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Review Article

BDNF, A Focus to Major Depression

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Abstract: Major depressive disorder is characterized, among other symptoms, by depressed mood and anhedonia associated with a high rate of suicidal ideation. In recent years, research has shown reduced expression of the brain-derived neurotrophic factor (BDNF) in limbic areas of individuals with depression. This reduction of BDNF is reversed by antidepressants in animal models of stress. Stress is one of the main triggers of mood disorders such as depression. Also, administration of BDNF increases the number of serotonergic fibers and serotonergic innervation, indicating an increase of serotonin in the synaptic cleft by this neurotrophin. Thus, BDNF appears to be one of the targets of antidepressant drugs for the increase of monoamines and remission of symptoms of major depression. The purpose of this review was to show the evidence that indicates BDNF as a molecular substrate for vulnerability to depression and the response of this substrate to the antidepressants.

Keywords: Major depressive disorder, Brain-derived neurotrophic factor (BDNF), Serotonin, Antidepressive agents.

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1. Introduction

Major depressive disorder is one of the most significant psychiatric disorders for public health worldwide. And it is predicted that this pathology, which is associated with morbidity and mortality **[1-3]**, will become the first leading cause of disability and disease spending in developed countries until 2030 [4].

Major depression is not yet the target of pharmacological treatment that benefits all patients and therapeutic responses require weeks of treatment [5]. In addition, the pathophysiology of major depression is not well understood. However, new studies have been done in search of other treatments and mechanisms for this disease. One of the molecules that has been described to be part of one of these mechanisms is the Brain-derived neurotrophic factor (BDNF) [6].

BDNF is one of the members of the neurotrophin family that among other functions promotes the maintenance and survival of neuronal cells [7,8]. And, this neurotrophin is reduced in depressed patients and in the post-mortem brain of victims of depression [9]. In addition, the data indicate that BDNF is intensely reduced in stress conditions, which is one of the main triggers of depression [9-11] and, in limbic areas such as hippocampus. On the contrary, its expression is increased with the use of antidepressive agents [12-15].

The purpose of this review was to show the evidence that indicates BDNF as a molecular substrate for vulnerability to depression and the response of this substrate to antidepressants.

2. Major depressive disorder

Major depression, also known as unipolar depression [16] is one of the most common psychiatric disorders [17]. Its etiology is undefined, but there are several clues that it can be triggered by several factors. These include genetic factors [4,18], disease such as cancers [19], recent stressful events such as divorce and grief [20,21] or remote as childhood

adversity - for example, sexual and physical abuse, neglect in food care and supportive as well as divorce itself and also grief [21,22]. The diagnosis of major depression is subjective and is made according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V). The criteria indicate that 5 out of 9 symptoms to be investigated should be present for a period of 2 weeks in a patient with this condition [23,24,25]. These symptoms are depressed mood, anhedonia, changes in appetite and weight loss, frequent insomnia, agitation or retardation, fatigue or loss of energy, feeling of worthlessness and excessive guilt. In addition, decreased ability to think, concentrate or decide [4,25,26,27]. In addition to the DSM-V, there is also another form of diagnosis of the severity of depression, which is the Hamilton depression scale. This scale is highly validated for this purpose [3,26,27].

Major depression is known to be more prevalent in women and Caucasians [17]. But its pathophysiology is not completely understood [18]. However, it is well established that depression is implicated in a reduction of monoamines dopamine [28], noradrenaline [29] and in particular serotonin [30]. Clinical observation of the effects of antihypertensive reserpine led to the "monoaminergic hypothesis", which consists in reducing these monoamines in depressed patients [31].

These monoaminergic neurotransmitters dopamine, 5-HT and norepinephrine are responsible for modulating emotional stimuli such as mood [32,33]. From the theory of monoamines began the development of drugs that would increase the availability of monoamines, especially 5-HT [31]. The decisive mechanisms by which antidepressive agents efficacy occurs are not yet well established [6]. But evidence indicates that one of the effects of antidepressant drugs is to increase monoamine levels in the synaptic cleft [5,31].

Treatment of major depression, which is associated with a high rate of suicidal ideation, resulting in about 15% death [3], includes electroconvulsive therapy, administration of psychoactive drugs such as lithium [34,35], tricyclic antidepressants, monoamine oxidase inhibitors (MAO), selective serotonin reuptake inhibitors (SSRIs) [36,37] and the use of certain substances such as L-tryptophan and L-5-hydroxytryptophan, which are present in some foods. Tryptophan is the precursor of serotonin (5-HT) [38]. 5-HT as well as norepinephrine are the main target monoamines of antidepressant drugs [39]. And, monoamine-based treatment remains the most recommended therapy for depression. But due to the clinical efficacy of antidepressant drugs arising after weeks of treatment or majority of patients failing to achieve complete remission, and as one third of them fail to respond to current drugs, new therapeutic targets are required for the clinical treatment of major depression disease [5].

