Brain-Derived Neurotrophic Factor/TrkB Signaling in the Pathogenesis and Novel Pharmacotherapy of Schizophrenia

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Key Words

Brain-derived neurotrophic factor • Schizophrenia • TrkB • Treatment

Abstract

The role of neurotrophins, predominantly brain-derived neurotrophic factor (BDNF), has been implicated in the pathophysiology as well as treatment outcome of schizophrenia. Both human and rodent studies indicate that the beneficial effects of antipsychotic drugs are mediated, at least in part, through BDNF and its receptor, TrkB. This review will discuss the available data on the levels of BDNF and TrkB in subjects with schizophrenia and in animals with and without conventional antipsychotics. The data concerning the impact of the antipsychotic drugs on BDNF/TrkB signaling will also be discussed. More importantly, this review will provide future perspective on BDNF/TrkB signaling as a novel molecular target to correct the pathogenesis and improve the long-term clinical outcome by treatments with conventional and adjunctive drugs.

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Introduction

A large number of neurotrophins have been demonstrated to play important role in the survival and development of neurons and in the establishment and maintenance of synapses during development and in adults [1–4]. Among these, the most studied are the brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophins 3 and 4 (NT-3 and NT-4), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF). A growing area of investigation within the field of schizophrenia research is the role of neurotrophins, particularly BDNF and NGF, in both pathophysiology and therapeutics of the illness. Understanding the possible defects in neurotrophin signaling may help to explain the well-demonstrated neurodevelopmental deficits in schizophrenia and may give possible clues for novel therapeutic strategies for the treatment of this disorder.

Two recent articles have reviewed the changes reported in the levels of BDNF and NGF in peripheral as well as postmortem tissue samples from subjects with schizophrenia and addressed the important role of these neurotrophins in schizophrenia [5, 6]. The present review will address the role of BDNF signaling via its receptor, TrkB, in the pathophysiology as well as treatment outcome of

schizophrenia. Furthermore, this review will provide the basis for BDNF/TrkB signaling as a potential molecular target for novel pharmacotherapy for the restoration of neuropathology and improved long-term clinical outcome of schizophrenia.

BDNF and Brain

BDNF is a small dimeric protein that is widely expressed throughout the adult mammalian brain (in different cell types such as neurons, astrocytes, microglia and endothelial cells), including the cerebral cortex, hippocampus, basal forebrain, striatum, hypothalamus, brainstem, and cerebellum [7]. BDNF immunoreactivity primarily localizes to soma, dendrites, and fibers, suggesting possibility roles in synaptic plasticity [8] and processes such as learning, memory, and age-related memory deficits [9]. In addition, in rat hippocampal and cortical areas – cingulate, parietal, and entorhinal cortex – and amygdala, BDNF immunoreactivity has also been observed in soma nuclei [10]. BDNF is a key regulator of the survival and differentiation of specific neuronal populations, including hippocampal and cortical neurons, cholinergic, nigral dopaminergic and 5-HT neurons [6].

BDNF/TrkB Signaling

BDNF signaling has been fairly well investigated both in vivo and in vitro experimental systems. The cellular response to BDNF depends on its differential actions on relative levels of its two receptors, full-length (TrkBFL) and truncated (TrkBtc) isoforms [11]. TrkBtc, which lacks the kinase domain, may inhibit BDNF signaling by sequestering BDNF so that it cannot bind TrkBFL [12] or by acting as a dominant-negative inhibitor of TrkBFL signaling via formation of heterodimers [13, 14]. The ratio of truncated to full-length receptors thus seems to be extremely important in the biological role of BDNF [15]. BDNF binding to TrkBFL induces receptor dimerization that triggers its intrinsic protein tyrosine kinase activity, leading to autophosphorylation at multiple tyrosine residues in the cytoplasmic domain of the receptor. These phosphotyrosine motifs serve as docking sites for the recruitment of proteins that contain a SH2 domain or phosphotyrosine-binding domain. These include enzymes such as Src, phospholipase C- γ (PLC- γ), and phosphatidylinositol-3 kinase (PI3K), which are activated by tyrosine phosphorylation, and adaptor proteins such as Grb2

(growth factor receptor-bound protein 2), which link receptor tyrosine kinases to downstream signaling pathways [16].

