

● INVITED REVIEW

Therapeutic potential of brain-derived neurotrophic factor (BDNF) and a small molecular mimics of BDNF for traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is a major health problem worldwide. Following primary mechanical insults, a cascade of secondary injuries often leads to further neural tissue loss. Thus far there is no cure to rescue the damaged neural tissue. Current therapeutic strategies primarily target the secondary injuries focusing on neuroprotection and neuroregeneration. The neurotrophin brain-derived neurotrophic factor (BDNF) has significant effect in both aspects, promoting neuronal survival, synaptic plasticity and neurogenesis. Recently, the flavonoid 7,8-dihydroxyflavone (7,8-DHF), a small TrkB agonist that mimics BDNF function, has shown similar effects as BDNF in promoting neuronal survival and regeneration following TBI. Compared to BDNF, 7,8-DHF has a longer half-life and much smaller molecular size, capable of penetrating the blood-brain barrier, which makes it possible for non-invasive clinical application. In this review, we summarize functions of the BDNF/TrkB signaling pathway and studies examining the potential of BDNF and 7,8-DHF as a therapy for TBI.

Key Words: 7,8-dihydroxyflavone; brain-derived neurotrophic factor; tropomyosin related kinase B (TrkB) receptor; traumatic brain injury; neuroregeneration; neuroprotection

Introduction

Traumatic brain injury (TBI) is a global public health issue with few treatment options available (Chauhan, 2014). With approximately 10 million people affected by TBI annually, it is a major cause of death and disability worldwide, and the World Health Organization projects that it will surpass the mortality and morbidity of many diseases by the year 2020. It is difficult to quantify the full magnitude of TBI, as multiple factors influence it being underreported, including mild head trauma, the most common brain injury that is often not reported and not physically observed, but may lead to memory or cognitive deficits at a later time (Hyder et al., 2007).

TBI is the loss or alteration of brain function generated by an external force (Menon et al., 2010). TBI can be diagnosed with symptoms and signs that are temporally close to the external insult, including damage to blood vessels, axons, neurons, and glia, which are considered primary damages. Following primary injury, which refers to the immediate death of cells on impact from the external disruption, secondary injury is the result of a series of biochemical changes in the surrounding area of the primary injury that induces further tissue damage leading to functional deficits (Stoica and Faden, 2010).

Thus far, there is no effective treatment for TBI. Current therapies are primarily focused on reducing the extent of secondary insult and enhancing the regeneration process. Strategies that have neuroprotective effects, salvaging the injured brain tissue in the early stages post-injury and promoting regeneration at the recovery stage, are desirable. The brain-derived neurotrophic factor (BDNF) and its high affinity receptor tropomyosin-receptor-kinase B (TrkB) play a critical role in promoting neuronal survival, plasticity, and memory function (Park and Poo, 2013; Leal et al., 2015). Therapeutic potential of BDNF and its mimics have been reported in many neurological conditions including TBI. This review summarizes the signaling pathway of BDNF/TrkB and studies targeting this signaling pathway for treating TBI.

Neurotrophins and the Receptors

Neurotrophins are endogenous peptides secreted from neuronal and glial cells, and are associated with regulating the function, survival, and development of individual cells and neuronal networks across the entire brain. More specifically, neurotrophins regulate synaptic plasticity, protect neurons from oxidative stress and apoptosis, and can stimulate neurogenesis (Skaper et al., 1998; Leal et al., 2015; Kuipers et

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al., 2016). The neurotrophin family members include nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5), which are classified together based on their structural similarity to NGF, the first neurotrophin discovered (Skaper, 2012).

Neurotrophins are able to exert their neuroprotective effects through the transmembrane receptors they bind to and the signaling cascades they initiate. There are two main classes of transmembrane neurotrophin receptors, which include the Trk family of tyrosine kinase receptors, TrkA, TrkB, and TrkC, and the p75^{NTR} neurotrophin receptor (p75^{NTR}), a member of the tumor necrosis-factor family (Marco-Salazar et al., 2014). NGF preferentially binds to TrkA, BDNF and NT-4/5 to TrkB, and NT-3 to TrkC, all with high affinity, while each of these neurotrophins binds with low affinity to p75^{NTR} receptors (Skaper, 2008; Marco-Salazar et al., 2014). Additionally, p75^{NTR} contributes to proper Trk receptor function, and promotes ligand binding of neurotrophins with their correct Trk receptor (Skaper, 2012). Once bound to their Trk receptors, neurotrophins activate a cascade of events through Ras, phosphatidylinositol 3-kinase (PI3K), phospholipase-C γ (PLC γ), and mitogen-activated protein kinase (MAPK) signaling pathways (Skaper, 2008).

