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REVIEW

Brain-derived neurotropic factor and GABAergic transmission in neurodegeneration and neuroregeneration

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Abstract
Neurotoxicity induced by stress, radiation, chemicals, or metabolic diseases, is commonly associated with excitotoxicity, oxidative stress, and neuroinflammation. The pathological process of neurotoxicity induces neuronal death, interrupts synaptic plasticity in the brain, and is similar to that of diverse neurodegenerative diseases. Animal models of neurotoxicity have revealed that clinical symptoms and brain lesions can recover over time *via* neuroregenerative processes. Specifically, brain-derived neurotropic factor (BDNF) and gamma-aminobutyric acid (GABA)-ergic transmission are related to both neurodegeneration and neuroregeneration. This review summarizes the accumulating evidences that suggest a pathogenic role of BDNF and GABAergic transmission, their underlying mechanisms, and the relationship between BDNF and GABA in neurodegeneration and neuroregeneration. This review will provide a comprehensive overview of the underlying mechanisms of neuroregeneration that may help in developing potential strategies for pharmacotherapeutic approaches to treat neurotoxicity and neurodegenerative disease.

Key Words: *brain-derived neurotropic factor; neurotoxicity; gamma-aminobutyric acid-ergic transmission; neurodegenerative diseases; neural regeneration*

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Introduction
Exposure to neurotoxicity induced by radiation, chemical and neurotoxic agents is common in today's modern society. Many people suffer from neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and multiple sclerosis (MS). The causes of neurotoxicity and neurodegenerative diseases vary; however, these conditions commonly share pathological processes, including synaptic dysfunction, neurovascular dysfunction, neuroinflammation, and neuronal death (Mattson and Duan, 1999; Mattson, 2000; Bito and Takemoto-Kimura, 2003; Amor et al., 2010).

To study neurotoxicity and neurodegenerative diseases, several models using neurotoxins have been developed. Kainic acid (KA), an analog of excitotoxic glutamate, can elicit selective neuronal death in rodent brain, resulting in pathological changes that partially mimic neurodegeneration in the central nervous system (CNS) (Wang et al., 2005). KA-induced neurodegeneration in rodents has been used as a model to explore the pathogenesis of excitotoxicity in neurodegenerative diseases (Zheng et al., 2011). Trimethyltin (TMT), a neurotoxic organotin compound, selectively affects neurons in the limbic system, particularly in the hippocampus, and is a useful agent for studying hippocampal neurodegeneration (Chang and Dyer, 1983; Balaban et al., 1988; Ishida et al., 1997; Ishikawa et al., 1997; Lee et al., 2016). Dopaminergic neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that stimulate the expression of inducible nitric oxide synthase are used to induce pathogenic neurodegeneration that mimics PD (Liberatore et al., 1999; Blum et al., 2001). In addition to neurotoxin treatment, genetically modified animal models are widely used to study human neurodegenerative diseases. For example, transgenic (Tg) mice overexpressing human tau protein have consistently demonstrated neurological deficits and neuronal loss linked to the appearance of neurofibrillary tangles (NFTs). NFTs are a common neuropathological feature found in AD, and have been implicated in mediating neurodegeneration and dementia in AD and other tauopathies (Arriagada et al., 1992; Gomez-Isla et al., 1997; Guillozet et al., 2003). MitoPark mice, which have a disruption in the gene encoding mitochondrial transcription factor A in dopaminergic neurons, showed diverse features of PD, such as progressive motor deficits, neuronal loss, and protein inclusion (Langley et al., 2017). In addition, diverse types of genetic HD models, including R6/2, YAC 128, and BACHD mice, exhibited pathological hallmarks of HD, such as chorea, psychiatric disturbance, gradual dementia, and death. Thus, these models are generally used to study HD (Heng et al., 2008; Liang et al., 2014).

