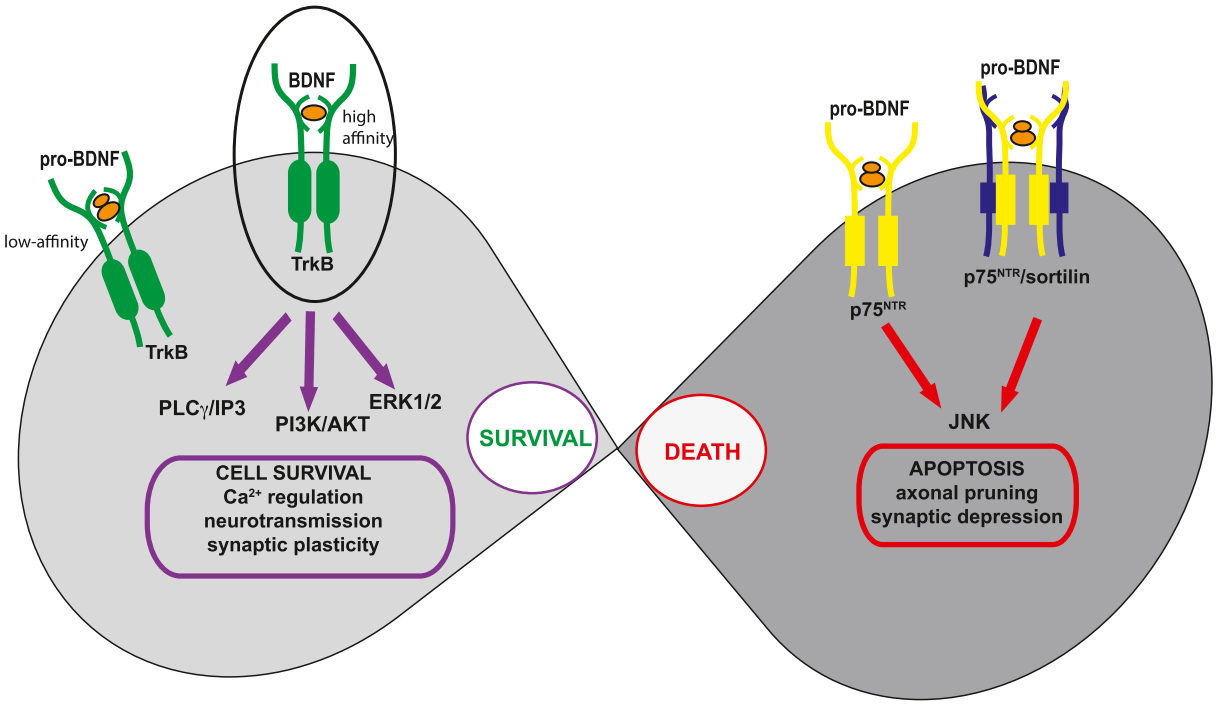

Fig. 1. The balance between pro-survival and pro-apoptotic signaling induced by BDNF receptors.
Pro-survival effect: BDNF binding to full-length receptor TrkB, leads to receptor dimerization and autophosphorylation of intracellular tyrosine residues, triggering three different signaling pathways: MAPK/ERK crucial for neuronal proliferation, differentiation and survival; PI3K / Akt involved in survival and axonal/dendritic growth; and phospholipase C (PLC) to promote survival and synaptic plasticity. By binding to the low-affinity TrkB receptor, pro-BDNF activates signaling cascades involved in neuronal survival. Pro-apoptotic effect: pro-BDNF binds with high-affinity to $p75^{NTR}$, whose activation requires the recruitment of sortilin to the receptor, leading to apoptotic cascade activation by c-Jun N-terminal kinase (JNK) or stress-activated protein kinase.

3. BDNF is a critical regulator of neuronal maturation and synaptic plasticity

Brain development is orchestrated by cell-autonomous programs, environmental factors, and the formation and refinement of appropriate synaptic connections; in the rodent cerebellum these coordinated events also occur during the first three weeks of postnatal life, while in the hippocampus they persist throughout life (Jiang and Nardelli, 2016). Therefore, the cerebellum is among the first brain areas to initiate cell differentiation and one of the last to fully mature in postnatal life (Wang and Zoghbi, 2001; Marzban et al., 2015; Rahimi-Palaei et al., 2018), while the hippocampus remains structurally plastic throughout adult life (Bayer and Altman, 1974; Mallard et al., 2000).

For these reasons, we have decided to focus our attention both on cerebellar development, as it provides an excellent model system to study how BDNF participates in the formation and modulation of brain circuits during postnatal development, and on the hippocampal brain region, which represents an elective structure to investigate dynamics concerning adult neurogenesis and the subsequent integration of newborn neurons into existing circuitry.