BDNF and its Downstream Pathways

Among neurotrophins, BDNF is the most widely studied due to its potent effects at synapses and wide expression in the brain. Two different classes of receptors are responsible for mediating BDNF signaling: p75^{NTR} and TrkB (Lu et al., 2008). BDNF has a $K_d = 9.9$ nM for the TrkB receptor and a $K_d \sim 1.0$ nM for the p75^{NTR} demonstrating its binding selectivity and affinity for each of the receptor types (Bernard-Gauthier et al., 2013). It is through its high affinity for TrkB that BDNF is able to provide neuronal survival, neuronal plasticity, and neurogenesis (Lu et al., 2008). The p75^{NTR} receptor is more associated with apoptosis. ProBDNF binds to the p75^{NTR} receptor while the mature form of BDNF has a high affinity to TrkB (Bollen et al., 2013). However, the mature form of BDNF can bind to p75^{NTR} receptor when there are high concentrations of BDNF (Boyd and Gordon, 2001). Both of the BDNF receptors can be found in the same cell, coordinating and modulating neuronal responses. Furthermore, the signals generated by each receptor can augment each other or go against each other, fluctuating between an enhancing and suppressing relationship (Kaplan and Miller, 2007).

Upon binding to the TrkB receptor, BDNF induces dimerization and autophosphorylation of the receptor, which causes internalization of the TrkB receptor and initiates intracellular signaling cascades (Levine et al., 1996) (**Figure 1**). These signaling cascades include the phosphatidylinositol-3-kinase (PI3K) pathway, the PLC γ pathway, and

the MAPK pathway. The PI3K pathway activates protein kinase B (Akt), which ultimately promotes cell survival by inhibiting Bad and consequently allowing the expression of anti-apoptotic proteins, such as Bcl2 (Yoshii and Constantine-Paton, 2010). Phosphorylation of Akt at the proper site also results in the suppression of pro-apoptotic proteins, pro-caspase-9 and Forkhead (Kaplan and Miller, 2007). Upregulated Bcl2 levels are correlated with positive outcomes, such as attenuated cell death and a better prognosis (Nathoo et al., 2004). The PLC γ pathway leads to the release of intracellular calcium stores *via* activation of the inositol triphosphate (IP3) receptor, and helps to increase calmodulin kinase (CamK) activity, and thus synaptic plasticity *via* the transcription factor CREB (cyclicAMP response element binding protein). The MAPK pathway, also referred to as extracellular related signal kinase (ERK) pathway, aids in cell growth and differentiation. A PLC γ mediated response is likely responsible for quick, short-term actions, while MAPK and PI3K pathways involve long-term transcriptional effects (Yoshii and Constantine-Paton, 2010).

Function of BDNF and TrkB Pathways in the Central Nervous System

BDNF and TrkB pathway have profound effects in regulating cell survival and other biological processes. BDNF is important for neurite and axonal growth (Yoshii and Constantine-Paton, 2010), and is required for the survival and development of dopaminergic, GABAergic, serotonergic, and cholinergic neurons (Pillai, 2008).

Activation of the TrkB pathways has been shown to improve cognition, and has also been correlated with an increase in synaptic density (Castello et al., 2014). BDNF and TrkB are upregulated in areas where there is neuronal plasticity occurring. Due to this relationship, BDNF is considered a molecular mediator in the function and structure of synaptic plasticity, and plays a pivotal role in memory formation as well as memory consolidation (Zeng et al., 2012). Even a disruption in the pathway that transports and produces BDNF can result in the clinical symptoms of deteriorating memory and cognitive dysfunction (Leal et al., 2015). Clinical studies have shown a causal relationship between lower levels of BDNF and cognitive declines observed in aging, schizophrenia, and Rett syndrome (Zuccato et al., 2011; Autry and Monteggia, 2012; Soares et al., 2016).

The cellular basis for learning and memory is considered to be at the synapses within the hippocampus. BDNF is a key molecule which controls neuronal differentiation and survival, synaptic formation and plasticity, as well as activity-dependent changes in synaptic structure and function (Park and Poo, 2013). Long-term potentiation (LTP) is a specific form of plasticity that occurs in the hippocampus and is the cellular basis of learning and memory. BDNF is a major regulator for the induction and maintenance of LTP in

the hippocampus and other brain regions (Leal et al., 2014, 2015). Studies have established that adult neurogenesis in the hippocampus is involved in learning and memory functions (Aimone et al., 2006; Deng et al., 2009). BDNF and TrkB signaling influences adult neurogenesis by mediating neuronal differentiation and survival of newly generated neurons (Scharfman et al., 2005; Chan et al., 2008; Gao and Chen, 2009). The influence of BDNF and TrkB signaling on neurogenesis likely contributes to its function on learning and memory.

