NEURAL REGENERATION RESEARCH
August 2014, Volume 9, Issue 16
www.nrronline.org

INVITED REVIEW

Possible protective action of neurotrophic factors and natural compounds against common neurodegenerative diseases

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doi:*10.4103/1673-5374.139474*
http:*//www.nrronline.org/*

Accepted: *2014-06-28*

Abstract

It has been suggested that altered levels/function of brain-derived neurotrophic factor (BDNF) play a role in the pathophysiology of neurodegenerative diseases including Alzheimer's disease. BDNF positively contributes to neural survival and synapse maintenance *via* stimulating its high affinity receptor TrkB, making upregulation of BDNF and/or activation of BDNF-related intracellular signaling an attractive approach to treating neurodegenerative diseases. In this short review, I briefly introduce small natural compounds such as flavonoids that successfully increase activation of the BDNF system and discuss their beneficial effects against neurodegeneration.

Key Words: *neurodegenerative diseases; BDNF; TrkB; natural compounds; neuroprotection*

Funding: *This study was supported by the grant from Grant-in-Aid for Scientific Research (B) (JSPS KAKENHI Grant Number 24300139), and for Challenging Exploratory Research (JSPS KAKENHI Grant Number 25640019) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.*

Numakawa T. Possible protective action of neurotrophic factors and natural compounds against common neurodegenerative diseases. Neural Regen Res. 2014;9(16):1506-1508.

Introduction

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family (consisting of nerve growth factor, BDNF, neurotrophin-3, and neurotrophin-4), has been intensely studied concerning its positive effect on survival promotion and synaptic regulation in the central nervous system. TrkB, a high affinity receptor for BDNF, and its downstream signals including phosphoinositide 3-kinase (PI3K)/Akt, extracellular signal-regulated kinase (ERK) and phospholipase Cγ pathways, are activated to maintain neuronal survival and regulate synaptic plasticity (Kuczewski et al., 2010; Numakawa et al., 2013). Evidence suggests that decreased BDNF and TrkB-related signaling are involved in the pathogenesis of neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD), establishing this neurotrophin as a therapeutic target in treating neurodegeneration (Allen et al., 2011; Lu et al., 2013). As a result, the biological mechanisms of small chemicals and natural compounds that can stimulate the BDNF/TrkB system have attracted researchers.

Beneficial effect of natural compounds in PD models

Dopamine toxicity and resultant oxidative stress are involved in the pathogenesis of PD. In order to make *in vitro* and *in vivo* models of PD, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) have been applied to cell cultures and animals (Bové and Perier, 2012). Therefore, the potential effect of natural compounds obtained from plants on neural cells under dopamine toxicity has become an interesting issue. Puerarin derived from kudzu roots exerts a protective effect on neurons in the substantianigra (SN) after 6-OHDA-induced tissue lesion (Li et al., 2013). Puerarin treatment increases both dopamine concentration and BDNF levels in SN neurons in addition to improving Parkinson-like behavior evoked by apomorphine (Li et al., 2013). Recently, Wei et al. (2013) observed that increased levels of glutathione, an endogenous antioxidant, play a role in cell protection by using (2S)-5,2′,5′-trihydroxy-7-methoxyflavanone (TMF), a natural chemical from abacopterispenangiana, in differentiated PC12 cells under dopamine exposure. They also found that TMF reversed reduction of spatial learning, memory and hippocampal BDNF expression in mice receiving D-galactose treatment (Wei et al., 2013).

Neuroprotection by flavonoids in AD models

Given that a growing body of evidence suggests that oxidative stress is also implicated in the pathophysiology of AD, natural antioxidants (including polyphenols) obtained from fruits, nuts, leaves and roots of plants are extensively examined. It is possible that bioactive nutrients are effective for prevention of neurodegeneration (Essa et al., 2012). Specifically, flavonoids, a major population of polyphenols obtained from plants, are speculated to be effective for treatment of

