INTRODUCTION

Major depressive disorder (MDD), a common disease that severely restricts psychosocial functioning and affects normal life, is one of the leading contributors to the global disease burden and is expected to become the leading cause of disability worldwide by 2030. The cardinal symptoms of MDD include depressed mood, anhedonia, irritability, difficulty concentrating, disrupted sleep, appetite and cognition and a tendency to commit suicide.1,2,3 Approximately 264 million people globally are affected by a depressive disorder. The number of cases of depression increased by almost 50% from 1990 to 2017, so this condition has been regarded as an important public health problem.4,5 The development and course of major depression disorder (MDD) are likely to be mediated by a complex interaction between genetic and environmental factors, and the associated heterogeneity of the disease makes it difficult to develop effective treatments.2

At the molecular level, depression is associated with atrophy and loss of nerve cells in the brain, particularly the hippocampus and prefrontal cortex.1,4 As growth factors, neurotrophins (NTs) promote the survival of nerve cells and induce differentiation of mature neurons from progenitor cells and have been advanced as critical modulators of depression.1,6 NTs, comprised of a family of structurally and functionally similar proteins, are critical to neuronal survival, synaptic function, neurotransmitter release and elicit plasticity and growth of axons within the adult central and peripheral nervous system. Accumulating studies have shown that NTs, especially mature NTs, are correlated with depression.1

NT-3 may exert antidepressant actions through its effects on monoamine neurotransmitters (serotonin and noradrenaline) and by regulating synaptic plasticity, neurogenesis, brain-derived neurotrophic factor signaling, and the hypothalamic-pituitary-adrenal (HPA) axis.5

Based on those mentioned above, this literature review aims to establish the role of Neurotropin-3 as the pharmacological target for handling depression.

Neuroanatomical Evidence

Four brain regions and neurocircuits are involved in depression, namely the amygdala, hippocampus, prefrontal cortex, and ventral striatum.

Amygdala

The amygdala is an integral part of the limbic system implicated in cognitive and emotional processing, particularly fear and anxiety. This implies that this
structure has a central role in regulating emotion and, consequently, mood-related pathology. Although volumetric magnetic resonance imaging (MRI) studies so far revealed contrasting results, with studies showing either an increase or a decrease in amygdalar volume in depressed patients, most of the functional MRI (fMRI) studies showed an increased activity of the amygdala in depressed patients during encoding of negative but not neutral or positive stimuli.

Hippocampus
The hippocampus is also a major structure within the limbic system, which is highly vulnerable to stress and other environmental factors. This region is critical in diverse cognitive processes and the regulation of emotions. MRI analyses revealed reduced hippocampal volume in patients suffering from first episodes and recurrent depression. Besides, a correlation between volume reductions and the total duration of major depression has been reported more than 20 years ago. These results have been further confirmed by several meta-analyses that show, e.g., a decreased hippocampal volume only in MDD patients having suffered from depression for 2 years or who had more than one episode or evidencing deficit in hippocampal volume deficits in recurrent but not in first-episode MDD patients although this last study gave rise to some debate. It has also been proposed that reductions in hippocampal volume may not antedate illness onset but that hippocampal volume may decrease most in the early years after illness onset.

Prefrontal Cortex
The PFC is functionally connected with several brain structures for processing sensory input and mediating executive motor functions. The ventromedial PFC and the orbitofrontal cortex are involved in the cognitive processing of emotional stimuli originating from the limbic system (e.g., amygdala, ventral striatum, hippocampus, and hypothalamus). They are especially engaged in memory consolidation and retrieval. As such, the PFC plays a major role in regulating the appropriate emotional response, such as fear or anxiety. Moreover, the PFC has been associated with decision-making, personality expression, social behavior, and hedonic responses. Neuroimaging studies showed a reduction in the size of multiple areas of the PFC in subjects diagnosed with MDD. In line with those studies, post-mortem brain analysis of depressed patients revealed reduced neural cell size, neural and glial cell densities, and synapse number in the dorsolateral and subgenual PFC. The PFC is strongly connected with the amygdala and the hippocampus, and the activity of its different subdivisions has been widely studied in depressed patients.

