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BDNF Protein and Anxiety Disorders

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Abstract

An increase in the prevalence of anxiety disorders (ADs), in individual, social, and economic losses, due to the high prevalence, chronicity, and disability of the individual besides the growth of multiple environmental stressors that are related to lifestyles, has been observed, which are all more harmful to one's health, and associated with genetic inheritances, among other factors. This reality may contribute to the risk of losing neurological functions, for example, cognition and memory, as well as to the development of more severe psychiatric disorders, with high levels of heritability and risk of suicide. Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophins in the human brain. Studies with neurotrophins allowed the introduction of one more hypothesis, called neurotrophic hypothesis, that would explain the physiopathology of mental disorders (MD), where deficits of neuroplasticity would occur and cause atrophy of certain regions of the brain (mainly cortical and the hippocampus), contributing to the development of mental disorders. Knowing the neurobiology of the ADs, as well as its relation to BDNF levels, may contribute to preventive actions regarding the said disorder in the general population. The objective of this chapter is to analyze the relation between levels of BDNF and AD.

Keywords: anxiety disorders, BDNF, mental disorders, neurobiology, neurotrophic theory

1. Introduction

Anxiety disorders (ADs) have become a significant public health issue worldwide, with individual, social, and economic losses, due to their high prevalence, chronic condition, and the individual's disability [1].

This reality may contribute to the risk of losing neurological functions, for example, cognition and memory, as well as to the development of more severe psychiatric disorders, with high levels of heritability and risk of suicide.

Anxious disorders like panic disorder (PD) with or without agoraphobia, generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias (SPs), and separation anxiety disorder are the most prevalent mental disorders (MD) and are associated with immense healthcare costs and a high burden of disease [1].

The word anxiety is derived from Latin *anxietatis* (desire, worry); *anxi* (contract, narrow); *anxietas* (narrowing); and *anxia* (craving, vulgar Latin) and is considered

a physiological manifestation when facing some type of danger (real or imaginary), with adaptability in forming responses to threatening stimuli, in order to foment the individual's safety and survival, leading to an unpleasant somatic and psychological experience [2].

When the severity, frequency, and persistence of the anxious symptoms become inconsistent with the presented circumstances, and the anxious reaction causes the behavior to be dysfunctional, then these are characterized as the anxiety disorders, which present high levels of morbidity, with a possible increase in mortality [1], since 6.1% of suicide cases are associated with AD [3].

Mental disorders were only recognized as a serious public health problem in 1996, in a study conducted by researchers from Harvard University and the World Health Organization (WHO), when out of the 10 main causes of disability worldwide, 5 were associated with mental disorders [4]. In the metropolitan region of São Paulo, 29.6% of individuals presented mental disorders with anxiety disorders being the most common, affecting 19.9% of the population, occurring twice as much in females [5]. Among the types of anxiety disorders, it is estimated that up to 5% of the population suffers from generalized anxiety disorder [1].

Generalized anxiety disorder, a type of AD, has high rates of comorbidity and stands out from mood disorders and other types of anxiety disorders. A recent study indicates that in 67% of the cases, GAD precedes (or is concomitant) depressive disorders (unipolar), 17% have bipolar disorder, and only 16% have no lifetime mood disorder and can be considered a risk factor. Furthermore, it is also associated with renal and cardiovascular diseases, rendering a more reserved prognosis in either situation [5, 6].

According to Bandelow and Michaelis, 33.7% of the world population suffers from anxiety disorders; however, it is difficult to find reliable evidence to demonstrate the evolution of this prevalence. Because the patients with anxiety disorders are mostly treated as outpatients, they probably receive less attention from clinical psychiatrists [1].

Epidemiological data from the National Comorbidity Survey suggest that 67% of the individual with GAD have depressive disorder (unipolar), 17% have bipolar disorder, and only 16% have no lifetime mood disorder [6].

ADs are highly comorbid with other mental problems like additive psychiatric disorders, leading to disability and impairment in quality of life [6].

Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophins in the human brain. Studies with neurotrophins allowed the introduction of one more hypothesis, called neurotrophic hypothesis, that would explain the physiopathology of mental disorders, where deficits of neuroplasticity would occur and cause atrophy of certain regions of the brain (mainly cortical and the hippocampus), contributing to the development of mental disorders [7]. Knowing the neurobiology of the AD, as well as its relation to BDNF levels, may contribute to preventative actions regarding the said disorder in the general population. The objective of this chapter is to analyze the relation between levels of BDNF and AD.

2. Methods

The two main types of review articles are commonly found in the scientific literature: systematic and narrative review of the literature. These two types of review articles have distinct characteristics and goals. The review of narrative or traditional literature, when compared to systematic review, presents a more open theme. This makes part of a specific and well-defined problem difficult and does not require a strict protocol for its preparation. The search for sources is not predetermined and

specific and is generally less comprehensive. Studies on BDNF protein and anxiety disorders are the focus of this narrative review of the literature [8].

3. Clinical picture

For the individual, anxiety is a form of protection, a defense mechanism, with an important role in the preservation of life, with symptoms that are somatic (breathing discomfort, tachycardia and precordial chest pain, excessive perspiration, increased peristalsis, epigastric pain, nausea, pallor or skin redness and flushing, paresthesia, chills, muscular changes, headache, dizziness, dry mouth, inability to remain seated or immobile for very long, etc.) and psychic (feeling of internal unrest, insomnia, feeling of oppression and discomfort, exaggerated worry, insecurity, irritability, undefined uneasiness, difficulty concentrating, depersonalization and derealization, among others). The effects of anxiety on thought, perception, and the learning process may be quite intense.

Anxiety tends to produce confusion and perspective distortions, not only in terms of time and space but also of people and the significance of events. These distortions may cause interference in learning, lowering concentration, reducing memory, and impairing the capability of association.

Pathological anxiety constitutes an inadequate response to a certain stimulus, as a result of its greater intensity and duration. Pathological anxiety paralyzes the individual, not allowing him/her to be prepared and to face threatening situations, differentiating itself from normal anxiety by the assessment of the intensity from the patient, his/her family, as well as from the physician [1]. The state of anxiety, its traits, and the ADs are differentiated by the degree of impairment and the duration of the anxiety symptoms on the individual. The state of anxiety is normally defined as a measure of acute or intermediate level of anxiety. Now, the anxiety trait is considered a tendency of the individual to produce an anxious response to environmental events. And, lastly, the anxiety disorders are the most severe, due to the excessive worry and fear and the greater duration and complexity of the anxious symptoms, which are dysfunctional and accompanied by impairment [8].

4. Classification

There are two types of international classification for anxiety disorders. According to the International Classification of Diseases, 10th edition, and more utilized in clinical psychiatry, there are seven main anxiety disorders: specific phobias, social phobia, panic disorder, generalized anxiety, obsessive-compulsive disorder, reaction to severe stress, and mixed anxiety-depressive disorder [9].

On the other hand, with the main goal of research purposes, the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-V), classifies the most important ADs as (1) generalized anxiety disorder, (2) panic disorder, (3) agoraphobia, (4) separation anxiety disorder, (5) social anxiety disorder or social phobia, (6) specific phobias, and (7) selective mutism [10].

5. Etiology

Biologically, the etiology of anxiety, with complex neurobiological mechanisms, according to the literature in neuroscience [2] seems to be related to the noradrenergic, GABAergic, and serotonergic systems and the frontal lobe and limbic

systems. The anxious patients tend to have increased sympathetic tone, causing delays in adapting to changes in the autonomic nervous system [1].

However, studies with neurotrophins gave rise to one more hypothesis that would explain the physiopathology of mental disorders in general, called the neurotrophic hypothesis, where deficits in the neuroplasticity would occur as well as cause atrophy of certain brain regions, mainly the cortex and hippocampus [7]. Nevertheless, there are gaps in the literature on whether the ADs take this explanation into consideration.