The role of PLC in BDNF-mediated signaling is well known. Two important second messengers, inositol triphosphate and diacylglycerol are generated upon PLC activation [17]. The inositol triphosphate causes release of stored intracellular calcium, and diacylglycerol activates protein kinase C (PKC). BDNF has been shown to activate these second messengers rapidly in cells [18]. The regulation of cell survival and cell death is of extreme importance in both the development of an organism and in the physiologic functions of the adult. PI3Ks play an important role in mitogenic signaling and cell survival, cytoskeletal remodeling, metabolic control and vesicular trafficking [19]. PI3K forms 3'-phosphorylated phosphoinositides, which allow the activation of several proteins, including Akt [20]. Activation of the Akt pathway provides cells with a survival signal that allows them to withstand apoptotic stimuli [21].

Growth factor activation of MAP (mitogen-activated protein) kinases requires Ras family small GTP-binding proteins. Ras proteins act as a major point of convergence in RTK signaling and play an important role in the transduction of extracellular signals [22]. Ras small GTP-binding proteins are membrane-bound intracellular signaling molecules that mediate a wide variety of cellular functions, including proliferation, differentiation, and survival. The best characterized effector of Ras is the serine/threonine kinase Raf. Upon activation, Raf phosphorylates MEK (mitogen/extracellular-signal-regulated kinase kinase) on Ser₂₁₈ and Ser₂₂₂ leading to its activation, which then activates MAP kinase or extracellular signal-regulated kinase (ERK) via phosphorylation on both threonine and tyrosine (Thr₁₈₃-Glu-Tyr₁₈₅) [23]. The two isoforms of ERK, 44 and 42 kDa, respectively, translocate to the nucleus, where they can activate a variety of proteins through phosphorylation on serine or threonine.

BDNF and Schizophrenia

Defective neurodevelopment as the pathogenesis of schizophrenia is based on extensive neuroimaging and neurobehavioral studies in young, first episode–drug naïve psychotic patients [24–28]. In addition, postmortem studies have provided evidence for neuropathological abnormalities that have a neurodevelopmental origin [29–31]. These studies indicated altered neural plasticity (i.e. altered neural proliferation and migration), delayed my-

elination, reduced neuropil and synapse and possibly enhanced cell vulnerability. BDNF has been found to play vital role in neural development, survival and repair in the central nervous system (CNS) [32, 33].

Clinical Studies

There is evidence from a variety of sources (postmortem, functional genetics, and clinical studies) that BDNF levels are disrupted in schizophrenia brains [5]. Postmortem studies have shown that BDNF protein levels, as measured by ELISA, were increased in cortical areas and decreased in hippocampus in schizophrenia [34]. Immunohistochemical studies [35] have shown increased expression of both BDNF and TrkB-positive neurons in the hippocampus of subjects with schizophrenia, whereas another study [36] reported elevated BDNF levels and decreased TrkB levels in the hippocampus of subjects with schizophrenia. Both BDNF and TrkB mRNA levels were significantly decreased in the prefrontal cortex of subjects with schizophrenia [37–39]. Though there are discrepancies among these reports from postmortem studies, overall these studies point to altered BDNF signaling in schizophrenia.

Several studies have indicated altered expression of BDNF in the blood of subjects with schizophrenia. BDNF reductions were observed in the serum of subjects with schizophrenia [40–42]. In a recent study [43], we found significantly decreased levels of plasma BDNF in subjects with first-episode psychosis in comparison with normal healthy controls. Additionally, plasma BDNF levels showed a significant negative correlation only with positive symptom scores at baseline and no significant correlations were found with any of the cognitive performance test battery or motor function test scores. Low BDNF levels at the onset of psychosis suggest that it may contribute to the pathogenesis of schizophrenia and/or perhaps could be a helpful neurobiological marker for possible early treatment intervention.

Studies have also evaluated the possible association of BDNF gene polymorphisms to increased risk of schizophrenia [44–46]. A number of studies have reported significantly increased frequency of the T allele (C-270T polymorphism, which is located in the 5' noncoding region of the BDNF gene and influences changes in BDNF expression) in schizophrenic patients [47, 48], but a few studies did not [49–52]. Val66Met, a frequent nonconservative polymorphism, which results in an amino acid change at codon 66 (valine to methionine) in the human

BDNF gene has been reported recently in schizophrenia. This functional polymorphism has been reported to affect the ability to perform tasks of verbal episodic memory and hippocampal function [44]. A number of studies have investigated the association between methionine or A allele at codon 66 and schizophrenia. A few studies among them found positive association [53], a few others found an opposite association [54, 55]. Although both positive [53] and negative [54, 55] associations have been reported, most studies to date found no association between the Val66Met polymorphism and schizophrenia [44, 50, 52, 56–59].

