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Long-Term Adaptive Changes Induced by Antidepressants: From Conventional to Novel Therapies

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1. Introduction

Major depressive disorder (MDD) is a devastating disease in terms of human suffering, health costs and economic burden to society. As described in the Diagnostic and Statistical Manual of Mental Disorders, various symptoms can be observed in depressed patients including disheartened mood, loss of interest or pleasure (anhedonia), feeling of guilt or worthlessness, disturbed sleep or appetite, low energy, poor concentration and suicidal ideation. The prevalence of MDD in the general population is 4.4% to 5% with an annual incidence of 2.4% to 3.8% [1]. Regional variation in the 12-month prevalence of the major depressive episodes was also noted, ranging from 2.2% in Japan to 10.45% in Brazil with similar averages of 5.5% in developed and 5.9% in developing countries [2]. In the USA, 59% of MDD patients experience severe degree of functional impairment, making depression the largest contributor to work loss [3, 4]. Furthermore, MDD was strongly associated to self-perceived stress, childhood adversity, working status and quality of life [5-7]. According to the estimation results reported in the global burden of disease study (a study measuring disability-adjusted life-years, DALY), MDD will have become the leading cause of disability in developed countries by the year 2030 [8], indicating that the situation is not likely to improve unless something changes. A major contributor to this crisis is the lack of adequate medication to treat a large proportion of patients. Indeed, 20% do not respond to antidepressants (ADs) recommended as “first-line” drugs, 40% do so only partially, and among responders, there is a time lag of several weeks to months before a meaningful clinical effect can be observed. Failure of clinical recovery with the first AD treatment used and high risk of relapses are also common features. A common

trait of all conventional ADs is that they have a similar mode of action, which is an enhancement of synaptic transmission of the monoamines serotonin (5-HT) and/or norepinephrine (NE) [9]. In fact, development of AD medications was largely based on the monoaminergic theory of depression that links the pathophysiology of this illness to a deficiency on cerebral 5-HT and/or NE levels. Hence, 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. Although effective, the severe side effects and toxicity of MAOIs and TCAs limited their usefulness. Later, drugs with more novel approaches, including selective 5-HT reuptake inhibitors (SSRIs), NE reuptake inhibitors (NRIs) and combined-action 5-HT/NE reuptake inhibitors (SNRIs) have been introduced, but as well as the prior generation of ADs, they act through the modulation of monoamine transporters, which may explain their suboptimal 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.

Nevertheless, the complexity and heterogeneity of symptoms of MDD makes incompatible the association of a disease with a single pathophysiological disturbance. Hence, years of research and efforts gave rise to a multitude of hypotheses trying to explain the different facets of this disorder. For example, studies have associated depression with abnormalities in the hypothalamus-pituitary-adrenal axis activity including elevated concentrations of the corticotropin-releasing hormone in the cerebrospinal fluid, increased volumes of adrenal gland and pituitary and an impairment of corticosteroid receptor signaling [10, 11]. Also, extensive studies reported circadian rhythms deregulations in depressed patients, as well as an AD effect of drugs that are capable to resynchronize this biological rhythm (i.e. agomelatine) [12, 13]. Pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factors (TNF)- α were also implicated in depressive disorders [14, 15]. Other possible mechanisms that have been suggested to be involved in the etiology and treatment of MDD include deficit in the gamma-aminobutyric acid (GABA) transmission [16], dysfunction of glutamatergic system [17], acetylcholine imbalance [18], estrogens [19, 20] and so many others [21]. In spite of these hypotheses, one of the oldest, "the monoaminergic hypothesis of depression" which assumes that MDD is caused by an imbalance in serotonergic, norepinephrinergic and possibly dopaminergic functions, is still driving clinical development of ADs since the empirical discovery of MAOIs and TCAs. Although these monoamines are undoubtedly involved, it is now recognized that, following AD administration, changes in the levels of monoamines and subsequent adaptive processes, in particular a change in the sensitivity of some of monoamine receptors, are not sufficient on their own to explain the mechanism of action of ADs. Indeed, it is difficult to correlate the time of the delayed clinical onset of AD action (several weeks) with the increase in synaptic levels of monoamines, as this change occurs already after the initial dose of the drug. In the last decade, investigations focusing on mood disturbances have been extended to brain neuroplasticity, leading to the "neurogenic and neurotrophic hypothesis of depression".

This latter postulates that development of MDD is, at least partially, related to a reduced neuroplasticity and/or depletion of neurotrophic factors which can lead to a structural deformity and functional impairment of the central nervous system.

The monoaminergic hypothesis of depression is still valid today, and intense research keeps focusing on the 5-HT system, its implication in the pathophysiology of depression and in the mode of action of ADs. Extensive data reported a number of cellular and molecular adaptive changes of the 5-HT system both at pre- (i.e. autoreceptor desensitization) and postsynaptic levels (i.e. stimulation of hippocampal neurogenesis and normalization of neurotrophins levels) following long-term treatment with various classes of ADs [22-24]. These neuroadaptations occurred with a time course consistent with the observation of a significant AD action. Naturally, a number of questions has to be asked; how the 5-HT system reacts in case of depression and after AD treatment? Which cellular and molecular actors are implicated in such reaction? Which brain areas are prevalent in these responses? To address these questions and others, the present chapter aims a better understanding of the biological basis of pharmacological treatments of depression. Attention will be paid to the neuroadaptive consequences of combination strategies (i.e. adjunction of antipsychotics) as well as promising targets on AD development (5-HT₇ receptor antagonism, 5-HT₄ agonism).

2. Neuroadaptations according to the monoaminergic hypothesis

2.1. Chronic effects of the first generation of ADs on the 5-HT system

MAOIs and TCAs were the first ADs discovered and they have proven their efficacy for treating MDD, particularly atypical depression, anergic bipolar depression and treatment-resistant depression. However, they are not supported as first-line drugs in clinical use due to life-threatening interactions with a variety of medications and common food as well as lethal cardiac irregularities [25, 26]. 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) [27-29], which is reversed by an injection of the 5-HT_{1A} receptors antagonist, WAY-100635 [28, 30].