Use of the aforementioned animal models in numerous studies has revealed some of the mechanisms and pathol-

ogies of neurotoxicity and neurodegenerative diseases. Brain-derived neurotropic factor (BDNF) and gamma-aminobutyric acid (GABA) are well known to be related to neuronal survival, neuronal protection, and synapse recovery (Levine et al., 1995; Ganguly et al., 2001; Baydyuk and Xu, 2014). BDNF and GABAergic transmission are thus believed to contribute to the etiology and regenerative processes of neurodegenerative diseases. However, the regulatory mechanisms and interactions between BDNF and GABA in neurodegenerative diseases are not yet fully understood.

This review summarizes prior studies that have elucidated the role of BDNF and GABAergic transmission in neurotoxicity and neurodegenerative disease, and the potential interactions between BDNF and GABAergic transmission in neuroregenerative processes. This review will provide a comprehensive overview of the underlying mechanisms of neuroregeneration to help develop pharmacotherapeutic strategies to treat neurotoxicity and neurodegenerative diseases.

BDNF

BDNF plays pivotal roles in maintaining neuronal function and structure, and supports cellular functions, such as growth, differentiation, and survival in neurons (Maisonpierre et al., 1990). BDNF is synthesized and released in an activity-dependent manner (Lu, 2003), and binds to high-affinity receptors, namely tropomyosin receptor kinase B (TrkB) (Klein et al., 1993). Binding of BDNF to TrkB receptors activates diverse intracellular signaling, including Ras and extracellular signal-regulated kinase (Erk)1 and 2, phospholipase C-γ (PLC-γ), phosphatidylinositol 3-kinase (PI3K), and protein kinase C (PKC) (Nakagawara et al., 1994; Zirrgiebel et al., 1995). Several transcription factors, including c-Jun, c-Fos, and early growth response 1 (Egr-1), are then induced, and cyclic adenosine 3′,5′-monophosphate (cAMP) response element binding protein (CREB) is activated (Nakagawara et al., 1994; Gaiddon et al., 1996; Finkbeiner et al., 1997). In addition to the high-affinity TrkB receptors, BDNF binds to low-affinity receptor p75 neurotrophin receptor (p75NTR) (Berg et al., 1991; Casaccia-Bonnefil et al., 1996), which is known to potentiate Trk-induced survival activity via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation (Maggirwar et al., 1998; Chittka and Chao, 1999; Hamanoue et al., 1999).

Several studies have reported that changes in BDNF levels occur during neurotoxicity and in neurodegenerative diseases (Ballarin et al., 1991; Lee et al., 2016; Tanila, 2017). Clinical human studies as well as genetic and experimental animal studies have suggested that decreased BDNF levels are associated with synaptic and neuronal loss and cognitive impairment in aging and AD (Tanila, 2017). In patients with AD, the expressions of the precursor form of BDNF (proBDNF) and mature BDNF decreased in the parietal cortex and hippocampus (Phillips et al., 1991; Holsinger et al., 2000; Michalski and Fahnestock, 2003; Peng et al., 2005). Systemic administration of BDNF is not considered to be a suitable approach due to its short plasma half-life and poor blood-brain barrier penetration (Nagahara and Tuszynski, 2011). However, neural stem cell injection, which leads to upregulation of hippocampal BDNF, rescues the cognitive phenotype in aged amyloid-β precursor protein (APP)/presenilin (PS)1/tau Tg mice *via* increased synaptic density and restoration of hippocampal-dependent cognition (Blurton-Jones et al., 2009). Therefore, the indirect elevation of BDNF levels in the CNS is considered to be a novel treatment strategy for AD.