BDNF and Traumatic Brain Injury

By virtue of its role in neuronal differentiation, survival, and plasticity, it is no surprise that BDNF plays an important role following TBI. In response to TBI, the mRNA expression level of BDNF is transiently and significantly increased. Studies have reported that within hours post-injury, the expression level of BDNF mRNA is significantly upregulated in the injured cortex and in the hippocampus (Yang et al., 1996). The level of BDNF declines at 24 hours post-injury, and is no longer significant at 36 hours post-injury (Oyesiku et al., 1999). Following injury, the mRNA expression level of TrkB receptor is also transiently upregulated in the hippocampus and dentate gyrus (Merlio et al., 1993). This transient surge of BDNF and its receptor following TBI suggests that BDNF acts as an endogenous neuroprotective response attempting to attenuate secondary cell damage following TBI (Mattson and Scheff, 1994).

The importance of the BDNF/TrkB signaling pathway in regulating CNS function has led to many studies exploring the therapeutic potential of BDNF/TrkB for various neurological diseases, including TBI. The therapeutic potential of BDNF is restricted due to its short half-life (< 10 minutes) and inability to cross the blood-brain barrier (BBB) because of its large size (27 kDa) (Price et al., 2007). Thus far, direct application of BDNF for TBI has not been efficacious in experimental TBI studies. However, limited studies have shown when delivered indirectly, BDNF can significantly improve functional recovery of injured animals. In a recent study, poly(lactic-co-glycolic acid) nanoparticles coated with surfactant poloxamer 188 was used to deliver BDNF to the injured brain by receptor-mediated transcytosis (Khalin et al., 2016). Following intravenous injection of nanoparticle-bounded BDNF, increased BDNF levels were found in the brain, and animals had improved neurological and cognitive functions following a weight-drop injury in mice (Khalin et al., 2016).

The Molecule 7,8-Dihydroxyflavone

Compared to BDNF, small compounds such as TrkB agonists that mimic BDNF's neurotrophic signaling without its pharmacokinetic barriers may have greater therapeutic potential. In an effort to search for small molecules mimicking BDNF function, Jang and colleagues conducted

a series of cell-based TrkB receptor-dependent survival assays to screen chemical libraries and resulted in the discovery of a flavone derivative, 7,8-dihydroxyflavone (7,8-DHF) (Jang et al., 2010). 7, 8-DHF is a polyphenolic compound found in fruits and vegetables, which mimics BDNF functions due to its ability to bind to TrkB (Chen et al., 2011; Zeng et al., 2012). 7,8-DHF specifically binds to the receptor extracellular domain of TrkB with high affinity, and induces the receptor dimerization and autophosphorylation (Jang et al., 2010), initiating activation of the downstream signaling pathways as described above in BDNF/TrkB pathway (**Figure 1**).

Compared to BDNF, 7, 8-DHF-induced TrkB receptor phosphorylation lasts much longer. Additionally, TrkB receptors activated by 7,8-DHF are not degraded, but instead are recycled to the cell surface after internalization, as opposed to BDNF activated TrkB receptors, which are tagged for ubiquitination and degraded after internalization (Liu et al., 2014). Internalization is a vital part of initiating signal transduction for the neurotrophin-Trk complex. 7,8-DHF can successfully mimic BDNF-TrkB internalization in neurons, producing endosomes with TrkB as early as 10 minutes, as BDNF does, and producing a more robust endocytic response than BDNF at 60 minutes (Liu et al., 2014).

7,8-DHF has a longer half-life compared to BDNF (134 minutes in plasma following 50 mg/kg oral administration versus less than 10 minutes) (Zhang et al., 2014). It is considerably smaller than BDNF, with a molecular size of 254 Da compared to BDNF's 27 kDa, which allows for greater permeability crossing the BBB (Liu et al., 2014). It is orally bioactive with an oral bioavailability of 5% (Zhang et al., 2014; Liu et al., 2016).

