

Review Article

Neuroadaptations of the 5-HT System Induced by Antidepressant Treatments: Old and New Strategies

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Abstract

Major Depressive Disorder (MDD) is a common illness worldwide with severe socioeconomic consequences. Several hypotheses have been formulated to explain the pathophysiology of depression as well as the mechanism of action of antidepressants but two of them had attracted much attention. The dominant monoaminergic hypothesis of depression links the pathophysiology of MDD to a deficiency on cerebral serotonin (5-HT) and/or Norepinephrine (NE) levels; however, the relatively new neurogenic and neurotrophic hypothesis raises the possibility of an impaired neuroplasticity and/or depletion of neurotrophic factors in specific networks resulting on their structural deformity and functional impairment. An enormous body of evidence reported particular neuroadaptations following chronic administration of antidepressant drugs. In this review, we describe major adaptive changes in pre- and post-synaptic 5-HT neurotransmission as well as alterations in gene transcription and neurotrophic factors in response to long-term treatment with conventional antidepressants, new putative ones or novel promising drug candidates, all acting via 5-HT system.

Keywords: BDNF; Dorsal raphe nucleus; Hippocampus; Major depressive disorder; Monoaminergic hypothesis of depression; Neurogenesis; Serotonin; VEGF; 5-HT_{1A} receptors

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Introduction

Major Depressive Disorder (MDD) is a common illness worldwide and has a profound impact on public health. According to the Diagnostic and Statistical Manual (DSM IV-TR, [1]) of Mental Disorders, MDD is described as a depressed mood or loss of interest or pleasure (anhedonia) for more than two weeks. In addition, individuals experiencing MDD exhibit five or more symptoms (among nine possible symptoms listed in the DSM IV-TR definition) that cause significant impairment at the social, occupational and educational levels. These symptoms may include weight loss or gain, low energy, insomnia or oversleeping, psychomotor agitation or retardation, low self-esteem or suicidal ideation. A recent study estimates the prevalence of MDD at 4.4% to 5% in the general population with an annual incidence of 2.4% to 3.8% [2]. In this context, nearly one in four women and one in six men experience depression during lifetime [3]. The 12-month prevalence of MDD ranges from 2.2% in Japan to 10.45% in Brazil with similar averages of 5.5% in developed and 5.9% in developing countries [4].

The most contemporary theory of depression is the notion that stress can initiate cognitive and possibly biological processes that increase risks for the disorder. In fact, major stressful life events are one of the best predictors of an impending onset of depression and include childhood abuse [5], childhood low socioeconomic status [6], workplace mobbing [7], poor working conditions [8], loss (e.g. death of a close person) [9], humiliation (especially partner-initiated separation) [9], concomitant pathologies such as traumatic injuries [10] and cancer [11], and other stress sources. Significant socioeconomic consequences of MDD have been noted in the form of substantial loss in life quality [12], absenteeism and poor work performance [13-15], higher pharmaceutical costs [16], higher suicide risks and mortality [17-18].

Due to the high prevalence of depressive disorder, the antidepressant drugs have become one of the most common medications in western countries, with as an example of 6% of users in France [19]. However, only a small proportion of MDD patients receive adequate treatment, with only one third reported a complete remission after trial of a first antidepressant followed by progressively lower response rates with each subsequent antidepressant trial [20]. Even among responders, there is a time lag of several weeks to months before the meaningful clinical response can be observed. These drawbacks are largely due to the absence of diversity in the mode of action of conventional antidepressants, which act principally via an enhancement of synaptic transmission of the monoamines serotonin (5-HT) and/or Norepinephrine (NE) [21]. The development of this type of medications was indeed largely based on the monoaminergic hypothesis of depression that links the pathophysiology of depression to a deficiency on cerebral 5-HT and/or NE levels. The first generation of ADs, Monoamine Oxidase Inhibitors (MAOIs) and Tricyclic Antidepressants (TCAs) inhibit the breakdown of 5-HT, NE and dopamine in presynaptic neurons and block the presynaptic uptake of 5-HT and NE through high-affinity 5-HT (SERT) or NE (NET) transporters, respectively. The severe side effects and toxicity of these drugs urge the development of novel drugs with a better profile,

including selective 5-HT reuptake inhibitors (SSRIs), NE Reuptake Inhibitors (NRIs) and combined-action 5-HT/NE reuptake inhibitors (SNRIs). However, this new generation of antidepressants acts through the modulation of monoamine transporters as the older one, which may explain their sub-optimal therapeutic efficacy. A number of emerging ADs that target monoamine transmission attempt to act on existing targets in more synergic ways (combining 5-HT reuptake inhibition with inhibition of autoreceptors) or to broaden the spectrum of monoamine systems targeted (dopamine, melatonin) to either enhance efficacy or speed response.