The long-lasting developmental time sequence exposes these two brain structures to an extended window of vulnerability to dysfunctions (Altman and Bayer, 1997; Middleton and Strick, 1998; Lavezzi et al., 2006; Fiorenza et al., 2021), which might contribute to neurodevelopmental disorders.

3.1. Pleiotropic effect of BDNF on the postnatal cerebellum: role on cell survival, migration and synaptogenesis

BDNF and its TrkB receptor are highly expressed in the postnatal cerebellum, with a spatiotemporal distribution that coincides with the main modifications characterizing the complex cerebellar maturation program (Lindholm et al., 1997; Bosman et al., 2006).

As it is known, granule cells (GCs) represent the most abundant neuronal type in the cerebellar cortex. During the first week of postnatal life, GC precursors (GCPs) intensely proliferate in the cerebellar outer granular layer (EGL); subsequently, they exit the cell cycle, initiate to differentiate and migrate radially along Bergmann glial processes towards their final destination, the inner granular layer (IGL), leaving their axons – named parallel fibers - in the molecular layer (ML) (Carletti and Rossi, 2008). In rodents, GC migration and maturation are completed at three weeks of age, which coincides with the disappearance of EGL in the adult cerebellar cortex (Espinosa and Luo, 2008).

The trophic effect of BDNF on GCs, both *in vitro* and *in vivo,* was described long time ago (Segal et al., 1992; Lindholm et al., 1993). *In vitro* studies showed that NMDA receptor activation on the GC membrane induced the synthesis and release of BDNF, which in turn promoted their survival and differentiation (Burgoyne et al., 1993).

Preclinical studies over the past two decades have demonstrated that BDNF knockout mice show an increase of GCP death, causing a reduction of the number of mature GCs and IGL thickness (Minichiello and Klein, 1996).

BDNF acts also as a chemotactic factor, stimulating GCs migration along Bergmann glia, in response to the BDNF concentration along the migratory path, from the EGL to IGL (Borghesani et al., 2002). In response to this gradient, phosphorylated TrkB is endocytosed in endosomes that accumulate in or near the main GCs process, orienting them to the source of BDNF in the IGL (Zhou et al., 2007). Furthermore, the activation of TrkB induces an autocrine release of BDNF from GCs that had already reached the IGL, which sustains the BDNF gradient itself (Sadakata et al., 2004; Zhou et al., 2007). Thus, paracrine/autocrine BDNF release and TrkB endocytosis promote polarized migration of GCs along the BDNF gradient.

The pro-BDNF and its $p75^{NTR}$ receptor are also highly expressed in the cerebellum and have an opposite role on GCs migration compared to the mature BDNF (Carter et al., 2003). Indeed, pro-BDNF has been

shown to inhibit GC migration, both *in vivo* and *in vitro,* by antagonizing the positive roles of BDNF/TrkB on GC migration. This function is mediated by its p75 ^{NTR} receptor, as indicated by the suppression of the pro-BDNF effect on cell migration observed in p75$^{NTR-/-}$ mice (Xu et al., 2011).

Contrary to the well-established role of BDNF in the survival/differentiation of GCs (Segal et al., 1995; Zhou et al., 2007), controversial results have been reported on Purkinje cells (PCs). For example, a study has shown that BDNF expression levels do not affect PC survival during the first postnatal week (Rakotomamonjy and Ghoumari, 2019). Other reports have shown that BDNF promotes the survival of purified *in vitro* PCs, while apparently it has no neurotrophic effect on *in vivo* PCs (Morrison and Mason, 1998; Ghoumari et al., 2002).

Furthermore, it has been demonstrated that BDNF secreted by GCs regulates, also, PC differentiation (Baptista et al., 1994), but even in this instance, the results are controversial. In fact, in BDNF$^{-/-}$ mouse models or in models of TrkB inactivation, some authors have reported an altered arborization of PCs (Minichiello and Klein, 1996; Schwartz et al., 1997; Carter et al., 2002), due to a strong reduction of the primary dendrite of these cells, which determines the consequent lack of the typical ramifications in the dendritic tree of adult PCs (Larkfors et al., 1996; Schwartz et al., 1997). Other authors found no irregularities in dendritic differentiation of PCs, both in BDNF and TrkB mutant mice (Jones et al., 1994; Bosman et al., 2006).

On the other hand, *in vitro* studies have shown that BDNF and TrkB modulate the dendritic development and spine density of PCs. However, BDNF treatment of primary culture of purified PCs did not elicit the generation of mature dendrites and spines, whereas chronic treatment with BDNF of GCs/PCs co-cultures increased the number of PC dendritic spines and synapses, suggesting a critical role of neuronal activity in mediating this BDNF response (Shimada et al., 1998; Tanaka et al., 2008).