Ventral Striatum
A preponderant role for the ventral striatum has also been reported in major depression. The fundamentals of the natural reward system are attributed to the dopaminergic connections between the ventral tegmental area (VTA) and the nucleus accumbens (NAc). In this respect, the NAc and the VTA may mediate the anhedonic symptoms of depression. Depressed patients show an attenuated activation of the VTA-NAc pathway or the NAc itself compared to normal patients in fMRI analyses. In rodent models of depression, reduced dopaminergic activity in the NAc with a disturbed burst firing of VTA neurons was also observed.

Neuroplasticity Dysfunction in Depression
Neuroplasticity can be defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function, and connections. Neurogenesis is one of the mechanisms of neuroplasticity. The formation of newborn neurons in proliferative areas. The regions identified so far in the erodent adult brain are the subventricular zone (SVZ) and the subgranular (SGZ) of the dentate gyrus (DG) in the hippocampus. Another plasticity mechanism is the modification of mature neuronal morphology, involving axonal and dendritic arborization and pruning, an increase in spine density and synaptogenesis. At a functional level, long-term potentiation (LTP) is the main mechanism mediating plasticity. The transcriptional regulation of genes involved in neuroplasticity by epigenetic mechanism also contributes to synaptic plasticity. Altogether, these processes mediated the dynamic and adaptive changes in synaptic strength.

Neurogenesis and Depression
The most commonly studied brain region in neurogenesis research is the hippocampus. Several factors have been demonstrated to regulate hippocampal neurogenesis,
including exercise, hormones and environment (hippocampus-dependent learning), suggesting that neurogenesis is closely related to some physiological mechanisms. Some negative stress and adverse experiences can lead to a significant decrease in the proliferation of granulosa cells, thereby affecting the function of the brain and hippocampus, among which the effect on memory is of great concern. At the same time, chronic antidepressant treatment can reverse this effect.

Studies show reduced hippocampal volume in depressed patients. Meanwhile, a reduced hippocampal volume and a decrease in neurogenesis can be observed in animal models. Although it is debatable whether hippocampal shrinkage results from depression or a preexisting vulnerability marker for depression, it does suggest that structural changes in the brain may be closely related to environmental factors, genetic risk, and outcome. Patients with the short (S) variant tri-allelic polymorphisms of the serotonin transport gene (5-HTTLPR) promoter region were more likely than those with only one risk factor (genetic or environmental) to have smaller hippocampal volumes when experiencing childhood stress.

Synaptic Plasticity and Depression

Stressed rodents display abnormal patterns of synaptic plasticity in brain areas, including the hippocampus and prefrontal cortex. N-methyl-d-aspartic acid (NMDA) receptor antagonist ketamine has a long-lasting antidepressant effect and can reverse depressive symptoms by improving the abnormal plasticity of glutamate synapses. Repeated stress lowers the dendritic complexity of the prefrontal cortex and hippocampal neurons and the selective deletion of excitatory synaptic markers. As with stressed rodents, synaptic markers in the frontal limbic region change in MDD patients. These data support the hypothesis that depression is caused by abnormal synaptic plasticity in the affected area. Using the developing visual cortex, studies have shown that long-term use of the antidepressant fluoxetine can reactive the plasticity of the adult cortex, which is difficult to distinguish from the plastic enhancement usually found in the juvenile cortex. When this promoted state of plasticity is combined with rehabilitation, plastic networks can reorganize so that impaired vision of one eye due to developmental visual deprivation, can be fully restored. Plenty of evidence showed a significant reduction in hippocampal volume in depression patients. These changes may result from a neurodegenerative reaction to increased glucocorticoid levels in depression.