3. Brain-derived neurotrophic factor

BDNF is one of the member of the neurotrophin family, which is also constituted of nerve growth factors (NGF), neurotrophin 3 (NT-3), and NT-4/5. They are proteins synthesized from a pro-protein, which cleaves to form mature neurotrophins and that these pro-proteins are about 32 kDa [40]. Mature BDNF weighs 14 kDa and is a 119-129 amino acid homodimeric [41]. After being translated into the rough endoplasmic reticulum, pro-BDNF is cleaved forming mature BDNF and transported to the Golgi complex. It is suggested that cleavage of pro-neurotrophins is mediated by proteases such as convertases and furin. These are found in the Golgi complex and in the vesicles themselves containing BDNF [41,42]. Evidence indicates that neurotrophins including BDNF are addressed from the Golgi complex to vesicles from which they are secreted (Figure 1) [41].

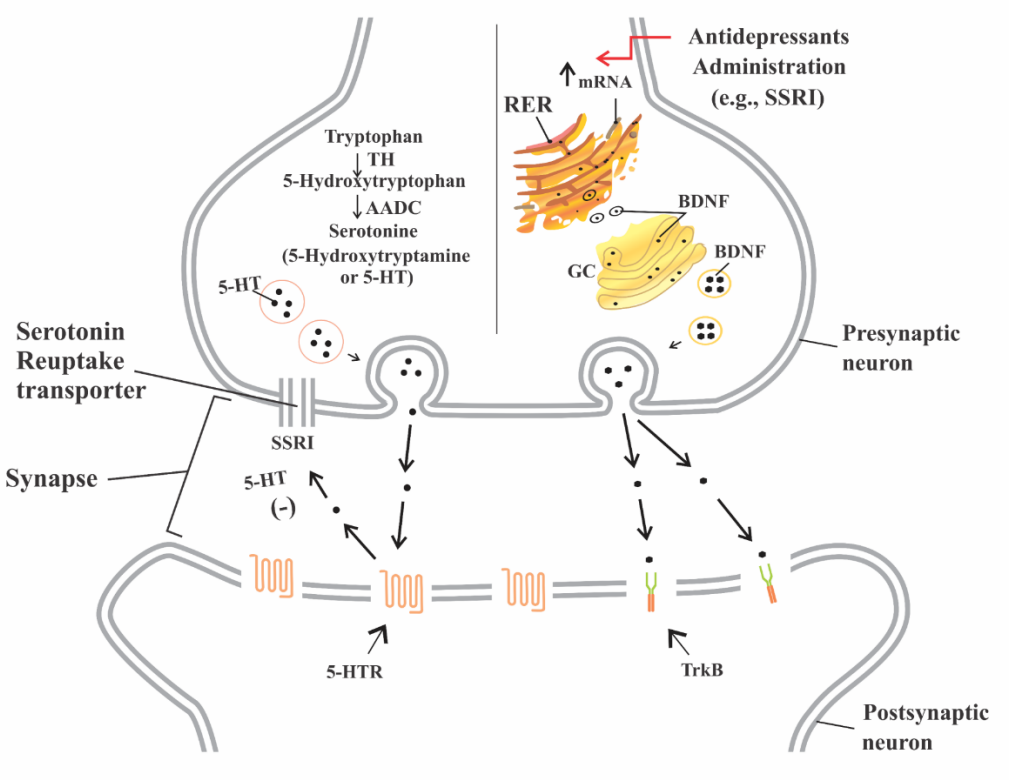

Figure 1. Synthesis of BDNF by administration of antidepressants. Antidepressant drugs, in addition to promoting an increase in serotonin activity in the synaptic cleft, also promote the synthesis and consequent release of BDNF by the cell, which culminates in several cellular changes triggering the improvement or remission of depressive symptoms. **TH:** tryptophan hydroxylase; **AADC:** aromatic L-amino acid decarboxylase; **5-HT:** 5-hydroxytryptamine or serotonin; **SSRI:** selective serotonin reuptake inhibitors; **5-HTR:** 5-hidroxy-triptamin receptor; **TrkB:** tropomyosin type B kinase activity; **BDNF:** brain-derived neurothrophic factor; **GC:** golgi complex; **RER:** rough endoplasmic reticulum; **mRNA:** messenger ribonucleic acid.

