



Role of Brain-derived Neurotrophic Factor in the Pathophysiology of Depression



Tridip Chatterjee* and Ashim Kumar Basak

Department of Molecular Biology, Institute of Genetic Engineering, India

Submission: March 16, 2017; Published: April 25, 2017

*Corresponding author: Tridip Chatterjee, Department of Molecular Biology, Institute of Genetic Engineering, 30 Thakurhat Road, Kolkata-700128, West Bengal, India, Tel: +91-09831325280; Email: ctrkidip@gmail.com

Abstract

Brain-derived neurotrophic factor (BDNF) is a crucial growth factor in the central nervous system (CNS) as it is required for the development of this system as well as synaptic plasticity of the brain that underlie the learning and memory process. Furthermore, this neurotrophic factor is also implicated in mood regulation. Thus the deficiency of BDNF signaling in the brain may give rise to cognitive dysfunction and anhedonia, the important features of depression. Monoamine neurotransmission deficiencies form an important basis for the pathogenesis and maintaining the characteristic features of depression. However, in addition to monoamine neurotransmission deficiencies, BDNF deficiencies have also been noticed in depression patients. Furthermore, anti-depression treatment mediates the depression reducing effects by increasing BDNF output in brain. Thus BDNF deficiencies in brain may be an important contributor in the pathogenesis of depression.

Keywords: BDNF; Depression; Antidepressant

Introduction

Depression or major depressive disorder (MDD) is one of the common and neuropsychiatric disorder affecting more than 10% world population [1]. In this disease activities of specific circuits in the brain neuronal network are altered owing to undesirable molecular and cellular alterations caused by some adverse environmental stimuli such as stress [1,2]. These alterations in brain regions can give rise to cognitive dysfunctions like poor concentration, difficulty in making decision, memory and executive dysfunctions etc., the fundamental features of depression [3]. Patients with severe depression are also at high risk of suicidal act [4]. Many factors can contribute to MD and no one factor is solely responsible for it [5]. In this review, we will provide a simple background idea on the role of BDNF in the development of depression.

Role of BDNF in the Pathogenesis of Depression

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that direct growth and differentiation in the developing nervous system. BDNF regulates synaptic transmission and activity-dependent plasticity and promotes long-term potentiating (LTP) required for memory formation [6,7] indicating its importance in cognitive function. Animal and human studies report that stress, a major contributor of depression, causes the reduced expression of BDNF in

hippocampus, the brain region implicated in learning. Moreover, serum or plasma BDNF levels are also found to be decreased in untreated depression patients [8]. BDNF influences CNS neurons via activation of the TrkB receptor. Phospholipase C gamma (PLC gamma), phosphoinositide 3-kinase/Akt (PI3K/Akt), and extracellular signal-regulated kinase (ERK) signals are stimulated after TrkB activation, which maintains cell survival and regulates synaptic function. Thus it has been suggested that an alteration in BDNF expression/ function contributes to the pathophysiology of psychiatric diseases including depression [9].

Genetic polymorphism and epigenetic regulation of BDNF expression in depression

Molecular pathophysiology of depression is very complex. Post-mortem data from depressed humans show that depression is associated with a decrease in the amount of BDNF in the hippocampus. Neuronal secretion of BDNF occurs through regulated (activity-dependent) and constitutive secretory pathways. Regulated secretion is modulated by the interactions of proteins in the Golgi apparatus with the pro-domain of BDNF, the site of a single-nucleotide polymorphism (G196A) in humans that results in the substitution of valine at amino-acid residue 66 with methionine.

The Met-66-containing BDNF variant has impaired intracellular trafficking. Met-66 BDNF is not properly sorted within the cell, causing it to be distributed throughout the cell body outside of the vesicles. In addition, less BDNF is secreted from the nerve terminal. Knock-in mice that homozygously express Met-66 BDNF have normal responses in the forced-swim test, but these mice show more anxiety like behavior and greater resilience to behavioral and molecular changes after social defeat, implicating this BDNF polymorphism in the pathophysiology of psychological disorders that are influenced by stressful life events.

BDNF gene expression is controlled by multiple promoters. Reduced expression of BDNF and increased promoter methylation of BDNF exons have been reported in the brain and blood of patients with depression [10]. Human BDNF gene has 11 exons and nine functional promoters that are used tissue and brain-region specifically [11]. Postmortem brain samples from suicide victims showed a statistically significant increase of DNA methylation at specific CpG sites in BDNF promoter/exon IV compared with non-suicide control subjects [12].

Epigenetic regulation of BDNF can also occur through other ways. For example, the methyl-CpG binding protein 2 (MeCP2), by virtue of its ability to add methyl groups in the genome and for recruiting the type I histone deacetylase (HDAC1) Sin3A can exert long-term inhibition of the BDNF [13].

Histone acetyltransferases (HATs) and deacetylases (HDAC) are the enzymes responsible for the addition and removal of acetyl groups respectively from lysine residues on the histone N-terminal tails. In doing so, the former and the later enzymes exerts stimulatory and inhibitory influences in gene expressions [14].

Exposure to stressful life events during pregnancy exerts profound effects on neurodevelopment and increases the risk for several neuro developmental disorders including depression in off springs. It has been shown that offspring resulted from mice with gestational stress exhibited depressive-like and anxiety-like behaviors. Stress-offspring showed decreased expression of BDNF that was accompanied with increased expression of HDAC [10]. Furthermore, HDAC inhibitor, sodium butyrate (SB) and trichostatin A (TSA), valproic acid (VPA) increased BDNF transcripts in brain astrocytes in a time-dependent manner [15]. All these instances indicate that BDNF dysregulation exerts an important contribution to the pathophysiology of depression.