In MDD, neuroplasticity changes based on neuroimaging and post-mortem human studies indicate that structural changes are often observed during this pathology. Structural MRI studies have revealed reduced hippocampal volume in individuals during a depressive episode compared to patients in remission, increased hippocampal dendritic atrophy and cell death, and reduced LTP and BDNF expression. While MRI studies were rather consistent with a reduced DG size in patients with depression or anxiety disorders, post-mortem studies in depressed patients showed important disparities regarding neurogenesis, showing either no difference or a decrease in the number of DG progenitor cells. Although these findings make it tempting to speculate on reduced levels of neurogenesis in MDD, further investigations making use of more specific techniques are needed better to understand the dynamics of adult neurogenesis in MDD.

However, other attempts to measure human brain plasticity during MDD have demonstrated functional alterations such as those observed at the LTP level. For example, visual-evoked potential amplitudes in the visual pathway were, compared to matched control subjects, decreased in patients with depression and also in bipolar disorder patients. In preclinical depression-like models, consistent data had also reported a decrease in the proliferation and survival of hippocampal neurons when the HPA axis was dysregulated. Hence, impaired neurogenesis was observed in rodent models of depressive-like behavior using proliferation and survival cell markers such as BrdU, Ki-67, or DCX.

Neurotrophins (NTs)

Currently, four classical neurotrophins have been identified in mammals and rodents: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3 and NT-4/5. Other neurotrophins, such as NT-6 and NT-7, were also found in zebrafish. NTs are synthesized primarily as precursor form in vivo, and proNTs are cleaved to generate mature NTs by proteases, such as furin and proconvertase, in the Golgi apparatus or secretory vesicles. Plasmin and matrix metalloproteinases (MMP) are necessary for converting proNTs to NTs when proNTs are processed incompletely and released from vesicles. The secretion of NTs consists of constitutive and regulated secretory pathways. Both pathways exist in neuronal cells, while nonneuronal cells depend mostly on constitutive pathways. Unlike other neurotrophins, BDNF is preferentially sorted into the regulated pathway in response to neuronal activity, so BDNF plays an important role in

Figure 2. Pro- and mature NTs and their receptors. Precursor and mature forms of NTs (NGF, BDNF, NT-3 and NT-4/5) can combine with p75NTR, while Trk receptors tend to combine with mature NTs, and each Trk subtype bind to their neurotrophin selectivity. TrkA was shown to be a receptor for NGF, TrkB was indicated as the receptor for BDNF and NT-4/5, and TrkC was the receptor for NT-3.
learning and memory.\textsuperscript{1,11}

Neurotrophin-3 (NT-3) is a peptide that belongs to a family of secreted proteins known as neurotrophins that also includes brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and neurotrophin (NT)-4/5. Neurotrophins bind to two different classes of cell surface receptors: i) low-affinity pan75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor (TNF) receptor superfamily, and ii) a family of tropomyosin receptor kinases (Trk)-A, Trk-B and Trk-C. Trk receptors and p75NTR are highly expressed in human cortical and hippocampal brain areas.\textsuperscript{5} NT-3, encoded by the NTF3 gene in the human chromosome 12, plays important roles in neurobiological processes implicated in mood and anxiety disorders, notably neurogenesis. NT-3 is widely expressed in the dentate gyrus of the hippocampus, a crucial neurogenic niche. By binding mainly to Trk-C, NT-3 regulates neurogenesis and facilitates hippocampal plasticity. Based on the concept that changes in synaptic plasticity and neurogenesis underlie mood and anxiety disorders pathophysiology. NT-3 signaling might be a promising therapeutic target.\textsuperscript{5,12}

**NT-3 regulation in neuroplasticity**

NT-3 is widely expressed in the dentate gyrus of the hippocampus and facilitates hippocampal plasticity by regulating neurogenesis through the activation of tyrosine kinase neurotrophin receptors such as TrkC and TrkB. It has been reported that NT-3 has a direct role in the proliferation, survival, or differentiation of hippocampal progenitor cells in vivo. Indeed, hippocampal atrophy and atrophic changes in the frontal cortex have been consistently demonstrated as one of the eminent pathophysiological findings in depression, which have also been correlated with clinical variables such as duration of depression. Therefore, the currently available findings suggest that NT-3 is involved in the mechanism of antidepressants, at least as a critical modulator in certain phases of synaptic plasticity and neurogenesis in the critical neuronal structures of the hippocampus.\textsuperscript{12}