Despite the emergence of alternative hypotheses, the monoaminergic one still dominates the research of the physiopathology and pharmacotherapy of MDD. It does not only propose the crucial involvement of monoamines in the therapeutic effects of antidepressant drugs but also suggests that depression is directly related to decreased monoaminergic transmission. The considerable potential of this hypothesis has been reinforced by the discovery of many adaptive changes, especially in the sensitivity of monoamine receptors, occurring after chronic antidepressant treatments in a time course consistent with their therapeutic action. Nevertheless, recent emphasis on neuronal circuits catalyzed a shift in our comprehension of MDD physiopathology. In particular, neurogenic and neurotrophic hypothesis of depression raises the possibility of an impaired ability of genes in specific networks, especially the hippocampus, to encode environmental stimuli and stressful events. This leads to a reduced neuroplasticity and/or depletion of neurotrophic factors, resulting in a structural deformity and functional impairment of the central nervous system.

In order to better understand the biological basis of antidepressant treatments, especially those that act through the 5-HT system, this review summarizes some of the most documented neuroadaptations, in respect to both the monoaminergic and neurogenic/neurotrophic hypothesis of depression. Attention will be paid to the neuroadaptive consequences of combination strategies (e.g. adjunction of antipsychotics), promising targets on AD development (5-HT₇ receptor antagonism, 5-HT₄ agonism) as well as new multimodal antidepressants.

Neuroadaptations of the 5-HT System

Effects of MAOIs and TCAs

MAOIs and TCAs were the first drugs discovered to be effective in the treatment of MDD. The use of older non-selective MAOIs (tranylcypromine and phenelzine) was now limited to cases of refractory depression because of serious side effects, especially cardiovascular reaction following ingestion of tyramine-containing food known as cheese effect [22,23]. These negative effects were attributed to the lack of MAO-A/MAO-B selectivity and the inhibition of other enzymes such as the drug metabolizing cytochromes P450. However, recent development of reversible MAO-A inhibitors with low tyramine-potential property and the discovery that selective MAO-B inhibitors do not cause cheese effect have facilitated the re-introduction of these drug class for the treatment of MDD.

Early preclinical studies showed that acute administration of MAOIs (pargyline, tranylcypromine, phenelzine and iproniazid) and TCAs (clomipramine, imipramine, amitriptyline and nortriptyline) suppresses the firing activity of 5-HT neurons in the Dorsal Raphe Nucleus (DRN) [24-26], which can be reversed by an administration

of the 5-HT_{1A} receptors antagonist, WAY-100635 [26,27]. After long-term treatment with MAOIs, a complete recovery of the firing activity of DRN 5-HT neurons is obtained [28]. This is a consequence of a desensitization of the somatodendritic 5-HT_{1A} autoreceptors as the agonist 8-OH-DPAT failed to affect the DRN 5-HT firing activity [28,29]. Similarly, a desensitization of these 5-HT_{1A} autoreceptors was observed in MAO-A mutant mice [30]. Interestingly, such desensitization was attributed to an altered receptor-G protein interaction rather than a simple down-regulation, since the agonist-stimulated [35S]-GTPγS binding in the dorsal raphe was shown to be reduced after chronic administration of MAOIs such as clorgyline [31]. In contrast, chronic MAOIs do not desensitize terminal 5-HT autoreceptors. In this context, it has been shown that long-term administration of the MAOI MDL72394 had no effect on the number of 5-HT_{1B} binding sites or the ability of the 5-HT_{1B} agonist RU24969 to reduce extracellular levels of 5-HT in the rat frontal cortex [32,33]. At the postsynaptic level, it has been demonstrated that the selective and potent 5-HT_{1A} antagonist WAY-100635 significantly increased the firing of CA3 pyramidal neurons in the hippocampus of rats chronically treated with the MAO-A inhibitor befloxatone, indicating an enhancement of the tonic activation of postsynaptic 5-HT_{1A} receptors [34]. This was associated with an unaffected autoradiographic labeling of these postsynaptic receptors after repeated treatments with clorgyline [31]. Taken together, these adaptive changes, obtained after a chronic MAOI administration, are associated with the enhancement of the 5-HT neurotransmission in the brain (Figure 1) [31-34]. This data was supported by the enhanced extracellular 5-HT amounts in the ventral hippocampus, frontal cortex and DRN found in MAO-A knock-out mice compared to wild-type littermates [30].

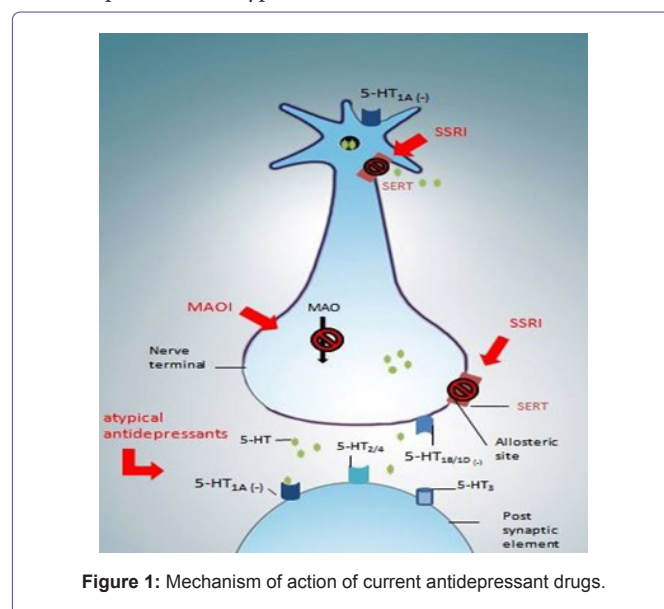


Figure 1: Mechanism of action of current antidepressant drugs.