Antidepressant treatment increases BDNF output

BDNF and its receptor TRKB are expressed in multiple regions in the adult brain, where they influence diverse roles like neuronal activity, function and its survival throughout life. The presence and activity of BDNF in many brain areas suggest a potential role of this molecule in the pathogenesis and treatment in psychiatric disorders [16]. It has been reported that chronic antidepressant administration increases the expression of BDNF in the hippocampus and prefrontal cortex in the brain.

Furthermore, animal experimentations show that BDNF infusions produce an antidepressant response in behavioral models, including the forced swim and learned helplessness paradigms [17]. It has been reported that a single bilateral infusion of BDNF into the ventricles or directly into the hippocampus caused rapid and sustained antidepressant-like effect. Importantly, disruption of BDNF signaling by genetic manipulation caused the attenuation of antidepressant-like response to conventional antidepressants. Additionally, low dose ketamine, an antagonist of the NMDA receptor that induces a rapid antidepressant effect in patients with treatment-resistant depression is also mediated by increased BDNF signaling. Ketamine increases BDNF translation in hippocampus, leading to enhanced synaptic plasticity and synaptic strength [18]. All these instances imply that BDNF is essential for normal brain functioning and interference of BDNF activity predispose the pathogenesis of depression.

Discussion

Deficiency of BDNF signaling seems to have an important role in the development of depression due to altered synaptic plasticity in the brain. Genetic polymorphism and epigenetic regulations may negatively regulate the expression of this important neurotrophic factor in the brain that may underlie depression. Thus BDNF as well as the drugs those increase BDNF in the brain offer promise for the treatment of depression.

References

1. (2013) New Molecular Mechanism of Depression Revealed. *Bulletin of the Chinese Academy of Sciences* 27: 4.
2. Krishnan V, Nestler EJ (2010) Linking Molecules to Mood: New Insight into the Biology of Depression. *Am J Psychiatry* 167(11): 1305-1320.
3. Papazacharias A, Nardini M (2012) The relationship between depression and cognitive deficits. *Psychiatria Danubina* 24(Suppl 1): 179-182.
4. Takahashi Y (2001) Depression and Suicide. *JMAJ* 44(8): 359-363.
5. (2017) Depression. *Epilepsy Newfoundland and Labrador, Canada*.
6. Murray PS, Holmes PV (2011) An Overview of Brain-Derived Neurotrophic Factor and Implications for Excitotoxic Vulnerability in the Hippocampus. *International Journal of Peptides* 2011(2011): 0-12.
7. Mizuno M, Yamada K, Olariu A, Nawa H, Nabeshima T (2000) Involvement of Brain-Derived Neurotrophic Factor in Spatial Memory Formation and Maintenance in a Radial Arm Maze Test in Rats. *20(18): 7116-7121*.
8. Lee BH, Kim YK (2010) The Roles of BDNF in the Pathophysiology of Major Depression and in Antidepressant Treatment. *Psychiatry Investig* 7(4): 231-235.
9. Numakawa T, Adachi N, Richards M, Chiba S, Kunugi HE, et al. (2012) Brain-derived neurotrophic factor and glucocorticoids: reciprocal influence on the central nervous system. *Neuroscience* 239: 157-172.
10. Zheng Y, Fan W, Zhang X, Dong E (2016) Gestational stress induces depressive-like and anxiety-like phenotypes through epigenetic regulation of BDNF expression in offspring hippocampus. *Epigenetic* 11(2): 150-162.
11. Pruunsild P, Kazantseva A, Aid T, Palm K (2007) Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Timmusk Genomics* 90(3): 397-406.

12. Keller S, Sarchiapone M, Zarrilli F, Videtic A, Ferraro A, et al. (2010) Increased BDNF promoter methylation in the Wernicke area of suicide subjects. *Arch Gen Psychiatry* 67(3): 258-267.
13. Martinowich K, Hattori D, Wu H, Fouse S, He F, et al. (2003) DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. *Science* 302(5646): 890-893.
14. Verdone L, Caserta M, Di Mauro E (2005) Role of histone acetylation in the control of gene expression. *Biochem Cell Biol* 83(3): 344-353.
15. Wu X, Chen PS, Dallas S, Wilson B, Block ML, et al. (2008) Histone deacetylase inhibitors up-regulate astrocyte GDNF and BDNF gene transcription and protect dopaminergic neurons. *Int J Neuropsychopharmacol* 11(8): 1123-1134.
16. Nagahara AH, Tuszynski MH (2011) Potential therapeutic uses of BDNF in neurological and psychiatric disorders. *Nat Rev Drug Discov* 10(3): 209-219.
17. Pittenger C, Duman RS (2008) Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. *Neuropsychopharmacology* 33(1): 88-109.
18. Björkholm C, Monteggia LM (2016) BDNF-a key transducer of antidepressant effects. *Neuropharmacology* 102: 72-79.



This work is licensed under Creative Commons Attribution 4.0 License
DOI: [10.19080/GJIDD.2017.01.555558](https://doi.org/10.19080/GJIDD.2017.01.555558)

**Your next submission with Juniper Publishers
will reach you the below assets**

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
(Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
<https://juniperpublishers.com/online-submission.php>