BDNF which is a neuropeptide synthesized and released by neuronal and muscle cells [41,43,44] as well as by glial cells, astrocytes, microglia and oligodendrocytes[45] can be secreted by a constitutive pathway, in which the vesicular content has its activity-dependent release and, by another pathway whose exocytosis is dependent on Ca^{2+} [41]. According to Lessmann and Brigadski (2009), after the release of BDNF, it can be re-endocytosed and vesiculated, restarting the secretion process.

In addition, pro-BDNF can also be released and perform functions distinct from mature BDNF. For example, while pro-BDNF has the function of initiating apoptosis, BDNF is involved in the process of neurogenesis. However, there are reports that mature BDNF is the main form to be released. On the contrary, it was also shown that half of the BDNF released in hippocampal cultures was pro-BDNF [41].

O BDNF is involved with cell growth, differentiation, maintenance and survival. In addition, it plays an important role in the synaptic function of the peripheral and central nervous system and synaptic plasticity during development and adulthood [7,25,46,47]. Several studies indicate that BDNF also plays an important role in depression and in the mechanisms of antidepressants [6,48]. It has been described as a probable biomarker of diagnostic for depression [49]. This neurotrophin was purified in 1982, from the pig brain, as a cell survival promoting factor for sensory neurons [3,42].

To perform its functions, NGF binds to the receptor with tropomyosin type A kinase activity (TrkA), NT-3 binds to the TrkC receptor, and NT-4/5 and BDNF have TrkB as their

receptor [46]. But NT-4/5 binds with low affinity to TrkB [5] whereas BDNF has high affinity for its tyrosine kinase receptor (Figure 2) [49].

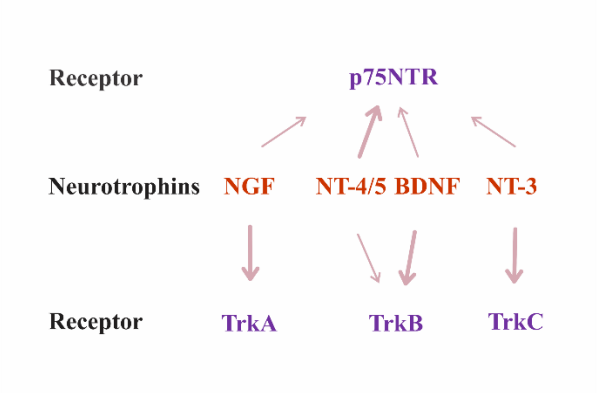

Figure 2. Neurotrophins family and their receptors. In performing its functions, NGF binds to the receptor with tropomyosin type A kinase activity (TrkA), NT-3 binds to the TrkC receptor, and NT-4/5 and BDNF have TrkB as their receptor. But NT-4/5 binds with low affinity to TrkB, whereas BDNF has high affinity for this receptor. Neurotrophins also have one receptor in common, the low affinity nerve growth factor receptor or the p75 neurotrophin receptor (p75NTR), which regulates the same intracellular pathways. **NGF:** nerve growth factors; **NT-3, 4/5:** neurotrophin 3, 4 and 5; **BDNF:** brain-derived neurothrophic factor.

The TrkB receptor contains intrinsic tyrosine kinase activity located in an intracellular domain [50]. When activated, this receptor is dimerized and autophosphorylated and thus appears to regulate the signaling of several pathways. These include the mitogen-activated protein kinase (MAPKs), extracellular signal-regulated protein kinase (ERK2), phospholipase Cy (PLCy), and phosphatidylinositol-3-kinase (PI3K) pathways [51]. Neurotrophins also have one receptor in common, the low affinity nerve growth factor receptor or the p75 neurotrophin receptor (p75NTR), which regulates the same pathways [51,52]. Pro-BDNF binds preferentially to this receptor more than TrkB [53].

Due to the negligible expression of BDNF mRNA in postsynaptic neurons, it has been indicated that this protein comes from presynaptic neurons [41]. According to some authors, BDNF vesicles are specifically located in the presynaptic terminals [54] and BDNF secretion has been demonstrated in both axons and dendrites of neurons in the hippocampus [55,56].

There are reports that BDNF is one of the most widely expressed neurotrophins in the brain [9] with special abundance in the cerebral cortex and hippocampus [17,57]. It is also present in the prefrontal cortex [7,9], cerebellum [4], amygdala [58-60] and hypothalamus [4,58]. These areas are involved with the pathophysiology of depression [61-64].