In PD, BDNF also has potent effects on the survival and morphology of dopaminergic neurons, and therefore the loss of BDNF is likely to contribute to the death of dopaminergic neurons (Howells et al., 2000). Clinically, reduction in BDNF mRNA and protein expression has been observed in the substantia nigra of patients with PD (Howells et al., 2000). Laboratory animal models using MPTP, which induces hallmark symptoms of PD including loss of dopaminergic neurons in the midbrain (Meredith and Rademacher, 2011) showed decreased BDNF protein levels in the lesioned striatum when compared with the same brain regions on the intact side (Kaur and Prakash, 2017). Inversely, over-expression of BDNF in dopaminergic neurons recovers the striatal innervation, dendritic spines and motor behavior in a rat model of PD (Razgado-Hernandez et al., 2015). Degeneration of striatal neurons and reduction in cortical BDNF mRNA and protein levels were observed in a mouse model of HD (Group, 1993; Perez-Navarro et al., 1999; Perez-Navarro et al., 2000; Zuccato et al., 2001; Zuccato and Cattaneo, 2007). The levels of transcripts encoding BDNF exons II, IV, and VI were reportedly to be reduced in R6/2 mice (Zuccato et al., 2005). In addition, previous studies regarding multiple sclerosis (MS), a major inflammatory demyelinating disease, also showed decreased plasma BDNF levels, with the exception of a transitory elevation during relapses (Lassmann et al., 1998; Azoulay et al., 2005; Blanco et al., 2005; Vacaras et al., 2017). Together, these reports suggest that reduction in BDNF levels is a common mechanism underlying the development of diverse neurodegenerative diseases (**Table 1**).

To provide advanced insights into the detailed mechanisms of neurodegeneration, animal models treated with diverse neurotoxins have been widely used (Geloso et al., 2011). Neurotoxins such as KA and TMT induce significant cell death and neuroinflammation, which subsequently result in neurodegeneration. Previous studies have observed the rapid elevation of BDNF levels in neurotoxin-treated neurodegeneration models (Ballarin et al., 1991; Sathanoori et al., 2004; Kim et al., 2014; Lee et al., 2016). Although neurotoxins induce rapid BDNF elevation, neurotoxin-treated models also showed a gradual decrease in BDNF levels over time (Kim et al., 2014), which is similar to the patterns observed in many neurodegenerative models (as summarized in **Table 1**). The elevation of BDNF in the acute phase of neurotoxin administration is interpreted by two conflicting points of view. First, from a pathogenical view, increased levels of BDNF following neurotoxin administration might increase the severity of excitotoxicity by increasing synaptic activity (Bathina and Das, 2015). Another viewpoint is related to the protective effects of elevated BDNF against

Table 1 The modulation of BDNF in various neurodegenerative models

	Model	Modulation of BDNF	References
AD	Patients with AD	BDNF mRNA, proBDNF, BDNF ↓	Michalski and Fahnestock (2003); Peng et al. (2005)
		BDNF mRNA ↓ (parietal cortex)	Holsinger et al. (2000)
		BDNF mRNA ↓ (hippocampus)	Phillips et al. (1991)
	Aged Tau/PS1/APP 3xTg mice	Hippocampal BDNF (NSC treatment) ↑	Blurton-Jones et al. (2009)
PD	Patients with PD	BDNF mRNA, BDNF ↓ (substantia nigra)	Howells et al. (2000)
	MPTP-induced model	BDNF ↓ (lesioned striatum)	Kaur and Prakash (2017)
	Rotenone-induced model	BDNF ↓ (plasma), BDNF ↑ (colon)	Johnson et al. (2015)
HD	QA-induced HD model	BDNF, striatal neurons ↓	Perez-Navarro et al. (2000)
	R6/2 Tg mice	Bdnfexon II, IV, VI, BDNF ↓	Zuccato et al. (2005)
MS	Patients with MS	BDNF ↓ (plasma)	Vacaras et al. (2017)
	Patients with rrMS	BDNF ↓ (serum and CSF)	Azoulay et al. (2005)
Others	KA-induced model	BDNF mRNA ↑(acute phase)	Sathanoori et al. (2004)
	TMT-induced model	BDNF mRNA PI 1–2 d↑, PI 4–8 d ↓	Kim et al. (2014)

AD: Alzheimer's disease; APP: amyloid-β precursor protein; BDNF: brain-derived neurotrophic factor; HD: Huntington's disease; KA: kainic acid; MS: multiple sclerosis; MPTP:1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NSC: neural stem cell; PD: Parkinson's disease; PI: post-injection; proBDNF: precursor form of BDNF; PS1: presenilin 1; QA: quinolinic acid; rrMS: relapsing-remitting MS; Tg: transgenic; TMT: trimethyltin.