Dopamine Hypothesis and Schizophrenia

The dopamine hypothesis of schizophrenia postulates that hypofunction of the cortical and prefrontal dopamine systems contributes to negative symptoms and cognitive disorders, and that hyperactivity of the subcortical and limbic dopamine systems causes positive symptoms in schizophrenia [60, 61]. Overall analysis of dopamine receptors in the brain indicate that the striatum, limbic system, and the cortex have more receptors than the rest of the brain, regardless of pathology [62] and the prefrontal cortex of schizophrenic patients has decreased levels of D1, D3, and D4 receptors [62, 63].

Though all current antipsychotic drugs act primarily through dopamine receptors the existing drugs are poorly tolerated and exhibit little differences in efficacy [64]. Moreover, it is very difficult to explain the pathophysiology of schizophrenia completely by a single molecular event as schizophrenia is a heterogeneous group of disorders [65]. Because of the limitations of this approach, there is a critical need for studies designed to identify other molecular targets for the development of therapeutics. Increasing reports of anomalies observed in BDNF/TrkB signaling in schizophrenia indicate that various components of this system may serve as such molecular targets.

BDNF and GABAergic System in Schizophrenia

GABAergic interneurons play an important role in modulating the cortical signal transduction operative in information processing by regulating pyramidal neuron firing rates [66]. Postmortem studies have shown reduced GABA uptake bilaterally in the hippocampus and amygdala and in the left temporal cortex [67], GABA_A receptor

upregulation in the prefrontal cortex (PFC), caudate nucleus [68] and in the dorsolateral prefrontal cortex, of patients with schizophrenia [69]. Moreover, decreased GAD65 as well as GAD67 mRNA expression in prefrontal and other neocortical association areas of schizophrenics has been reported in different studies that used postmortem tissue from different brain banks [70]. Studies have also reported increased GAD67 mRNA and protein levels in prefrontal and primary sensory (visual) cortices of elderly schizophrenia subjects [71]. Since a reduction of GABAergic neurons results in a loss of the key modulatory inhibition of the pyramidal and interneuron processes, which may mediate the central executive function of working memory in schizophrenia subjects, several studies have looked at the effect of GABAergic agents in the treatment of schizophrenia [72–73].

A number of studies have shown that BDNF is a potent neurotrophic factor for GABAergic striatal neurons. When administered to cultured striatal neurons, it increases their cellular GABA content, the frequency of parvalbumin and calbindin neurons, and the levels of neuropeptide Y and somatostatin [74–75]. Moreover, BDNF infusion in normal rats increased the mRNA levels of GAD67 in substantia nigra and BDNF has been shown to increase GAD expression [76]. Interestingly, the decreases in spine density and GAD67 mRNA levels found in the PFC of subjects with schizophrenia are strongly correlated with decreases in mRNA levels of BDNF [37]. In addition, genetically engineered mice with altered BDNF/TrkB signaling showed changes in overall GABA/GAD levels in cerebral cortex [37, 77]. These studies suggest the role of the BDNF signaling pathway in the regulation of expression of GABA-related proteins.

BDNF and Animal Models of Schizophrenia

BDNF levels have been extensively studied in various animal models of schizophrenia. The neonatal ventral hippocampal lesion (NVHL) in animals produces a variety of behavioral and neurochemical abnormalities resembling phenomena observed in schizophrenia [78–79] such as hyperlocomotion, excessive reactivity to stress, and deficits in sensorimotor gating and social interactions [80–83]. It has been shown that animals with neonatal ibotenic acid lesions of the ventral hippocampus or amygdala have decreased BDNF mRNA levels in the prefrontal cortex and hippocampus [84]. Gestational methylazoxymethanol acetate (MAM) exposure has been suggested to produce neural and behavioral abnormalities

similar to those seen in schizophrenia [85]. It was found that injection of MAM during early rat brain development induced deficits in both the acquisition and retention phases of the Morris maze and these behavioral changes were associated with significant changes in BDNF [86]. In addition, chronic administration (8 days) of *d*-amphetamine has been shown to reduce BDNF levels in the occipital cortex and hypothalamus in rats [87]. Moreover, administration of NMDA receptor antagonist, MK-801 in rats decreased BDNF mRNA in the hippocampus and in the superficial layers of the cerebral cortex [88].