**NT-3 increases the level of BDNF**

It has also been shown that an infusion of NT3 increases the level of BDNF mRNA expression and produces BDNF-like effects, inducing cortical tyrosine kinase (TK) B phosphorylation. In addition, NT-3 has been reported to modulate BDNF signaling in differentiating hippocampal neurons. BDNF has been implicated in the pathogenesis of depression and the therapeutic mechanism of antidepressants, as evidenced by the number of preclinical and clinical studies. For example, BDNF significantly increases the level of 5-hydroxyindoleacetic acid (5-HIAA) and/or the 5-HIAA/5-hydroxytryptamine (5-HT) ratio in the hippocampus, cortex, striatum, nucleus accumbens, substantia nigra, and hypothalamus. It also alters the dopaminergic activity, primarily within the striatum and cortex. In preclinical studies, antidepressants, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs), elevate the BDNF mRNA levels in the hippocampus. In addition, BDNF has demonstrated antidepressant-like behavioral effects in the modified rat-forced swimming test by showing reduced immobility and increased swimming. Therefore, NT-3 might be involved in the fundamental molecular events in the treatment of depression by regulating or boosting important neurotrophic factors such as BDNF.\textsuperscript{12}

**NT-3 increases the turnover of 5-HT and levels of noradrenaline**

NT-3 promotes the noradrenergic neuronal cells of the locus ceruleus (LC). These findings are particularly intriguing in that the monoamine hypothesis is the prevailing pathogenesis of depression and the main therapeutic mechanism of contemporary antidepressants such as tricyclic antidepressants (TCAs), SSRIs, and SNRIs. Preclinical studies have shown that simultaneously targeting a subset of 5-HT receptors and α-adrenergic receptors may play a key role in modulating antidepressant activity. Indirect activation of the neurotransmitter receptors by antidepressants might increase the endogenous levels of available monoamines in the synapses of specific depression-related brain regions. Furthermore, NT-3 can accelerate the regrowth and sparing of 5-HT innervation from various neurotoxic insults.\textsuperscript{5,12}

**NT-3 increases the level of extracellular signal-related kinase (ERK) phosphorylation**

NT-3 markedly enhances the level of extracellular signal-related kinase (ERK) phosphorylation associated with various growth factors, hormones, and neurotransmitters. This strongly supports the existence of a specific receptor for NT3 (e.g., G-protein coupled receptor) and suggests that multiple signal transduction mechanisms might be activated by NT3, which may be involved in the action mechanism of antidepressants. Preclinical studies have shown that antidepressant-induced neurotrophin signaling may trigger the formation and stabilization of the synaptic connectivity, which gradually leads to clinical antidepressive effects and mood recovery.\textsuperscript{5,12}

**NT-3 in the ventral tegmental area (VTA)**

NT-3 mRNA has also been found in the ventral tegmental area (VTA), which is important in the reward process. Recent preliminary evidence suggests that NT3 may participate in a certain step in regulating the mesoaccumbens dopamine system on initiating behavioral sensitization through activating the mitogen-activated protein (MAP) kinase signal transduction cascade. This indicates that NT-3 has potential psychostimulant activity. This is interesting when considering the findings that psychostimulants may be effective in augmenting the treatment response in patients who have failed to respond adequately to antidepressants.\textsuperscript{5,12}

**NT-3 associated with the HPA axis**

Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis after multiple stressors is consistent with the results from previous preclinical and clinical studies in depression. In this regard, the compensatory elevation of
NT-3 after an aberration of the HPA axis may support the potential role of NT-3 in treating depression, which is in line with the antidepressant effect involving the normalization of the HPA feedback loop. NT-3 is also expressed in the noradrenergic neuron of the LC, and recurrent immobilization stress increases the NT-3 mRNA levels in the LC. It was also reported that high levels of endogenous glucocorticoids are involved in the increase in NT-3 mRNA. Levels in the LC. Given that NT-3 is stress-responsive and neurotrophic to LC, NT-3 may play a role in the effects of stress and antidepressants on mood.5,12