7,8-DHF is a selective TrkB agonist which is able to activate TrkB receptors without binding to p75 receptors, initiating signaling pathways that only influence neuroprotection, plasticity, and neurogenesis without activating the apoptotic processes (Bollen et al., 2013). The binding of 7,8-DHF to the TrkB extracellular domain activates signal cascades that induce autophosphorylation of TrkB, leading to activation of MAPK, PI3/Akt, and ERK1/2 signal pathways in a time frame that is comparable to BDNF and in a dose-dependent manner (Liu et al., 2010; Jiang et al., 2013).

Therapeutic Potential of 7,8-DHF for TBI

Since its discovery, 7,8-DHF has been documented in providing neuroprotection and neuroplasticity in animal models of various neurological diseases and disorders including TBI. In particular, the beneficial effect of 7,8-DHF has been observed in animal models of Parkinson's disease (Sconce et al., 2015), Alzheimer's disease (Castello et al., 2014; Zhang et al., 2014), amyotrophic lateral sclerosis

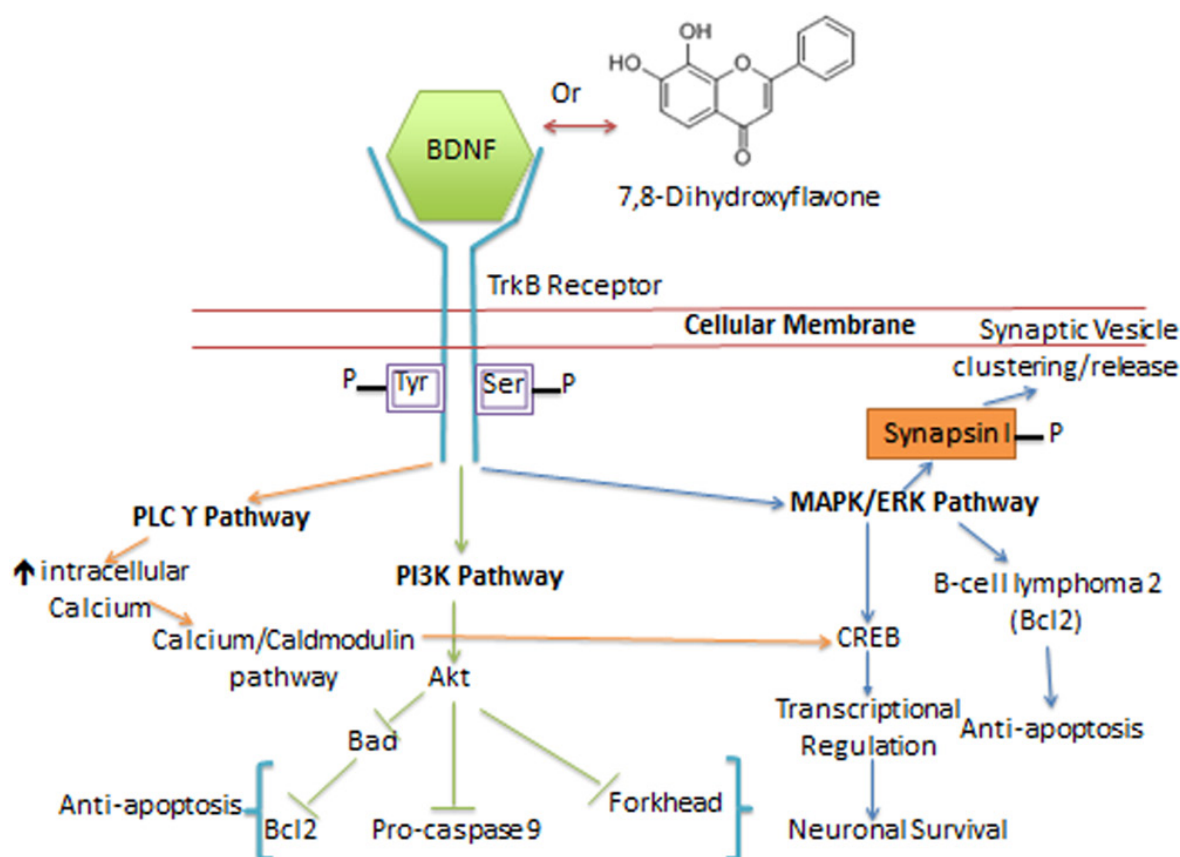


Figure 1 The activation pathways of the TrkB receptor.