neurotoxins (Casalbore et al., 2010; Corvino et al., 2013). Additionally, Lee et al. (2016) have reported that BDNF treatment significantly reduced neurotoxin-induced cell death *via* the activation of ERK signaling. Many *in vitro* and *in vivo* experiments have shown the protective effects of BDNF in striatal neurons and the therapeutic effects of BDNF or BDNF mimetics (Nakao et al., 1995; Ventimiglia et al., 1995; Bogush et al., 2007). Although further comprehensive studies investigating the precise protective/pathogenic roles of elevated BDNF levels in the acute phase of neurodegenerative process are needed, BDNF seems to play mainly a protective role against neuronal insults. As summarized in **Table 1**, those studies could provide fundamental data on the role of BDNF in neurodegeneration, and could be useful for the development of novel strategies aimed at increasing BDNF levels in the aforementioned neurodegenerative diseases to ultimately influence the clinical treatment of these conditions.

GABAergic transmission

GABA is the major inhibitory neurotransmitter that activates GABAergic systems (Watanabe et al., 2002; Jin et al., 2003a; Wu et al., 2007b). The GABAergic system plays a pivotal role in maintaining equivalent neurotransmission in the CNS (Barbin et al., 1993; Behar et al., 1996; Taketo and Yoshioka, 2000; Pallotto and Deprez, 2014). Moreover, neuronal networks, including neural migration, differentiation, proliferation, and neurite outgrowth facilitation, are modulated by GABA synthesis, transport, release and reuptake, and GABA receptor composition (Jin et al., 2003b; Wu et al., 2007a). The synthesis of GABA is catalyzed by glutamic acid decarboxylase (GAD), which plays a key role in the regulation of GABAergic transmission (Wu et al., 2007b). GABA transporters, including the GABA transporter (GAT) and the vesicular GABA transporter (VGAT), act to store synthesized GABA and mediate the release and reuptake of GABA from synapses (Nelson and Blaustein, 1982). The action of GABA is terminated by its reuptake from the synaptic cleft *via* membrane-bound GATs, which has been observed in both presynaptic and postsynaptic membranes of differentiated neurons and in the surface of glial cells (Minelli et al., 1995, 1996).

GABAergic transmission is mediated by two distinct receptor classes: ionotropic GABA A receptors ($GABA_A$Rs) and metabotropic GABA B receptors ($GABA_B$Rs) (Couve et al., 2000; Sieghart and Sperk, 2002; Bettler and Tiao, 2006). $GABA_A$Rs are hetero-pentameric chloride channels that mediate fast synaptic inhibition. $GABA_A$Rs are composed of five subunits selected from at least 19 $GABA_A$R subunits. Interestingly, there is accumulating evidence that individual $GABA_A$R subunits are associated with distinct neuronal structures and subcellular distributions, and that their differential activation is closely correlated with distinct pharmacological and behavioral phenotypes (Rudolph et al., 2001; Kittler et al., 2002; Sieghart and Sperk, 2002). $GABA_A$Rs are relevant drug targets for anti-convulsant, anxiolytic, and sedative-hypnotic agents (Monteleone et al., 1990; Olsen and Avoli, 1997; Sieghart and Sperk, 2002). $GABA_B$R is a G protein-coupled receptor in the CNS that is implicated in neurological and psychiatric disorders (Barnard et al., 1998; Bowery et al., 2002; Calver et al., 2002). Therefore, elucidating the modulatory mechanisms of the GABAergic system should be prioritized to understand the inhibitory role of GABA in diverse neurologic conditions. However, the modulation of GABA signal-related molecules in neurodegeneration is not completely understood.

