● REVIEW

The role of the TrkB-T1 receptor in the neurotrophin-4/5 antagonism of brain-derived neurotrophic factor on corticostriatal synaptic transmission

Elizabeth Hernández-Echeagaray[*]
Unidad de Investigación en Biomedicina FES-Iztacala, Universidad Nacional Autónoma de México, México

Abstract

This manuscript reviews the function and fundamental characteristics of the neurotrophins and their receptors to introduce the reader to the differential effects exhibited by the neurotrophins; brain-derived neurotrophic factor and neurotrophin 4/5 when acted together after sequential presentation. The neurotrophin 4/5 exhibits an inhibitory action on the modulatory effect of brain-derived neurotrophic factor in corticostriatal synapses when they are administered sequentially (brain-derived neurotrophic factor to neurotrophin 4/5). This inhibitory effect has not been previously documented and is relevant for these neurotrophins as both of them stimulate the TrkB receptor. The additive effect of these neurotrophins is also discussed and occurs when neurotrophin 4/5 exposure is followed by brain-derived neurotrophic factor in a mouse model of striatal degeneration. Occlusive and additive effects of both neurotrophins are accompanied by changes in the expression of the TrkB receptor isoforms, specifically TrkB-T1 and TrkB-FL, as well as differences in phosphorylation levels of the TrkB receptor. The results of the experiments described raise several questions to inquire about the role that TrkB-T1 receptor plays in striatal physiology, as well as the functional relevance of the interaction of brain-derived neurotrophic factor and neurotrophin 4/5 in the brain and more specifically at the striatal circuits in normal as well as pathological conditions.

Key Words: *brain-derived neurotrophic factor; neurotrophin 4/5; occlusive; striatum; synergic; TrkB-FL; TrkB-T1*

Neurotrophins

Brain-derived neurotrophic factor (BDNF) and neurotrophin-4/5 (NT-4/5) are trophic factors that together with nerve growth factor (NGF) and neurotrophin 3 (NT-3) belong to the neurotrophin family (Hohn et al., 1990; Kaplan and Miller, 2000; Reichardt, 2006). Like other trophic factors, neurotrophins are peptides which originate in specific tissues and execute their activity through membrane receptors of the target cells. Neurotrophins regulate development, differentiation, growth, and survival of various neuronal populations in the nervous system, through activating intracellular signaling pathways. In addition, neurotrophins participate in synapse formation, synaptic modulation and neuronal plasticity (Yuen and Mobley, 1996; Schuman, 1999; Alberch et al., 2002; Reichardt, 2006).

For neurotrophins to perform their cellular functions, they must interact with two classes of transmembrane receptors: the family of tropomyosin receptor kinases (Trks) and p75 receptors (Minichiello, 2009). Trk receptors are high affinity receptors, and each of the neurotrophins bind to one or more specific receptors: NGF activates the TrkA receptor, while NT-3 mainly activates the TrkC, and together with BDNF and NT-4/5, the TrkB receptor (Barbacid et al., 1994). Although the TrkA, TrkB and TrkC receptors are transcribed from separate *loci*, they are genetically homologous and structurally similar (Bibel and Barde, 2000; Huang and Re-

ichard, 2001; Bartkowska et al., 2010).

Tropomyosin Receptor Kinase Receptors

Trk receptors are composed of an extracellular region, a transmembrane region, and a cytosolic domain containing tyrosine kinase. The extracellular region is crucial for the recognition and binding of neurotrophins, which causes receptor dimerization. It is characterized by a group rich in cysteines (domain 1), followed by three leucine rich repeats (domain 2), another group of cysteines (domain 3), and two immunoglobulin domains (domains 4 and 5) that have been reported as the binding sites for neurotrophins (Ng et al., 2006; Josephy-Hernandez et al., 2017). Each receptor crosses the membrane only once and the tyrosine kinase domain is within the cytoplasm, followed by the carboxyl end. The tyrosine kinase domain is indispensable for the initiation and propagation of the signal as this region contains the tyrosine residues (Chao, 2003). As noted above, Trk receptors dimerize in response to neurotrophin binding which triggers the trans-activation of the tyrosine kinase domain and initiates a massive cascade of signaling pathways. Thus, immediately after trans-activation, several residues of the tyrosine kinase domain in the receptor are phosphorylated (Y^{515} and Y^{816}). Phosphorylation of these residues is required to complete the trans-activation of Trk receptors, and serve as coupling sites for adapter proteins, which are essential