Antipsychotic Treatment Effects on BDNF Levels

Significant evidence indicates an effect of antipsychotic drugs on BDNF in human as well as rodent studies.

Human Studies

The effect of antipsychotic drugs on BDNF levels has been studied using serum or plasma samples from schizophrenia and control subjects. Serum BDNF levels of chronic schizophrenic patients on clozapine were higher than in patients on risperidone, but not statistically higher compared to patients on typical antipsychotics [41]. Another study [89] reported that antipsychotic treatment for 6 weeks did not influence serum BDNF levels compared to drug-free levels. The above two studies suggest that risperidone treatment is not associated with increases in serum BDNF levels, whereas higher doses of clozapine treatment are associated with higher BDNF levels. A few studies have investigated the effect of antipsychotic medications on plasma BDNF levels in subjects with schizophrenia. Treatment with olanzapine for 8 weeks did not alter the plasma levels of brain-derived neurotrophic factor in schizophrenia subjects compared to age- and sex-matched control subjects [90]. Risperidone treatment for 4 weeks did not find any change in the plasma BDNF levels in schizophrenia subjects [91]. The mean dose of risperidone used was 3.8 ± 1.4 mg/day.

Rodent Studies

Previous studies have reported that short-term treatment with antipsychotics differentially affects the expression of BDNF in rat brain [92–98]. Typical antipsychotics, such as haloperidol, seem to reduce BDNF expression in the rat brain [99], whereas atypical antipsychotics, including clozapine and olanzapine, might ele-

vate BDNF expression in the rat brain [100]. Previous studies from our group have shown that post-treatment with the atypical antipsychotic olanzapine markedly restored reductions in both BDNF and TrkB receptors in the hippocampus associated with haloperidol treatment [93]. Moreover, we found that chronic exposure to haloperidol, but not the atypical antipsychotics olanzapine, clozapine and risperidone, impaired spatial learning performance in rats [101, 102]. This is consistent with the clinical reports indicating that atypical antipsychotics (compared primarily to haloperidol) are more effective in reducing negative symptoms and improving cognitive performance [103, 104]. The data on neuroprotective effect of atypical antipsychotics is also supported by the potential of quetiapine in preventing immobilization stress-induced decrease in levels of BDNF mRNA [105].

The impact of antipsychotics upon BDNF levels has also been addressed in animal models of schizophrenia. Both clozapine and haloperidol significantly reduced expression of BDNF in the hippocampus, but not in the prefrontal cortex, following neonatal lesion of the ventral hippocampus [99]. The studies on the effects of the concomitant administration of haloperidol or olanzapine with the N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 on BDNF expression showed that MK-801 reduces the hippocampal expression of the neurotrophin; this effect was exacerbated by haloperidol, but it was normalized by olanzapine [106]. Studies were also done using a repeated restraint stress animal model to observe the changes in the expression of BDNF and B cell lymphoma protein-2 (Bcl-2) in hippocampal neurons of rats [107]. The data indicate that repeated restraint stress decreased the levels of expression of BDNF and Bcl-2 in hippocampal neurons and administration of olanzapine for 1 week returned the expression of Bcl-2 to its prestress level, and the administration for 3 weeks caused an excessive expression of BDNF in hippocampal neurons.

Most of the antipsychotic treatment studies in rodents have investigated the acute or short-term effect of antipsychotics on brain BDNF levels. Since antipsychotics are likely to be used for the very-long-term (over 10–50 years) management of schizophrenia, it is important to investigate the differential effects of these antipsychotics on the expression of BDNF with chronic treatment. In this regard, our group has investigated the long-term treatment effects of various antipsychotics, both typical as well as atypical on brain BDNF levels in rats. We found reduced BDNF expression in rat hippocampus with haloperidol, but not with olanzapine after 90 days of treatment [108]. Moreover, post-treatment of haloperidol-treated rats with

olanzapine reversed haloperidol effects on BDNF expression in hippocampus. We also observed a corrective effect of atypical antipsychotics on BDNF expression following switching from typical antipsychotics (haloperidol and chlorpromazine) to atypical antipsychotic (olanzapine and risperidone) [108]. But prolonged treatment in rats (180 days) resulted in BDNF reduction in hippocampus and striatum even with atypical antipsychotics indicating that atypical antipsychotics may positively influence BDNF levels early during chronic administration, this effect may disappear with time (and even negative effects may occur with more extended periods of treatment) [109]. Such differences between typical and some atypical drugs regarding neurotropic and neuroprotective mechanisms can have implications on the clinical course of the disorder and on brain loss associated with schizophrenia [110].