BDNF and its downstream signaling pathway are also implicated in synapse pruning (Johnson et al., 2007) of supernumerary climbing fibers (CFs) afferents, innervating PCs. CFs, originating in the inferior olive and providing the earliest glutamatergic inputs to cell body of PCs undergo significant structural remodeling during the first weeks of postnatal life (Llinàas and Sugimori, 1980). In rodents, around the third postnatal day (P3), the number of CFs innervating a PC is typically 5, while few days later CFs that have not grown on the apical dendrite are progressively lost and no longer elicit postsynaptic responses (Scelfo and Strata, 2005; Bosman et al., 2008). Thanks to this pruning remodeling, by the end of the third week, each PC is innervated by a single *CF* (Strata and Rossi, 1998; Scelfo et al., 2003; Hashimoto and Kano, 2005).

Disruption of the pruning process in the developing cerebellum is associated with impaired motor coordination, as observed in BDNF knockout and hypomorphic or null mice for TrkB (Kashiwabuchi et al., 1995; Riva-Depaty et al., 1998). Both these mouse models display ataxia and impaired pruning of *CF*–PC synapses, leaving PCs multi-innervated by CFs beyond the normal developmental time frame (Schwartz et al., 1997; Choo et al., 2017).

BDNF also plays an important role in the organization of synaptic connectivity within the glomerulus (Chen et al., 2016). It is well known that after migration into the IGL, GCs receive excitatory inputs from mossy fibers (MFs) (Rabacchi et al., 1999; Lackey et al., 2018), which project into the cerebellar cortex from a different set of sensory and motor structures throughout the brain stem and spinal cord (Kalinovsky et al., 2011; Delvendahl and Hallermann, 2016). After arriving at the IGL, MFs establish synaptic contacts with GC dendrites and axon terminals of Golgi cells (Eccles et al., 1967; Balmer and Trussell, 2019). Thus, the cerebellar "glomerulus" is a complex synaptic area with two different axonal (mossy and Golgi) and dendritic (granule and Golgi) endings involved and represents the first "processing station" for afferent nerve fibers entering the cerebellum (Hàmori and Szentàgothai, 1966). Within the glomerulus GABAergic and glutamatergic synapses exist between inhibitory Golgi cells-GCs and MFs-Golgi cells, respectively (Mapelli et al., 2014).

Interestingly, some reports have highlighted that excitatory MFs express high BDNF levels and that the release of BDNF from their axons is necessary to promote the formation of GABAergic synapses and also control their own differentiation, in an autocrine manner (Chen et al., 2011, 2016). BDNF and TrkB receptor are necessary not only for the assembly of GABAergic synapses, but also for their maintenance, regulating the localization of important postsynaptic proteins (Chen et al., 2011). Indeed, BDNF improves the localization and clustering on GC dendrites of postsynaptic scaffolding proteins, as gephyrin, but also cell adhesion molecules, as contactin-1. Accordingly, conditional mutants in which BDNF has been eliminated from the cerebellum after birth display a reduced localization of gephyrin on dendrites of GCs and a subsequent perturbation of the differentiation of GABAergic synapses in the postnatal cerebellar glomeruli (Chen et al., 2016). Lastly, TrkB$^{-/-}$ mice show a reduction in the number of GABAergic boutons (Rico et al., 2002), while a moderate reduction in the synaptic density of cerebellar glomeruli was observed only in conditional TrkB mutants (Carter et al., 2002; Rico et al., 2002).

These data indicate that BDNF is closely involved in the early development of GCs, as well as in the organization of connectivity within the cerebellar cortex and in the modulation of glutamatergic and GABAergic synapses (Chen et al., 2016).

3.2. *The interplay between BDNF and synaptic dynamics: focus on hippocampus*

The neural and functional changes that occur during development and in adulthood are crucial examples of plasticity or " *ability to adapt* " (Bishop, 1982), which is the most important and fascinating feature of the central nervous system (CNS). Synaptic plasticity specifically refers to the ability of synapses to change strength and efficacy over time, in response to extrinsic or intrinsic stimuli (Cramer et al., 2011). It is well established that long-term potentiation (LTP) is the major form of synaptic plasticity and that it is associated with the formation of new synapses, changes in the number and morphology of dendritic spines (Lynch, 2004; Holtmaat and Caroni, 2016), postsynaptic density (PSD) remodeling (Bourne and Harris, 2008) and learning and memory processes (Muller et al., 2002).

In the 1990s, several groups intensively studied the role of BDNF in synaptic plasticity, focusing primarily on the hippocampus (Kang and Schuman, 1995; Kang et al., 1997; Kafitz et al., 1999). BDNF was found to be a positive modulator of LTP (Chen et al., 1999), regulating both the induction and maintenance of LTP in excitatory glutamatergic synapses in the hippocampus and in different brain areas (Rex et al., 2006). Further demonstration that BDNF is involved in synaptic plasticity is provided by BDNF knockout mice, in which hippocampal LTP is compromised but recovered upon BDNF stimulation (Ernfors et al., 1994; Korte et al., 1995; Patterson et al., 1996).

