THE PHARMACODYNAMICS OF MEDICATIONS USED IN PSYCHIATRIC DISORDERS

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Brain-derived neurotrophic factor and schizophrenia

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Abstract

Schizophrenia is a severe disorder affecting approximately 1% of the population. Historically, alterations of dopaminergic function were considered the primary cause of schizophrenia. However, for many patients, drugs that alter dopaminergic function do not consistently lead to resolution of the symptoms of schizophrenia. Thus, there is an increased interest in pathophysiologic processes that result in altered neurodevelopment and plasticity associated with schizophrenia. Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in neurogenesis, synaptic plasticity, cognition, and neurotransmission. Genetic polymorphism, expression, and function of BDNF have been implicated in psychiatric diseases, including schizophrenia. This review discusses BDNF, its role in neurologic processes, and the evidence implicating BDNF in schizophrenia.

Keywords: schizophrenia, brain-derived neurotrophic factor, BDNF

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Introduction

Schizophrenia is a chronic disorder affecting 1% of the population. Although alterations in dopaminergic function have been found in schizophrenia, administration of dopamine antagonists is ineffective or suboptimal in more than 30% of patients with schizophrenia.[1] Alternate theories of schizophrenia point to neurodevelopmental abnormalities as a potential cause. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor essential for development of the central nervous system and modulation of neuronal connections that may be involved in the pathophysiology of schizophrenia.

Background

Neurotrophins are a family of proteins involved in the growth and survival of neurons. During brain development neurotrophins support neuronal growth, differentiation, and survival. Long-term effects of neurotrophins, such as axonal and dendrite growth, synaptic structure and connections, and neuroplasticity, are dependent on gene regulation.[2] Short-term cytoplasmic effects of neurotrophins influence neuronal differentiation, modulation of neuronal excitability, and synaptic transmission.[2] In animal models, lack of neurotrophins is associated with decreased synaptic connectivity.[2] Thus, neurotrophins appear necessary for the proper function of synapses that may be directly related to symptoms of schizophrenia.[3,4]

Brain-derived neurotrophic factor is the most widely studied neurotrophin and is expressed in the periphery and central nervous system. It is involved in brain development, including neurogenesis, and neuronal differentiation, maturation, and survival.[2,3] In the adult brain, BDNF is important for neuronal plasticity, apoptosis, modulation of neurotransmitters, and survival of dopaminergic, cholinergic, and serotonergic neurons, which have been implicated in memory and cognitive changes in schizophrenia.[3-6] Brain-derived neurotrophic factor also promotes cellular and molecular functions related to neurotransmitter release.[3,4] Aberrant function of BDNF could lead to changes in neuronal cell development,

survival, plasticity, and synaptic connectivity. It has been posited that such changes in plasticity and neurotransmission are important for higher cognitive functions often impaired in those with schizophrenia.[3-5]

BDNF and Psychotic Symptoms

Animal models have demonstrated BDNF is important for the development and activation of neurotransmitters associated with psychosis.[2,7-11] Neurodevelopmental models suggest reduced concentrations of BDNF modify synaptic efficiency and connectivity, which alters neurotransmission and results in signs and symptoms consistent with schizophrenia.[2,10-13] Models of drug-induced psychosis (ie, phencyclidine, dizocilpine, ibotenic acid) demonstrate decreased BDNF mRNA concentrations are associated with psychotic symptoms.[9-11] This suggests early life changes in BDNF are associated with impaired neurotransmission and psychotic symptoms later in life.

BDNF and the Environment

Transcription of BDNF is a complex process that involves activation of a multistep signal cascade. When induction of BDNF transcription is activity triggered, only certain mRNA isoforms are produced.[14-16] Neuronal activity induced by seizures and sensory stimuli through *N*-methyl-D-aspartate receptor and L-type voltage-gated calcium channels leads to changes in BDNF gene expression through initiation of this activity-triggered transcription signal cascade, which may result in expression of a limited range of mRNA isoforms that increase the risk of developing schizophrenia.[14-16] Such epigenetic regulation of BDNF expression is consistent with the theory that schizophrenia is a result of both environmental and genetic influences.[17]