AD. Indeed, the antioxidant effect of flavonoids in neurodegenerative diseases such as AD has been demonstrated (Albarracin et al., 2012). In addition, other mechanisms behind neuroprotection have been proposed. Although it is well known that an aggregation of 42 residue amyloid-protein is implicated in the onset of AD, catechol-type flavonoids diminish aggregation *via* acting on the lysine residue of amyloid-protein (Sato et al., 2013). Using amyloid precursor protein/presenilin-1 double transgenic mice, Zhao et al. (2013) demonstrated that apigenin, 4′,5,7-trihydroxyflavone, improves deficits in learning and memory in these mice while rescuing downregulation of BDNF and its downstream signaling including ERK and cAMP response element-binding protein (CREB). Rutin(3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside) administration also increases hippocampal expression of ERK1, CREB and BDNF genes, and improves memory deficits of amyloid-injected rats (Moghbelinejad et al., 2014). Recently, we also found that flavonoids extracted from Iris Tenuifolia (IT; plant observed in Mongolian and East Asian regions) protected cultured cortical neurons against oxidative stress, and the neuroprotection by IT flavonoids was completely dampened by an inhibitor for Src homology 2 domain-containing phosphatase 2 (shp2) (Jalsrai et al., 2014). In our cultures, IT flavonoids indeed caused phosphorylation (activation) of shp2, although no change in levels of BDNF was observed (Jalsrai et al., 2014). Importantly, Jang et al. (2010) demonstrated that 7, 8-dihydroxyflavone acts as a potent TrkB agonist and is neuroprotective in a PD model using MPTP administration. A recent study demonstrated efficacy of 7, 8-dihydroxyflavone on recovery from deficits in spatial memory in a mouse model of AD-like neuronal loss (Castello et al., 2014). Detailed characterization of various flavonoids (radical scavenger properties, involvement in intracellular signaling, production of BDNF, *etc.*), and specificity to particular brain regions with respect to neuroprotection should be clarified in future studies. Specifically, the effect of flavonoids on BDNF production or direct stimulation of TrkB as an agonist should be considered separately, in order to explore novel drugs targeting the BDNF/TrkB system.

HD and small molecules targeting BDNF

It is also suggested that decreased expression of BDNF plays a role in the pathogenesis of HD, and that application of BDNF (including gene delivery with viral systems) is effective towards improving HD-like behaviors using animal models (Sari et al., 2011). Furthermore, as huntingtin regulates intracellular transport of BDNF (Gauthier et al., 2004), the relationship between HD and BDNF function is very close. Because peripheral BDNF application has poor brain penetration, small molecules aimed to upregulate the endogenous BDNF/TrkB system are powerful therapeutic tools for neurodegenerative diseases such as HD. Simmons et al. (2013) showed that TrkB and downstream Akt and PLCγ were activated in the striatum of R6/2 mice after 7-week treatment with LM22A-4. LM22A-4 decreased aggregated huntingtin in striatal and cortical neurons of R6/2 mice, which have about 130 CAG repeats of human huntingtin (Simmons et al., 2013). Recently, a report has demonstrated significant improvements in aggregation of huntingtin and downregulation of BDNF transcripts in R6/2 mice after knock-down of histone deacetylase 4 (HDAC4), which is shown to associate with huntingtin (Mielcarek et al., 2013). Because HDAC4 is a potential target for HD (Mielcarek et al., 2013), possible alterations in the expression of HDAC4 serve as an attractive marker when applying natural compounds or small molecules stimulating BDNF signaling. Because mutant huntingtin, which causes polyglutamine expansion, negatively affects intracellular BDNF transport resulting in loss of neurotrophic maintenance by BDNF (Gauthier et al., 2004), natural compounds that have high specificity for the BDNF/TrkB system may be promising drugs for HD treatment.

As described above, evidence suggests that natural and small compounds activating the BDNF/TrkB system are promising therapeutic targets for the treatment of neurodegenerative diseases. On the other hand, Todd et al. (2014) demonstrated that an antibody which acts as an agonist for TrkB exerts a beneficial effect on the BDNF/TrkB system although both 7,8-dihydroxyflavone and LM22A-4 failed to prevent cell death in rat striatal neurons, implying that much more *in vitro* and *vivo* studies to characterize the functioning of natural compounds as TrkB agonists are needed. Recently, glial production and secretion of growth factors including BDNF, stimulated by a variety of flavonoids, has been reported (Xu et al., 2013). In treating HD, the transplantation of stem cells overexpressing growth factors is considered to be a novel approach to improve disease symptoms (Maucksch et al., 2013). In addition, involvement of altered BDNF forms (proBDNF precursor or mature BDNF) in the pathophysiology of mental disorders and AD has been suggested (Carlino et al., 2013). Precursor proneurotrophins, before proteolysis into mature neurotrophins, bind to the low affinity common receptor p75 with high affinity, ultimately causing cell death (Lee et al., 2001; Teng et al., 2005). To accelerate development of novel therapeutic agents for neurodegenerative diseases, not only are investigations of underlying mechanisms of BDNF upregulation in neurons necessary, but also studies investigating natural compounds using another cell population (glia and neural stem cells) and biosynthesis of BDNF (pro or mature forms).

Conflicts of interest: *None declared.*

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