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Mini Review

BDNF: An Emerging Prognostic Marker in Bipolar Disorder: Mini Review

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Abstract

Brain Derived Neurotropin Factor (BDNF) is a well-known potential biomarker used in studying the neurophysiological mechanisms either as a diagnostic or prognostic marker. Current research is trying to explore its putative role in chronic psychiatric illness termed Bipolar Disorder (BD). BDNF has been found to be expressed in Bipolar Disorder at various time variants based on the disease severity.

Various studies have been conducted using differential approach to evaluate the pathophysiology behind the variation in the disease severity and its correlation with BDNF expression in the clinical outcome.

Due to an existence of substantial variations in the clinical outcome and heterogeneous pathophysiology of the disease, no research has come up with prompt conclusion in relevance to diagnostic or prognostication. The aim of this mini review is to highlight the core relationship of BDNF in BD using peripheral molecular marker and its role in the disease specificity in relation to the disease severity, its relevance in the future direction implementation.

ABBREVIATIONS

BDNF: Brain Derived Neurotropic Growth Factor; BD: Bipolar Disorder, PT: Physical Therapy, VEGF: Vascular Endothelial Growth Factor; IGF-1: Insulin Growth Factor, NT-3: Neurotrophin-1; GDNF: Glial Cell Line Derived Neurotropin Factor, NT: Neurotropin, GWAS: Genome Wide Association Studies; SNP: Single Nucleotide Polymorphism

INTRODUCTION

Bipolar Disorder (BD), one of the main psychological disorder exhibits with cognitive dysfunction in a variety of domains even during periods of clinical remission is known to cause the mortality of 9 – 15% amongst the patients by committed suicide [1,2]. Heterogeneity in the disease pathophysiology affects activity of daily living in person suffering from bipolar disorder.

Various biological and non-biological markers like neuroimaging, peripheral biomarkers, genetic markers have been studied to figure out the prompt conclusive evidence but are unable to predict the cause and difference in differentiating the complete diagnosis of Type I and Type II disorder [3]. Anti-inflammatory cascades which acts as a primary line of defense like cytokines, neurotropin, and endothelial growth factors VEGF, GDNF, NT-3, 4, IGF-1 studied have also come out with the mixed results.

Differential cognitive deficits assigned to functional, metabolic and structural changes especially in the pre frontal cortex, hippocampus and amygdala inducing changes in the mood disorders, activation of inflammatory cascade followed by blood brain barrier disruption, Glutamate receptors activation and its correlation with BDNF expression with differentiated pattern of cortical, neuroanatomical and functional response which is still inconclusive and is needed to be explored [4].

Profound existence of various molecular and imaging techniques have been conducted but are not able to reveal conclusive remarks with, yet still failed to differentiate the complete diagnosis and its differentiation [3].

BDNF, a well- known regulatory mediator in neuroplasticity is known to cross blood brain barrier, but its correlation with respect to disease severity in BD is conflicting because of its response at various disease time lines [20].

The aim of this mini review is to explore the role of BDNF in Bipolar Disorder to explore the correlation and the expression of various biological metabolites by using various pharmacological and non-pharmacological approaches and its relevance with respect to disease severity and outcome.

Role of BDNF at genetic level

Recent candidate gene and genome wide association studies (GWAS) have revealed the presence of 8 loci and its association with Bipolar Disorder and have concluded their heterogeneous expression as polygenic \ and its correlation in the genetic variation with a change in the environmental factors causing disease progression [5-8]. Imaging studies reveals that genetic load of the brain function affects task related recruitment with