A prolonged administration of MAOIs induces a complete recovery of the firing activity of DRN 5-HT neurons, an effect attributable to a desensitization of the somatodendritic 5-HT_{1A} autoreceptors since the reducing effect of 5-HT_{1A} receptors agonists is completely abolished (Figure 1) [31-33]. Accordingly, a reduction of the ability of 8-OH-DPAT to inhibit forskolin-stimulated adenylate cyclase activity [34] and an increase of the ED₅₀ for 8-OH-DPAT induced lower lip retraction [35] were reported after chronic treatment with MAOIs (MDL 72394, clorgyline or tranylcypromine) in rats. This desensitization of 5-HT_{1A} autoreceptors seems to occur at the level of receptor-G protein interactions rather than their simple downregulation. In fact, an autoradiographic study showed that the 5-HT_{1A} agonist-stimulated [³⁵S]-GTPγS binding is reduced in rats treated for 21 days with clorgyline [36]. Importantly, such chronic treatment with MAOIs was shown to increase the extracellular

concentrations of 5-HT, an effect greater in raphe nuclei than in their projection areas [37]. A microdialysis study measuring the extracellular levels of 5-HT in the frontal cortex of rats reported that chronic administration of the reversible MAOI MDL72394 significantly increased 5-HT amounts, without having any effect on the ability of the 5-HT_{1A} and 5-HT_{1B} agonist RU24969 to reduce these levels [38], suggesting that the sensitivity of these autoreceptors are not affected by chronic treatment with MAOIs. This is supported by data from an electrophysiological study demonstrating that long-term administration of clorgyline increased the efficacy of the stimulation of the 5-HT pathway to suppress the firing activity of CA3 pyramidal neurons of the dorsal hippocampus, whereas the enhancing effect of the antagonist of the terminal 5-HT autoreceptors methiothepin remained unchanged [39]. However, it is for high interest to note that long-term treatment with the reversible MAO-A inhibitor befloxatone resulted in a tonic activation of postsynaptic 5-HT_{1A} receptors located on the dorsal hippocampus CA3 pyramidal neurons since the highly potent and selective antagonist, WAY-100635, markedly increased the firing activity of these neurons (Figure 2) [40]. It is also noteworthy that MAO-A knock-out mice exhibit high extracellular amounts of 5-HT and an overall decrease of 5-HT_{1A} receptors density, including raphe autoreceptors as well as hippocampus and spinal cord postsynaptic receptors [41, 42]. In summary, chronic treatment with MAOIs does desensitize inhibitory 5-HT_{1A} autoreceptors, keep sensitivity of terminal 5-HT autoreceptors unaltered and enhance the tonic activation of postsynaptic 5-HT_{1A} receptors. Similarly to MAOIs, chronic treatment with TCAs (imipramine, iprindole, desipramine and femoxetine) did not change the mean firing rate of the DRN 5-HT neurons in comparison to controls [31]. However, the responsiveness to intravenous injection of the 5-HT agonist LSD or the effectiveness of microiontophoretic application of 5-HT and LSD were not altered by such treatment [31], suggesting that the sensitivity of the 5-HT autoreceptors is not modified. The 5-HT_{1A}/G-protein coupling is usually assessed by measuring [³⁵S]-GTPγS binding induced by 5-HT_{1A} receptor activation [43]. It was reported that chronic treatment with the TCA amitriptyline did not alter the 5-HT_{1A} agonist-stimulated [³⁵S]-GTPγS binding in dorsal and median raphe nuclei [44, 45], further confirming an absence of desensitization of the somatodendritic 5-HT_{1A} autoreceptor following chronic TCAs. In contrast, the same treatments have different effects on postsynaptic levels. Indeed, long-term application of imipramine increased the responsiveness of postsynaptic CA3 hippocampus pyramidal neurons to the microiontophoretic application of 5-HT or 8-OH-DPAT [46]. In accordance, Rossi et al. [45] showed that chronic administration of amitriptyline increased the 5-HT_{1A} receptor-stimulated [³⁵S]-GTPγS binding in the hippocampus, without affecting the binding of [³H]8-OH-DPAT (indicating the number of 5-HT_{1A} receptors in the coupled high-affinity agonist state). These authors suggest that, in absence of an increase in the binding of [³H]8-OH-DPAT, the increased capacity of 5-HT_{1A} receptors to activate G proteins in CA1 and dentate gyrus of the hippocampus may be due to regulatory changes at the level of the G protein, e.g. phosphorylation [45]. In summary, chronic TCA treatment does not desensitize inhibitory 5-HT_{1A} autoreceptors and enhance the sensitivity of postsynaptic 5-HT_{1A} receptors in the hippocampus.

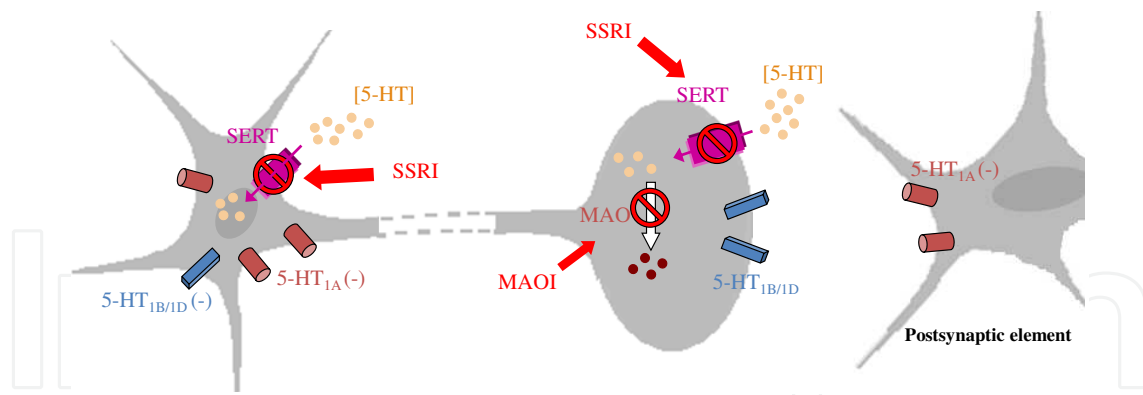


Figure 1. Representation of the effects of the serotonergic antidepressants on 5-HT neurotransmission. Monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) act on the 5-HT system, respectively, by inhibiting the 5-HT degradation and by blocking the 5-HT transporter (SERT). Their administration induces the raise of extracellular levels of 5-HT which activate 5-HT receptors. In the raphe nuclei, the somatodendritic 5-HT_{1A} autoreceptors negatively control the firing activity of the 5-HT neurons, while the 5-HT_{1B/1C} autoreceptors control the 5-HT release. Long-term administration of both classes of antidepressants desensitize 5-HT_{1A} autoreceptors. Modified from Faure et al. [22].