As shown with MAOIs, long-term administration of TCAs induced a recovery of the mean firing rate of the 5-HT neurons in the DRN [29]. In contrast, an intravenous injection of the 5-HT agonist LSD or microiontophoretic application of 5-HT or LSD still decreased this firing, suggesting that the sensitivity of 5-HT autoreceptors is not modified [29]. In this context, no changes were observed in i) 5-HT_{1A} density or mRNA expression in the DRN [35,36] or in ii) 5-HT_{1A} agonist-stimulated [35S]-GTPγS binding in dorsal and median raphe nuclei [37,38]. These latter data suggest that neither down

regulation nor desensitization of somatodendritic 5-HT_{1A} autoreceptors occurred after chronic TCA treatments. Similarly, the sensitivity of terminal 5-HT_{1B/1D} autoreceptors seem to be unaffected since subcutaneous injection of the 5-HT_{1B/1D} antagonist GR127935 leads to an increase of 5-HT levels in the hippocampus and frontal cortex of rats chronically treated with the TCA clomipramine [39]. Initial observations reported that long-term administration of TCAs sensitized postsynaptic 5-HT receptors responsiveness in forebrain structures including hippocampus, amygdala, lateral geniculate nucleus and cerebral cortex [40-43]. Subsequently, long-term application of imipramine was shown to enhance the responsiveness of postsynaptic CA3 hippocampus pyramidal neurons to the microiontophoretic application of 5-HT or 8-OH-DPAT [44]. In support, chronic administration of amitriptyline increased 5-HT_{1A} agonist-stimulated [35S]-GTPγS binding in the hippocampus without affecting the binding of [3H]8-OH-DPAT [38], indicating a hypersensitivity of postsynaptic 5-HT_{1A} receptors non-associated with a change in the number of binding sites. It is noteworthy that no effect was observed on 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} or 5-HT₇ mRNA expression in any hippocampal sub region [36]. In summary, as MAOIs treatments, TCAs induce a net increase of 5-HT neurotransmission in the brain.

Effects of SSRIs

There is no doubt that the reduction in cardiac arrhythmias and other potential lethality played a major role in opening the door to the exponential growth of second-generation antidepressant prescription. These antidepressants include SSRIs which are considered nowadays as first-line treatment options. They comprise fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram and escitalopram, and they primary act via the blockade of SERT, thus enhancing the extracellular 5-HT amounts in the brain and leading to a cascade of events at the pre- and post-synaptic levels (Figure 1). Their behavioral efficacy in animal models of depression (chronic mild stress, learned helplessness), and in screening tests detecting antidepressant-like responses (forced swim and tail suspension tests) are well documented [45].

It is extensively reported that acute administration of SSRIs produces a strong and transient increase of extracellular 5-HT levels, thus activating somatodendritic 5-HT_{1A} autoreceptors which reduce the firing activity of DRN 5-HT neurons [46-49]. In this context, an elegant immunoelectron microscopy study demonstrated that a single injection of the SSRI fluoxetine in rats induces a decrease in the 5-HT_{1A} immunogold labeling of the plasma membrane of the DRN dendrites and a concomitant increase in their cytoplasmic labeling, without any change in hippocampal dendrites [50]. In agreement, a reduction of the *in vivo* binding of the 5-HT_{1A} Positron Emission Tomography (PET) radioligand [18F]MPPF in the DRN, but not in the hippocampus, was observed one hour after fluoxetine injection [50]. Taking together, these data indicate an internalization of the somatodendritic 5-HT_{1A} autoreceptors. Importantly, similar autoreceptor sequestration was reported in the DRN of human volunteers after taking a single dose of fluoxetine [51]. Effects of a subchronic treatment with SSRIs on the 5-HT firing activity did not differ from those of an acute administration [52-53]. However, chronic treatments with these drugs produced a recovery of the 5-HT firing activity accompanied with a desensitization of the body 5-HT autoreceptors as shown for example by a decrease in the action of 8-OH-DPAT to reduce 5-HT levels [54-56]. Surprisingly, it has been reported that neither the number of 5-HT_{1A} receptor-labeled

