Role of Brain Derived Neurotrophic Factor in Psychotic and Mood Disorders

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Saad Mohamed Alshemy

Contents

List of abbreviations

AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
AMPA	α-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid
BBB	Blood Brain Barrier
BD	Bipolar Disorder
BDNF	Brain Derived Neurotrophic Factor
BrdU	5-Bromo-2-deoxyuridine
CNS	Central Nervous System
CRH	Corticotrophin Releasing Hormone
CT	Computed Tomography
CUS	Chronic Unpredictable Stress
DL-PFC	Dorso-Lateral Pre-Frontal Cortex
ERK	Extracellular Regulated Kinase
FGF	Fibroblast Growth Factor
GABA	Gamma Amino Butyric Acid
GCL	Granular Cell Layer
GMP	Guanosine Mono-Phosphate

HPA	Hypothalamic Pituitary Adrenal Axis
IGF 1	Insulin-like Growth Factor 1
IGFBP	Insulin-like Growth Factor Binding Protein
ILC	Infra Limbic Cortex
IP3	Inositol Tri-Phosphate
LTM	Long Term Memory
LTP	Long Term Potentiation
L-LTP	Late-phase Long Term Potentiation
Mb	Million base
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribo-nucleic Acid
MS	Multiple Sclerosis
NGF	Nerve Growth Factor
NMDA	N-Methyl-D-Aspartate
NIMH	National Institute of Mental Health
NO	Nitric Oxide
NT3	Neurotrophin 3
NT4	Neurotrophin 4
NTR	Neurotrophin Receptor
PI3K	Phosphatidyl-Inositol 3 Kinase
PKG	Protein Kinase G

PLC	Pre- Limbic Cortex
PNS	Peripheral Nervous System
PD	Parkinson’s Disease
PV	Parvalbumin
SGC	Soluble Guanyl Cyclase
SGZ	Sub-Granular Zone
SNP	Single Nucleotide Polymorphism
SNpc	Substantia Nigra pars compacta
TNF	Tumor Necrosis Factor
TrK	Tyrosine Kinase
VEGF	Vascular Endothelial Growth Factor
VIP	Vaso-active Intestinal Peptide

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Introduction

Introduction

Neurotrophins are a family of closely related proteins that were identified initially as survival factors for sensory and sympathetic neurons, and have since been shown to control many aspects of survival, development and function of neurons in both the peripheral and the central nervous systems **(Reichardt, 2006).** There are many types of neurotrophins like: Nerve growth factor (NGF), Proapoptotic receptors (P75), Antiapoptotic receptors (TrkA), Glial cell line-derived neurotrophic factors (GDNF), Brain derived neurotrophic factor (BDNF), Neurotrophins 3,4, and 5 (NT-3,4, and amp-5), Ciliary neurotrophic factor (CNTF), Insulin like growth factors (ILGF 1 and 2), Fibroblast growth factor (FGF) and Epidermal growth factor (EGF) **(Stahl, 2009).**

Brain derived neurotrophic factor **(BDNF),** a member of the neurotrophin family, promotes neuronal survival and regulates the proliferation and differentiation of nerve cells in the peripheral and central nervous systems **(Hartmann et al., 2001)**. BDNF has important regulatory effects on the serotonergic (**Mossner et al., 2000**), glutamatergic (**Falkenberg et al., 1996**) and dopaminergic (**Guillin et al., 2001**) neurotransmitter systems. BDNF is also involved in hippocampal long-term potentiation, which is related to learning and memory (**Yamada et al.,2002**). In addition, brain-derived neurotrophic factor (BDNF) plays an important role in the

survival, differentiation, and outgrowth of selected peripheral and central neurons throughout adulthood.

Because of its important role in the development of the dopamine system, it appears to play an important role in the pathophysiology of schizophrenia (**Davis et al.,1991**), which is a syndrome of unknown etiology characterized by disturbances in cognition, emotion, perception, thinking, and behavior. Schizophrenia is well established as a brain disorder, with structural and functional abnormalities visible in neuroimaging studies and a genetic component, as seen in twin studies. The disorder is usually chronic, with a course encompassing a prodromal phase, an active phase, and a residual phase. The active phase has symptoms such as hallucinations, delusions, and disorganized thinking. The prodromal and residual phases are characterized by attenuated forms of active symptoms, such as odd beliefs and magical thinking, as well as deficits in self-care and interpersonal relatedness. **(Sadock & Sadock, 2010)**.

BDNF has also been implicated in such disorder. One study reported elevated BDNF levels in the cingulated cortex and the hippocampus of schizophrenic patients (**Takahashi et al., 2000**), whereas two other studies showed reduced BDNF in the prefrontal cortex (**Weickert et al., 2003**) and the hippocampus (**Durany et al., 2001**) of patients with schizophrenia. Based on the neurodevelopmental hypothesis [**Jones and Murray, 1991**] and the

dopamine theory [**Davis et al., 1991**] of schizophrenia, BDNF abnormalities may increase vulnerability to the illness.

On the other hand, bipolar disorder (BPD), is a disorder of mood in which both manic & depressive symptoms occur either in separate episodes or mixed together or in a recurrent alternating unpredictable sequence. It includes bipolar 1 disorder which is characterized by a well-designed, at least, 1 manic episode lasting for at least 1 week. On the other hand, bipolar 2 disorder is characterized by depressive episodes & hypomanic episodes during the course of the disease. (**Sadock & Sadock, 2007**).

Although these episodes are usually interspersed with periods of relatively normal mood, BPD is the cause of significant suffering for both patients and their families. BPD leads to limited functioning, which often results in decreased productivity in both the personal and the professional arenas of the patient's life. The prognosis for patients with BPD is poor, with high rates of relapse, lingering residual symptoms, cognitive impairments, and diminished well-being. Moreover, individuals with BPD frequently have coexisting medical conditions, such as obesity, cardiovascular disease, diabetes mellitus, and thyroid dysfunction, all of which are exacerbated by their BPD symptoms. **(Keri Martinowich et al., 2009).**

There is a growing evidence suggesting that BDNF is involved in the pathophysiology of mood disorders. **(Liu et al. 2009).** Moreover, histological and behavioral research in bipolar disorder (BD) implicates structural abnormalities in the hippocampus. Brain-derived neurotrophic growth factor (BDNF) protein is associated with hippocampal development and plasticity, and in mood disorder pathophysiology. **(Chepenik et al.,2010).**

Major depressive disorder is characterized by a combination of symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy once-pleasurable activities. Major depression is disabling and prevents a person from functioning normally. An episode of major depression may occur only once in a person's lifetime, but more often, it recurs throughout a person's life **(Wakefield et al., 2007)**. In addition, Brain derived neurotrophic factor (BDNF) is the most studied neurotrophin in the pathophysiology of MDD. Postmortem studies have found that depressed subjects have decreased hippocampal and cortical BDNF levels and BDNF has been found to be down regulated by stress, which has been directly implicated in the pathophysiology of depression. **(Machado-Vieira et al., 2009).**

Rationale of the work

1. Is there a relation between brain derived neurotrophic factor and psychotic and mood disorders ?
2. Does identifying the role of BDNF in psychotic and mood disorders can affect the treatment and follow up of these disorders ?