The balance between neuronal excitation and inhibition in neuronal networks is crucial for normal brain function. The dysfunction of neuronal electrical excitability may play an important role in neurodegenerative disease. GABAergic systems have recently become an increasing area of interest in AD research (Rossor and Iversen, 1986; Andrews-Zwilling et al., 2010). In the human APP Tg mouse, inhibitory hippocampal circuits are altered by the sprouting of collat-

eral mossy fibers onto GABAergic basket cells (Palop et al., 2007). Tau/PS2/APP 3xTg mice demonstrated significant neurodegeneration of GABAergic septo-hippocampal projection neurons as well as that of their target cells, GABAergic hippocampal neurons (Bowery and Brown, 1974). APP-induced impairment of GABAergic interneurons suggests that dysregulation of the excitatory/inhibitory neurotransmitter balance contributes to neurodegeneration in AD (Wang et al., 2014; Villette and Dutar, 2017). Oyelami et al. (2016) reported the functional and transcriptional deficits in GABAergic pathways in prefrontal cortex in aged APP/PS1 Tg mice. They observed significant decreases in various GABA-related genes, such as *Gabra1, 3, 4, 5, Gabrb2, 3, Gabrg2, Gabarapl1*, and *Gabarap*, and the changes in synaptic function in the prefrontal cortex of 8-month-old APP/PS1 Tg mice (Oyelami et al., 2016). However, VGAT and GAD are not altered in patients with AD or in APP/PS1 Tg mice (Mitew et al., 2013). Therefore, understanding the molecular details involved in the alteration of GABAergic transmission may provide insight into the pathogenesis of AD.

Similarly, patients with PD exhibited significantly decreased levels of GABA in the cerebrospinal fluid (CSF) (de Jong et al., 1984). A (3-chlorophenyl)[3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2(1H)-isoquinolinyl]-methanone (CIQ)-induced PD model also showed depressed GABAergic transmission *via* a cholinergic mechanism in medium spiny projection neurons in the striatum (Feng et al., 2014). In addition, HD caused by expansion of the CAG repeat in exon 1 of the *huntingtin* gene induced loss of GABAergic medium spiny neurons in the striatum (Kremer et al., 1994; DiFiglia et al., 1997). Furthermore, a pattern of neurodegeneration of GABAergic striatal efferent projection neurons observed in patients with HD, are closely correlated with increasing clinical neuropathological HD grade (Glass et al., 2000). Following quinolinic acid (QA)-induced degeneration of the striatonigral pathway, there was marked loss of GABA immunoreactivity and 59% increase in the density of $GABA_A$Rs in the substantia nigra pars reticulate (Nicholson et al., 1995). Moreover, QA injection rapidly induced an increase in $GABA_B$R subunit 1 or 2 immunoreactivity in the lesioned striatum, despite the neuronal loss (Rekik et al., 2011), indicating that it may be upregulated by reactive astrocytes. GABA insufficiency has also been identified in MS patients. The sensorimotor GABA concentration was abnormally lower in individuals with the secondary progressive form of MS, suggesting that decreased GABA levels are involved in worse motor function (Demakova et al., 2003; Cawley et al., 2015).

Additionally, other neurodegenerative models using neurotoxins, such as KA, induce loss of GABA and GAD when injected into rodent striata (Young et al., 1988). The mRNA levels of $GABA_A$R subunits γ2 and δ also decrease significantly in the hippocampus following TMT-induced seizure (Kim et al., 2015). In 4-aminopyridine-induced excitotoxicity, GABA-mediated transmission may paradoxically boost neuronal hyperexcitation (Pena and Tapia, 2000). As summarized in **Table 2**, the number of GABAergic neurons is decreased in neurodegenerative stimulation. Thus, the decrease in the number of GABAergic neurons induces an imbalance of excitatory/inhibitory neurotransmission, which is considered a main causal factor in many neurodegenerative diseases. This suggests that the stable maintenance of GABAergic transmission may be a protective/therapeutic solution in neurodegenerative disease.

Correlation between the BDNF and GABAergic systems

BDNF is synthesized by both neurons and glia and is involved in survival, differentiation, and regeneration of neurons *via* TrkB binding. BDNF is one of the crucial mediators of long-term potentiation at glutamatergic and GABAergic synapses in the CNS (Korte et al., 1995; Figurov et al., 1996; Lu, 2003). BDNF is attributed to mostly increased presynaptic transmitter release. Specifically, the acute effects of BDNF enhance glutamatergic transmission and reduce GABAergic transmission in the CNS (Zafra et al., 1991; Tanaka et al., 1997). Thus, BDNF could influence GABAergic transmission positively or negatively through various intracellular signaling pathways triggered *via* TrkB or $p75^{NTR}$.