Increased activity in emotion-processing brain regions in patients who have an anxiety disorder could result from decreased inhibitory signaling by g-aminobutyric-acid (GABA) or increased excitatory neurotransmission by glutamate [11].

The connection between the sympathetic nervous system and the psyche is best seen in anxiety and especially in social phobia. The hippocampus may predominantly control the avoidance components of phobic anxiety by the serotonergic system, with other regions, such as the dorsomedial hypothalamus, controlling the escape components with the cholinergic system. Furthermore, the autonomic dysfunction and the overactivity of the sympathetic nervous system appear to induce many of the symptoms of anxiety, such as sweating, trembling, and heart racing [12].

There is increasing evidence that development and maturation of neuronal connectivity are critical components in the pathophysiology of essentially all neuropsychiatric disorders. As neurotrophins have been implicated in brain development and in particular in the plasticity and maturation of neuronal circuits, it is understandable that neurotrophins have been popular candidate genes for psychiatric diseases [13]. However, there are gaps in the literature on whether anxiety disorders include this explanation.

6. Genetic predisposition and precursor factors

More well-defined classifications tend to standardize the studies on ADs, contributing toward the biological evidence associated with these disorders, as well as making the “phenotypic complexity” a challenge to genetic psychiatry [14].

Upon including twins and their biological families, a meta-analysis indicated a heritability between 30 and 40% for anxiety disorders [15]. Now, a longitudinal study estimated a heritability ranging from 72 to 89%. The results of this study also showed a “developmental dynamic” pattern, for, over time, there is a mitigation of the genetic influence as a risk factor for anxious and depressive symptoms [16], leading one to ponder over the influence of protective factors in the prognosis of ADs.

7. Environmental factors

Individuals with AD present attentional bias to the threatening stimulus, which increases the vulnerability to stress, considering these “complex disorders,” due to being influenced by multiple factors that flee from what are called “deterministic effects” of the genes, therefore making them liable to modulation by interference [2].

According to an experimental study with laboratory animals, stress by social subjugation is able to foster hyperalgesia with a decrease in the BDNF levels; this condition is more evident in “susceptible” subjects rather than in “resilient” ones [17], reinforcing the complex multifactorial theory that the neurobiological response to stress is not only genetic but also environmental.

BDNF exons decrease markedly after high corticosterone levels. BDNF levels are controlled by epigenetic mechanisms with extinction assisted by partial NMDA receptor agonists (e.g., D-cycloserine) and histone deacetylase inhibitors [18].

Environmental factors, via epigenetic factors, control the alterations of BDNF gene expression, especially when young. Harmful environmental influences while growing can cause a decrease in BDNF expression in adulthood, in addition to the serotonin transporter and FKBP5, leading to problems in patient response to drug and behavior therapies [19, 20].

Problems during youth lead to DNA methylation of BDNF promoter IV and a decrease in prefrontal cortex total BDNF mRNA [21]. However, after exercise and a healthy environment, total BDNF mRNA in the hippocampus increases due to increases in histone acetylation at promoter IV or decreases in its methylation [19].

In response to fear conditioning, the levels of BDNF exon mRNAs change markedly. As an example, after fear conditioning using light shock, exon I and III mRNA levels increase markedly, different from the exons II and IV which remain constant [18].

Several psychological factors have been associated with increased risk for anxiety disorders. Among the most intensively researched has been the concept of anxiety sensitivity (AS). AS has been defined as the individual response to physiological alterations associated with anxiety and fear. Patients with anxiety disorders have exaggerated psychological reactions that are reflective of misinterpretation of bodily cues such that the patient misperceives these sensations inappropriately as being harmful and dangerous, leading in a circular fashion to increased anxiety and fear. AS is associated with a selective cognitive bias toward threat. AS predicts the frequency and intensity of panic attacks [21].