dendrites in the DRN nor the density of somatodendritic 5-HT_{1A} receptor labeling on the plasma membrane of these dendrites was significantly different from control after SSRI (fluoxetine) treatment [57]. This is in keeping with the lack of changes in the *in vivo* binding of [18F]MPPF in the DRN and hippocampus of rats [57] as well as in the [18F]MPPF binding potential in any cat brain region after chronic treatment with fluoxetine [58]. These data suggest the presence at the plasma membrane of DRN 5-HT neurons of uncoupled 5-HT_{1A} autoreceptors from their G-proteins (inactivated state). In fact, it is widely admitted that after activation, many G-protein coupled receptors internalize and recycle back to the membrane as fully competent receptors. However, after chronic treatment, the repeated activation and internalization of the pool of functional 5-HT_{1A} autoreceptors apparently led to their replacement by a pool of inactivated receptors that recycle to the plasma membrane of DRN 5-HT neurons. In this context, it has been shown that after chronic fluoxetine, the 5-HT_{1A} agonist-stimulated [35S]-GTPγS binding was reduced [31,37,59], which is surprisingly not the case after chronic sertraline or citalopram [60,61]. This indicates that this class of antidepressants produces a differential functional regulation of 5-HT_{1A} autoreceptors. Desensitization of terminal 5-HT_{1B/1D} receptors with no change on their binding sites was also reported after chronic SSRI treatment [62,63]. Repeated administration of fluoxetine produced a desensitization of these terminal autoreceptors in both hippocampus and frontal cortex, but not in the hypothalamus [63,64], suggesting that the regulation of extracellular levels of 5-HT may be subject to different autoregulatory mechanism depending on the brain region. At the postsynaptic level, 5-HT_{1A} heteroreceptors are known not to desensitize [34,62], where they are coupled to Gao protein [65]. For instance, electrophysiological recordings in brain slices from rats chronically treated with fluoxetine showed no change of the 5-HT_{1A}-evoked responses of CA1 pyramidal cells in the hippocampus [62]. However, after long-term treatment with paroxetine, the selective 5-HT_{1A} receptor antagonist WAY100635 markedly increased the firing activity of CA3 pyramidal neurons, a disinhibition not shown in control rats or in those treated with non-antidepressant drugs [34,66]. This indicates that SSRIs (as well as MAOIs and TCAs) might alleviate depression by enhancing the tonic activation of forebrain postsynaptic 5-HT_{1A} receptors [34].

SERT, the site of action of SSRIs, similarly undergoes adaptive changes during SSRI treatment. Increases [67], decreases [68-70] or no change [71,72] in density of SERT binding sites have been reported in the DRN and various territories of 5-HT innervations. However, an elegant study using immunoelectron microscopy in rats indicates that there is an internalization of SERT at cell bodies and dendrites of DRN neurons as well as at their axon terminals in the hippocampus after chronic, but not acute, treatment with fluoxetine [51]. Furthermore, a reduction in the overall density of labeling in both DRN and hippocampal terminals was observed, suggesting that SERT was not only internalized, but also degraded, in the course of the chronic fluoxetine treatment [51]. This is in agreement with earlier studies showing a desensitization and a downregulation of SERT following repeated administrations of paroxetine or sertraline [68,69]. Other neuroadaptive changes were reported after chronic fluoxetine such as a desensitization of 5-HT₇ receptors [53] and a downregulation of their binding sites in the hypothalamus [73], as well as a downregulation of 5-HT₄ binding sites in the CA1 field of the hippocampus [74].

Effects of novel strategies

The moderate efficacy of the antidepressants cited above and their delayed onset of action urged the search of new therapeutic strategies. Indeed, the majority of depressed patients do not fully recover with an initial conventional antidepressant treatment. Alternatives include escalating the dose of the initial antidepressant, switching to an alternative medication, combining two antidepressants with different mechanisms of action, etc. One promising therapeutic strategy in this context is adding an augmentation agent such as an atypical antipsychotic (e.g. aripiprazole, quetiapine, risperidone and olanzapine) to a conventional antidepressant (e.g. SSRI). The use of second-generation antipsychotics as adjuvants to SSRIs has been investigated and approved for clinical use to treat depression, particularly treatment-resistant depression, late-life depression and co-morbid MDD and alcohol dependence [75-77]. The combination of an SSRI and an antipsychotic has been proven to be more effective than a SSRI alone in patients with MDD [78]. Despite the established efficacy of this combinatory therapy, its mechanism of action is not entirely understood. For instance, electrophysiological studies showed that when escitalopram and quetiapine were co-administered for either 2 or 14 days, the 5-HT spontaneous firing activity is reduced while the overall 5-HT neurotransmission is enhanced as indicated by the increase in tonic activation of postsynaptic 5-HT_{1A} receptors located on the CA3 pyramidal neurons in the hippocampus [79]. Importantly, addition of quetiapine to escitalopram regimen not only reversed the inhibitory action of the latter upon NE spontaneous firing activity (which is likely contributing to the limited benefits of SSRIs in some patients, as well as to some of their side effects), but also significantly increased it above control levels [79]. This action is believed to be mediated by a direct antagonism of 5-HT_{2A} receptors, located on GABA neurons that inhibit the firing rate of NE neurons [80]. Hence, the effectiveness of such combination therapy can be explained by its positive effect on both 5-HT and NE neuronal tone [79]. Similarly, long-term co-administration of risperidone and escitalopram dampens the spontaneous firing activity of 5-HT neurons [81] however, both dopamine outflow and NMDA receptor-mediated transmission in the rat PFC are increased [82]. These data suggest that the effectiveness of these combination treatments can be explained by an increase of several brain neurotransmissions rather than only an enhancement of the 5-HT one. In our opinion, such antidepressant strategy is more adequate to treat MDD regarding the heterogeneity of the related symptoms and paves the way to new therapies that consider this disease as several sub-components rather than a unitary construct.