The binding of BDNF or 7,8-DHF leads to auto-phosphorylation of the intracellular domain of the receptor and activation of the downstream pathways. 1) The MAPK pathway. Activation of this pathway stimulates anti-apoptotic proteins, including Bcl2 and cAMP response-element binding protein (CREB). CREB is required by neurotrophin mediated neuronal survival. Activation of the MAPK pathway also stimulates extracellular signal related kinase (ERK), which induces phosphorylation of Synapsin I mediating the clustering and release of synaptic vesicles. 2) Activation of the PI3K pathway, which activates Akt. Akt inhibits apoptosis by inhibiting activation of antiapoptotic proteins including Bad, Pro-caspase 9 and Forkhead. PI3K = phosphatidylinositol 3 kinase; Akt = Protein Kinase B, PKB; Bad = Bcl2 associated death promoter. 3) The Phospholipase C-gamma (PLC γ) pathway. PLC- γ can lead to an increase in intracellular calcium levels, which activates the calcium/calmodulin pathway leading to CREB activation. 7,8-DHF: 7,8-Dihydroxyflavone; BDNF: brain-derived neurotrophic factor; MAPK: mitogen-activated protein kinase; TrkB: tropomyosin related kinase B.

(Korkmaz et al., 2014), Huntington’s disease (Jiang et al., 2013), stroke (Wang et al., 2014), depression and Rett syndrome (Liu et al., 2010), and TBI (Wu et al., 2014; Agrawal et al., 2015).

In recent years, the therapeutic potential of 7,8-DHF for TBI has been explored in several types of TBI models, and the underlying mechanisms were explored as well. In an *in vitro* stretch injury model, 7,8-DHF treatment can attenuate stretch injury induced cytotoxicity and apoptosis in cultured primary neurons (Wu et al., 2014). In a mouse focal controlled cortical impact (CCI) injury model, intraperitoneal injection of 7,8-DHF at the dose of 20 mg/kg beginning at 10 minutes following moderate CCI injury, and subsequent single daily doses for 3 days had significant beneficial effects including reducing brain edema, cortical contusion volume, neuronal cell death and apoptosis, as well as improving motor functions of injured animals (Wu et al., 2014). The neuroprotective effect of 7,8-DHF was also observed when

the initial treatment was delayed starting at 3 hours following TBI as demonstrated by reduced cortical lesion volumes (Wu et al., 2014).

In a fluid percussion injury (FPI) rat model, animals that received 7,8-DHF following injury at the single daily dose of 5 mg/kg for 7 consecutive days had enhanced learning and memory functions (Agrawal et al., 2015). In both the CCI and FPI studies, enhanced phosphorylation of TrkB receptor and activation of downstream signaling proteins such as Akt and CREB was observed, confirming that the protective effect of 7,8-DHF for TBI was through activation of TrkB receptor (Wu et al., 2014; Agrawal et al., 2015).

At the dose of 5 mg/kg giving at 1, 24, 48 and 72 hours following TBI in a mouse CCI model, 7,8-DHF can also prevent dendritic degeneration of cortical neurons and improve motor functional deficits (Zhao et al., 2016a). Pretreatment of 7,8-DHF before TBI in the mouse CCI model can enhance neuroprotection by reducing inju-

ry-induced neuronal cell death of immature neurons in the dentate gyrus of the hippocampus (Chen et al., 2015). When given post-TBI, 7,8-DHF also protects newly generated immature neurons in the dentate gyrus of the hippocampus from injury-induced cell death and promotes their dendritic development in a mouse CCI model (Zhao et al., 2016b).

Our lab has recently found that in a rat CCI model, 5-day treatment of 7,8-DHF at the dose of 5 mg/kg started either at 1 hour or 2 days post-injury could provide protective effect with reduced lesion volume and neuronal cell loss in the hippocampus, as well as improved motor and cognitive functions (unpublished data).

Apart from direct neuronal function, 7,8-DHF has also demonstrated a role in modulating inflammation. In cultured murine microglial cells, 7,8-DHF can inhibit transcription activities of nuclear factor- κ B and MAPK signaling, and thus reduce the production of iNOS (inducible nitric oxide synthase), COX-2 (cyclooxygenase-2), tumor necrosis factor- α and interleukin- 1β following lipopolysaccharide-stimulation (Park et al., 2014). This anti-inflammation effect of 7,8-DHF likely contributes to its beneficial effects following TBI.

Conclusion and Perspectives

In summary, 7,8-DHF has proven a viable therapy option for TBI and multiple degenerative neurological disorders. Through its activation of the TrkB receptor and downstream signaling pathways, it promotes survival and dendritic integrity of neurons, reduces injury-induced tissue damage, and ameliorates motor and cognitive functional impairments. Its ability to cross the BBB and broad therapeutic potential in the CNS makes it a valuable compound deserving further examination for its application in TBI and other neurological diseases in clinic.

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