for the initiation of the downstream signaling cascade. This association occurs mainly through phosphotyrosine binding adapter proteins or through the homology domain to Shc. These clusters cause the activation of several intracellular signals such as the mitogen-activated protein-Ras kinases, phosphatidylinositol 3-kinase and C-γ phospholipase pathways (Dolcet et al., 1999; Ng et al., 2006; Reichardt, 2006; Josephy-Hernandez et al., 2017). Although dimerization of the receptors appears to be the necessary condition for their phosphorylation and intracellular activation, it has been recently noted that TrkB may be present as monomers and activated in the presence of a neurotrophin (Simi and Ibañez, 2010) or pre-formed as an inactive dimer, and BDNF induces changes in the TrkB conformation leading its activation (Shen et al., 2019).

The TrkB receptor gene can give rise to several mRNA transcripts. Two of them encode the complete form of TrkB, a catalytic full-length form of TrkB (TrkB-FL) and a truncated version with the tyrosine kinase region TrkB-TK. Other transcripts give rise to TrkB isoforms that lack the intracellular domain and have no tyrosine kinase activity; these isoforms are known as truncated TrkB receptors – the TrkB.T1, TrkB.T2 and TrkB.T-Shc (Klein et al., 1990, 1991; Gupta et al., 2013).

Although the catalytic form of TrkB, the TrkB-FL, is considered to be the one that mediates the main biological actions of BDNF, the TrkB-T1 isoform is the predominant isoform in the adult brain, and has been shown to antagonize the TrkB-FL receptor (Eide et al., 1996). This antagonism can be produce by sequestering the neurotrophin or by modulating the kinase activity (Baxter et al., 1997). Therefore, it is plausible that the stimulation of each of these isoforms leads to different physiological effects.

Neuromodulatory Effects of Brain-Derived Neurotrophic Factor and Neurotrophin-4/5

The effects of BDNF and NT-4/5 on synaptic transmission were first observed in neuromuscular synapses (Lohof et al., 1993). Subsequently it was shown that in various regions of the nervous system such as the visual cortex (Carmignoto et al., 1997) and the hippocampus (Lessman et al., 1994; Levine et al., 1995, 1996, 1998), BDNF and NT-4/5 enhanced synaptic transmission (Wang et al., 1998). Nonetheless, BDNF also decreases synaptic transmission (Lessman and Heumann, 1998; Matsumoto et al., 2006).

BDNF and NT-4/5 act directly on synaptic communication efficacy, acting at the presynaptic and/ or post-synaptic level (Levine et al., 1995; Lessmann and Heumann, 1998; Boulanger and Poo, 1999; Edelmann et al., 2014). The effects of NT-4/5 and BDNF on synaptic communication are related to the activation of the TrkB receptor (Lessman et al., 1994; Levine et al., 1995, 1996; Kang et al, 1996). However, the biological actions of BDNF and NT-4/5 also depend on the region of the nervous system, the intrinsic properties of the different neuronal types, the temporal phase of the transmission, and age of the experimental subjects.

Our work has focused on knowing the synaptic effects that these two neurotrophins exert on cortico-striatal connections. BDNF is anterogradely transported from the cerebral cortex and then released into the striatum (Altar et al., 1997; Altar and DiStefano, 1998), while NT-4/5 appears postnatally in the rodent striatum. We have shown that BDNF and NT-4/5 are differentially expressed in the striatum, a long during postnatal development; BDNF expression decreases while NT-4/5 increases (Zermeño et al., 2009). This difference in the expression of BDNF and NT-4/5 caught our attention from the very beginning, as both neurotrophins activate the same receptor.