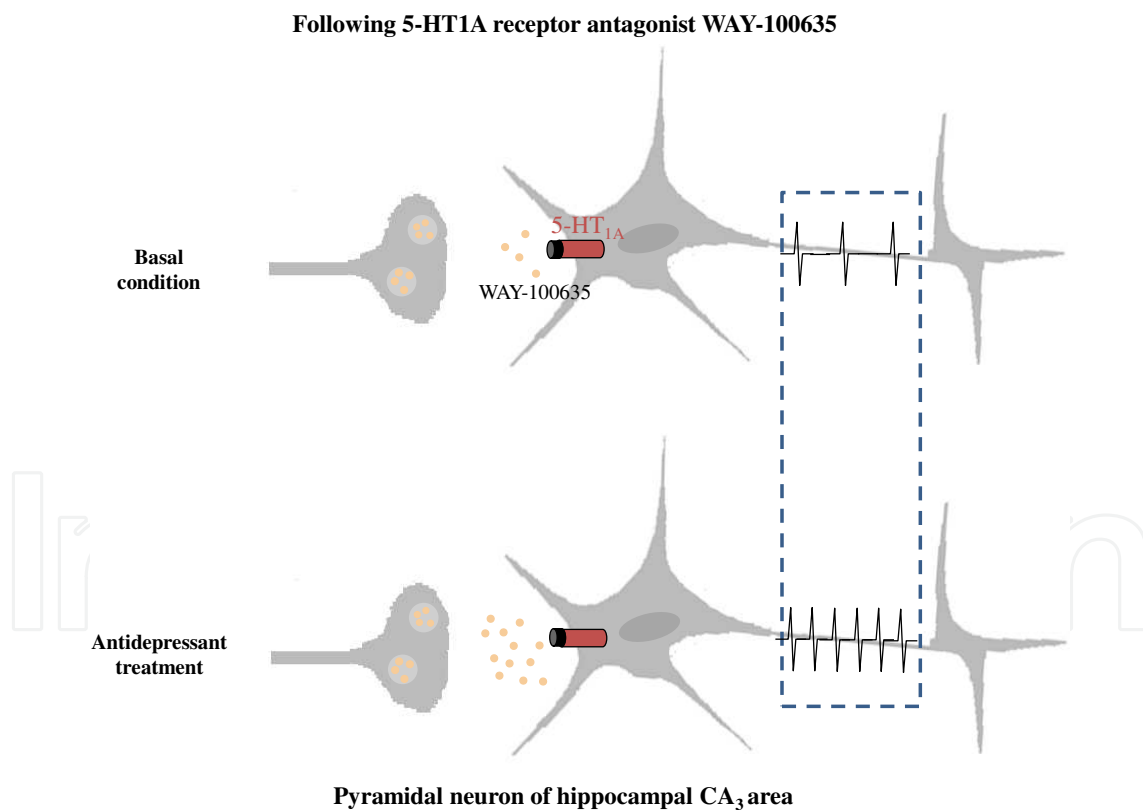


Figure 2. Representation of the effect of antidepressant treatments on hippocampal neurons. The raise of extracellular 5-HT levels decreases the firing activity of hippocampus CA₃ pyramidal neuron and this is mediated by postsynaptic 5-HT_{1A} receptors. In control animals, no or low firing activity increase is observed after administration of the antagonist WAY-100635. However, in antidepressant-treated animals, WAY-100635 disinhibits pyramidal cells, suggesting that antidepressants increase 5-HT tone in the hippocampus. Modified from Blier and de Montigny [201].

