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BDNF-TrkB Signaling and Neuroprotection in Schizophrenia

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Abstract

Neurotrophins such as brain-derived neurotropic factor (BDNF), play critical role in neuronal survival, synaptic plasticity and cognitive functions. BDNF is known to mediate its action through various intracellular signaling pathways triggered by activation of tyrosine kinase receptor B (TrkB). Evidence from clinical as well as pre-clinical studies indicate alterations in BDNF signaling in schizophrenia. Moreover, several antipsychotic drugs have time-dependent effects on BDNF levels in both schizophrenia subjects and animal models of schizophrenia. Given the emerging interest in neuroplasticity in schizophrenia understanding the neuroprotective and cell survival roles of BDNF signaling will enhance our knowledge of its diverse effects, which may lead to more effective treatments for schizophrenia. This article will present an overview of recent findings on the role of BDNF signaling in the pathophysiology and treatment of schizophrenia, with a special focus on its neuroprotective effects.

Keywords

Brain-derived neurotrophic factor (BDNF); tyrosine kinase receptor B (TrkB); schizophrenia; Antipsychotic; Neuroprotection

1. Introduction

Schizophrenia is a chronic, severe, and debilitating mental illness that is characterized by disintegration of thought processes and of emotional responsiveness. Although the cause and pathophysiology of schizophrenia are still not clear, evidence suggest that impairments in neurodevelopmental processes as a result of genetic and environmental insults lead to the development of schizophrenia pathophysiology. Neurotrophic factors play important roles in neurodevelopment and adult brain plasticity. They are large family of dimeric polypeptides, namely nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3) and NT-4/5 and are known to play critical role in neuronal growth, differentiation, survival as well regulation of neuronal structure and function (Huang and Reichardt, 2001; Lewin and Barde, 1996; Maisonpierre et al. 1990). Their function requires activation of various intracellular signaling pathways through binding of specific Trk receptors such as TrkA, TrkB and TrkC for NGF, BDNF and NT-3 respectively (Arevalo and Wu, 2006; Biffo et al., 1995). In

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Conflict of Interest
There is no conflict of interest.

addition, chronic stress, a major vulnerability factor in neuropsychiatric disorders including schizophrenia has been shown to alter neurotrophin function (de Kloet et al., 2005; Gatt et al., 2009).

2. BDNF and schizophrenia

There is accumulating evidence indicating altered BDNF levels in subjects with schizophrenia. Serum BDNF levels in schizophrenia subjects were found lower in many studies (Chen da et al., 2009; Grillo et al., 2007; Ikeda et al., 2008; Jindal et al., 2010; Rizos et al., 2010; Toyooka et al., 2002; Vinogradov et al., 2009; Xiu et al., 2009; Zhang et al., 2008) except a few studies reported higher BDNF levels (Gama et al., 2007; Reis et al., 2008). Studies have reported significant decreases in plasma BDNF levels in schizophrenia subjects as compared to control subjects (Buckley et al., 2007b; Palomino et al., 2006). Similarly, BDNF levels were also found lower in CSF samples from schizophrenia subjects (Pillai et al., 2010; Issa et al., 2010). Postmortem studies have shown increases in parietal cortex and frontal cortex, whereas decrease in temporal cortex and occipital cortex in BDNF levels as measured by ELISA (Durany et al., 2001). BDNF protein levels were significantly lower in prefrontal cortex samples from schizophrenia subjects (Issa et al., 2010; Weickert et al., 2003). BDNF mRNA expression was also found lower in the prefrontal cortex of schizophrenia subjects (Hashimoto et al., 2005; Pillai, 2008; Weickert et al., 2003). Studies have reported mixed results on BDNF levels in hippocampus (Iritani et al. 2003; Takahashi et al., 2000; Thompson Ray et al., 2011). A recent meta-analysis demonstrated that peripheral BDNF levels are reduced in drug-naive and medicated schizophrenia samples when compared with age-matched healthy controls. Moreover, alterations in BDNF levels were found to be increased with age, independent of medication dosage (Green et al., 2011). As suggested in the recent review articles (Buckley et al., 2011; Favalli et al., 2012) the inconsistency found in BDNF levels between different studies could be due to differences in the methodology, sample population, different stage of illness, gender and subtype and medication history. Therefore, more detailed placebo-controlled studies with larger sample sizes on standardized antipsychotic therapy are warranted.