In order to avoid usual molecular targets of conventional antidepressants, many promising candidates have been identified to develop fast-acting and more effective antidepressants, including 5-HT₄ receptors and 5-HT₇ receptors [53,83]. It has been previously shown that a subchronic treatment (3 days) with the 5-HT₄ agonist RS67333 induced a desensitization of somatodendritic 5-HT_{1A} autoreceptors [83], increased tonic activation of hippocampal postsynaptic 5-HT_{1A} receptors [83], increased basal 5-HT levels and decreased its metabolite 5-HIAA levels in the rat ventral hippocampus [84]. Furthermore, co-administration of the SSRI citalopram and 5-HT₄ receptor agonists RS6733 or prucalopride for only 3 days exhibited similar neuroadaptive changes of the 5-HT system than those obtained after 2 to 3 weeks of citalopram application, except that the tonus of the hippocampal 5-HT_{1A}

heteroreceptors was two to three times higher [85]. This clearly indicates an important increase of the 5-HT neurotransmission following adjunctive SSRI/5-HT₄ agonist treatment.

A new trend in pharmacotherapy research is the multi-target approach that may prove successful in order to find new and more effective therapies for the complexity of MDD. In this category, vilazodone, a 5-HT_{1A} receptor partial agonist and SSRI [86-88], offers a new therapeutic possibility [89,90]. It has been shown that vilazodone induces an elevation of 5-HT amounts in the medial and the lateral cortex that is six-fold higher than those induced by SSRIs paroxetine, citalopram or fluoxetine [86]. Using *in vivo* electrophysiology in the DRN of anesthetized rats, the sensitivity of 5-HT_{1A} autoreceptors of 5-HT neurons was tested by determining the intravenous dose of the agonist 8-OH-DPAT required to suppress the basal firing rate of these neurons by 50% (ID₅₀) after acute or subchronic (3 days) treatment with vilazodone [91]. While paroxetine or fluoxetine did not affect the ID₅₀ value of 8-OH-DPAT, acute and subchronic administrations of vilazodone significantly increased this value, even after 24 hours in the case of a subchronic treatment [91]. This result suggests that this antidepressant induces a rapid but also prolonged inhibition of 5-HT_{1A} autoreceptors, which can occur by either direct interaction with these receptors or their desensitization [91]. Undoubtedly, further studies are needed to determine other effects of this new antidepressant on the 5-HT system. Another multimodal-acting antidepressant is vortioxetine which acts as a 5-HT₃, 5-HT₇ and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and SERT inhibitor [92-94]. Strikingly, 1-day treatment with vortioxetine is sufficient to induce a recovery of the 5-HT neuronal firing activity in the DRN, an effect observed after 14 days of fluoxetine treatment [93]. This markedly faster recovery was associated with 5-HT₃ receptor antagonism and reduced SERT occupancy [93]. Additional data showed that acute or subchronic 3-day administration of vortioxetine caused robust dose-dependent increase of extracellular 5-HT levels in the ventral hippocampus and the median PFC, with a greater effect on the former compared to the latter [92]. This increase seems to occur at low levels of SERT occupancy. Further research is required to establish the full effects of the unique pharmacological and neurochemical profile of this antidepressant.

Taken together, these data indicates that a change in the 5-HT receptor sensitivity at the presynaptic and/or postsynaptic level can be a common mechanism of action of the 5-HT antidepressants. These neuroadaptations took place in a time course consistent with the onset of action of each antidepressant strategy. Such neuroadaptive changes are a major argument supporting the monoaminergic hypothesis. However, a growing body of evidence also shows that downstream antidepressant actions include adaptations of signal transduction pathways and gene expression, notably neurotrophic factors and hippocampal neurogenesis [95-97], which favour the neurotrophic and neurogenic hypothesis of depression. In the following part of this review, we will describe the neuroadaptive changes seen after 5-HT antidepressant treatment according to this theory.