Compared to the slow effect that BDNF exerts on neuronal survival/differentiation, the modulatory activity it plays on synaptic transmission is very rapid (seconds or minutes), instead (Blum et al., 2002).

In the hippocampus, BDNF released from pre- and postsynaptic sources regulates synaptic activity and plasticity through autocrine and paracrine mechanisms (Björkholm and Monteggia, 2016) (Fig. 2). The most remarkable outcome of BDNF is the increase of the frequency of miniature excitatory postsynaptic currents (mEPSCs) (Taniguchi et al., 2000; Tyler and Pozzo-Miller, 2001), indicating an intensification of excitatory neurotransmission from presynaptic terminals.

Regarding BDNF presynaptic release at the glutamatergic synapses, following its synthesis in the cell soma, the BDNF is transported in large dense core secretory vesicles to the presynaptic terminals, where activity-dependent exocytosis is regulated by the influx of Ca^{2+} through L-type voltage-gated calcium channels (Tyler and Pozzo-Miller, 2001). BDNF released into the synaptic cleft can simultaneously induce retrograde and anterograde signals (Fig. 2).

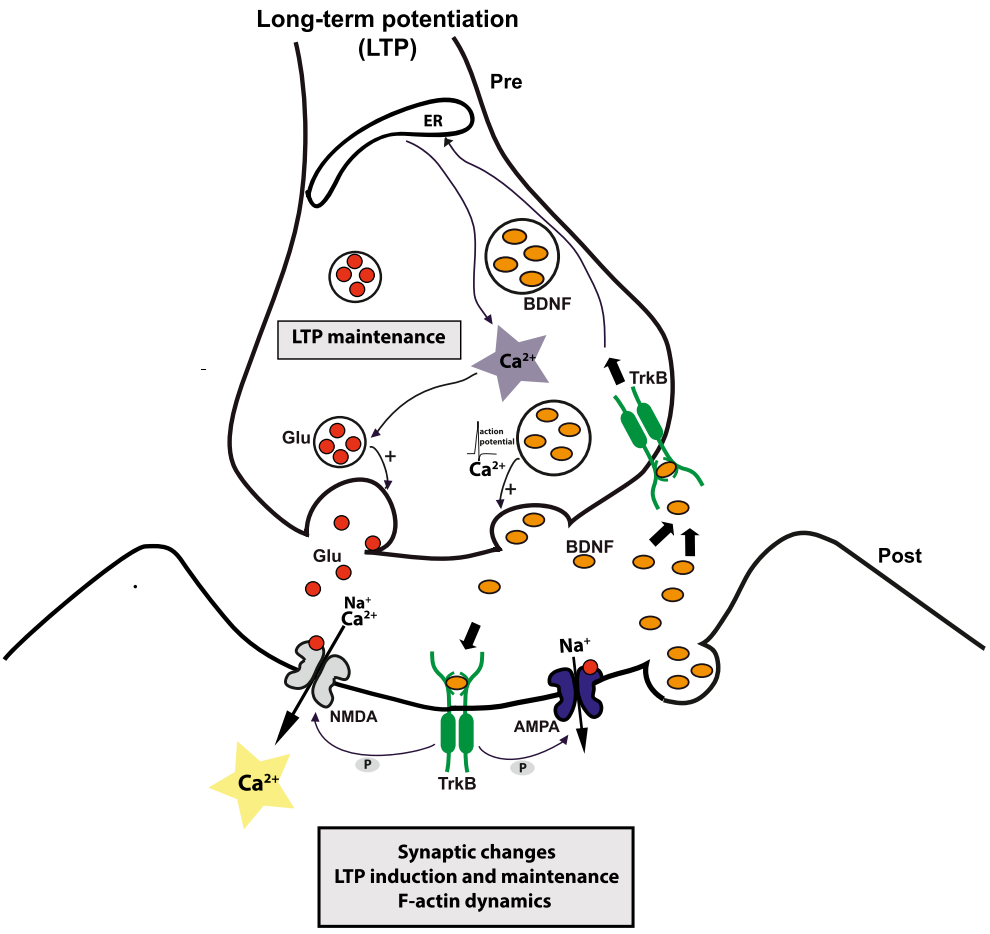

Fig. 2. Schematic representation of BDNF/TrkB signaling at the synapse. BDNF is a key regulator of LTP induction and maintenance, modulating synaptic strength through pre- and postsynaptic mechanisms. The influx of Ca^{2+} through L-type voltage-gated calcium channels triggers the exocytosis of BDNF that once released into the synaptic cleft can simultaneously induce retrograde and anterograde signals. In the presynaptic membrane, the binding of BDNF to the TrkB receptor increases the level of cytosolic Ca^{2+} by release from intracellular deposits, improving vesicular release of glutamate. In the postsynaptic membrane, the activation of TrkB receptor induces phosphorylation of NMDA and AMPA receptors leading to a potentiation of postsynaptic influx of Ca^{2+} and Na^{+}, respectively. This results in an increase in the frequency and amplitude of mEPSC and facilitates the induction and maintenance of LTP. Abbreviations: TrkB = tyrosine kinase receptor B; ER: endoplasmic reticulum; NMDA = *N*-methyl-D-aspartate receptor; AMPA = α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptor; P = Phosphorylation; Glu = glutamate; LTP = long-term potentiation; mEPSC = miniature excitatory postsynaptic currents.

