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Inducing neuronal regeneration and differentiation via the BDNF/TrkB signaling pathway: a key target against neurodegenerative diseases?

Mirjana Antonijevic, Patrick Dallemagne, Christophe Rochais*

Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins, a specific polypeptide growth factor, which plays a crucial role in the proliferation, differentiation, survival, and death of neurons and non-neuronal cells. It is not only essential to maintain the balance between death on one side and survival of neurons on the other, but also it mediates additional higher-order activities such as learning, memory, and behavior. It is initially synthesized as a precursor protein, proBDNF, that can be secreted as it is or it can be cleaved intracellularly by furin and proconvertases, or extracellularly by extracellular proteases such as matrix metalloprotease-9 and matrix metalloprotease-2, or plasmin to give mature BDNF.

BDNF exerts its biological activities through two receptors: tropomyosin-related kinase B (TrkB) and the structurally unrelated p75 neurotrophin receptor (p75^{NTR}). However, it has been shown that the influence of BDNF on neuronal growth, development, plasticity, synaptogenesis, adult neurogenesis, and myelinations is exerted via activation of the TrkB receptor and its various signaling cascades (mitogen-activated protein kinase, phosphatidylinositol 3-kinase, and phospholipase C- γ) (Tejeda and Díaz-Guerra, 2017; Ferreira et al., 2018).

The TrkB receptor can be expressed as the full-length receptor (TrkB-FL) and as a truncated, non-active isoform (Tejeda and Díaz-Guerra, 2017). It was shown that, in neurodegeneration, the TrkB-FL is being downregulated due to calpain-degradation (Tejeda et al., 2019), which can represent a potential challenge in the activation of this receptor in order to trigger its influence on neuronal survival.

Even though the involvement of neurotrophins in many pathophysiological conditions has been known for years, we have decided to focus only on their roles in the neurodegenerative ones since they represent one of the major threats to human health, because they are worldwide rising diseases. The death of neurons is one of the main events occurring in neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, and Huntington's disease), but that is the final outcome caused because of the neuronal damage. In order to treat these diseases, it is suggested to induce regeneration and development of

already damaged neurons and not only to prevent neuronal death. In this perspective article, we will try to summarize and point to the potential role of the BDNF/TrkB signaling pathway in the regeneration of the neurons.

Myelin represents a sheet of modified plasma membrane, wrapped around the axon and has a crucial role in enabling rapid nerve impulse conduction in both the peripheral and central nervous systems, and provides trophic and metabolic support to the axons. It is also a primary target of the immune system in multiple sclerosis (Fletcher et al., 2018). Several studies have shown the effect that BDNF has on the myelination process, via TrkB activation (Fletcher et al., 2018). Namely, the proposed mechanism is that BDNF/TrkB signaling, actually the cascade that activates the mitogen-activated protein kinase/Erk pathway, as a final outcome, has the promotion of the differentiation of premyelinating oligodendrocytes and myelination both *in vitro* and *in vivo*. The same results have been reported when, instead of BDNF, small molecules activators of the TrkB receptor are used (Fletcher et al., 2018). Because the TrkB receptor is localized on oligodendrocyte cells, it was shown that, after following a demyelinating lesion, this receptor can positively regulate the expression of myelin and can cause remyelination (Huang et al., 2020). The recent study has also reported that it is crucial to preserve myelin integrity after traumatic brain injury (Fletcher et al., 2021). Indeed, after administration of the TrkB receptor activator, LM22A-4, to mice that suffered a traumatic brain injury, myelin integrity was preserved, cortical atrophy was prevented, while gliosis was reduced (Fletcher et al., 2021). These studies show that the TrkB receptor can be a target of great interest when it comes to the reparation of damaged myelin, especially if we take into consideration that this is one of the main events in multiple sclerosis.

In addition to its influence on myelination, it is proven that BDNF/TrkB signaling pathway can induce axonal regeneration. Namely, a previous study has shown that administrating the recombinant human BDNF, at the site where the axon was cut can enhance axonal regeneration (English et al., 2022). Small molecules, 7,8-dihydroxyflavone and deoxygedunin, which activate the TrkB receptor, have the same effect

on axonal regeneration (English et al., 2022). These molecules do not promote endogenous BDNF, since they enhanced regeneration in BDNF-knockout mice, while in the TrkB knockout mice, they could not. This led us to conclude that for inducing axonal regeneration, the presence of intact TrkB receptor is mandatory. It is believed that the phosphatidylinositol 3-kinase signaling pathway is the one in charge for axonal regeneration (Tejeda and Díaz-Guerra, 2017). The downside of applying BDNF or small molecules to induce axonal regeneration after injury is the fact that they had to be administered locally, during the surgical intervention. However, recently it has been described that oral treatments of R13 (a prodrug of 7,8-dihydroxyflavone), can stimulate both sensory and motor axonal regeneration (English et al., 2022). The potential of activating the TrkB receptor and its influence on axonal regeneration is of great value and interest, since it could lead to the development of the treatments used to treat severe mechanical damage of the spinal cord. This could be a promising cure for patients who have suffered injuries to the spine in different accidents.