Neurotrophic and Neurogenic Adaptations Induced by 5-HT Antidepressants

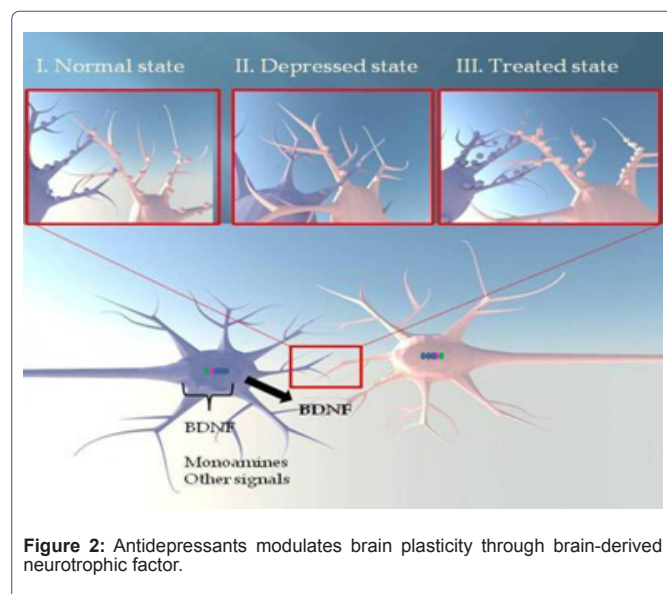
In quest for elucidating the neurobiological basis of MDD, neurotrophic factors as well as hippocampal neurogenesis have emerged as serious candidate substrates for both the etiology and

the treatment of MDD. Modifications involving cell proliferation and plasticity in some brain limbic structures as the hippocampus, the frontal cortex and the amygdala have been identified in both depressive state and following antidepressant treatments [95-97].

Neurotrophins

Neurotrophins are a group of proteins implicated in neuronal survival, synaptic function and synaptic plasticity [98]. They are important regulators of cell fate decisions, axon growth, dendrite pruning, the patterning of innervations and the expression of proteins crucial for the normal neuronal function such as neurotransmitters and ion channels [98]. The functional significance of altered neurotrophic factor expression was highlighted by studies showing a dystrophic action of stress and depression in key brain regions including the hippocampus, the frontal cortex and the amygdala, and in turn, antidepressant treatment can block or reverse this action. The mechanism underlying the actions of such medications are still under investigation, but up regulation of neurotrophins seems to be a part of the long-term adaptations that are required for the therapeutic actions of these treatments.

Brain-Derived Neurotrophic Factor (BDNF): BDNF is the most studied neurotrophin in the context of MDD (Figure 2). A reduced expression of BDNF in different brain areas (hippocampus, prefrontal cortex, substantia nigra) was detected in a plenty of animal models of depression including Olfactory Bulbectomy (OBX) and Unpredictable Chronic Mild Stress (UCMS) [99-101] as well as in genetic models of depression such as Flinders Sensitive Line [102] and Wistar-Kyoto rat strain [103]. Also, patients with MDD showed lower BDNF mRNA levels and plasma levels compared with healthy controls [104-106]. Moreover, human BDNF gene polymorphism Val66Met was suggested to be related to the pathogenesis of MDD and seems to affect clinical response to antidepressant treatment [107-109].



Antidepressants could oppose or reverse the action of stress on the 5-HT system via a positive effect on cerebral BDNF. Indeed, it has been reported that chronic treatment with different classes of antidepressants (SSRIs fluoxetine and escitalopram, MAOIs tranylcypromine and phenelzine, TCA desipramine) increases BDNF brain levels [101,110-113]. A very recent study reported that long-term administration of the SSRI escitalopram to mice,

experiencing postnatal maternal separation plus 4 weeks of UCMS in adolescence, induced an elevation of BDNF levels in the hippocampus [114]. This result was obtained when stressed mice were treated either during or following exposure to stress, demonstrating that antidepressants are capable of blocking and reversing the negative effect of stress via BDNF actions [114]. Such modulation of BDNF concentrations seemed to be time-dependent. Indeed, a previous study monitoring BDNF mRNA in the rat hippocampus reported that daily oral administration of fluoxetine decreased this expression after 4 days, had no effect after 7 days and enhanced it after 14 days [110]. This biphasic response can be explained by a differential transcript regulation since rat BDNF gene expresses four mRNA isoforms that are modulated by different signaling cascades. In this context, acute injection of fluoxetine or tranylcypromine was reported to decrease exon V and IV mRNAs without affecting those of exon I or III, whereas prolonged treatment enhanced expression of exon V and exon I mRNAs without changing those of exon III or IV [115]. Clinical data are in accordance with preclinical results and show an increase of serum or platelet BDNF levels following several weeks of antidepressant treatment. For example, depressed patients showed an elevated plasma BDNF level after chronic treatment with SSRI paroxetine or citalopram compared to drug-free patients [104,116]. Interestingly, a recent pilot study showed that plasma BDNF of depressed patients increased rapidly (within 7 days) after the initiation of an antidepressant (including SSRIs and TCAs) treatment, and in turn, the absence of this early increase seemed to indicate that the selected treatment will not be effective [117]. This suggests a valuable clinical utility of peripheral BDNF measurement as surrogate marker of antidepressant efficacy [117].