Presynaptically, the BDNF binding to TrkB receptor activates the PLC pathway, which in turn increases the level of cytosolic Ca^{2} by the release from intracellular deposits, independent of voltage-gated calcium channels (Amaral and Pozzo-Miller, 2012).

Postsynaptically, BDNF/TrkB signaling causes NMDA receptor phosphorylation by a member of the Src kinase family (Fyn-kinase) (Amaral et al., 2007), resulting in increased NMDA receptor responses and Ca^{2} influx (Carvalho et al., 2008; Edelmann et al., 2015). Furthermore, to increase the frequency and amplitude of the mEPSC, BDNF upregulates both the amount of AMPA receptor subunit glutamate receptor 1, 2 and 3 (GluR1; GluR2, GluR3) on postsynaptic membrane (Carvalho et al., 2008), and their rapid translocation to the cell surface in response to BDNF stimulation (Narisawa-Saito et al., 2002).

Interestingly, the use of a virus-mediated approach to delete TrkB specifically in the CA1 and CA3 regions of the Schaffer collateral pathway, showed that TrkB at presynaptic terminals is necessary for the maintenance of LTP, while at the postsynaptic side it is required for both LTP induction and maintenance (Lin et al., 2018). Furthermore, in organotypic sections of developing hippocampus (postnatal day 12–14), tetanic stimulation can cause short-term potentiation but cannot generate LTP (Figurov et al., 1996). However, if the sections are treated with exogenous BDNF for a few hours, the same stimulation paradigm induces LTP, demonstrating how BDNF allows for greater responsiveness of synapses to stimulation patterns that typically induce synaptic plasticity (Kovalchuk et al., 2002). In addition, hippocampal slices from adult mice, treated two min before and two min after LTP induction with an antibody against BDNF, showed markedly reduced synaptic enhancement (Kossel et al., 2001).

Pivotal mechanisms involved in LTP induction are the regulation and remodeling of the cytoskeleton and protein synthesis at spines (Lee et al., 2009; Nakahata and Yasuda, 2018). The effect of BDNF in regulating LTP-related cytoskeletal changes is well documented (Matsuzaki et al., 2004; Bramham, 2008; Murakoshi and Yasuda, 2012). Although the initial characterization of mice harboring a null mutation of BDNF gene showed no effect on spine density (Korte et al., 1995), subsequent studies have demonstrated that BDNF can modify the structure of spines (Tanaka et al., 2008). Indeed, it was observed that primary culture of hippocampal neurons from rats, exposed to BDNF displayed an increase of dendritic spines positive to F-actin, indicating that actin polymerization is among the effects of BDNF exposure (Rex et al., 2007). The activation of the mTOR signaling upon BDNF binding to the TrkB receptor boosts protein synthesis at the level of dendritic spines, confirming the role of this neurotrophin in dendritic growth and spine formation (Danzer et al., 2004; Kellner et al., 2014).

In vitro and *in vivo* studies have shown that, in pyramidal neurons in which SNARE-dependent vesicular release was inhibited by botulinum neurotoxin C, the addition of exogenous BDNF resulted in an increase in the number of immature spines (long and thin), demonstrating that BDNF is able to increase the density of spines, regardless of synaptic transmission (Tyler and Pozzo-Miller, 2003). Consistent with these data, the addition of exogenous BDNF to hippocampal neurons cultured in a medium containing a high level of magnesium, a condition that is known to enhance BDNF expression levels (Afsharfar et al., 2021), resulted in a significant increase of the proportion of mature spines (large heads) compared to immature ones (small heads) (Zagrebelsky et al., 2020).

Finally, mice lacking BDNF die during the second postnatal week (Ernfors et al., 1994; Rios et al., 2001), showing a strong reduction of dendritic arborization of hippocampal neurons (Gao et al., 2009; Wu et al., 2019), while the abrogation of BNDF function by inactivating antibodies results in an inadequate mature phenotype of hippocampal

neurons, with a reduction of spine head diameter and an increase of spines length (Kellner et al., 2014).