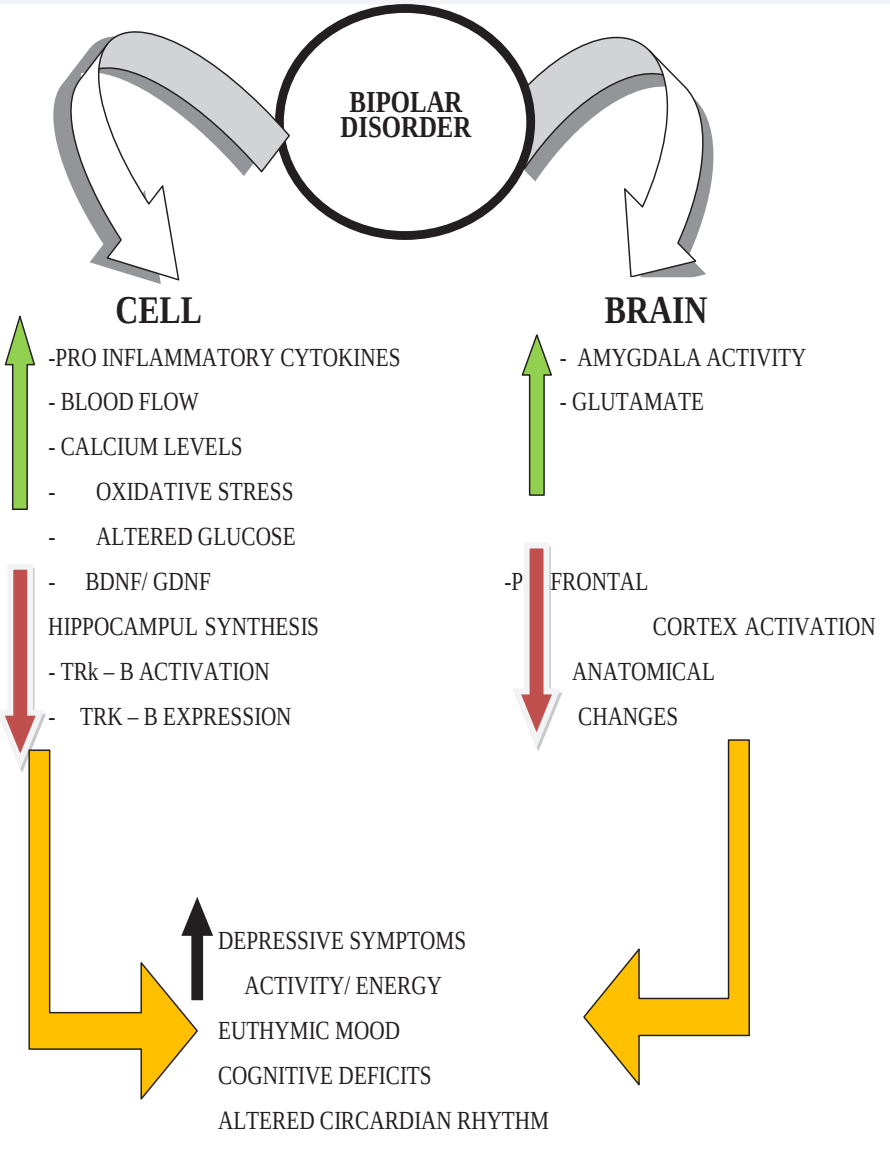

Figure 1 Integrated view of cellular and brain functionality in bipolar disorder and its clinical implementation (adapted).

the frontal areas more prominent. Imaging techniques using Diffusion Tensor Imaging coupling tract based spatial statistics have concluded with an involvement of dysmyelination in the pathogenesis of BD. ANK3 and ZNF804A polymorphism has shown the risk alleles with abnormal white matter integrity [9].

Interventional approach using antidepressant treatment response with both milnacipran and fluvoxamine has been found to be associated with genetic polymorphism BDNF G196A polymorphism and rs908867 [10, 11].

Role of peripheral biomarkers in BD

Various clinical studies have been conducted in ruling out the disease specific pathophysiology using peripheral molecular growth factors but, the development of a single, specific prognostic biomarker is still questionable due to the disease heterogeneity. BDNF is known to be highly expressed in the brain areas involved with regulation of cognition and emotion but on the other hand is negatively correlated with manic and depressive symptoms [12,13]. The expression level of BDNF has also been found to vary based on the disease severity with 100% sensitivity at early stages [14]. Study conducted in 2014 by Chatterji et al shows BDNF expression across mood variation and its relationship with cognitive functions for one year and has emphasized on long term follow up studies on BDNF in BD across changes in the mood state. Neuroimaging studies in using the genetic neuroimaging paradigms in BD patients have shown reduction in the hippocampal volume amongst the individuals carrying BDNF Val66Met allele as compared to the non-carriers which might help in ruling out the mechanistic insights for BD [15].

Role of BDNF in cognition

There is recent interest on role of BDNF in BD. Five year term clinical study conducted by Bauer et al., 2014, [16] concluded

that reduced levels of BDNF, peripheral inflammatory cytokines and oxidative stress is associated with bipolar disorder, depression, mania and poor cognitive performance which might be related to polymorphisms in inflammatory responsive genes. Genetic polymorphism Val66Met is found to be associated with neurocognition domain carrying the higher percentage under memory domain followed by an executive function domain, attention and concentration domain, yet unable to clarify the effect of Met allele [17]. Larger studies are required to detect the association between BDNF polymorphism, BDNF levels, brain abnormalities and cognition in BD [18].