Activation of the TrkB receptor signaling pathway also has a pro-neuronal effect on the damaged retinal ganglion cells, because it can promote its regeneration and further development (Han et al., 2018). Not only that the activation of the BDNF/TrkB pathway is capable of promoting the regeneration of damaged neurons, it can also induce neuronal outgrowth, such as dendritic branching of hippocampal neurons, most likely through regulation of the Rab5-Rab11 endosomal system (Moya-Alvarado et al., 2018), via one of the signaling pathways (mitogen-activated protein kinase)/ERK or phosphatidylinositol 3-kinase (Tejeda and Díaz-Guerra, 2017). It was reported recently that this activation of the TrkB pathway on the neuronal differentiation, can be also obtained by small molecules, activators of the TrkB receptor, instead of BDNF (Antonijevic et al., 2023).

Among all these effects that the BDNF/TrkB signaling pathway has on neuronal regeneration and development, this pathway has also been reported to influence synaptogenesis most likely via the phospholipase C- γ signaling pathway (Tejeda and Díaz-Guerra, 2017). Research has shown that BDNF and some small molecules (such as amitriptyline and 7,8-dihydroxyflavone), activators of the TrkB receptor, can protect and repair cochlear synapses in noise-induced synaptopathy (Fernandez et al., 2021).

Taken all together, we can see that in many studies the protective role that BDNF/TrkB signaling has is without any doubt. Not only that this pathway is capable of saving neurons from death, it is also inducing myelination, regeneration of the axons, differentiation of neurons, and restoring synapses (Figure 1).

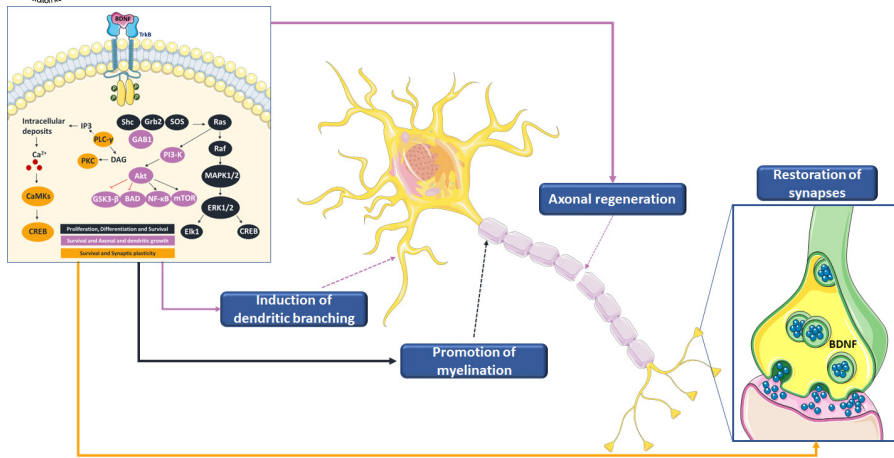


Figure 1 | Representation of the influence of the BDNF/TrkB signaling pathway on dendritic branching (purple arrow), myelination (dark blue arrow), axonal regeneration (purple arrow), and synapse restoration (orange arrow). Created with Microsoft PowerPoint and Servier Medical Art free images (<https://smart.servier.com/>). Akt: Protein kinase B (purple); BAD: Bcl-2 antagonist of cell death (purple); CaMKs: Ca(2+)/calmodulin-dependent protein kinases (orange); CREB: cAMP response element-binding protein (orange); DAG: diacylglycerole; Elk1: ETS like-1 protein (dark blue); ERK1/2: extracellular signal-regulated protein kinases 1 and 2 (dark blue); GAB1: GRB2-associated-binding protein 1 (purple); Grb2: growth factor receptor-bound protein 2 (dark blue); GSK3-β: glycogen synthase kinase 3 β (purple); IP3: inositol-1,4,5-trisphosphate; MAPK1/2: mitogen-activated protein kinase 1 and 2 (dark blue); mTOR: mammalian target of rapamycin (purple); NF-κB: nuclear factor kappa-B (purple); PI3-K: phosphatidylinositol 3-kinase (purple); PKC: protein kinase C (orange); PLC-γ: phospholipase C-γ (orange); Raf: rapidly accelerated fibrosarcoma kinases (dark blue); Ras: low-molecular-weight GDP/GTP-binding guanine triphosphatase encoded by the Ras gene (dark blue); SOS: son of sevenless (dark blue).

Neurodegenerative diseases are multi-factorial diseases, in which the goal, for the moment, is to stop the progression of it. But we must think in advance and if we are able to eventually find a cure to stop the disease, we will need a treatment that will induce the regeneration of already damaged neurons that are left, followed by its differentiation. The signaling pathway that the TrkB receptor has represents an extremely interesting target in the development of potential therapies for neurodegenerative conditions because of its wide range of influences on the neurons, and could be one of the key pieces of the puzzle in this quest. What makes this quest even harder, is the debate currently existing in the field, in which the mechanism of action of some activators is questioned (Pankiewicz et al., 2021) (are the discovered small molecules actually direct activators of the TrkB receptor or are causing activation of it through indirect communication). Despite this, one thing remains, is that the BDNF/TrkB pathway still represents an interesting target and gives hope in the fight against neurodegeneration.

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