Therefore, BDNF is now considered the most critical factor regulating the growth/branching of dendrites and axons (Suzuki et al., 2007) and its contribution depends on TrkB activation (Chakravarthy et al., 2006; Tanaka et al., 2008; Burk et al., 2018). Accordingly, the inhibition of TrkB receptor prevents BDNF activity (Tyler and Pozzo-Miller, 2001) and spine growth (Kellner et al., 2014). The acute infusion of BDNF to hippocampal neurons results in TrkB activation and spine head enlargement, while gradual addition of BDNF is accompanied by spine neck lengthening, subsequent to ERK1/2 activation (Ji et al., 2010). It has been shown that exposure of mature pyramidal hippocampal neurons to BDNF induces an increase in the density of dendritic spines (Gottmann et al., 2009) through activation and endocytosis of TrkB, which by axonal transport reaches the PSD region (Ji et al., 2005; Andreska et al., 2020). TrkB receptor together with the PSD95 scaffold protein anchor the AMPA and NMDA receptors to the postsynaptic membrane (Chen et al., 2015).

While BDNF/TrkB signaling positively regulates dendritic spine structure and plasticity, pro-BDNF and its $p75^{NTR}$ receptor exert an opposite effect, inducing a significant reduction in dendritic spine density (Buhusi et al., 2017), which is associated with an increase in the number of immature spines, also known as stubby spines (Chapleau and Pozzo-Miller, 2012). Zagrebelsky and colleagues have shown that $p75^{NTR}$ activation negatively impacts on dendrite morphology and spines number of hippocampal neurons, contributing to spines retraction and reducing dendritic complexity (Zagrebelsky et al., 2005). Furthermore, the activated $p75^{NTR}$ receptor contributes to long-term depression (LTD) in several cerebral areas (Woo et al., 2005; Park and Poo, 2013) and induces NMDA and AMPA receptors endocytosis (Kojima and Mizui, 2017).

In brief, in the mature hippocampus, BDNF/TrkB together with pro-BDNF/$p75^{NTR}$ generate a cloud of local BDNF, which acting at both pre/post-synaptic sides, regulates synaptic turnover, plasticity and produces more stable synaptic connections.

3.3. Misregulation of BDNF in neurodevelomental disorders

The increasing prevalence of neurodevelopmental disorders, in particular autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD), are an urgent concern for society and require more research on identifying etiological and predictive factors.

As described above, a great deal of evidence has shown that BDNF plays a vital role in brain development favoring the growth and differentiation of new neurons and synapses (Lee and Kim, 2010; Phillips, 2017) and alterations in BDNF expression levels represent a shared risk of vulnerability to neurodevelopmental disorders (Autry and Monteggia, 2012; Cattaneo et al., 2016). Therefore, it is not surprising that the therapeutic potential of BDNF has captured attention and the dysregulation of its signaling cascades, in terms of increases or decreases, is commonly present in disorders, such as ADHD and ASD (Wang et al., 2019) and autism spectrum disorder (ASD) (Campbell et al., 2006; Hashimoto et al., 2006).

It has been proposed that BDNF is associated with the pathogenesis of ADHD (Tsai, 2003), one the most common behavioral/neurodevelopmental disorder present in adolescents and adults (Pastor et al., 2015). This pathology is characterized by symptoms of inattention, impulsivity and locomotor hyperactivity and commonly treated using drugs that increase dopamine (DA) levels in the brain (Sharma and Couture, 2014; Nùñez-Jaramillo et al., 2021). Altered serum levels of BDNF are present in both adolescents and adult patients with ADHD (Corominas-Roso et al., 2013) while treatments with psychostimulants and antidepressants, commonly used to increase DA levels, increase the expression levels of BDNF and its TrkB receptor, particularly in the hippocampus, amygdala, nucleus accumbens (NAc) and caudato-putamen (Fumagalli et al., 2010; Amiri et al., 2013).

Based on this evidence, it has been proposed that the expression levels of BDNF may explain the altered homeostasis of the DA system observed in patients with ADHD (Galvez-Contreras et al., 2017).

The BDNF regulates the survival and differentiation of midbrain DA neurons both *in vivo* and *in vitro*, modulating DA release through the activation of its TrkB receptors (Knüsel et al., 1991; Guillin et al., 2001). As observed in retinal cells, the BDNF increases DA release within minutes upon binding to TrkB receptor (Neal et al., 2003). Subsequent events such as PLC-γ activation, IP3 production and calcium release from the ER, represent the trigger for BDNF-induced DA release (Neal et al., 2003).

Preclinical studies in DA retrograde transporter knockout mice showed a decrease of the BDNF level in the frontal cortex (Fumagalli et al., 2003), which is detrimental for brain maturation and generates a persistent impairment in synaptic plasticity associated with cognitive impairment (Jeong et al., 2014), aggression, anxiety, and locomotor hyperactivity (Liu et al., 2015). These mice exhibit the behavioral characteristics typical of ADHD patients; moreover, mice with BDNF conditional deletion in the postnatal brain also displayed increased anxiety and hyperactivity (Rios et al., 2001).

