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Review

7,8-Dihydroxyflavone as a pro-neurotrophic treatment for neurodevelopmental disorders

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ABSTRACT

Neurodevelopmental disorders are a group of conditions that arises from impairments of the central nervous system during its development. The causes of the various disorders are heterogeneous and the symptoms likewise are multifarious. Most of these disorders currently have very little available treatment that is effective in combating the plethora of serious symptoms. Brain-derived neurotrophic factor (BDNF) is a fundamental neurotrophin with vital functions during brain development. Pre-clinical studies have shown that increasing BDNF signalling may be a potent way to prevent, arrest or even reverse abnormal neurodevelopmental events arising from a variety of genetic or environmental causes. However, many difficulties make BDNF problematic to administer in an efficient manner. The recent discovery of a small BDNF-mimetic, the naturally occurring flavonoid 7,8-dihydroxyflavone (7,8-DHF), may provide an avenue to allow efficient and safe activation of the BDNF pathway in tackling the symptoms of neurodevelopmental disorders. Here, evidence will be provided to support the potential of 7,8-DHF as a novel treatment for several neurodevelopmental disorders where the BDNF signalling pathway is implicated in the pathophysiology and where benefits are therefore most likely to be derived from its implementation.

Contents

1. Introduction

Neurodevelopmental disorders arise from abnormal impairments or retardation of early central nervous system maturation

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processes owing to a variety of reasons, including genetic mutations, prenatal stress, infection and alcohol exposure. Due to its fundamental nature, these disorders result in a wide array of behavioural symptoms, depending on the severity and timing of the neurodevelopmental insult.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that also contains nerve growth factor, neurotrophin 3 and 4 (E. J. Huang and Reichardt, 2003; Thoenen, 2000). Since its discovery in 1982 (Barde et al., 1982), BDNF has received considerable attention from the research community due to its plethora of vital developmental functions, both embryonic and postnatal. These include its essential participation in the promotion of early neuronal survival, circuitry and synaptic growth and maturation (Buchman and Davies, 1993; Cohen-Cory et al., 2010; Lindsay, Barde, et al., 1985; Lindsay, Thoenen, et al., 1985; Nikolakopoulou et al., 2010; Wright and Ribera, 2010) as well as important and sustained neurotrophic function in adulthood, where BDNF sustains neuronal homeostasis, growth and survival (Ernfors et al., 1994; Hetman et al., 1999), regulates synaptic plasticity (L. J. Goodman et al., 1996; Inagaki et al., 2008; Novkovic et al., 2015; Pang and Lu, 2004; Patterson et al., 1996; Tanaka et al., 2008) and promotes adult neurogenesis by enhancing proliferation (Pencea et al., 2001; Rossi et al., 2006; H. Scharfman et al., 2005; Zigova et al., 1998), differentiation (Chan et al., 2008) and survival (J. Lee et al., 2002) of new-born cells. Therefore there is great potential for BDNF as a therapeutic target for neurodevelopmental disorders with origins in early brain development. Our goal in this review is to address whether naturally occurring molecules, especially the recently discovered flavonoid, 7,8-dihydroxyflavone (7,8-DHF), represent avenues for the safe activation of the BDNF pathway.

2. BDNF and its receptor

The importance of BDNF in the pathophysiology of multiple neurodevelopmental disorders including schizophrenia, autism and Rett's syndrome is evidenced by post-mortem and blood sampling of patients that have discovered reduced levels of BDNF gene and protein expressions. Further insights from animal and cellular models reveal that besides absolute expression, BDNF trafficking and downstream signalling are also disarranged in neurodevelopmental disorders, as will be discussed later in the review.