Switching Antipsychotic Drugs

The practice of switching drugs is commonly related to the reduced efficacy as well as increased side effects of typical antipsychotics. Godleski et al. [111] evaluated whether patients stabilized on depot antipsychotic medication could be successfully transitioned to oral olanzapine. The data indicate that oral olanzapine patients demonstrated significant clinical improvement over the depot control group from baseline to 3-month endpoint. There are no studies done in patients to determine the effects of switching antipsychotic drug in patients. Our studies in rats have demonstrated the potential of switching antipsychotic drugs from one to other, could sustain BDNF levels. Our data on switching rats treated with haloperidol for 90 days to either risperidone or olanzapine for the next 90 days showed the potential of risperidone as well as olanzapine to bring back haloperidol-induced low BDNF levels to control values, which may be one of the mechanisms for the beneficial effects observed in clinical practice with switching of drugs [108].

BDNF – a Possible Molecular Target for Developing Novel Therapeutic Strategies in Schizophrenia

The prevention of the neuropathological events in schizophrenia is a major therapeutic objective and it is equally important to make sure that the conventional treatment strategies (use of antipsychotics) do not exacerbate the pathology. As discussed above, atypical anti-

psychotics have been suggested to have a more favorable profile (at least based on short-term treatment studies) as compared to typical antipsychotics in the treatment of schizophrenia. However, based on several rodent studies, it is difficult to differentiate both classes of antipsychotics on their long-term treatment effects, since both typical as well as atypical antipsychotics induce adverse neurochemical as well as cognitive effects on long-term treatment. The data from various studies investigating the effect of antipsychotic drugs on brain BDNF levels suggest that all antipsychotics may upregulate BDNF levels when treated for a short period of time, but long-time treatment with antipsychotics, in particular typical antipsychotics, does not sustain brain BDNF levels (rather downregulates its expression in brain). Since antipsychotics are likely to be used for the very-long-term (over 10–50 years) management of schizophrenia, it is important to investigate the possible ways by which BDNF levels can be sustained in the brain.

Adjunctive or Add-On Therapies

In addition to switching the drug, adjunctive or add-on different drug has been very actively sought in order to improve the efficacy or ameliorate the side effects of the primary drug in schizophrenia. We have hypothesized that the use of adjunctive or add-on drugs that can sustain/restore the BDNF levels will be the future major breakthrough in the treatment of schizophrenia. The direct delivery of neurotrophins (themselves) like BDNF to the brain remains a major challenge, however, due to permeability of the blood-brain barrier. An alternative approach to directly administering BDNF is to increase BDNF activity in the brain by agents that can easily enter in the CNS.

Erythropoietin

Recombinant human erythropoietin (rhEPO) treatment has recently been reported to have neurotropic effects (i.e. to increase the expression of BDNF in the brain) [112]. Furthermore, several studies have shown that rhEPO is a potent neuroprotective agent against neural dysfunction resulting from a variety of neural insults [113–116]. A recent study in rats from our laboratory indicates that EPO co-treatment prevented the HAL-associated decrease in the BDNF protein levels and also significantly increased BDNF levels above vehicle treatment [117]. Therefore, sustained or increased brain BDNF by exogenous rhEPO co-treatment has the potential to prevent and/or reverse neuropathological events in schizophrenia. In support of this possibility, a recent clinical

add-on therapy, rhEPO with antipsychotic medication, showed significant improvement in cognitive function in chronic schizophrenia patients [118]. In addition, rhEPO has therapeutic advantages over other neurotropic factors in terms of delivery to their target cells in the brain and clinical tolerability [119, 120].