2.2. Chronic effects of the SSRIs on the 5-HT system

SSRIs represent the first-line ADs in clinical use nowadays, mainly due to their relatively lower burden of adverse effects and safety in overdose. SSRIs include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram and more recently vilazodone [47, 48]. These drugs are believed to exert their effects by blocking SERT, which induces an increase of 5-HT synaptic levels. In turn, the chronic enhancement of 5-HT bioavailability produces numerous neuroadaptive changes leading to an enhancement of the 5-HT neurotransmission (Figure 1) [22, 40, 49]. In particular, it was widely reported that acute administration of SSRIs inhibits the firing activity of the 5-HT neurons in DRN, resulting from an enhancement of somatodendritic 5-HT release which activates the 5-HT_{1A} autoreceptors [50-55]. However, immunoelectron microscopy studies using specific antibodies showed a significant decrease of the 5-HT_{1A} immunogold labeling of the plasma membrane of the DRN dendrites and an increase in their cytoplasmic labeling after a single injection of the SSRI fluoxetine in animals, indicating an internalization of these autoreceptors under acute conditions [56, 57]. Importantly, a very recent double-blind positron emission tomography study investigated the binding of the 5-HT_{1A} radioligand [¹⁸F]MPPF in human volunteers after taking a single tablet of fluoxetine or placebo. This study clearly demonstrated that in DRN, and nowhere else in the brain, a significant decrease in [¹⁸F]MPPF binding potential between fluoxetine and placebo [58]. In animals, this autoreceptor internalization seems to be very transient since a microdialysis study reported that administration of a 5-HT_{1A} receptor agonist a few hours after single injection of fluoxetine reverses the SSRI-induced increase in the 5-HT levels [59]. Short-term treatment with SSRIs also reduced the firing activity of the DRN 5-HT neurons [50]. Only chronic (2 to 3 weeks) treatments with these drugs completely recover the 5-HT firing activity, and this is accompanied with a desensitization of the somatodendritic 5-HT_{1A} autoreceptors [50, 51, 60, 61]. Interestingly, when rats chronically treated with fluoxetine were challenged with a single dose of 8-OH-DPAT, there was no internalization of the 5-HT_{1A} autoreceptors in keeping with their desensitized form [62]. In fact, after such treatment, neither the density of the 5-HT_{1A} autoreceptors on the plasma membrane of DRN neurons nor the [¹⁸F]MPPF binding were changed [56, 58, 62, 63]. One explanation is that, after repeated internalization and retargeting, functional 5-HT_{1A} autoreceptors are replaced by receptors uncoupled from their G proteins (inactivated form of the receptor) on the plasma membrane of DRN 5-HT neurons [62]. However, controversial results have been reported about the effects of chronic SSRI treatment on the functional status of the 5-HT_{1A} autoreceptors. An attenuation of 8-OH-DPAT-mediated [³⁵S]-GTPγS stimulation has been consistently observed in the DRN by certain groups after chronic fluoxetine [36, 44, 49, 64, 65], while others reported no change in this parameter after chronic sertraline or citalopram [63, 66]. These findings raised the possibility that SSRIs may not be a homogenous class of AD drugs with regard to the mechanism by which the function of somatodendritic 5-HT_{1A} autoreceptors is regulated. Thus, at least in the case of fluoxetine, acute and chronic treatments seem to induce two distinct types of 5-HT_{1A} autoreceptor desensitization: one rapid and reversible (associated with the internalization of the functional pool of membrane-bound receptors), the other being progressive and long-lasting, no longer accompanied with receptor sequestration, but which probably resulted from the reiteration of this process throughout the course of chronic fluoxetine treatment [58]. Another

picture can be drawn for the postsynaptic 5-HT_{1A} heteroreceptors. In fact, neither acute nor chronic treatment with SSRIs induced a change in the subcellular distribution of the 5-HT_{1A} receptors in dendrites or in the *in vivo* binding of the 5-HT_{1A} radioligand [18F]MPPF in projection areas, particularly hippocampus and frontal cortex [56, 62, 63]. Such differences between 5-HT_{1A} receptors in DRN and projection areas were explained by a differential coupling, the autoreceptors being coupled to G α_{i3} while heteroreceptors are coupled to G α_o protein [67]. However, agonist-induced [³⁵S]-GTP γ S binding data showed an increase [36, 63, 64] or no change [44, 49, 68] after long-term SSRI treatment, further adding complexity to the whole picture. Importantly, long-term application of SSRIs produced an increase in tonic activation of pyramidal neurons, indicated by the disinhibition of firing rate in response to the antagonist WAY-100635 (Figure 2) [40, 51]. This further supports the increase of the efficacy of the 5-HT neurotransmission seen *in vivo* (enhancing the effectiveness of the stimulation of the 5-HT pathway to suppress the firing activity of CA3 pyramidal neurons) and *in vitro* (increasing the electrically-evoked release of tritiated 5-HT from preloaded hippocampal slices) [46, 69]. More recent studies noted a decrease in the density of the 5-HT₄ receptor binding in the CA1 field of hippocampus of rats as well as in several areas of the striatum after a 21-day treatment with the SSRI fluoxetine [70]. The activity of these postsynaptic receptors in the hippocampus, measured as the excitatory action of the 5-HT₄ agonist zacopride in pyramidal cells of CA1 evoked by Schaffer collateral stimulation, was attenuated also after such chronic treatment [70]. This suggests a net decrease in the signalisation pathway of 5-HT₄ receptors after chronic SSRI treatment. In addition, desensitization of the 5-HT₇ receptors [71] and downregulation in the 5-HT₇ binding site in the hypothalamus [72] were reported following chronic treatment with fluoxetine.

Another interesting consequence of chronic, but not acute, treatment with SSRIs is a reduction of the surface expression of SERT. In fact, electron microscopy studies reported that long-term administration of fluoxetine induced an internalization of SERT in both cell bodies and axon terminals of 5-HT neurons [58]. Moreover, the total amounts of SERT immunoreactivity is also reduced, suggesting that, rather than a simple internalization, a long-term degradation of this protein happened in the course of the treatment [58].

2.3. Chronic effects of new antidepressant strategies

The suboptimal efficacy and the delayed onset of action of different classes of ADs raises the necessity to find new strategies to treat depression, especially treatment-resistant depression and depressive episodes associated with bipolar disorders. For example, a number of second-generation antipsychotics have been investigated and approved for use as augmentation agents in combination with currently approved first-line ADs such as adjunctive aripiprazole, olanzapine or quetiapine to standard doses of SSRIs [73-75]. The effect of such combination on the 5-HT system is yet not well described in the literature, and only very recent preclinical studies began to investigate their mechanisms of action. For example, Chernoloz et al. [76] showed in rats that long-term administration (14 days) of quetiapine alone or in combination with the SSRI escitalopram led to significant inhibition of the spontaneous firing activity of the DRN 5-HT neurons, while escitalopram alone (as previously described for SSRIs) induced a

recovery of this neuronal activity at this time point. Co-administration of quetiapine and escitalopram for 14 days produced an increase in tonic activation of postsynaptic 5-HT_{1A} receptors located on the dorsal hippocampus CA3 pyramidal neurons, but in the same range as that obtained with chronic escitalopram alone [76]. The enhancement in 5-HT transmission produced by this combination was attributable to the attenuated inhibitory function of α_2 -adrenergic receptors on 5-HT terminals and possibly to direct 5-HT_{1A} receptor agonism by quetiapine [76]. Similarly, risperidone co-administered with escitalopram for 14 days was shown to prevent the restoration of the 5-HT neuronal firing rate, obtained with the SSRI alone [77]. Therefore, it might be suggested that risperidone co-administrated with the SSRIs increases 5-HT neurotransmission by indirect action on the 5-HT system. Indeed, Marcus et al. [78] reported that adjunctive low-dose of risperidone to escitalopram significantly enhanced both dopamine outflow and NMDA receptor-mediated transmission in the medial prefrontal cortex (PFC) of rats. Taken together, these results pointed out the possibility that, rather than a direct action on the 5-HT system, combining an SSRI and an antipsychotic of second-generation implicate multiple neurotransmitter systems to exert their beneficial effects.