**NT-3 on the vegetative function**

The effect of NT-3 on vegetative functions such as sleep has been demonstrated in preclinical studies. The duration of nonrapid eye movement sleep (NREMS) was increased by intracerebroventricular injection of two doses of NT-3 (50 ng and 500 ng). However, only the higher dose produced a statistically significant result.12

**NT-3 as Therapeutic Target in Mood Disorders**

NT-3 stimulates neurogenesis, regulates monoamine neurotransmitters like serotonin (5-HT) and noradrenaline, and enhances the expression of other neurotrophins such as NGF and BDNF. All these NT-3 associated effects seem to support, at least in part, the mechanisms of action of antidepressants and mood stabilizers, making NT-3 a molecular target for developing antidepressant strategies.5

The main therapeutic mechanism of currently available antidepressants like tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRI) is based on the regulation of monoaminergic neurotransmission. Chronic infusion of NT-3 into the rat midbrain increases the turnover of 5-HT and the levels of noradrenaline in multiple CNS regions such as the neocortex, basal ganglia, and hippocampus. Infusion of NT-3 into the adult rat neocortex also accelerated the regrowth of serotonergic nerve fibers following neurotoxic insults with parachloroamphetamine. The implant of genetically modified fibroblasts that constitutively express high levels of NT-3 in the rat LC prevented degeneration of noradrenergic neurons in a 6-hydroxydopamine toxic model.5,13,14

Accordingly, NT-3 might be a valuable and specific therapeutic target for conditions. Involving the LC, such as mood disorders. Moreover, NT-3 regulates norepinephrine transporter (NET) expression during embryonic development and, in turn, promotes noradrenergic cell differentiation in the LC from quail embryos. These studies indicate that NT-3 contributes to maintaining the integrity of monoamine nuclei and, hence, the CNS levels of monoamine neurotransmitters.5,12,15,17

More direct evidence of NT-3 contribution to antidepressant effects was provided by an elegant study that showed that rats receiving a single bilateral infusion of NT-3 (0.25 ug/side) in the dentate gyrus of the hippocampus did not display depression-like behavior in the learned helplessness paradigm. The potential antidepressant effect of NT-3 was also investigated in CUS- the induced model of depression in response to treatment with compounds other than antidepressants. Daily intragastric administration of SYJN (1300 or 2600 mg/kg/day), a Chinese herbal formula, during 4 weeks of CUS restored NT-3 protein and mRNA expression levels in rats’ hippocampus and frontal cortex and prevented depression-like behaviors. More recently, a subcutaneous high dose of vitamin D3 (5.0 mg/kg), like the SSRI fluoxetine, increased NT-3 levels in the hippocampus and improved depression-like profile induced by chronic unpredictable mild stress (CUMS) for 28 days in long-term (3 months) ovariectomized adult rats. Vitamin D3 treatment also decreased corticosterone/ACTH levels, an index of hypothalamic–pituitary–adrenal (HPA) axis activity. Changes in the HPA axis in response to multiple stressors are consistent with data from studies on depression. Therefore, NT-3 increase as a compensatory mechanism to the dysregulation of the HPA axis provides further support for the role of NT-3 as a potential target for depression.5,13,14

This study is limited to a literature review; for future references, it needs more clinical studies that are well prepared because it lacks preclinical studies based on the environmental and genetic models, which are deemed necessary before progression to clinical study.

**CONCLUSION**

NT-3 is thought to play a role in the neurobiological processes implicated in depression and is a potential pharmacological target. NT-3 may exert antidepressant actions through its effects on monoamine neurotransmitters (serotonin and noradrenaline) and by regulating synaptic plasticity, neurogenesis, BDNF signaling and the HPA axis. The mechanisms underlying NT-3 anxiolytic properties require further exploration and definition. More preclinical studies based on environmental and genetic models are necessary before progression to clinical studies.

**CONFLICT OF INTEREST**

There is no conflict of interest in this paper.

**ETHICAL CONSIDERATIONS**

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All of the authors contributed evenly to the making of this literature review.

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