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Review

The role of BDNF in the pathophysiology and treatment of schizophrenia

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ABSTRACT

Brain Derived Neurotrophic Factor (BDNF) has been associated with the pathophysiology of schizophrenia (SCZ). However, it remains unclear whether alterations in BDNF observed in patients with SCZ are a core part of disease neurobiology or a consequence of treatment. In this manuscript we review existing knowledge relating the function of BDNF to synaptic transmission and neural plasticity and the relationship between BDNF and both pharmacological and non-pharmacological treatments for SCZ. With regards to synaptic transmission, exposure to BDNF or lack of this neurotrophin results in alteration to both excitatory and inhibitory synapses. Many authors have also evaluated the effects of both pharmacological and non-pharmacological treatments for SCZ in BDNF and despite some controversial results, it seems that medicated and non-medicated patients present with lower levels of BDNF when compared to controls. Further data suggests that typical antipsychotics may decrease BDNF expression whereas mixed results have been obtained with atypical antipsychotics. The authors found few studies reporting changes in BDNF after non-pharmacological treatments for SCZ, so the existing evidence in this area is limited. Although the study of BDNF provides some new insights into understanding of the pathophysiology and treatment of SCZ, additional work in this area is needed.

1. Introduction

Schizophrenia (SCZ) is a devastating major mental illness that affects 1% of the world population and is associated with personal and family suffering, high suicide rates and disruption in social functioning (Ross et al., 2006). However, despite much research, the etiology remains poorly understood. While antipsychotic treatment can be very effective, nearly 40 percent of patients achieve only a partial response and 10 percent experience no response at all (Pantelis and Lambert, 2003). Better understanding of the pathophysiological mechanisms is therefore necessary to design better, targeted treatments, to enhance outcomes for these patients.

It is well known that neurotrophic factors, such as Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin-3 (NT-3) and Neurotrophin-4/5 (NT4/5) promote the growth, differentiation and survival of nerve cells during development and are also involved in the maintenance and plasticity of adult neurons (Huang and Reichardt, 2001; Lewin and Barde, 1996; Maisonpierre et al., 1990). Therefore, primary alterations in the activity of these molecules could lead to inappropriate alterations in cortical circuitry and synaptic transmission in the developing brain, which could then translate into the neural dysfunction underlying psychiatric disorders.

BDNF was the second neurotrophic factor to be characterized after NGF. BDNF is the most widely distributed neutrophin in the CNS and it is highly expressed in the prefrontal cortex (PFC) and hippocampus (Pezawas et al., 2004), where it has been shown to have long-term effects on neuronal survival, differentiation and synaptic plasticity (Pang et al., 2004; Nawa et al., 2000). This review is intended to summarize existing findings about the role of BDNF in the pathophysiology and treatment of SCZ. First, we will review the role of BDNF in synaptic neurotransmission, with special emphasis on GABA and glutamate, two neurotransmitter systems that play a crucial role in the pathophysiology and treatment of SCZ (Lewis et al., 2005), as well as dopamine, since this neurotransmitter has a dominant role in the development of SCZ, regarding the patophysiology, symptoms and medication. Second, we will review the role of BDNF in relation to neuronal plasticity in SCZ. Third, we will review literature evaluating the effects of pharmacological and non-pharmacological treatments in SCZ on BDNF modulation of synaptic transmission which is a differential of this review from others previous published (Buckley et al., 2007, 2011; Green et al., 2011). Finally, we will discuss future studies suggesting novel methods though which BDNF may be targeted as part of treatment for SCZ.

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2. BDNF

BDNF is a basic dimeric polypeptide located on chromosome 11p13. It is initially synthesized as a larger protein precursor and cleaved to form mature BDNF, which is approximately 13 kDa in size (Maisonpierre et al., 1991). BDNF binds at least two receptors, TrkB and p75 (Barbacid, 1995a,b; Chao et al., 1998). TrkB is a tyrosine kinase receptor that, when activated, phosphorylates tyrosine residues and activates a number of intracellular cascades (e.g. calcium influx) (Kaplan and Miller, 2000; Maisonpierre et al., 1991) involved with cellular survival, growth and differentiation (Fig. 1) (Huang and Reichardt, 2001). There are other related Trk receptors,