Among novel targets to develop more efficacious and fast-acting ADs, 5-HT₄ and 5-HT₇ receptors are promising candidates [71, 79]. For example, brain regional changes in the binding of the 5-HT₄ receptors were found in murine models of depression-related states including olfactory bulbectomy model, glucocorticoid receptor heterozygous mice and Flinders sensitive line depression model [80, 81]. Lucas et al. [79] showed in rats that a 3-day treatment with the 5-HT₄ receptor agonist RS67333 modifies several rat brain parameters considered as key markers of AD action, which are changed only after 2 to 3 weeks with classical ADs. These changes include desensitization of the 5-HT_{1A} autoreceptors and increased tonus on hippocampal postsynaptic 5-HT_{1A} receptors [79]. Accordingly, subchronic (3 days) administration of RS67333, but not acute, increased basal 5-HT levels and decreased its metabolite levels 5-HIAA in the rat ventral hippocampus [82]. Furthermore, a 3-day co-administration of the SSRI citalopram and a 5-HT₄ receptor agonist, RS67333 or prucalopride, resulted in an increase of DRN 5-HT neuron mean firing activity, displaying a similar, or even slightly superior, firing amplitude obtained with each agonist alone [83]. At the postsynaptic level, this translated into the manifestation of a tonus on hippocampal postsynaptic 5-HT_{1A} receptors, which was two to three times stronger when the 5-HT₄ receptor agonist was combined with citalopram [83]. This suggests an important increase on the 5-HT neurotransmission following adjunction of an SSRI to a 5-HT₄ receptor agonist, clearly indicating a rapid AD-like potential of these agonists.

Moreover, antipsychotics (lurasidone, amisulpride), as well as a novel AD-like multimodal 5-HT agent (Lu-AA21004), have been proved to be potent 5-HT₇ antagonists [84-88]. Furthermore, genetic deletion of this receptor confers to mice AD-like behaviors including decreased immobility in the forced swim and tail suspension tests as well as shorter and less frequent episodes of rapid eye movement sleep [89], indicating that antagonists might have therapeutic value as ADs. In this context, we showed that a 1-week treatment with the selective 5-HT₇ receptor antagonist, SB-269970, did not alter 5-HT firing activity but desensitized somatodendritic 5-HT_{1A} autoreceptors and enhanced the tonic activation of

postsynaptic 5-HT_{1A} receptors in the hippocampus [71]. Taken together, these findings show that new AD strategies targeting 5-HT receptor manipulation resulted in similar adaptive changes of the 5-HT system than those produced by classical ADs, except that they took place faster in both pre- and postsynaptic levels.

In summary, a change of 5-HT receptor sensitivity that occurs only after chronic treatment seems to be a common mechanism of AD action, which takes place depending on the delay onset of action of each 5-HT AD. This represents the major argument supporting the 5-HT hypothesis of depression. However, it became obvious that depression involves further modifications besides those at the 5-HT system. Several studies emerged to assess new pharmacological models that may help to better understand the mechanisms and pathophysiological changes leading to a depressive behaviour.

3. Neurogenic and neurotrophic adaptations induced by 5-HT antidepressants

Recent studies indicate that an impairment of cellular and synaptic plasticity in specific areas of the brain, especially the hippocampus and PFC, may be a core factor in the pathophysiology of depression. The abnormal neuronal plasticity including neurogenesis, axon branching, dendritogenesis and synaptogenesis was suggested to be related to alterations in the level of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) which plays a central role in the adaptation of neural networks. Numerous studies reported that AD treatments may act by normalizing neurotrophic levels in the brain and enhancing neurogenesis and synaptogenesis, leading to a gain of function in neuronal networks altered by depressive states. In the following paragraphs, we enumerate the chronic effects of the previously cited AD strategies on the cellular and synaptic plasticity, as well as neurotrophin expression. A critical view of the role of each parameter on the etiology of depression and AD action is also described.

3.1. Neurogenesis

The first evidence of newly generated neurons in the adult central nervous system was reported in 1965 when Altman and Das [90] used ³H-thymidine to label proliferating cells in the rat dentate gyrus (DG) of the hippocampus. Subsequent studies confirmed the existence of this hippocampal neurogenesis in adulthood in several species including humans [91, 92], using the new tool bromodeoxyuridine (BrdU), a thymidine analog that labels dividing cells in S-phase [93]. In the hippocampus, progenitor cells are located in the subgranular zone (SGZ) where they divide and a subset of the new cells survive, migrate into granule cell layer and differentiates into neurons. An excellent review of Hanson et al. [94] described the timeline of cell division and maturation as well as markers of cells from different stages of neurogenesis in the SGZ. The subventricular zone (SVZ) was also identified as a highly neurogenic area of the adult brain [95], although other regions retain the potential to generate new neurons [96-98].