BDNF may affect GABAergic transmission, subsequently modulating CNS function, neuronal survival, and plasticity. BDNF binds to TrkB, which couples to the PLC-γ/PKC-δ and ERK/mitogen-activated protein kinase (MAPK) pathway. Activated PLC-γ could induce PI3K activation which increases intracellular Ca^{2+} concentrations (Yamada et al., 1991); consequently, BDNF disrupts $GABA_A$R function through elevated intracellular Ca^{2+} concentration (Tanaka et al., 1997). BDNF-TrkB signaling also affects the presynaptic concentration of GABA through the activation of GAT-1 (Vaz et al., 2011). These alterations are presumably caused by the upregulation of GAD67 mRNA and neuronal GAT-1. GATs are located in the plasma membrane of neurons and astrocytes and are responsible for the termination of GABAergic transmission. BDNF enhances GAT-1-mediated GABA transport in astrocytes and/or neurons, which requires an active A_{2A} receptor. In primary hippocampal neurons, BDNF reduces GABAergic miniature inhibitory postsynaptic currents and causes reduction in $GABA_A$R subunit α2, β2, β3, and γ2 immunoreactivity (Brunig et al., 2001). Moreover, BDNF upregulates the expression of $GABA_A$R α4 by Egr-3 stimulation related to PKC pathway activation (Roberts et al., 2005, 2006). BDNF has been shown to selectively regulate $GABA_A$R transcription through activating the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway and BDNF treatment of hippocampal neurons stimulated phosphorylation of STAT3, induced increases in inducible cAMP early repressor (ICER) expression, and decreased transcription of *Gabra1* (Lund et al., 2008). BDNF increased $GABA_A$R subunit α4 expression, but decreased $GABA_A$R subunit α1 levels in hippocampal neurons, suggesting that BDNF has a potential role in differentially regulating the expression of extrasynaptic and synaptic $GABA_A$Rs (Roberts et al., 2006). The influence of BDNF on GABAergic transmission is not only limited to

Table 2 Modulation of the GABAergic system in various neurodegenerative diseases

	Model	Modulation of the GABAergic system	References
AD	Tau/PS2/APP 3xTg mice	GABAergic septo-hippocampal projection neurons and GABAergic hippocampal neurons ↓	Bowery and Brown (1974)
	Aged APP/PS1 Tg mice	*Gabra1, 3, 4, 5, Gabrb2, 3, Gabrg2,Gabarapl1, Gabarap* ↓	Oyelami et al. (2016)
PD	Patients with PD	GABA ↓ (CSF)	de Jong et al. (1984)
	CIQ-induced model	GABAergic transmission ↓ (striatum)	Feng et al. (2014)
HD	Patients with HD	Neurodegeneration of GABAergic striatal efferent projection neurons	Glass et al. (2000)
	QA-induced model	GABA ↓, $GABA_AR$, $GABA_BR$ subunit 1, 2 ↑	Nicholson et al. (1995); Rekik et al. (2011)
MS	Patients with MS	GAD, GABA ↓ (blood)	Demakova et al. (2003)
	Patients with rrMS	GABA ↑ (sensorimotor cortex) with worsening of performance	Bhattacharyya et al. (2013)
	Patients with spMS	GABA ↓ (sensorimotor cortex)	Cawley et al. (2015)
Others	KA-induced model	GAD, GABA ↓	Young et al. (1988)
	TMT-induced model	$GABA_AR$ subunit γ2, δ ↓	Kim et al. (2015)

AD: Alzheimer's disease; APP: amyloid-β precursor protein; CIQ: (3-chlorophenyl)[3,4-dihydro-6,7-dimethoxy-1-[(4-methoxyphenoxy)methyl]-2(1H)-isoquinolinyl]-methanone; CSF: cerebrospinal fluid; GABA: γ-aminobutyric acid; $GABA_AR$: GABA A receptor; $GABA_BR$: GABA B receptor; GAD: glutamic acid decarboxylase; HD: Huntington's disease; KA: kainic acid; MS: multiple sclerosis; PD: Parkinson's disease; PS1: presenilin 1; PS2: presenilin 2; QA: quinolinic acid; rrMS: relapsing-remitting MS; spMS: secondary progressive MS; TMT: trimethyltin.