BDNF is mapped to chromosome 11 p in humans (Jones and Reichardt, 1990; Maisonpierre et al., 1991) and its expression is regulated in a neuronal activity-dependent manner through calcium mediated mechanisms (Tabuchi, 2008). BDNF's importance is reflected in its highly conserved state across vertebrate species (Gotz et al., 1992) and the fact that BDNF knock-out mice show severe deficiencies in brain development and early lethality with most dying in the second postnatal week (Ernfors et al., 1994). BDNF exhibits highly complex regulation of its expression. It has been found to have 11 exons and 9 functional promoters that direct tissue, brain-region and cellular spatial specificity (Aid et al., 2007; Chiaruttini et al., 2008; Pruunsild et al., 2007). BDNF is synthesized as a 35 kDa prepro isoform, which may then be cleaved to form a 28 kDa proBDNF or the biologically active 13.5 kDa mature BDNF. Mature BDNF acts mainly through its high-affinity receptor, tropomyosin-related kinase receptor (TrkB) (Strohmaier et al., 1996), which is also regulated in an activity dependent manner (Nagappan and Lu, 2005). Binding of mature BDNF to TrkB causes autophosphorylation of the receptor and initiates a number of pro-survival intracellular signalling pathways including phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK) and phospholipase Cγ (PLCγ) (Kuczewski et al., 2010; Numakawa et al., 2013; Patapoutian and Reichardt, 2001; Reichardt, 2006).

3. BDNF as therapeutic

BDNF's wide range of diverse and fundamental roles in brain development has rendered abnormalities in its signalling as a focus on the pathogenesis of neurodevelopmental disorders. Studies have confirmed BDNF as being implicated in a wide spectrum of neurological and neurodegenerative diseases, such as mood disorders and neurological disorders (Autry and Monteggia, 2012; Balaratnasingam and Janca, 2012; Boulle et al., 2012; Duman, 2004; Lu et al., 2013). Furthermore, it has been shown in rodent models that BDNF expression is sensitive to early environmental challenges and is reduced by a variety of adverse influences known to be risk factors for neurodevelopmental disorders such as maternal nutrient deficiency (Sable et al., 2011, 2014), prenatal alcohol exposure (Caldwell et al., 2008; Feng et al., 2005; Maier et al., 1999) and early life stress (Roceri et al., 2002).

As such, the potential application of BDNF as an overarching therapeutic target for various central nervous system disorders has been gathering momentum (Lu et al., 2013; Pezet and Malcangio, 2004). However, the direct administration of BDNF in patients faces multiple hurdles. Oral administration of BDNF is broken down by the digestive enzymes and systemic administration is impeded by the very short half-life of BDNF (less than 1 min in rat plasma), its poor ability to cross the blood–brain barrier and its poor brain intraparenchymal penetration after direct infusion into the ventricles (Morse et al., 1993; Pardridge, 2007; Pardridge et al., 1998; Poduslo and Curran, 1996). Drugs such as antidepressants, which have been shown to possess the ability to increase BDNF, have delayed action, low efficacy and also come with unwanted psychotropic effects and adverse reactions (Ferguson, 2001; Kozisek et al., 2008; Malberg and Blendy, 2005; Stassen et al., 1997; Uher et al., 2009). For these reasons, the recently identified small molecule flavonoid, 7,8-DHF, a BDNF mimetic, may prove to be the answer to the obstacles adumbrated above. Its particular properties, discussed in detail later in this review, including its ability to cross the blood brain barrier efficiently while maintaining stability via oral administration, allow it potentially to circumvent the major complications facing direct BDNF infusion. Thus 7,8-DHF may offer clinicians a new weapon against neurodevelopmental disorders by targeting the alluring signalling pathway of the vital neurotrophic factor BDNF in an efficient manner. With increasingly earlier detection, early implementation of suitable treatment may ameliorate, prevent or even reverse adverse sequelae.

4. Flavonoids

Flavonoids are a common class of phytochemicals ubiquitously found in plants and are the most common group of polyphenolic compound in the human diet (Kozlowska and Szostak-Wegierek, 2014; Spencer, 2008b). In recent years, the cognitive-enhancing and neuroprotective roles of various food items and beverages have been explored including *Camellia sinensis* (tea) (Wierzejska, 2014), *Vitis Vinifera* (grapes) (Georgiev et al., 2014), *Theobroma cacao* (cocoa) (Sokolov et al., 2013) and various berries (Cherniack, 2012) – all of which are bountiful sources of polyphenols.

Flavonoids have been found to possess multiple beneficial effects including antioxidant, anti-inflammatory, estrogenic and anti-tumour properties (Harborne and Williams, 2000; Solanki et al., 2015). But above all, flavonoids may enhance neuro-cognitive performance through their ability to modulate intracellular pro-survival signalling cascades such as extracellular signal-regulated kinase (ERK)1/2, protein kinase B (PKB/Akt), protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3K) signalling pathways (Mansuri et al., 2014). These activations lead to, among other things, up-regulation of the anti-apoptotic protein Bcl-2 and