The hippocampal neurogenesis was shown to be implicated in the pathophysiology of depression (Table 1). Clinical studies showed that patients suffering from MDD had lower hippocampal volume than healthy subjects [99, 100], that may be linked to increased neuronal atrophy. Only patients who remitted after 8 weeks of AD treatment present larger hippocampal volume in comparison to subjects who did not remit [101]. A more evident correlation came firstly from the preclinical study of Santarelli et al. [102]. In this study, mice treated 28 days with the SSRI fluoxetine exhibited an increase in the number of BrdU-positive cells in the SGZ of DG with a concomitant decrease in the latency to feed in the novelty suppressed-feeding (NSF) paradigm. However, ablation of cell proliferation in the SGZ, but not the SVZ, following X-ray treatment suppressed behavioral responses to chronic fluoxetine [102]. The requirement of hippocampal neurogenesis for therapeutic efficacy of ADs was subsequently confirmed in non-human primates [103]. Consistent with the time course of their therapeutic action, only chronic treatment regimen with MAOIs [104, 105], TCAs [106, 107], SSRIs [61, 102, 105, 108], putative fast-acting AD drugs including 5-HT₄ agonists [79] and 5-HT₇ antagonists [71] and finally adjunctive strategies (olanzapine plus fluoxetine) [108] increased the cell proliferation in the SGZ of the hippocampus at comparable extent. This indicates that upregulation of hippocampal neurogenesis may be a common denominator of the mechanism of action of ADs. Although the function of these newly generated cells in the adult brain is still unclear, it has been suggested that young granule cells constitute a distinct population exhibiting a greater degree of plasticity than mature neurons. In particular, they display a reduced threshold to induction of long-term potentiation (LTP) [109], and 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 [110].

Given the emergence of new data, the initial research cited above suggesting a model of hippocampal degeneration as basis of depression and reversal by ADs through neurogenesis seems to be uncertain. In fact, as chronic ADs, mood stabilizers (lithium) and atypical antipsychotics induce hippocampal cell proliferation [108, 111-113], but whether these drugs can be used as monotherapy in depression is an area of debate and clinical data failed to support it. It is also noteworthy that, even in the famous study of Santarelli et al. [102], X-ray of hippocampus suppressing neurogenesis in non-treated rats failed to induce a depressive-like behavior. Accordingly, cyclin D2 (a protein involved in the cell cycle regulation) knock-out mice, specifically lacking adult brain neurogenesis, showed normal anxiety levels in the open-field and elevated plus maze [114]. In contrast, increasing hippocampal neurogenesis in mice was not reported to produce anxiolytic or AD-like behavioral effects [115]. These latter reports add complexity to the understanding of the role of altered neurogenesis in the pathology of depression. That is why, some neuroscientists postulate that, beyond a simple increase of hippocampal neurogenesis in response to ADs, insertion of the newly generated neurons (even a small number) in functional neural networks especially through synaptogenesis, may be more relevant for the explanation of their mechanism of action.

In this context, an elegant theory in which neurogenesis is seen as an epiphenomenon of a more widespread alteration in dendritic length and spine number was already proposed [116].

According to this theory, exposure to chronic stress and stressful life events increases excitotoxic glutamatergic neurotransmission in multiple brain areas. To protect neurons from consequent apoptosis, dendrites retract and spine number decreases thus limiting the number of exposed glutamate receptors.

3.2. Synaptic plasticity and synaptogenesis

The regulation of synapse formation or synaptogenesis is a subcellular neuronal alteration that contributes to synaptic plasticity [117, 118], which defines the ability to integrate informations from different neuronal inputs and make the appropriate adaptive responses. An increase in functional synaptogenesis is typically accompanied by an increase in the number of dendritic spines, the physical site of synaptic connections [118, 119]. In recent years, it has become clear that spines are dynamic structures that undergo rapid remodeling important for synapse formation, function and plasticity [120, 121]. In the adulthood, spines continue to remodel in response to a variety of physiological stimuli. For example, synaptic activity that induces LTP, a long-lasting enhancement of synaptic strength, promotes spine enlargement and new spine formation [122], whereas activity that induces long-term depression (LTD), a persistent weakening of synaptic strength, causes spine shrinkage or retraction [123]. The potential role of spines and dendrites in MDD (Table 1) is supported by preclinical studies demonstrating that exposure to chronic stress negatively influence dendritic spine density and morphology in brain areas such as DG, CA1 and CA3 subfields of the hippocampus and PFC [124-126]. This includes a decrease in spine density, dendritic length and branch number [127, 128]. These effects could contribute to the reduction in volume of PFC and hippocampus determined by imaging the brains of depressed patients [100, 101, 129]. In accordance, a recent study revealed lower expression of synaptic function-related genes in the dorsolateral PFC of MDD subjects and a corresponding lower number of synapses [130].

As for neurogenesis, ADs regulate these different forms of synaptic plasticity. Synaptic communication is altered by chronic stress which impairs LTP and facilitates LTD induction in the CA1 of the hippocampus [131-133]. It has been reported that repeated application of the SSRI fluvoxamine (21 days) increased the extent of LTP induction in the CA1 region of rats that experienced chronic mild stress [131]. Using rats neonatally-exposed to clomipramine as an animal model of depression, Bhagya et al. [134] found that these animals displayed a decreased LTP in the hippocampal CA1 and a 14-day treatment with the SSRI escitalopram restored this LTP. Similarly, retrieval of LTP in the CA1 field of hippocampus was obtained in stressed animals after repeated application of other classes of ADs including the SNRI milnacipran and electroconvulsive stimulation (ECS) [132, 135]. In contrast, other groups described an impairment of LTP after chronic SSRI fluoxetine, TCA imipramine, SNRI venlafaxine or ECS, but in non-stressed animals [136-138], indicating a stress-dependent action of the ADs on hippocampal LTP. In the same way, chronic fluoxetine was reported to increase dendritic spine density and arborization of granule cells in the mouse hippocampus [139, 140]. Daily administration of fluoxetine to ovariectomized rats for 5 days was shown to induce a robust increase in pyramidal cell dendritic spine synapse density in the hippocampal CA1 field, with similar changes appearing in CA3 after 2 weeks of treatment [141]. This rapid

synaptic remodelling might represent an early step in the fluoxetine-induced cascade of responses that spread across the entire hippocampal circuitry, leading to the restoration of normal function in the hippocampus [141]. In accordance, a recent study using ovariectomized hamsters exposed to diminished light at night displayed depressive-like behaviors and reduced hippocampal CA1 dendritic spine density, but a 2-week treatment with citalopram rescued this behavior and moderately improved the spine density in the CA1 but not fully restored it [142]. Also, chronic treatment with the TCA amitriptyline reversed the bullectomy-induced reduction in dendritic spine density in CA1, CA3 and dentate gyrus of hippocampus [143]. It has to be noted that single injection of the 5-HT₄ receptor partial agonist SL65.0155 does not promote spine growth in the naive mouse hippocampus [144], and the 5-HT₇ receptor agonist AS-19 increased neurite length and number in primary embryonic hippocampal neurons [145], still the characterization of the *in vivo* effects of their chronic manipulation is missing. It is obvious that the effects on synaptic plasticity of chronic treatment with different AD strategies will be an important area of further research.