Pharmkinetics and BDNF

Lithium Carbonate as mood stabilizers has proven in enhancement of BDNF gene polymorphism causing an up regulation of serum BDNF expression along with an improvement in the cognition in patients with BD. Other pharmacological treatments like valporic acid, fluoxetine, risperidone, lorazepam have shown an increase in the level of BDNF along with good prognosis in mood symptoms [19].

Role of BDNF in Exercise

Most studies revealed a high prevalence of metabolic syndrome in bipolar patients. Nonetheless, the relationship between metabolic syndrome and physical activity in this population is uncertain. Study done by Guan in 2010 [20] had shown higher rates of hyperglycemia, dyslipidemia, hypertension and metabolic syndrome in bipolar patients. Physical therapy acts a triggering response in the enhancement of hippocampal BDNF levels which not only stimulates neurogenesis but also acts as antidepressants. Supportive studies have revealed elevated BDNF level followed by change in the global wellbeing in the patients with BD ($p<0.05$) [17].

BDNF and Neuroplasticity

BDNF is highly expressed in the cerebral cortex and hippocampus, brain areas that are known to regulate complex brain functions such as memory and emotion. It has been demonstrated that BDNF plays a key role in long-term potentiation, and memory and is one of the most accepted models of learning and memory. Due to its LTP mechanism certain studies have hypothesized that abnormalities in the BDNF-signaling system might be implicated in the cognitive decline observed in BD, Major Depression and Schizophrenia, also act as an antidepressant and mood stabilizer and also has been found to be highly elevated in the cerebral cortex and Hippocampus post antidepressant regime [12].

Role of serum or Plasma BDNF in Bipolar

Serum BDNF supports the variation level based on mood level. It decreases at the beginning of mood episode and normalizes at Euthymia and again increases with response to treatment. Hence we might be able to say that BDNF may reflect dependent or independent marker of mood episodes in recovery. Compared to pro inflammatory markers levels, BDNF have shown the significant elevation in the BD and hence, therefore has been found to be negatively correlated with severity of manic and bipolar symptom [13].

Current status

Recent meta-analysis of genes and their association with cardio metabolic and mood disorders states a positive association of BDNF gene in mood disorders [21]. Transcription factor NF-kB and BDNF activated pathway in antidepressant action could also help in the development of antidepressant targeted molecule in future [22]. Peripheral serum BDNF concentrations were observed in affective BD and healthy controls. No significant changes were seen. Limitation lies in the potentiality of BDNF amongst the type of BD [23].

Published evidence shows that most of the BD patients lead a sedentary life, which has been associated with more medical comorbidities, poorer quality of life, worsening of functioning and more depressive symptoms in BD (Figure). The pathways of exercise causing neuronal plasticity in bipolar disorder are still unclear. The effects of exercise on BDNF levels in BD were poorly studied, despite its strong influence on brain functions. Aerobic exercise is known to elevate BDNF levels, associated with the chronic stress suppression, frequently found in bipolar patients [24].

CONCLUSION

Emerging role of BDNF as a mediator in the peripheral serum and plasma levels with supportive clinical studies has shown heterogeneous results. Statistically no significant change in the expression level on the basis of disease severity (cognitive functions) measurement has been observed.

BDNF might play as a marker of neuronal dysfunction, possibly mediating cognitive impairment in BD with pre-existing, pro-inflammatory and functional changes, which can be reversed by adequate established treatment targeting on neutralizing the events onset. Therefore, a deep understanding about the molecular determinants involved in BDNF-signaling cascades may provide a means for monitoring treatment response and disease progression as well as the development of novel agents for the treatment of BD.

There are certain comorbid factors responsible behind conflicting results with substantial variation in outcomes of BD and associations with BDNF. High variation in the mean expression of serum and plasma levels with Type I & II and severity of Bipolar has lead a major question on relation of BDNF in Bipolar recovery. Further limited studies have been conducted using therapeutic intervention for BD Symptoms and BDNF level. Various Interventional regimes along with some drugs (e.g. Resveratrol, Lithium) have shown positive correlation with the upregulation of anti-inflammatory BDNF expression with long term psychiatric treatment.

Non-pharmacological approach such as Physical therapy plays an effective role in reducing the depression and anxiety symptoms with a significant increase in the BDNF levels but no change in the peripheral BDNF levels in correlation to the affective states overall has been observed. Higher BDNF levels have been found to be associated with chronic BPD illness.

Evidence based prompt conclusion in evaluating role of BDNF as a multivariable diagnostic and prognostic marker using

subgroup analysis and its relation in substantially improving the quality of further research is warranted. More Longitudinal studies in studying the change in the magnitude of BDNF expression using large sample size with relevance to methodological issues in correlation with mood states are indeed needed.

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