There is a lack of data describing the effects of novel antidepressants targeting the 5-HT system on BDNF. Previous work from Li's lab [118] demonstrated that chronic restraint stress reduced BDNF expression in the rat hippocampus and that chronic administration of quetiapine or venlafaxine dose-dependently prevented this reduction. Interestingly, combination of lower doses of quetiapine and venlafaxine prevented BDNF decrease in stressed rats, whereas each of the drugs exerted mild or no effects [118]. These data suggest that both drugs share the hippocampus as their common target by enhancing hippocampal resilience, which may be impaired in MDD patients. In accordance, a clinical study assessing the efficacy of risperidone addition on sertraline-resistant patients showed that, 4 weeks after risperidone co-treatment, plasma BDNF levels were increased in responders (reduced HAM-D scores), whereas no change was observed in non-responders [119]. This supports the idea that enhanced levels of peripheral BDNF can represent a biological marker of the antidepressant response. Another study investigating the effects of a new promising target reported an enhancement of BDNF protein levels in the hippocampus of rats after only a subchronic application of the 5-HT₄ receptor agonist SL65.0155, which was not obtained using subchronic citalopram or clomipramine treatments [120], again in support of the fast-acting antidepressant profile of 5-HT₄ receptor agonists.

Vascular Endothelial Growth Factor (VEGF): A relatively newer candidate involved in the physiopathology of MDD is the Vascular Endothelial Growth Factor (VEGF). It is an important signaling protein implicated in the regulation of angiogenesis and neurotrophism and is synthesized by different cell types including astrocytes, ependymal cells and neuronal stem cells [121]. VEGF is involved in the neurovascular stem cell niche in the subgranular zone of the dentate

gyrus of the hippocampus and affects synaptic plasticity in hippocampus-dependent processes such as learning and memory [121]. Similarly to BDNF, VEGF protein expression was found to be downregulated in frontal and hippocampal regions in animal models of depression such as UCMS [122,123]. However, data in human are more inconsistent [124]. In fact, while some authors observed higher serum or plasma VEGF concentrations in drug-free depressed patients [125-127] and in patients with acute episodes of MDD or bipolar disorders [128], others reported no significant difference compared to healthy controls [129]. It has been suggested that an elevation of VEGF expression may be a repair response to the neural damage that underlies the pathogenesis of depression [130]. However, depressed patients who had attempted suicide [127] or had completed suicide [131] had lower serum or plasma VEGF levels compared with adequate controls, making these discrepancies very difficult to explain.

Numerous antidepressant treatments have been shown to affect VEGF signaling. Elegant studies from Duman's group reported that chronic treatment with SSRIs fluoxetine or sertraline, TCAs desipramine or amitriptyline and SNRI venlafaxine increases VEGF protein levels in the hippocampus [132,133]. Interestingly, such regulation seems to require the activation of the 5-HT_{1A} receptor subtype, at least, in the case of fluoxetine [133]. However, data reported in cultured cell systems are not consistent. For example, a treatment with the SSRIs fluoxetine or paroxetine in cultured cortical astrocytes leads to an up regulation of the VEGF mRNA levels whereas the TCAs imipramine and desipramine did not affect this expression [134]. The latter result suggests that SSRIs may contribute to normalize the trophic support to neurons in major depression by increasing the expression of this specific astrocyte-derived neurotrophic factor, while TCAs may involve other astrocytic mechanisms or other cell populations to accomplish their therapeutic effects [134]. Interestingly, it has been reported that, after a sub-acute treatment in rats, neither the SSRI citalopram nor TCA clomipramine affected the VEGF protein levels in hippocampal homogenates, unlike the 5-HT₄ receptor agonist SL65.0155 which increased these levels, accordingly to its fast-acting antidepressant profile [120]. The clinical data shed light to a more complex landscape. An eight-week treatment with paroxetine appeared to decrease VEGF mRNA levels in peripheral leukocytes of depressed patients in positive correlation with clinical improvement [125]. In the same class of antidepressants, escitalopram did not alter VEGF plasma levels in depressed patients after 12 weeks of treatment [129]. It has to be mentioned that this latter study was conducted in a very small sample (25 subjects) without control of the co-morbidities, cardiovascular diseases or confounding factors, making conclusions very hard to make [129].

It is of high interest to note that these neurotrophic factors and related signaling pathways are associated with antidepressant action and could operate as key modulators in the regulation of neurogenesis in the adult hippocampus [135]. The findings that antidepressants increase neurotrophic factor expression, particularly in the hippocampus, provide the background and the rationale for studies of adult neurogenesis and its implication on the etiology of depression and the antidepressant response.