Significant evidence suggests that ADs regulate synaptic plasticity and reorganization through the modulation of cell adhesion protein and synaptic function/structure related genes. In particular, the neural cell adhesion molecule NCAM is necessary for activity-dependent LTP in the hippocampus [146]. Its highly sialylated isoform PSA-NCAM promotes plasticity through the negatively charged PSA, postulated to be a spacer that reduces adhesion forces between cells allowing their dynamic changes [147]. It was reported that chronic treatment with the selective MAO-B inhibitor deprenyl, the TCA imipramine or the SSRI fluoxetine increased the expression of PSA-NCAM in the hippocampus and medial PFC [148-151]. Interestingly, chronic exposure to second-generation antipsychotics olanzapine or risperidone enhances PSA-NCAM expression in the PFC, but not in the hippocampus, suggesting that modulation of cell adhesion protein in the hippocampus may be specific to the mechanism of action of ADs [152, 153]. Moreover, an increased expression of synaptophysin, a glycoprotein localized in presynaptic vesicle membranes required for docking and fusion of neurotransmitter-containing synaptic vesicles as well as endocytosis [154], was observed in hippocampus and/or cerebral cortex of rats chronically treated with the MAOI tranylcypromine, the TCA amitriptyline or the SSRI fluoxetine [148, 155, 156]. Also, Arc (Activity-regulated, cytoskeletal-associated protein), a highly expressed protein in dendrites and postsynaptic densities [157] is implicated in LTP and spine size and type [158-160]. Repeated administration (14 days) of the SSRI paroxetine, the TCA desipramine or the MAOI tranylcypromine increased Arc mRNA and the number of Arc-immunoreactive cells in frontal and parietal cortex as well as in the CA1 region of the hippocampus, while acute injection had no effect [161].

How do ADs exert their effect on synaptic plasticity is a matter of discussion. Several putative mechanisms have been proposed in this context. However, the observation that antidepressants increased anti-apoptotic factors and the synthesis of neurotrophic factors raises the possibility that these drugs act via a mechanism of neuroprotection rather than a neuroregeneration [23]. Particular attention was given to neurotrophins such as brain-derived neurotrophic factor (BDNF).

3.3. Neurotrophins modulation by 5-HT antidepressants

Neurotrophins are growth factors with crucial roles in the formation and plasticity of neuronal networks [162], and BDNF is the most studied in this context. The dystrophic action of stress was reported in animal models of depression (Table 1). Animals exposed to chronic stress such as chronic mild stress or social deprivation displayed a decrease in the protein levels of BDNF and an increase of its receptor tyrosine-kinase TrkB in several brain regions including hippocampus (DG, CA1 and CA3), frontal cortex and midbrain [163-168]. BDNF-deficient mice or with specific knockdown of BDNF in the DG also displayed depressive-like behaviors [169, 170]. Accordingly, drug-free MDD patients showed lower serum or plasma BDNF levels in comparison to healthy subjects [171-174]. Moreover, human BDNF gene polymorphism Val66Met was suggested to be related to the pathophysiology of MDD and affect clinical response to AD treatment [175-177].

Studies	Stress type	Neuroplasticity consequence	References
<i>Preclinical</i>			
	Repeated restraint stress paradigm in rats	Reduction on the number and length of apical dendritic branches in mPFC	[127] [126]
		Atrophy of apical dendrites of CA3 pyramidal neurons	[201]
		LTP suppression in DG and CA3 in a site-specific manner	[202]
		Chronic unpredictable stress paradigm in rats	Dendritic atrophy in CA3 region
	Chronic corticosterone administration in rats	Atrophy in granule and CA1 pyramidal neurons	[125]
		Dendritic atrophy in CA3 area	
		Retraction of apical dendrites in mPFC	[205]
		Decrease in BDNF mRNA level in hippocampus and cerebral cortex	[204]
	Chronic sleep deprivation in rats	Decrease in hippocampal volume	[207]
		Suppression of cell proliferation in the hippocampus	[208]
		Impairment of LTP in the CA1 region	[209]
<i>Clinical</i>			
	Unipolar depression	Lower hippocampal volume	[99, 210]
		Volume reduction in orbitofrontal cortex, frontal cortex, hippocampus, striatum, and cingulate cortex	[128]

Studies	Stress type	Neuroplasticity consequence	References
	Recurrent MDD	Lower hippocampal volume	[211, 212]
		Reduced volume in dorsolateral prefrontal cortex	[213]
		Lower plasma BDNF	[172]
	First-episode depression	Lower hippocampal volume	[214, 215]
		Smaller left hippocampal volume only in males	[216]
		Lower plasma BDNF	[172]
	Late-life depression	Reduction in hippocampal volume	[217, 218]
		Specific reduction in left hippocampus	[219]
		Volume reduction in orbitofrontal cortex, putamen and thalamus	[217]
		Lower plasma BDNF	[220]
	Familial recurrent MDD	Smaller volume of the right hippocampus	[221, 222]
	Cumulative adversity (recurrent stressful life events)	Smaller volume in medial prefrontal cortex, insular cortex and subgenual anterior cingulate regions)	[223]

Table 1. Effects of chronic stress and depression on different neuroplasticity actors in the brain. mPFC: median prefrontal cortex. DG: dentate gyrus. LTP: long-term potentiation. BDNF: Brain-derived neurotrophic factor. MDD: major depressive disorder.