Cysteamine

A number of recent studies indicate that cysteamine might be a useful pharmacological alternative or adjunctive in the treatment of schizophrenia [121]. There are consistently replicated findings that systemic cysteamine treatment could attenuate the apomorphine-induced stereotypy as well as decreasing motor stimulant effects of amphetamine [122], decrease the amphetamine-induced locomotor activity [122, 123], and normalize deficits in prepulse inhibition induced by systemic injections of amphetamine [124]. Amphetamine is known to induce dopamine outflow in schizophrenia through alteration in the distribution of intracellular dopamine. Cysteamine treatment has been shown to completely prevent the 3-NP-mediated decrease of glutathione [125], whose levels are also low in prefrontal cortex (PFC) and CSF in schizophrenia patients [126]. Cysteamine administration also resulted in the depletion of norepinephrine, but increased dopamine levels in rodent brain cortex [127]. Cysteamine was also found to decrease weight gain and cataleptic behavior as well as preventing the increase of serum prolactin levels due to haloperidol administration in rats [128], which are the major beneficial properties of atypical antipsychotics. A recent study has shown that cysteamine increases brain as well as serum BDNF levels in rodent and primate model [129]. In addition, a cysteamine-induced increase in brain and serum BDNF levels was still detected after 12 weeks of continuous treatment, indicating that the efficacy of a repeated treatment is unlikely to diminish with time. Since BDNF-signaling pathway plays an important role in the neuroplasticity of schizophrenia, cysteamine may have potential to activate the BDNF signaling in schizophrenia.

Omega-3 Fatty Acids

The role of omega-3 fatty acids, predominantly docosahexaenoic acid (DHA) has been suggested for long time in the pathogenesis of schizophrenia [130–131]. Deficits in the levels of DHA in both peripheral and CNS membrane phospholipids have been consistently reported at the onset of psychosis as well as in chronic medicated patients. Since DHA is vital for brain development and function [132–136], its role in neurodevelopmental pa-

Fig. 1. Effect of antipsychotic drugs and adjunctive molecules on BDNF/TrkB signaling-mediated neuroplasticity in schizophrenia. The figure depicts the effect of antipsychotic drugs and adjunctive molecules on BDNF/TrkB signaling-mediated neuroplasticity in schizophrenia. BDNF regulates neuroplasticity by activating two major signaling pathways: the PI3K/Akt pathway, and the ERK pathway. Rodent studies indicate that acute treatment with antipsychotic drugs activates BDNF/TrkB signaling, whereas chronic treatment has either no effect or negative effects on this signaling pathway. The adjunctive or add-on drug therapy may be a potential way to activate BDNF/TrkB signaling and sustain or enhance neuroplasticity in schizophrenia. PIP2, IP3, DAG = Components of the PLC pathway; Ras GTP, MEK, ERK = components of the ERK-MAP kinase pathway; PI3K, Akt = components of PI3K/Akt pathway.

thologies and behavioral deficits in schizophrenia is implicated. DHA is continuously secreted by astrocytes, bathing the neuron where it participates in neuronal function and survival. Furthermore, neurotransmitter receptor-mediated release of DHA has been suggested to participate in gene activation for neural cell survival and neuroplasticity [131, 134, 135, 137]. Also, omega-3 polyunsaturated fatty acid (PUFA) deficiency in rats has been found to reduce the expression of BDNF in the frontal cortex, and that addition of DHA to cultured rat cortical astrocytes induced BDNF protein expression [138]. Thus, the increased BDNF by adjunctive use of omega-3 fatty acids (EPA and DHA) may be one of the mechanisms of reported improved clinical outcome in schizophrenia [130, 139].

Schizophrenia Therapeutic Perspective

Over 100 years, schizophrenia symptomatology is managed through behavioral and pharmacological means. Unfortunately, there is no treatment that significantly improves the quality of life of the schizophrenic subject. Current pharmacological treatments are based on neurotransmitter receptor regulation using short-term clinical trials. However, these medications are used for years throughout the life of an individual and long-

term use indicates either no response or serious side effects in subjects with schizophrenia. Neurodevelopmental deficits of schizophrenia at/predating the onset of illness indicate that treatment must be initiated very early and it must induce the neurorestoration through enhanced and sustained neuroplasticity. Existing evidence suggests that BDNF/TrkB signaling may be an important target to regulate neurorestoration. As discussed above, agents such as erythropoietin, cysteamine and DHA seem to have therapeutic potential as adjunctive or add-on drugs in the treatment of schizophrenia. As shown in figure 1, these agents can activate BDNF/TrkB signaling pathway that regulates neuroplasticity. Alterations in this signaling pathway can be studied in subjects with schizophrenia using lymphocytes collected at different stages of illness and with or without conventional treatments. BDNF/TrkB signaling pathway may thus hold considerable promise for the development of novel therapeutic strategies for the treatment of schizophrenia.

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