In addition, it has been shown that BDNF mRNA is expressed in several other parts of the body such as the heart, lung, kidney, testicles [65] and in the serum of patients with major depression [57,66]. BDNF reduction has been implicated with the pathophysiology of this disease [10,24,48].

Levels of mature BDNF can be measured in serum, plasma or whole blood and in blood cells, the platelets [57,67]. But although BDNF is expressed in these and most tissues of the body, and at relatively high levels, it can come from the brain [57]. Regarding serum BDNF, it can be detected by means of a simple test and the simplicity of this test in investigating BDNF levels is one of the factors that would indicate this as a clinically useful molecule to diagnose in individuals with major depression [3,57].

4. Brain-derived neurotrophic factor and Major Depressive disorder

Research has shown several evidence implying the involvement of BDNF in the pathophysiology of major depressive disorder. Studies have indicated that there is a reduction in serum BDNF levels in patients diagnosed with depression compared to control and that these levels are normalized after treatment with antidepressant drugs [54,68], electroconvulsive therapy [69,70] and physical activity [71,72], which is indicated for depressive patients [25].

Also, the data has shown that there is a reduction of BDNF in the prefrontal cortex, amygdala and hippocampus of patients with this patology [7,73,74] as well as in postmortem brain of victims of suicide and depression [9]. In addition, it has been observed that stress, one of the main triggers of mood disorders such as anxiety and depression [75,76] induces a decrease in BDNF [10,77]. In line with these data, exposure to stress factors, which is one of the most used approaches to model depression in experimental animals, promoted a decrease in the levels of BDNF and TrkB expression in the hippocampus, cortex and amygdala of animal models of stress such as social defeat, containment stress (immobilization) and maternal deprivation [75,78-80].

Treatment with SSRI antidepressants has been shown to increase the expression of the BDNF gene in the hippocampus of animal models of stress [13,81,82] and, BDNF decreased may be one of the causes of atrophy of neurons vulnerable to stress in the hippocampus [62]. In this context, the SSRI was able to reverse the atrophy of this brain area [83] probably by a neurogenesis-dependent mechanism [84]. It has also been observed in normal animals that administration of tricyclic antidepressants including imipramine and desipramine, the MAO inhibitor, tranylcypromine and SSRIs such as fluoxetine, paroxetine and sertraline increased BDNF levels in the rat brain [12,13,36, 81,85]. However, there are studies demonstrating that the BDNF mRNA levels decrease shortly after antidepressants administration [86,87].

The effects of antidepressants in BDNF knockout mice have also been observed. In addition to a blockage [88] or attenuation [74] of the effects of these substances, these animals exhibited similar behavior to anxiety and depression [89]. In another works, behavior similar to anxiety and depression was shown in heterozygous knockout mice for BDNF (BDNF +/-) after exposure to stress [6,90]. Furthermore, BDNF +/- mice exhibit resistance to the effects of antidepressants in the forced swim test [88] which, is one of the most well-established tests used for screening antidepressants [39]. However, Lindholm and Castren (2014) point out that BDNF +/- mice, which were exposed to tail suspension and forced swimming tests, do not exhibit depression-like behavior [89].

Cognitive, attention and memory deficits are related by depressed patients and, a deficiency in long-term potentiation (LTP) appears to be correlated with a change in the BDNF level [91,92]. According to Patterson et al. (1996), heterozygous knockout and knockout mice for BDNF showed suppression of LTP [92]. Also, knockout mice for TrkB subjected to trials of spatial memory task demonstrated decreased learning and a reduction in hippocampal LTP [93]. And, Martínez et al. (1998) report that a reduction in the number of synaptic structures was indicated in the hippocampus of TrkB knockout mice [94].

Also, the effects of BDNF administration in animals subjected to the forced swim test were observed. Hoshaw et al. (2005) indicated that BDNF, administered intracerebroventricular, unlike pharmacological antidepressants, which produce an acute effect in the forced swim test, induces a behavior similar to antidepressant (reduced immobility and increased swimming), which persists about 6 days after treatment [95]. In addition, it has been shown that both the chronic administration of BDNF peripherally, through the subcutaneous implantation of osmotic pumps [96] and centrally, through the administration of BDNF directly in the hippocampus and midbrain [89,97,98] promote behaviors similar to antidepressants in animal models of depression, such as the learned helplessness test, inescapable shock and forced swimming test.

In contrast, the infusion of BDNF to the nucleus accumbens (NAcc), an area of the brain involved in reward and hedonic behavior, increased shorter latency to immobility in the forced swim test, that is, depression-like behavior [25]. Also, direct injection of BDNF into the ventral tegmental area, which contains bodies of dopaminergic neurons, promoted depression-like behavior and blockade of BDNF signaling in the NAcc [99-101].