Given the difference in spatio-temporal expression, we wondered about the functional role of the individual and joint action of BDNF and NT-4/5 would be in modulating cortico-striatal synaptic transmission; This led us to describe that BDNF and NT-4/5 increase synaptic efficacy in the striatum if they act individually, but exert different effects when applied sequentially. Electrophysiological recordings in acute brain slices show that application of BDNF together with NT-4/5, maintain the effects previously generated by NT-4/5 in synaptic transmission, indicating that they act on the same mechanism. In contrast, the administration of NT-4/5 in the presence of BDNF causes antagonism in the synaptic effect generated by BDNF.

How Do We Explain That Neurotrophin-4/5 Antagonizes the Synaptic Effect of Brain-Derived Neurotrophic Factor?

Although several reports indicate that both neurotrophins have a similar effect on synaptic transmission, survival and neuronal growth (Gottmann et al., 2009), previous studies indicated that BDNF and NT-4/5 do not have identical effects on neurons (Ip et al., 1993; Mc Allister et al., 1995). We thought it biologically unlikely that two signaling molecules in the same region of the nervous system and coupling with the same receptor will always generate the same physiological effect. For example, it has been reported that the replacement of the BDNF gene with that of NT-4/5 does not favor the viability of mutated mice. These mice die in the early stages of embryonic development, while in mice where NT-4/5 was replaced by BDNF survived, and showed an increase in the rate of synapse formation compared with the control animals (Fan et al., 2000).

There is evidence suggesting that BDNF and NT-4/5 interact differently with the TrkB receptor. For example, the substitution of the cysteine[354] for a serine[354] in the second immunoglobulins motif of the extracellular domain of the TrkB receptor did not allow the morphological transformation of NIH3T3 cells produced by NT-4/5 in culture, while BDNF did transform them (Ip et al., 1993). Likewise, the mutation of the Shc adapter protein from the neurotrophins' TrkB binding site in mice did not allow the survival of sensory neurons that depend on NT-4/5. However, it did allow the survival of vestibular ganglion neurons that depend on a supply of BDNF (Minichiello et al., 1998). These experiments show that the TrkB receptor is differentially stimulated by BDNF and NT-4/5, and that each of these two neu-

rotrophins can trigger different synaptic signals, depending on the nature of their receptor stimulation. In our studies, when corticostriatal synapses were exposed to BDNF and NT-4/5 individually, they induced similar p-TrkB levels, thus demonstrating no differences in the activation of the TrkB receptor. However, when BDNF was followed by NT-4/5, the p-TrkB level was reduced. Furthermore, if the NT-4/5 was followed by BDNF, the p-TrkB level increased (Torres-Cruz et al., 2019a).

As mentioned above, the truncated isoform of TrkB, TrkB-T1 is a natural antagonist of TrkB-FL. This antagonism may result from the coupling of an orphan receptor of the TrkB-FL receptor with a orphan receptor of TrkB-T1; the dimerization of two truncated TrkB receptors; the sequestration of BDNF by TrkB-T1 (Fryer et al., 1997); the internalization of the TrkB-FL receptor by the truncated receptor (Biffo et al., 1995); or the activation of other intracellular signals that block phosphorylation from TrkB-FL (Chen et al., 2007). For example, the truncated isoform TrkB-Shc increases in response to exogenous BDNF exposure, apparently to regulate TrkB-FL activity (Wong and Gardner, 2012).

We speculated that BDNF and NT-4/5 exhibits differential interactions with the TrkB receptor isoforms. By evaluating the expression of the truncated isoform of the TrkB receptor in the presence of sequential administration of both neurotrophins, we demonstrate that NT-4/5 inhibits BDNF through up regulating TrkB-T1 and down regulating TrkB-FL (Torres Cruz et al., 2019a).

Experimental evidence demonstrates that BDNF is required for medium spiny neuron (MSN) survival and activity in the striatum. In a seminal work, Zuccato et al. (2001) established that the protein huntingtin regulates BDNF transcription in the cerebral cortex. The huntingtin becomes polyglutaminated in Huntington's disease (HD), and this mutation causes a reduction in BDNF production (Zuccato et al., 2001). BDNF is not involved in the early stages of MSNs' development, but it is required for their long-term survival. A lack of BDNF affects mainly the morphology of dendrites, which in turn affects synaptic stimulation and the neuronal firing of MSNs (Baquet et al., 2004).