3. DNA methylation of BDNF gene and its association with schizophrenia

Epidemiological studies support the theory that the interplay between an individual's genes and the environment plays a significant role in the onset of schizophrenia (Roth et al., 2009). Epigenetic mechanisms such as histone modifications and DNA methylation have been shown to play a pivotal role in psychiatric disorders such as schizophrenia. 'Epigenetics' is the study of heritable alterations in gene expression by mechanisms that do not cause direct changes to the underlying DNA sequence. DNA methylation is one of these epigenetic mechanisms shown to play a role in schizophrenia through a handful of candidate genes such as the reelin gene, the glutamic acid decarboxylase 67 gene (GAD67) and BDNF (Roth et al., 2009).

During DNA methylation, enzymes known as DNA methyltransferases (DNMTs) catalyze the addition of a -CH3 group to cytosine residues at the 5-position of the pyrimidine ring (Bird, 2002; Miranda and Jones, 2007). Cytosines that are followed by a guanine can be methylated, and these CpG dinucleotide sequences are typically found in and around gene regulatory regions in clusters known as CpG islands. DNA methylation usually occurring in these regulatory regions can lead to transcriptional suppression (Bird, 2002; Miranda and Jones, 2007). A number of studies have also shed light on the potential role of DNA methylation in the dynamic regulation of the BDNF gene in adults, and have highlighted the fact that altered BDNF regulation could contribute to schizophrenia (Lu and Martinowich, 2008).

It has been shown that DNA methylation plays a role in activity-dependant BDNF regulation (Martinowich et. al., 2003). It is also known that changes in methylation at the BDNF promoter and intragenic regions is associated to different behavioral trends such as fear learning, memory formation, stressful social interaction, etc (Lubin et. al., 2008; Roth et. al., 2009). Mill et. al. (2008) using a genome wide micro-array based approach, found alterations in DNA methylation in a number of genes including BDNF in major psychosis. In a recent study Gavin et. al. (2011) found an increase in protein levels and mRNA expression of a growth arrest and DNA-damage-inducible, beta (GADD45b) in patients with psychosis. They also found reduced GADD45b binding to the BDNF IXabcd gene promoter region and increased methylation (5-methylcytosine and 5-hydroxymethylcytosine) at the promoter in subjects with psychosis, in turn leading to reduced BDNF IXabcd mRNA expression. GADD45b is required for activity-induced DNA demethylation and it utilizes cytidine deaminases and thymidine glycosylases. Thus, DNA methylation might be involved in the dynamic regulation of BDNF activity in schizophrenia (Lu and Martinowich, 2008).

4. Polymorphisms of BDNF gene in schizophrenia

An important single nucleotide polymorphism (SNP) found in the BDNF gene is an amino acid change from a valine (Val) to a methionine (Met) at position 66 (Val66Met) in the prodomain of BDNF (BDNFMet) (Egan et al., 2003). This polymorphism has been found to decrease activity-dependant BDNF secretion (Chen et al., 2004) and shown to be associated with a number of neurological disorders in humans (Momose et al., 2002; Neves-Pereira et al., 2002; Sen et al., 2003; Sklar et al., 2002; Ventriglia et al., 2002). It has also been linked to affect hippocampal volume and memory function in humans (Egan et al., 2003). In vitro studies have shown that the variant BDNFMet leads to altered BDNF trafficking and less efficient BDNF sorting in neurons (Chen et al., 2004). BDNFMet mice exhibit increase in anxiety-related behavior when placed in conflict settings (Chen et al., 2006).