Intracortical infusion of BDNF in the adult rat was shown to produce a robust sprouting of 5-HT nerve terminals and accelerated the regrowth of 5-HT axons in basal conditions or following their destruction [178, 179]. AD treatments could oppose or reverse the actions of stress on the 5-HT system via a positive action on cerebral BDNF. Indeed, several studies showed that long-term AD treatments including SSRIs (fluoxetine) and MAOIs (tranylcypromine, phenelzine) increase BDNF levels in the brain [168, 180-182], although a time-dependent modulation seems to occur. Indeed, De Foubert et al. [182] demonstrated in rat hippocampus that a 4-day administration of the SSRI fluoxetine decreased BDNF mRNA levels, a 7-day treatment had no effect, but a 14-day treatment increased it. One explanation of this biphasic change in BDNF gene expression could be a differential transcript regulation, since the rat BDNF gene expresses four mRNA isoforms which can be modulated by different signaling cascades. In fact, a recent study demonstrated that acute injection of fluoxetine or tranylcypromine decreased total BDNF mRNA (exon V) as well as exon IV mRNA with no significant changes on exon I or III mRNAs [183]. In contrast, chronic administration of these two drugs enhanced expression of exon V and exon I mRNAs with no changes for exon III or IV [183]. It is of high interest to note that ADs, besides regulating BDNF levels in naive animals, normalize it under stress conditions. Hence, chronic treatment with fluoxetine increased the BDNF protein till control levels in the hippocampus of rats experiencing chronic mild stress [184], indicating that AD treatment can oppose the dystrophic actions of stress. Accordingly, clinical studies reported that untreated depressed patients showed a decrease of serum or platelet

BDNF levels before treatment, and a normalization of this parameter following several weeks of SSRI (escitalopram or paroxetine) administration accompanied with an improvement in depressive symptoms [185, 186]. Unfortunately, very few studies were conducted in this field using novel ADs targeting the 5-HT system. For example, subchronic administration (3 injections in 24h) of the 5-HT₄ receptor partial agonist SL65.0155, but not citalopram or clomipramine, was reported to enhance hippocampal BDNF protein levels in rats, further supporting a fast-acting AD profile of 5-HT₄ receptor agonists [187]. Also, Agostinho et al. [188] reported that combinatory treatment for 28 days with olanzapine and fluoxetine had no effect on BDNF protein levels but enhanced specifically in the PFC the protein levels of NT-3, a neurotrophin implicated in the pathophysiology of MDD [189]. However, these authors reported also that 28 days of fluoxetine administration did not increase BDNF proteins levels neither in the hippocampus nor in the PFC, even at high doses [188], raising some concern about this study. Obviously, more investigations are needed to characterize the exact effects on BDNF of these new treatment strategies.

4. Conclusion

The study of MDD is a real challenge for those who want to reveal the pathophysiological basis of this disease. The monoaminergic and neurotrophic/neurogenic hypotheses cited in this review give only a partial explanation of this basis. In the former, the function of a number of 5-HT receptors is still not yet elucidated and growing data implicate each receptor in a different way in the AD mechanism of action. In the latter, the role of new-added neurons in the hippocampus is still under investigation, although their integration in functional networks may confer additional plasticity to rescue stress effects. These hypotheses can be considered complementary as the activation of monoamine receptors may modulate the expression of intracellular proteins and neurotrophic factors, permitting the re-organization of complex neuronal networks involved in depression. Hence, ADs, particularly those targeting the 5-HT system, were shown to induce changes at the level of 5-HT autoreceptors localized in the raphe nuclei as well as the activation of neurotrophic factors expression and induction of cellular proliferation within projecting areas such as the hippocampus. Yet, combining these two hypotheses is not sufficient to fully explain the pathophysiology of depression, since conventional ADs were shown to modulate each factor (5-HT sensitivity, hippocampal cell proliferation, neurotrophic expression), but still displaying moderate efficacy to alleviate depression symptoms. Thus, the re-construction of a new and more convincing model is an urgent necessity.

While there has been a major emphasis on the co-incidental changes in neurotransmitters and the related receptors, neurogenesis and neurotrophic factors, less attention has been paid to changes in glia. These non-neuronal cells, particularly astrocytes, were long considered to have simple supportive role for neurons providing structure and adequate environmental conditions for neuronal functions. However, recent discoveries changed this view and led to a reconceptualization of neuronal signaling with astrocytes forming an integral part of the “tripartite synapse” along with the pre- and postsynaptic neurons [190]. In fact, glia was shown

to use variations in cytoplasmic calcium as a form of cellular excitability allowing signaling to other glia, neurons and blood vessels [191]. The astrocytes excitability can be triggered by various neurotransmitters receptors expressed on glia and, in turn, these cells can release a wide variety of gliotransmitters including glutamate, adenosine triphosphate and D-serine, which regulate synaptic transmission and plasticity [191] [192]. Strikingly, reductions in the density and ultrastructure of glial cells were detected in fronto-limbic regions in major depression [193, 194], indicating the relevance of studying these cells in the pathophysiological basis of MDD. Also, glial cells seem to play a central role in inflammation that contributes to the main symptom of depression [195, 196], while fluoxetine requires microglia to exert its neuroprotective action [184].

Being a heterogeneous condition, depression is unlikely to be explained by a single pathophysiological disturbance, hence, it is not expected that a single mechanism of drug action can be uniformly effective. A new vision in which neurons and glial cells are involved side by side will be more adequate to explain the heterogeneity of MDD. In the basis of very recent researches, a “network hypothesis”, in which information processing implicating neurons and glia within particular brain networks is altered in MDD and can be improved by AD treatment, can be proposed. Hence, Sheline et al. [197] reported, in depressed subjects, a dramatic increase in connectivity of three different brain networks: the cognitive control network, default mode network and affective network, with the “dorsal nexus”, a bilateral region of the dorsal medial PFC. Recent reports using subpsychomimetic doses of ketamine, an ionotropic glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, showed a rapid AD response in MDD subjects [198], which is hypothesized to be mediated by i) lower Glx/glutamate ratio in the PFC associated with reductions in glial cells in the same region [199] and, ii) decreased functional connectivity of the default mode network to the dorsal nexus [200]. More investigations are needed to define how brain networks can respond faster to this novel antidepressant, how neurons and glia are implicating in such process and how the involved mechanism can be used to the discovery of new treatment strategies in MDD.

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