Since a reduction in BDNF levels is associated with neurodegenerative pathologies, and occurs in the striatum in HD (Zuccato and Cattaneo, 2007), we studied whether BDNF and NT-4/5 exhibits occlusive or synergistic effects using a striatal degeneration model that mimics the early stages of HD. We observed that NT-4/5 antagonizes the effects of BDNF through activation of the truncated isoform of TrkB, as previously described (Torres-Cruz et al., 2019a); however, the treatment of NT-4/5 followed by the administration of BDNF produced a synergistic effect on synaptic activity (Torres-Cruz et al., 2019b).

Neurotrophins are involved in the regulation of neuronal activity. For the first condition (BDNF followed by NT-4/5), we believe that the antagonism of NT-4/5 maintains a baseline level of synaptic communication to avoid over-stimulation produced by BDNF. But it is also possible that as a result of different interactions with the TrkB receptor, once BDNF stimulates TrkB-FL, NT-4/5 exhibits more affinity with TrkB-T1 receptors. For the second condition, as BDNF level is reduced in striatal degeneration (Espíndola et al., 2012), we assume that NT-4/5 is not competing with BDNF to stimulate the TrkB-FL receptor, and therefore exhibits additive effects.

Although it has been shown that BDNF and NT-4/5 differentially affect the endocytic sorting of TrkB receptors (Proenca et al., 2016), the differential synaptic effects produced by BDNF followed by NT-4/5 and NT-4/5 followed by BDNF have not previously been described. More observations showing that the order of stimulation of these neurotrophins generate different responses by interacting with specific TrkB isoforms has also not been previously reported. The role of NT-4/5 in striatal physiology has not been explored in detail and we do not know why NT-4/5 prefers stimulating TrkB-T1 in the striatum (**Figure 1**). Furthermore, NT-4/5 antagonism of BDNF in healthy striata and in HD animal models opens up new questions about neurotrophin interactions in neuronal circuits. It is particularly important to understand under which physiological circumstances NT-4/5 is released after BDNF, what neuronal population releases NT-4/5, and whether NT-4/5 contributes to BDNF inefficacy in HD pathology. This information can be of potential clinical relevance for the treatment of HD and other pathologies where these two neurotrophins interact. Moreover, several questions need to be addressed in the future in relation to NT-4/5 function and the physiological role of the truncated isoforms of TrkB, especially because this receptor isoform is highly expressed in the adult brain.
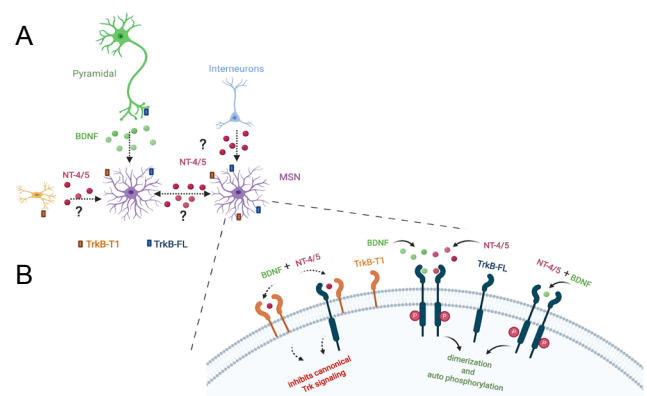
Figure 1 Activation of TrkB receptors by BDNF and NT-4/5.
(A) BDNF (green circles) is released at the corticostriatal synapses. It is unknown whether NT-4/5 (red circles) is coming from glial cells, striatal interneurons or MSN, but MSN expresses TrkB receptors stimulated by both neurotrophins. (B) BDNF or NT-4/5 activates TrkB receptors located on MSN, and leads to the auto phosphorylation of TrkB-FL receptors and signaling pathways activation. If NT-4/5 is followed by BDNF, TrkB-FL is also activated. If BDNF is followed by NT-4/5, TrkB-T1 is activated and inhibits canonical signal transduction. BDNF: Brain-derived neurotrophic factor; MSN: medium spiny neurons; NT-4/5: neurotrophin-4/5; TrkB: tropomyosin receptor kinase B; TrkB-FL: full-length form of TrkB; TrkB-T1: truncated form of TrkB.

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