The above section identifies several possible mediators of the psychobiological response to extreme stress and how each may contribute, alone or through functional interactions, to resilience or vulnerability to anxiety disorders. One prediction is that individuals in the highest quartile for measures of HPA axis, CRH, LC-NE, and estrogen activity and the lowest quartile for DHEA, NPY, galanin, testosterone, and 5-HT_{1A} receptor and benzodiazepine receptor function will have an increased risk for anxiety disorders. Other mediators that can be included for the characterization of the vulnerable or resilient profile are glutamate and neurotrophic factors, such as brain-derived neurotrophic factor, and neuropeptides, such as substance P and cholecystokinin [21].

8. Pharmacologic and non-pharmacologic treatments

Patients should receive “psychoeducation” about their diagnosis, the possible etiology, and the mechanisms of action of the available treatment approaches. The treatment plan should include psychotherapy, pharmacotherapy, and other interventions, which should be chosen after careful consideration of individual factors, e.g., the patient’s preference, the patient’s history with previous treatment attempts, illness severity, comorbidities such as personality disorders, suicidality, local availability of treatment methods, wait time for psychotherapy appointments, costs, and other factors [22].

For all types of anxiety disorder, cognitive-behavioral therapy is the type of psychotherapy for which there is the strongest evidence and which receives the highest-level recommendation [23].

Cognitive-behavioral therapy has been found to have a moderately strong beneficial effect against all types of anxiety disorder compared to a placebo drug

(Cohen's $d = 0.57$); the same is true of pharmacotherapy (e.g., sertraline, $d = 0.54$; venlafaxine, $d = 0.50$) [24, 25].

It is important to highlight that no articles were found that evaluated the effectiveness of Jungian and integrative psychotherapy.

Pharmacological treatments for anxiety disorders have become more tolerable, available, and numerous over the past half century. At the same time, research has yielded a vastly improved understanding of the neurobiological and physiological mechanisms involved in chronic anxiety and stress responses, suggesting new approaches to the treatment of anxiety disorders [26].

Numerous neurotransmitters play a role in normal states and in pathological anxiety states. Each of these systems is a potential target for pharmacological intervention, but relatively few classes of medications are used in clinical practice for the treatment of anxiety [27].

Due to their positive benefit/risk balance, selective serotonin reuptake inhibitors (SSRIs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) are recommended as first-line drugs. Patients should be informed that the onset of the anxiolytic effect of these antidepressants has a latency of 2–4 weeks (in some cases up to 6 weeks) [22].

We should continue to test alternative therapies for treating and preventing anxiety disorders and to help patients whose anxiety is resistant to conventional treatments; also, we need to consider the patient's feelings about mental illness and address their responses early in treatment. All of these measures will enhance the care of patients with anxiety [27].

9. Brain-derived neurotrophic factor

BDNF is one of the most abundant neurotrophins in the human brain, identified in 1982 by Yves Barde and Hans [17]. It is found in two distinct forms, pro-BDNF and the mature BDNF, which have antagonistic functions. The pro-BDNF is the precursor protein that is synthesized and undergoes cleavage to produce its mature form, BDNF, presenting greater physiological activity in the central nervous system [28, 29].

The pro-BDNF has high affinity to the p75 neurotrophin receptor, triggering pro-apoptotic effects and anti-plasticity [17]. On the other hand, the main receptor where the binding of the mature BDNF occurs is the tropomyosin-related kinase receptor type B (TrkB), distributed in the cortex, hippocampus, multiple bridged nuclei, and the spinal cord. When activated, this receptor causes a series of intracellular cascades that are responsible for growth, survival, and neural differentiation [15, 18].

Studies on neurotrophins allowed the release of one more hypothesis that would explain the physiopathology of mental disorders, called neurotrophic hypothesis, where deficits of neuroplasticity would occur and cause atrophy of certain regions of the brain (mainly cortical and the hippocampus), contributing to the development of mental disorders [7].