In rats and mice, the infusion of BDNF into the NAc or the ventral tegmental area has been shown to increase nigrostriatal dopaminergic activation, resulting in increased locomotor activity (Altar et al., 1992; Narita et al., 2003); furthermore, chronic treatment with BDNF (over two weeks) enhanced the reward response to cocaine through long-term adaptations within the mesolimbic DA system (Horger et al., 1999). Of note the increased response to cocaine in BDNF-treated animals persisted for more than one month after discontinuation of BDNF infusions (Horger et al., 1999; Corominas- Roso et al., 2007), indicating that these BDNF-induced neurochemical changes contribute to the consolidation of lasting neuroplasticity, at the basis of sensitized responses to psychostimulants.

Changes in BDNF levels have been reported in ADHD patients but the results were highly inconsistent; some studies reported elevated BDNF levels in serum or plasma of ADHD patients in comparison to healthy subjects (Shim et al., 2008; Li et al., 2014), while the exact opposite was reported by some studies (Corominas-Roso et al., 2013; Sahin et al., 2014; Saadat et al., 2015), and no differences were observed by others (Sargin et al., 2012; Scassellati et al., 2014).

The Val66Met polymorphism of the BDNF gene appears to be associated with an increased risk of anxiety disorder and increased liability to ADHD (Kent et al., 2005; Sànchez-Mora et al., 2010). This polymorphism, observed in over 25% of the human population, causes a change from valine (Val) to methionine (Met) at position 66 of the pro-BDNF protein. The Val66Met pro-BDNF isoform associates with a reduced neuronal activity-dependent secretion of BDNF, due to the reduced ability of BDNF to be sorted from Golgi to secretory vesicles (Verhagen et al., 2010; Dincheva et al., 2012; Hajek et al., 2012). Although some studies identified the Val66Met polymorphism as a possible genetic marker of susceptibility to ADHD (Lanktree et al., 2008; Ozturk et al., 2016), such association is controversial (Kwon et al., 2015; Liu et al., 2015).

Abnormalities in BDNF homeostasis are thought to contribute to a group of complex neurodevelopmental disorders, ASD, characterized by intellectual disability, severe delayed language development, impaired social interaction, and repetitive behaviors (Chaste and Leboyer, 2012; Skogstrand et al., 2019). Evidence from clinical studies suggest that abnormal activity of BDNF contributes to the pathogenesis of ASDs, identifying BDNF serum levels as prognostic or diagnostic markers of ASD (Bryn et al., 2015; Garcia Barbosa et al., 2020). Similarly to ADHD, studies analyzing systemic levels of BDNF in patients with ASD are conflicting; several reports detailed higher levels of BDNF in the blood (Nelson et al., 2001; Connolly et al., 2006; Kasarpalkar et al., 2014; Qin et al., 2016) and in the brains of children with ASD (Perry et al., 2001), while others have found reduced BDNF levels compared to healthy subjects (Hashimoto et al., 2006; Fuentealba et al., 2019; Skogstrand

et al., 2019).

More consistent observations were made by using mouse models of ASD, in which BDNF expression was downregulated in various brain areas with consequences on cognitive and behavioral performances (Branchi et al., 2006; Gould et al., 2011). Among these mouse models, adult mice lacking the homeobox domain of *engrailed-2* ($En^{-/-}$), landmarked by social behaviour deficits, locomotor impairment, and cerebellar hypoplasia, exhibited marked downregulation of the mRNA and the mature protein of BDNF in the neocortex but not in the hippocampus, compared to control mice (Zunino et al., 2016). Similarly, in prenatally valproate rats, which represent an established model of autism, BDNF transcription determined by *in situ* hybridization was found reduced in the hippocampus dentate gyrus and CA3 regions (Fuentealba et al., 2019). Conversely, a line of genetically modified mice that overexpress the BDNF transgene in forebrain neurons showed less obsessive-compulsive and anxious behaviors (Weidner et al., 2014).

Accumulating evidence shows that the cerebellum is structurally and functionally abnormal in patients with autism (Fatemi et al., 2012; Rogers et al., 2013) and it has been demonstrated that mutations of genes involved in cerebellar development are associated with changes in BDNF levels and susceptibility to autism (Rylaarsdam and Guemez-Gamboa, 2019). Chief among these genes are *secretion* Ca^{2+}*-dependent activator protein for secretion 2 (CAPS2)* and retinoic *acid-related orphan receptor alpha* (*RORα*) *(*Campbell et al., 2006; Wang et al., 2008; Sadakata and Furuichi, 2009; Sen et al., 2010). *CAPS2* contributes to cerebellar development, by improving the expression levels of BDNF and neurotrophin-3 (NT-3) (Sadakata et al., 2007; Sadakata and Furuichi, 2009), while cerebellar defects present in *RORα* mutant mice are in part induced by the altered expression of BDNF and NGF and NT-3 neurotrophins (Qiu et al., 2007).