The NAcc can be considered as a receptor area for dopaminergic cell projections located in the ventral tegmental area [99], which acts as a convergence site for stimuli from the amygdala, hippocampus, anterior cingulate area and part of the temporal lobe. From this nucleus, efferents depart for the hypothalamus, anterior cingulate area and frontal lobes. Due to its afferent and efferent connections, NAcc plays a relevant role in the regulation of emotion, motivation and cognition [99,102-104].

In addition, glutamatergic projections emerge from the medial prefrontal cortex, basolateral amygdala, and hippocampal formation, important regions for the emotional process and behavioral regulation and converge to the NAcc neurons, indicating that the NAcc can trigger an adequate emotional behavior [105].

Duman et al. (2007) point out that BDNF is implicated in antidepressant mechanisms [6]. In this context, there is an increase in the phosphorylation of TrkB in the hippocampus and cortex of rodents after the administration of antidepressants and this occurs in a period of hours [34,88]. Furthermore, after chronic treatment with antidepressants, an increase in the levels of BDNF and TrkB mRNA was detected in the cerebellum of patients with depression [106]. In addition, BDNF activity increases the number of serotonergic fibers [50] and serotonergic innervation [88] indicating an increase in the serotonin activity in the synaptic cleft by this neurotrophin.

The vast majority of drugs after the initial administration reach an initial target and thus a consequent acute effect. Antidepressant drugs, on the other hand, require continued administration for several weeks for the therapeutic effect to appear. Probably, this is due to the fact that after administration of antidepressants, they reach an initial target, such as an increase of monoamines, but also other indirect targets, for example, increase of the BDNF, TrkB and synapses plasticity for the remission of patients symptoms to occur [50,88], thus determining long-term adaptive effects (Figure 3).

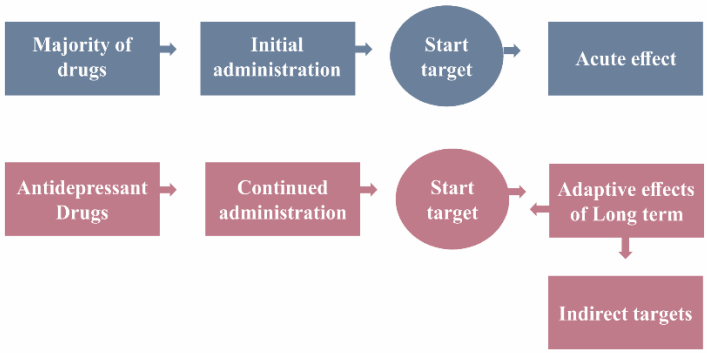

Figure 3. Antidepressant drugs, unlike other drugs, have indirect targets. The vast majority of drugs after the initial administration reach an initial target and thus a consequent acute effect. Antidepressant drugs, on the other hand, require continued administration for several weeks for the therapeutic effect to appear. This is due to the fact that after administration of antidepressants, they reach an initial target, such as an increase of monoamines, but also other indirect targets, for example, increase in BDNF, TrkB and synapses plasticity for the remission of patients symptoms to occur, thus determining long-term adaptive effects.

The TrkB receptor mediates the growth and plasticity of serotonergic neurons by BDNF [33]. 5-HT and BDNF are two signaling systems that perform regulatory functions in many neuronal functions, including survival, neurogenesis and synaptic plasticity [101]. And there are reports that the administration of SSRI antidepressants agents increases the expression of the BDNF gene [12,13,36,82,85,107]. And both acute and chronic administration of antidepressants promotes activation of TrkB [107].

In addition, it has been reported that the effects of antidepressants on TrkB and BDNF also imply their action on 5-HT. BDNF signaling increases the number of serotonergic fibers [50] and serotonergic innervation [88] and this suggests a consequent increase of activity of this monoamine in the synaptic cleft culminating in the improvement of the clinical condition of patients in particular with regard to symptoms of depressed mood and anhedonia.

5. Conclusion

The review results demonstrate the essential role of BDNF in the pathophysiology of depression and the increase in its levels in the face of different classes of antidepressants. All this indicates that the cause of depression is far from being just a deficiency of central monoamines and antidepressant drugs have another target in addition to monoamines which is BDNF. In addition, it appears to determine the long-term adaptive effects of these drugs. For this reason, since 30% of patients are unable to respond to current drugs and 70% do not reach complete remission [25], knowledge of the mechanisms that involve the pathophysiology of depression is important for the search for new pharmacological targets and most effective drugs for the treatment of this disease.

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