Data from studies on stress and BDNFMet polymorphism in humans indicate mixed results in part due to the variability of different kinds by genetic and environmental stressors in humans as well as the unreliability of questionnaire based approach to judge human emotional status (Gatt et al., 2009; Kim et al., 2010; Yu et al., 2012). However, in mice with BDNFMet polymorphism, chronic restrained stress has been shown to increase anxiety-like and depressive-like behaviors as well as impairs their working memory, (Yu et al., 2012) which can be attributed to the decreased levels of BDNF in their brains.

A number of studies have investigated the relationship between BDNFMet polymorphism and schizophrenia, but the results are mostly inconsistent. Some earlier studies have shown an association between schizophrenia and BDNFMet in humans (Neves-Pereira et al., 2005; Rosa et al., 2006); however, more recent studies did not find any direct correlation between BDNFMet polymorphism and susceptibility to schizophrenia (Yi et al., 2011; Zhang et. al., 2012). The BDNFMet polymorphism has been associated to a lower age at onset of schizophrenia in male patients from the Han Chinese population (Yi et al., 2011).

5. Neuroprotective roles of BDNF/TrkB signaling

BDNF and its high affinity TrkB receptor are broadly expressed in the developing and adult mammalian brain (Murer et al., 2001). BDNF induced activation of TrkB is essential to synaptic plasticity (Kuipers and Bramham, 2006) and contributes to the pathogenesis of schizophrenia. Studies have shown increases in two truncated TrkB Isoforms, (truncated TrkB [TrkB-TK-] and sarc homology containing TrkB [TrkB-Shc]), but decreases in full length TrkB levels in the prefrontal cortex of schizophrenia subjects (Wong et al., 2011; Weickert et al., 2005). Moreover, a non-significant decrease in TrkB immunoreactivity was found in the cerebellum of patients with schizophrenia (Soontornniyomkij et al., 2011).