Table 3 The mechanisms underlying BDNF modulation on the GABAergic system

Altered pathway induced by BDNF	Modulating target	References
Elevated intracellular Ca^{2+} concentration by TrkB activation	$GABA_AR$	Tanaka et al. (1997)
Enhanced GABA transport in astrocytes through ADORA2A signaling	GATs	Vaz et al. (2011)
Egr-3 stimulation related to PKC-MAPK pathway activation	$GABA_AR$ α4	Roberts et al. (2005, 2006)
JAK/STAT, *Gbara1*	$GABA_AR$ α1	Lund et al. (2008)
Increased GAD activity/elevated GABA uptake activity	GABA content	Mizuno et al. (1994)
Downregulated K^+-Cl^- cotransporter 2 (KCC2)	GABA receptors	Wardle and Poo (2003)

ADORA2A: Adenosine A_{2A} receptor; BDNF: brain-derived neurotrophic factor; Egr: early growth response protein; GABA: γ-aminobutyric acid; $GABA_AR$: GABA A receptor; GAD: glutamic acid decarboxylase; GAT: GABA transporter; JAK: Janus kinase; MAPK: mitogen-activated protein kinase; PKC: protein kinase C; STAT: signal transducer and activator of transcription; TrkB: tyrosine receptor kinase B.

direct regulatory mechanisms, but also includes indirect ionic concentrations.

BDNF indirectly modulates GABAergic transmission through the postsynaptic regulation of Cl^- transport (Wardle and Poo, 2003). Previous studies suggest that the acute postsynaptic downregulation of K^+-Cl^- cotransporter 2 (KCC2) activity may decrease the efficacy of inhibitory transmission. Moreover, BDNF contributes to the differentiation of striatal GABAergic neurons during development (Mizuno et al., 1994). BDNF injections into the cerebral ventricles of neonatal rats induced an increase in GABA content in the striatum (Mizuno et al., 1994). The elevation of GABA levels mainly resulted from the elevation of GAD activity and GABA uptake activity (Mizuno et al., 1994). Therefore, BDNF could alter diverse intracellular mechanisms, which might modulate pre/postsynaptic GABAergic transmission, as summarized in **Table 3**. The organization of evidence for the correlation between BDNF and GABA during neurodegeneration may be important to understand their underlying mechanisms of neurotoxicity and neurodegenerative diseases.

Based on its role in diverse neurodegenerative processes, BDNF typically enhances the release of presynaptic transmitters, including GABA; in general, its expression is downregulated, except during the acute phase, when it is upregulated. BDNF exhibits an acute excitatory effect *via* suppression of chloride-dependent fast GABAergic inhibition (Rivera et al., 2002; Canas et al., 2004). In pathological processes including chronic pain and seizure, BDNF/TrkB signaling contributes to downregulation of KCC2 protein expression and its transport function, leading to hyper-excitability (Kong et al., 2014; Tao et al., 2015). Thus, it was suggested that a temporary increase in BDNF during the acute phase of neurodegenerative processes involves hyper-excitability *via* suppression of chloride transport and decreased efficacy of inhibitory transmission. Additionally, increased BDNF likely disrupts the function of $GABA_AR$ by elevating the intracellular Ca^{2+} concentration (Yamada et al., 1991) during the acute phase, resulting in abnormally regulated GABAergic transmission. During the neurodegenerative period, decreased BDNF levels may cause decreases in the intracellular Ca^{2+} concentration, Egr-3 signaling in the post-synapse, as well as GAD65/67 in the pre-synapse (Brunig et al., 2001; Roberts et al., 2005, 2006; Lund et al., 2008; Vaz et al., 2011). Thus, downregulation of intracellu-