The main origin of these alterations is a decrease in the BDNF expression, caused by stress [19]. However, the association between the BDNF serum levels and mental disorders has yet to be completely clarified. There is evidence that the BDNF serum levels are reduced in patients with mental disorders, regardless of the diagnosis [7].

A meta-analysis that studied the peripheral values of BDNF in different mental disorders with the hypothesis of proving its nonspecificity obtained results pointing

to a valid reduction of BDNF levels in acute cases as well as in other periods of treatment (i.e., with symptom remission and in the presence of residual symptoms), in comparing groups of patients with healthy controls [30].

It is known that in a severe and prolonged state of stress, with sustained increase of glucocorticoid (GC) hormone levels due to the activation of the HPA axis, neuroplastic changes occur, as well as a decrease in the BDNF hippocampal levels. Thus, a persistence and intensity of stressors may produce hippocampal dysfunction, causing a decline in the inhibitory control that the hippocampus exerts over the HPA axis [31].

The BDNF has become an important tool in understanding cognitive deficits, especially those related to memory loss. One of the reasons to use this neurotrophin in these studies is its participation not only in processes of differentiation, neuronal survival, and synaptic plasticity but also in processes involving learning and memory [32].

The BDNF also enables the strengthening of connections between neurons (synapsis), mainly in the hippocampus, cortex, and basal forebrain—important regions for learning, maintaining memory, and higher thinking.

10. Changes in BDNF levels in psychiatric illnesses

The BDNF may cause neurogenesis mainly in the hippocampal region of adult brains. At the same time, in patients who suffer from psychiatric illnesses, a smaller hippocampus has been identified, associated with a decrease in BDNF plasma levels, than healthy individuals. Clarifying the exact mechanism of the action of BDNF will permit a better understanding of the cognitive deficits.

BDNF crosses the blood-brain barrier, possibly through its dosage in peripheral blood, whose serum levels correlate with the levels in the central nervous system [7]. However, this has not become a clinical reality, despite the biological plausibility, due to great heterogeneity between the studies, which presented low power of detection of differences and biases of publication, and influence of confounding variables (physical exercise, smoking, body mass index, laboratory techniques that lack standardization, kits that do not distinguish between pro-BDNF and mature BDNF). The high number of variations limits comparisons between the studies [7].

The regular practice of physical activity has been shown to be a prophylactic and therapeutic intervention for several dysfunctions, such as stress, by way of the increase in adaptive responses of the HPA axis, improvement of adaptive response to stress, and a decrease in anxiety.

It is believed that identifying variations of the epigenetic pattern of DNA and of the gene expression of rats exposed to stress, as well as rat practitioners and non-practitioners of physical activity, may reveal additional data that could be extrapolated to the human population, regarding the importance of physical activity in illness prevention [24].

The interest in knowing the molecular aspects of the effect of physical activity and/or exercise is evident; however, little is known yet regarding the epigenetic changes resulting from physical exercise [24].

Thus, several studies have been conducted to clarify the connection between the regular practice of physical exercise and the increased concentration of BDNF, making it necessary to shed light on the role of this gene in suppressing the harmful effects resulting from stressful situations [24].

11. Conclusion

There is evidence that it is important to study aspects in common of the neurobiology of anxiety disorders, and its relation to the BDNF protein, to obtain preventive measures in mental health.

Recent clinical trials, in animals and humans, increasingly seek an association between different spectra of mental disorders and BDNF levels and their subforms, in different collection sites, leading to the question of the possibility of using it as a biomarker of susceptibility to anxious disorders. The early titration and serialization of BDNF and subforms in families with a high probability of ED heritability are shown as a future perspective for primary and integrated actions in mental health, with modulation of gene expression, using the “dynamic developmental” pattern for a reduction of future medication for susceptible individuals, as well as the possibility of discovering acute illnesses early, with a positive change in the history of the disease and a reduction in social economic losses. From this perspective, we highlight the importance of further studies on the neurobiology of anxiety disorders, on BDNF protein and its physiology, and the association between both for preventive measures in mental health.

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