These studies suggest that blocking of excessive truncated TrkB or enhancement of full-length TrkB function can be used as a future therapeutic approach to restore the deficits in BDNF signaling in schizophrenia. In this regard, a recent study has shown the potential of cysteamine to ameliorate alterations in BDNF signaling and GAD67 expression in heterozygous reeler mice (Kutiyanawalla et al., 2011). BDNF/TrkB plays an important role in neuronal survival, morphogenesis, and plasticity. It is well known that binding of BDNF to TrkB elicits various intracellular signaling pathways, including mitogen activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), phospholipase Cγ (PLCγ), and phosphoinositide 3-kinase (PI3K) pathways (Schabitz et al., 2000; Wu and Pardridge, 1999 Berridge and Irvine, 1989; Schlessinger, 2000; Hetman et al., 1999). In addition, small G proteins such as Ras, Rap-1, and the Cdc-42-Ra have also been implicated as key molecules in BDNF/TrkB signaling (Huang and Reichardt, 2001). BDNF has been shown to prevent neuronal death caused by N-methyl d-aspartate receptor (NMDAR) blockade in corticostriatal organotypic cultures (Xia et al., 2010). The protective effect of BDNF against apoptosis requires the activation of the PI-3K/Akt and ERK pathways through the inhibition of GSK-3beta and activation of CREB. It has been observed that BDNF protects cortical neurons against camptothecin or serum deprivation induced apoptosis through the activation of ERK and PI3 kinase pathways (Hetman et al., 1999). Similarly, the neuroprotective effects of cystamine and erythropoietin against haloperidol-induced neuronal death were mediated through the activation of BDNF/TrkB signaling pathway in primary cortical neurons (Pillai et al., 2008a; 2008b). The protective effects of BDNF against glutamate (Almeida et al., 2005) and norepinephine (NE) (Chen et al., 2007) in hippocampal neurons were also found to be mediated through PI3K and MAPK signaling pathways. It has been shown that low level stimulation of NMDA receptors protects hippocampal neurons against glutamate excitotoxicity via a BDNF autocrine loop in hippocampal neurons (Jiang et al., 2005). BDNF and constitutive activation of Ras protein have been shown to prevent MK801-induced apoptotic neuronal death in immature neuronal cultures (Hansen et al., 2004). The above observations from animal studies are supported by postmortem evidence showing alterations in Akt and Erk signaling pathways in schizophrenia. A number of studies have reported decreases in AKT1 mRNA, protein, and activity levels in the prefrontal cortex and hippocampus, as well as in peripheral blood of individuals with schizophrenia (Emamian et al., 2004; Zhao et al., 2006; Thiselton et al., 2008). In addition, many studies have found genetic association between AKT1 genetic variants and schizophrenia (Emamian et al., 2004; Ikeda et al., 2004; Schwab et al., 2005; Bajestan et al., 2006). A recent study has shown an association between decrease in phosphorylated AKT--total AKT ratio and reduced hippocampal volume in first episode schizophrenia subjects (Szamosi et al., 2012). Significant decreases in protein levels of members in ERK signaling pathway such as Rap1, B-Raf, MEK1, MEK2, ERK1/2 and RSK1 were found in prefrontal cortex of schizophrenia subjects (Yuan et al., 2010). Since BDNF plays a vital role in activation of various survival signaling pathways, efforts have been made to identify the role of apoptotic mechanisms in the pathophysiology of schizophrenia (Berger et al., 2003). The ratio of the proapoptotic to antiapoptotic proteins is the key determinants for the apoptotic activation. The expression of Bcl-2, an antiapoptotic factor was found lower in postmortem temporal cortex of schizophrenia subjects (Jarskog et al., 2000). In addition, the Bax/Bcl2 ratio was found significantly higher in the temporal cortex of schizophrenia subjects (Jarskog et al., 2004). It is important to note that both Akt and Erk are also downstream signaling pathways to many other proteins implicated in schizophrenia pathophysiology such as neuregulin, DISC1 and reelin. Therefore, data from postmortem studies have some limitations in interpreting the roles of Akt and Erk to schizophrenia pathology. However, *in vitro* activation of Akt or Erk signaling pathway using postmortem samples or lymphocytes from schizophrenia and control subjects might give some answers to the specificity of these signaling pathways (Hahn et al., 2006).

6. Effects of antipsychotic drugs on BDNF levels

There is a growing literature from clinical and pre-clinical studies on the effects of antipsychotic drugs on BDNF levels.

6.1. Clinical Studies

The effects of antipsychotic drugs on BDNF levels have been studied using serum and plasma samples from schizophrenia and control subjects (Table 1). Serum BDNF levels were found directly correlated with clozapine daily dose in schizophrenia subjects (Pedrini et al., 2011). However, another study reported significant decreases in serum BDNF levels in chornic schizophrenia subjects on long term treatment with antipsychotics (Tan et al., 2005). No change in serum BDNF levels was found in schizophrenia subjects following 6 weeks of antipsychotic treatment (Pirildar et al., 2004). In contrast, a recent study found significant increase in serum BDNF levels following 4 weeks of antipsychotic treatment in schizophrenia subjects (Lee et al., 2011). Reduced serum BDNF levels were observed in patients with chronic schizophrenic disorder in relapse, but no significant change in BDNF levels was found following 6 weeks of treatment with typical (haloperidol) or atypical antipsychotics (risperidone, olanzapine and amisulpride) drugs (Rizos et al., 2010).A number of studies have investigated the effect of antipsychotic drugs on plasma BDNF levels in schizophrenia subjects. A recent study compared plasma BDNF levels at base line and after 1 year of olanzapine treatment in drug-naïve first episode subjects (Gonzalez-Pinto et al., 2010). They found significantly lower plasma BDNF levls at onset as compared to controls, but increased toward control values during olanzapine treatment. However, another study in drug-naïve first episode subjects did not find any significant change in plasma BDNF levels following 8 weeks treatment with antipsychotic drugs, risperidone, olanzapine or aripiprazole (Yoshimura et. al., 2010). Similarly, unchanged plasma BDNF levels was found in schizophrenia subjects following 8 weeks of olanzapine (Hori et al., 2007) or 4 weeks of risperidone (Yoshimura et al., 2007) treatment.