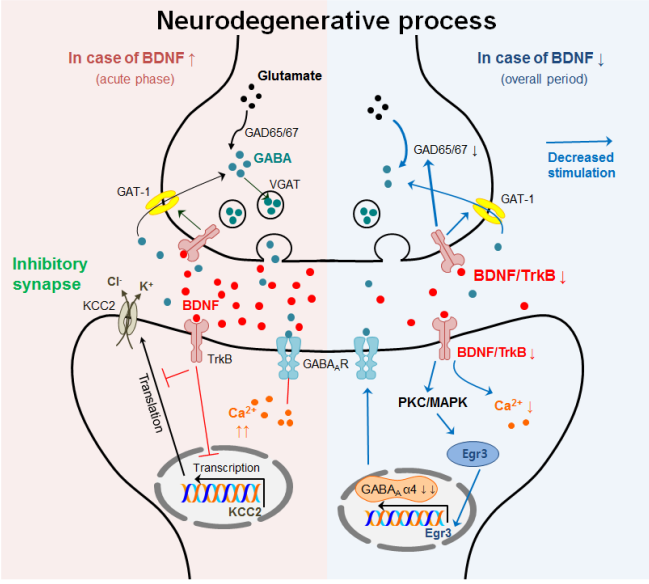

Figure 1 Summarized possible mechanisms between BDNF and GABAergic transmission during neurodegenerative process.
During neurodegenerative process, there is a close interaction between BDNF and GABAergic transmission. In inhibitory synapses, both increase and decrease in BDNF levels contribute to abnormal GABAergic transmission *via* alteration of GABA release and GAT-1-related transport of GABA, and abnormal regulation and decreased transcription of $GABA_AR$. It may interrupt the balance between excitatory/inhibitory neurotransmission, attributing to the underlying mechanisms of neurodegeneration. BDNF: Brain-derived neurotropic factor; Egr3: early growth response 3; GABA: gamma-aminobutyric acid; $GABA_AR$: GABA A receptors; GAD65/67: glutamic acid decarboxylase 65/67; GAT-1: GABA transporter 1; KCC2: K^+-Cl^- cotransporter 2; PKC/MAPK: protein kinase C/mitogen-activated protein kinase; TrkB: tropomyosin receptor kinase B; VGAT: vesicular GABA transporter.

lar signaling affecting GABA-related signaling may reduce the inhibitory efficacy of GABAergic transmission, leading to hyper-excitability. Therefore, the altered BDNF levels in neurodegenerative processes may perturb the balance in potentiation between glutamatergic and GABAergic synapses in the CNS. An imbalance in excitatory/inhibitory neurotransmission may be one of the key factors for neurodegeneration (as shown in **Figure 1**). Consequently, targeting the increased levels of BDNF in neurodegenerative diseases could result in a balance in neurotransmission and may further be used as an effective therapeutic strategy in diverse neurodegenerative conditions.

Conclusion

BDNF and GABAergic systems are involved in critical CNS functions, ranging from neuronal development and neuronal survival to learning and memory. In addition, BDNF and GABAergic systems have significant physiological and pathological roles in neurotoxicity and neurodegenerative diseases. In many neurodegenerative diseases, the levels of BDNF are generally decreased, although rapid elevation of BDNF levels occur in the acute phase in response to neuronal insults which may contribute to protective/regenerative processing. The overall reduction of BDNF results in diverse intracellular signalings, leading to an imbalance in excitatory/inhibitory neurotransmission, including dysregulation of GABAergic transmission. Therefore, the reduction of BDNF and the subsequent dysregulation of GABAergic transmission may be one of the major mechanisms of neurodegeneration. However, the relationship between BDNF and GABAergic systems remains largely unknown; therefore, further studies investigating the precise interactions between BDNF and GABAergic transmission are needed. Nevertheless, the substantial progress that has been made in the last few decades in elucidating the mechanisms of BDNF and GABAergic systems, may not only further extend our knowledge of normal CNS functions, but may also help to develop potential strategies for pharmacotherapeutic approaches in neurodegeneration.

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