BDNF and Genetics

Progressive changes in brain volume in schizophrenia have been associated with the Val66Met polymorphism of the BDNF gene.[18,19] The Val66Met polymorphism has also been associated with lower BDNF serum concentrations, which correlates with decreased hippocampal volume.[18-20] Given the similarities in brain changes associated with schizophrenia and the Val66Met polymorphism, it has been posited that the Val66Met genotype is associated with schizophrenia.[18-20] However, studies assessing the association of Val66Met polymorphisms with schizophrenia have reported mixed results. One meta-analysis[20] found that although overall hippocampal volumes were decreased in patients compared with controls, the effect was independent of Val66Met genotype, suggesting BDNF polymorphism may not be a risk factor for decreased hippocampal volume in schizophrenia. This was confirmed in a second meta-analysis,[21] which also failed to find an association. Conversely, although one meta-analysis reported an association of theVal66Met polymorphism with schizophrenia, another reported an association only in Asian, European, and Chinese populations.[22,23] In the largest meta-analysis[24] of 11 480 patients with schizophrenia and 13 490 controls, no association between the Val66Met polymorphism and schizophrenia was found. However, the Val66Met polymorphism may be associated with younger age of onset.[25-27]

Given BDNF's role in cognition and memory, it has been proposed that modulation of BDNF expression through the Val66Met genotype could account for cognitive symptoms associated with schizophrenia.[28] However, data are mixed on this topic. One study[29] reported an association of the Val66Met polymorphism with impaired cognitive function in bipolar disorder but not schizophrenia. Another study[30] reported a significant association of the Val66Met polymorphism and cognitive deficits in schizophrenia. Another study[31] reported the association was gender specific. A meta-analysis[32] of 12 studies of 1890 patients failed to find an association between the Val66Met allele and cognition.

There appears to be some relationship between the Val66Met polymorphism and schizophrenia. The exact nature of this relationship has yet to be elucidated. It does not seem that the Val66Met polymorphism of the BDNF gene is directly related to the development of schizophrenia.

It is unclear whether a link between the cognitive symptoms of schizophrenia and the Val66Met polymorphism exists. It may be genetic variation is associated with the clinical presentation of schizophrenia, rather than a direct cause.

BDNF as a Biomarker

Postmortem studies[33,34] of patients with schizophrenia demonstrated increased BDNF expression in the prefrontal cortex and hippocampus. One study[35] demonstrated decreased BDNF concentrations in the prefontal cortex compared with matched controls. However, studies of peripheral BDNF concentrations in patients with schizophrenia have reported mixed outcomes. Although most studies report decreased peripheral concentrations of BDNF, other studies[7,30,36,37] report elevated BDNF concentrations in patients with schizophrenia. Such differences in findings may be related to the nature of the populations studied (eg, medicated versus unmedicated, treatment-naive) or sampling source (eg, serum versus serum protein). A meta-analysis[7] of 17 studies of 1114 patients with schizophrenia and 970 age-matched controls reported a moderate reduction in peripheral BDNF concentrations in patients with schizophrenia, although the authors note significant heterogeneity in studies. This

finding was consistent in subanalyses of drug-naive patients versus controls and medicated patients versus controls. Another meta-analysis[36] of 35 studies included 2667 patients with schizophrenia and 2580 healthy controls also reported moderately reduced BDNF concentrations in patients with schizophrenia compared with controls. Sensitivity analyses found similar results, although the effect size was decreased from −0.7 (95% confidence interval [CI]: −0.45 to −0.94; $P < .001$) to −0.56 (95% CI: −0.33 to −0.8; $P < .001$). Subanalyses of first-episode and non–first-episode psychosis and drug-free and drug-naive patients had similar results. Although this is an interesting finding, presumably central concentrations would better reflect BDNF's role in schizophrenia However, it is unclear whether peripheral concentrations reflect central nervous system BDNF concentrations. Currently, peripheral BDNF concentrations are not a viable biomarker for schizophrenia.

BDNF and Antipsychotics

If schizophrenia is truly related to decreased BDNF concentrations, effective treatments would presumably reverse this trend. Therefore, antipsychotic effects on BDNF concentrations have been investigated. Some studies,[38-41] but not all, have not demonstrated an increase in BDNF following antipsychotic administration. Studies have failed to find an increase in BDNF with second generation antipsychotics on both chronic and first-episode patients treated for 8 weeks.[41] One meta-regression[7] of 8 studies failed to find an association between antipsychotic dose and BDNF concentrations. However, this meta-regression was likely underpowered to show an association. Another larger meta-regression[42] reported plasma, but not serum, BDNF concentrations rose after antipsychotic initiation, suggesting disparate results may be due to sampling techniques.

Conclusions

BDNF appears to be involved in numerous neuronal processes known to be associated with schizophrenia. Several animal models indicate that BDNF plays a role in schizophrenia. However, human data are mixed. Although it appears BDNF is implicated in schizophrenia, the data are far from conclusive as to the exact nature of the relationship or how to leverage this information into the diagnosis or treatment of patients with schizophrenia.

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