6.2. Pre-clinical Studies

Differential effects of typical and atypical antipsychotics on BDNF levels in rodents are summarized in Table 2. Typical antipsychotics such as haloperidol have been shown to reduce BDNF and TrkB protein levels in rat hippocampus (Parikh et al., 2004). No changes in BDNF protein levels was found in rat hippocampus following olanzapaine treatment for 45 days (Parikh et al., 2004). Interestingly, switching to olanzapine markedly restored haloperidol-induced reductions in both BDNF and TrkB receptors in rat hippocampus. Haloperidol significantly decreased BDNF concentrations in frontal cortex, occipital cortex and hippocampus after 29 days of treatment in rats (Angelucci et al., 2000). However, risperidone could reduce BDNF levels in the above regions only at higher doses. Both haloperidol and risperidone was unable to alter BDNF expression in hypothalamus and striatum (Angelucci et al., 2000). Olanzapine at a dose of 15 mg/kg body weight for 29 days significantly reduced BDNF protein levels in rat frontal cortex and hippocampus (Angelucci et al., 2005). In addition, reduced BDNF mRNA expression has been reported in rat hippocampus following haloperidol treatment (Lipska et al., 2001), whereas BDNF mRNA levels were elevated with atypical antipsychotics, like clozapine and olanzapine in the rat hippocampus (Bai et al., 2003). In chronic antipsychotic treatment studies, BDNF protein levels in rat hippocampus were unchanged with olanzapine both after 90 and 180 days of treatment (Pillai et al., 2006). BDNF protein levels were significantly lower in rat hippocampus following 90 days of haloperidol or chlorpromazine treatment and the reduction was continued up to 180 days. Furthermore, switching haloperidol treated rats after 90 days of treatment to either risperidone or olanzapine for the next 90 days significantly restored levels of BDNF in hippocampus. Olanzapine, but not haloperidol has

been shown to restore MK-801-induced reductions in BDNF protein levels in rat hippocampus (Fumagalli et al., 2003). Similarly, quetiapine treatment in rats was effective to attenuate the decreases in BDNF mRNA expression caused by immobilization stress in hippocampus and cortex (Park et al., 2006; Xu et al., 2002). Moreover, administration of ziprasidone significantly attenuated the immobilization stress-induced decrease in BDNF mRNA expression in rat hippocampus and neocortex (Park et al., 2009). The above studies suggest that atypical antipsychotics exhibit less deleterious effects on BDNF levels compared to typical antipsychotics and also capable of restoring the effects of typical antipsychotics. However, it is important to determine whether the beneficial effects of atypical antipsychotics will sustain over longer period of treatment (Terry and Mahadik, 2007).

7. Conclusion

There is growing interest in understanding the role of BDNF signaling in the pathophysiology of schizophrenia. Although most of the studies have found decreases in BDNF protein levels in peripheral samples from schizophrenia subjects the data on the effects of antipsychotic drugs on BDNF are not conclusive. TrkB signaling molecules such as Akt and Erk are linked to several cellular pathways involved in survival and apoptosis, and are also implicated in schizophrenia pathology. Given the limitations of the currently available antipsychotic drugs in the treatment of schizophrenia, in particular, treating cognitive deficits and negative symptoms, novel treatment avenues would be of great importance. Neuroprotective/neurotrophic compounds might be used as adjunctive therapeutic strategy for the treatment of schizophrenia.

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Highlights

Overview of BDNF/TrkB signaling in the pathophysiology of schizophrenia.

Pre-clinical and clinical studies indicate differential effects of antipsychotic drugs on BDNF/TrkB signaling in schizophrenia.

Neuroprotective/neurotrophic compounds should be tried as adjunct to conventional medications in schizophrenia.