BDNF also plays an important role in the onset and progression of the neurological phenotype of the Rett syndrome (RTT). The RTT is a complex autism spectrum disorder caused by loss-of-function mutations of the methyl-CpG-binding protein 2 (*MeCP2*) gene and characterized by respiratory problems, ataxia, seizures, anxiety, cognitive and motor disorders (Rett, 1966; Amir et al., 1999). The MECP2 protein, thanks to its binding domain to methylated CpG-enriched DNA sequences, is involved in the silencing of several genes by epigenetic mechanisms (Jones et al., 1998; Nan and Bird, 2001). However, MeCP2 has been shown to be a chromatin architecture modulator that can also act as a transcriptional activator, binding to the co-activator CREB (cAMP response element binding protein) (Chahrour et al., 2008). Among target genes regulated by MeCP2, *BDNF* is the main target (Chahrour et al., 2008; Su et al., 2015), representing the major deregulated factor in the brains of RTT patients and *MeCP2*-deficient mice.

Consistently, a growing body of evidence has demonstrated that BDNF mRNA and protein levels were reduced in several brain areas of $MeCP2^{-/-}$ mice, such as the brainstem and cerebellum (Wang et al., 2006; Kline et al., 2010) and in postmortem RTT subject brain samples (Deng et al., 2007). In addition, Chahrour and colleagues reported increased levels of BDNF mRNA expression in the hypothalamus in mice overexpressing MeCP2 (Chahrour et al., 2008). Interestingly, double knockout mice in which both the *Mecp2* and *BDNF* gene were deleted showed early disease onset RTT while conditional BDNF overexpression delayed disease onset (Chang et al., 2006). In addition to the dysregulation of BDNF expression, the loss of *MeCP2* appears to be also associated with alterations in the axonal transport of BDNF (Li and Pozzo-Miller, 2014). *In vitro* cultured cortical neurons isolated from *Mecp2* knockout mice showed a reduced rate of axonal transport of BDNF-containing vesicles, a deficit that can be rescued by the re-expression of *Mecp2*. These results were also confirmed *in vivo*, in the cortico-striatal axonal projections of *Mecp2*-deficient animals (Roux et al., 2012).

Moreover, several studies on glutamatergic hippocampal neurons have demonstrated that loss of MeCP2 protein leads to reduced dendritic complexity and arborization associated with a decreased dendritic length (Belichenko et al., 2009; Jentarra et al., 2010); however, little is known about the mechanisms behind this defective differentiation program. According to the role of BDNF in the regulation of dendritic spine formation and synaptogenesis (Yoshii and Constantine-Paton, 2010), the manipulation of BDNF-TrkB activity could represent a promising therapeutic strategy for ameliorating the progression of RTT disease.

4. Conclusions

For their genetic and phenotypic intricacy, neurodevelopmental disorders are challenging both in biological and medical terms.

Although BDNF/TrkB signaling is a key molecular pathway in brain development, synaptic plasticity and learning/memory processes, the specific role of BDNF in the onset of neurodevelopmental deficits remain still unclear. In humans, the relationship between cognitive deficits and BDNF is still correlational, essentially because the available techniques do not allow the determination of brain expression of BDNF *in vivo*. Despite this difficulty, numerous rodent studies have established the causal relationship between BDNF and important cellular and molecular neurodevelopmental processes, under conditions that increase or decrease BDNF expression.

Synaptic defects present in neurodevelopmental disorders such as ADHD and ASD could be rescued through the formation of new terminals and/or dendritic spines; in this context, BDNF appears to be a potent synaptic repair molecule, as observed in the cerebellum and hippocampus, where the role of this neurotrophin is critical for the correct regulation of the development and maturation of glutamatergic and GABAergic neurons, classically involved in these disorders.

Finally, BDNF expression is reduced in many neurodegenerative diseases, such as Spinocerebellar ataxia type 1 (SCA1) (Takahashi et al., 2012). In particular, in SCA1 mouse models, the administration of exogenous BDNF during the pre or post-symptomatic phases is able to improve motor deficits and cerebellar neuropathology, demonstrating the potential therapeutic role of BDNF (Mellesmoen et al., 2019; Sheeler et al., 2021).

However, in the future, we believe the crucial question will not be whether BDNF levels will be considered a diagnostic marker, but whether manipulating BDNF and its main intracellular signaling mechanisms will help to conceive new drugs and innovative strategies for these devastating diseases.

Author contributions

Sonia Canterini was responsible for the general idea, writing the manuscript and figure design, Serena Camuso contributed to the drafting of the manuscript, Piergiorgio La Rosa revised the manuscript and Maria Teresa Fiorenza contributed with advice and critical discussion. All authors read and approved the final manuscript and contributed to the conception of the work.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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