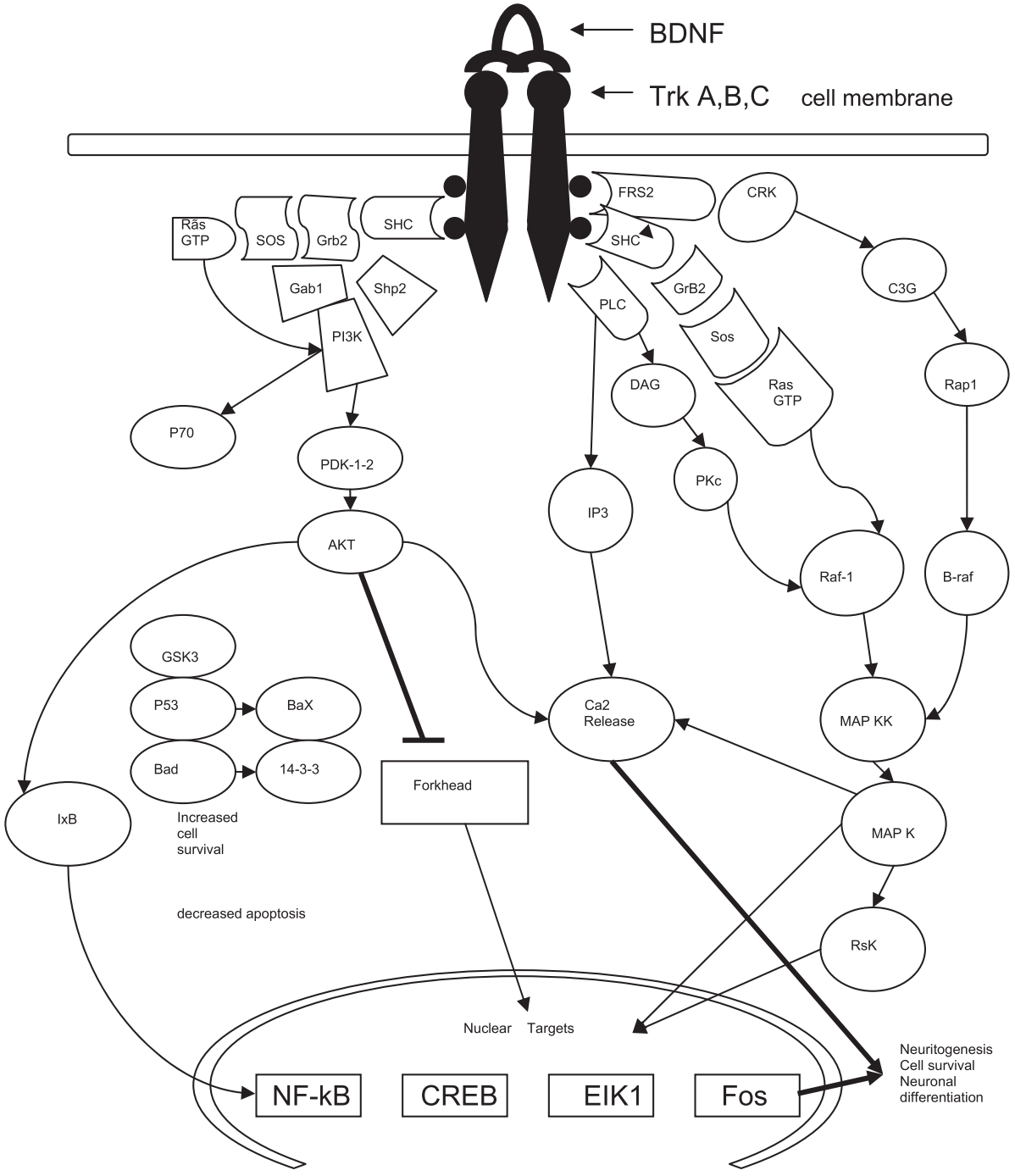

Fig. 1. Protective effects of BDNF Receptor activation by BDNF. Based on Scott Pollack et al.: Neurotrophin Receptor Activators Drug News Perspect 2002, 15(5): 268. TrKA,B,C: Neutrotrophic receptor family A,B, C; SHC = Src homology and collagen homology; SoS = Son of sevenless; Ras = Ros family small GTP binding protein; GTP = guanosine triphosphate; Gab-1 = Grb2-associated binder1; PLC = Phospholipase-C; CrK = Chicken tumor virus n°10 regulator of kinase; Rap-1 = member of RAS oncogene family; B-raf = v-raf murine sarcoma viral oncogene homolog B1/serine/threonine protein-kinase; DAG = diacilgycerol; IP3 = inositol triphosphate; GSK3 = glycogen synthase kinase 3; p70 = sh3 domain-containing 70 kDa protein; BAD = BCL2-associated agonist of cell death; 14-3-3 = cytosolic phospholipase A2; Forkhead = forkhead box protein; PI3 = Phosphatidylinositol 3; PKD1,2 = Polycistyn(transient receptor potential cation channel); AKT = Rac-alpha serine/threonine protein-kinase; PKC = Protein kinase C; MAPK = Mitogen-activated protein-kinase; MAPK = Mitogen-activated protein-kinase-kinase; RsK = Ribosomal protein S6 kinase; NF-kB = Nuclear Factor kappa B; CREB = cAMP-response element binding protein; ELK = member of ETS oncogene family; Fos = Fbj murine osteosarcoma viral oncogene homolog.