Table 1

Effects of antipsychotic drugs on BDNF levels: Clinical studies

Drug	Duration of Treatment	Tissue/region	Effect	Reference
Olanzapine/Risperidone/Quetiapine/Amisulpride/Haloperidol	4 week	Serum	Increase	(Lee et al. 2011)
Clozapine	Chronic medication	Serum	Increase	(Pedrini et al. 2011)
Haloperidol/Risperidone/Olanzapine/Amisulpride	6 week	Serum	Decrease	(Rizos et al., 2010)
Olanzapine	1 year	Plasma	Increase	(Gonzalez-Pinto et al. 2010)
Risperidone/Olanzapine/Aripiprazole	8 weeks	Plasma	Unchanged	(Yoshimura et. al., 2010)
Clozapine/Risperidone	12 weeks	Serum	Decrease	(Grillo et al. 2007)
Olanzapine	8 weeks	Plasma	Unchanged	(Hori et al. 2007)
Risperidone	4 weeks	Plasma	Unchanged	(Yoshimura et al. 2007)

Table 2

Effects of antipsychotic drugs on BDNF levels: Pre-clinical studies

Drug	Treatment time and dose	Tissue/region	Effect	Reference
Haloperidol	1.0 mg/kg once daily for 3 weeks	Hippocampus	Decrease	(Park et al. 2009) [a]
Haloperidol	1.0 mg/kg once daily for 3 weeks	Neocortex	Decrease	
Haloperidol	2 mg/kg per day for 45 days	Hippocampus	Decrease	(Parikh et al. 2004) [a]
Olanzapine	10 mg/kg per day for 45 days	Hippocampus	Unchanged	
Haloperidol	1.15 mg/100 g food/day for 29 days (Oral)	Frontal cortex, Occipital cortex, Hippocampus	Decrease	(Angelucci et al. 2000) [b]
Haloperidol/Risperidone	1.15 mg/100 g food/day for 29 days (Oral)	Hippocampus, Frontal cortex, Occipital cortex Hypothalamus, Striatum	Unchanged	
Risperidone	2.30 mg/100 g food/day for 29 days (Oral)	Hippocampus, Frontal cortex, Occipital cortex	Decrease	
Risperidone	2.30 mg/100 g food/day for 29 days (Oral)	Hypothalamus, Striatum	Unchanged	
Olanzapine	3 mg/kg body weight for 29 days (Oral) in drinking water	Hippocampus, Frontal cortex, Occipital cortex	Unchanged	(Angelucci et al. 2005) [b]
Olanzapine	15 mg/kg body weight for 29 days (Oral) in drinking water	Hippocampus, Frontal cortex	Decrease	
Olanzapine	15 mg/kg body weight for 29 days (Oral) in drinking water	Occipital cortex	Unchanged	
Haloperidol	0.5 mg/kg for 28 days/1 mg/kg for 28 days	Hippocampus	Decrease	(Lipska et al. 2001) [b]
Haloperidol	0.5 mg/kg for 28 days/1 mg/kg for 28 days	Frontal cortex	Unchanged	
Clozapine	10 mg/kg for 28 days	Hippocampus, frontal cortex	Unchanged	
Clozapine	10 mg/kg for 28 days	Hippocampus	Increased	(Bai et al. 2003) [b]
Olanzapine	2.7 mg/kg for 28 days	Hippocampus	Increased	
Olanzapine	10 mg/kg/day for 90 days	Hippocampus	Unchanged	(Pillai et al. 2006) [b]
Olanzapine	10 mg/kg/day for 180 days	Hippocampus, Striatum	Decreased	
Haloperidol	2 mg/kg/day for 90 days	Hippocampus	Decreased	
Haloperidol	2 mg/kg/day for 180 days	Hippocampus/Striatum	Decreased	
Risperidone	2.5 mg/kg/day for 90 days/2.5 mg/kg/day for 180 days	Hippocampus	Decreased	

[a] BDNF mRNA expression levels;

[b] BDNF protein levels.