Hippocampal neurogenesis

Neurogenesis in the mammalian brain occurs throughout life in two specific regions: Subventricular Zone (SVZ) lining the lateral

ventricle, and Subgranular Zone (SGZ) of hippocampal Dentate Gyrus (DG) [136]. In particular, hippocampal neurogenesis plays an important role in cognitive function and can be altered by several factors including chronic stress and antidepressant treatments. There is an enormous body of evidence that a depressed behavior in chronically stressed animals is accompanied with an impairment of hippocampal neurogenesis, and that antidepressants improve both parameters [137,138]. Although the lack of newly formed cells in the hippocampus was not causally involved in depression, as their absence does not trigger a depressive behavior, their loss has been shown to be causally involved in the ability of chronic antidepressants to achieve remission [139]. Clinical studies also showed volume reductions, hypothesized to be secondary to cell death and neurogenesis blockade, in the hippocampus of MDD patients [140-142], particularly in those who had experienced childhood maltreatment [143].

One of the most reproducible findings in antidepressant research is that different classes of antidepressants including TCAs, MAOIs and SSRIs increase hippocampal cell proliferation and neurogenesis [83, 139,144-146] after chronic, but not acute, treatment consistent with the time course for their onset of therapeutic action. Similar positive effects have been reported using novel therapeutic strategies. For example, quetiapine add-on therapy increased the number of newborn cells in the hippocampus of fluoxetine treatment-resistant rats that experienced UCMS [147]. Putative fast-acting antidepressants, including 5-HT₇ receptor antagonist SB-269970 [53] and 5-HT₄ receptor agonists RS67333 and prucalopride [83,85] induced an enhancement of hippocampal neurogenesis in a time course concordant with their onset of action. Very recently, a preclinical study using the multimodal antidepressant vortioxetine showed that a 21-day treatment with this drug was able to increase cell proliferation and survival and to stimulate the maturation of immature granule cells in the SGZ of the DG of the hippocampus [146] while a preliminary study revealed that such DG cell proliferation increase occurred after one day of treatment only [148]. Taken together, these data indicate that up regulation of hippocampal neurogenesis may be a common dominator of the mechanism of action of antidepressants. However, the function of these newly formed neurons is still not fully understood. Previous studies suggested that young granule cells constitute a distinct population that exhibit a greater degree of plasticity than mature neurons: i) they displayed a reduced threshold to induction of Long-Term Potentiation (LTP) [149], and ii) they can be tonically activated by ambient GABA before being sequentially innervated by GABA- and glutamate-mediated synaptic inputs, leading to marked defects in their synapse formation and dendritic development *in vivo* [150]. This hypothesis has to be confirmed by additional studies.

Conclusion

The list of neuroadaptations induced by 5-HT antidepressants mentioned in this review is certainly not exhaustive. Establishing the full profile of these neuroadaptive changes is necessary to better target the downstream common mechanisms. Although the monoamine imbalance is undoubtedly involved, the classical monoaminergic systems seemed to be simplistic over the years. The only elevation of monoamine neurotransmissions could not explain the temporal delay in the therapeutic action of antidepressants. In the same way, the neurogenic/neurotrophic hypothesis could not support the physiopathology of MDD or the antidepressant response by only the enhancement of neurotrophin expression and/or addition of new

cells to existing relevant networks. These two hypotheses can be considered complementary as activation of monoamine receptors may modulate the expression of intracellular proteins and growth factors, but still not sufficient to explain the heterogeneity of MDD symptoms and the failure of antidepressant effect in some cases. The elaboration of a putative more efficient model has to be addressed. Other hypotheses on MDD pathophysiology are currently under investigation, such as possible alterations of the glial system, or genetic and epigenetic modifications. The modulatory role of each candidate is still far from being understood. Future works will definitely come up with a new way to approach MDD in order to understand its etiology and to develop new therapeutics with broader efficacy.

Depression is associated with reduced levels of monoamines in the brain, such as 5-HT. Chronic administration of antidepressants can cause a number of changes in the brain, depending on the particular drug type. Selective 5-HT Reuptake Inhibitors (SSRIs) and Monoamine Oxidase (MAO) Inhibitors (MAOIs) enhance 5-HT extracellular levels by blocking the 5-HT transporter (SERT) or by inhibiting the 5-HT degradation, respectively. Chronic administration of these drugs desensitizes somatodendritic 5-HT_{1A} receptors and terminal 5-HT_{1B/1D} autoreceptors leading to an enhancement of 5-HT neurotransmission.

There is a possible contribution of neuronal plasticity in the action of SERT ligands.

- I. A normal hippocampal pyramidal neuron is represented. This neuron is regulated by Brain-Derived Neurotrophic Factor (BDNF), and can be innervated by monoaminergic and other signals.
- II. In depressed state, there is a decrease of brain levels of monoamines and neurotrophic factors inducing atrophy of dendritic arborization.
- III. Antidepressants might reverse the effects of stress. This can be observed by an increase in the length and density of dendritic extensions, promoting the formation of synaptic contacts. These effects could explain the onset of antidepressant response obtained with this type of SERT-targeting antidepressants.

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