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PHARMACOLOGICAL PROPERTIES AND INNOVATIVE THERAPEUTIC TARGETS OF NOVEL COMPOUNDS USED TO TREAT MAJOR DEPRESSION

Introduction: unmet needs in the treatment of major depressive disorder

Major depressive disorder (MDD) is one of the most common and disabling psychiatric conditions worldwide and is associated with significant disability and functional impairment [1-3]. Although many medications are available for this complex disorder [4], antidepressant treatment is mainly limited by: delay in the onset of therapeutic effects, poor adherence and adverse long-term effects (in particular weight gain and sexual dysfunction). In addition, according to the STAR*D trial of Nierenberg et al. [5], although most of the investigated patients responded to commonly available psychoactive treatments and achieved remission, they still suffered from at least one residual depressive symptom, which is a known predictor of relapse/recurrence in the long-term. Moreover, non-response to traditional antidepressants is another relevant issue, as more than 20% of MDD patients do not respond or don't recover completely from their illness. These individuals may be considered as affected by treatment-resistant depression [6].

Given that first-line antidepressant medications mainly target the reuptake or breakdown of monoamines, this further highlighted the need to extend the knowledge on MDD pathogenesis and to promote the translation of such findings into novel, effective therapeutic agents. Over the last two decades, research have discovered several novel molecular targets which may be actively involved in the pathophysiology of MDD [4 7 8]. This knowledge has provided intruiging insights into the development of novel antidepressant molecules, some of which have already passed rigorous clinical testing.

The aim of the present review was to summarize the relevant research on novel molecular/cellular targets and recently marketed antidepressant medications which may change the landscape of the treatment of major depression in the near future.

Overview of current treatment strategies with available antidepressant medications

The pharmacological treatment of depression had its inception more than fifty years ago, when tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were introduced in the clinical world. Later, the 1980s saw the marketing of SSRIs, which presented with a great

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advantage in terms of safety and tolerability [9]; in the early 1990s serotonin and norepinephrine reuptake inhibitors (SNRIs) were introduced, including venlafaxine, desvenlafaxine and duloxetine [10], together with modern SSRIs such as sertraline, paroxetine, and citalopram. The latter are generally regarded as first-line treatment for a depressive episode, but, as stated above, they result in the remission of only a subset of patients.

Whereas, the following treatment options are currently reccomended for patients that do not respond to antidepressant treatment: 1) revision of the psychiatric diagnosis; 2) medication augmentation; 3) switch to another antidepressant medication [11]. The substitution of first-line antidepressant with another first-line medication is currently the most commonly used therapeutic strategy. However, two consecutive trials with different psychoactive medications usually require approximately 6 weeks, and the delay in achieving adequate antidepressant effects is associated with relevant drop-out rates from treatment (al least 50% of patients), which commonly occurs within the first months of treatment [12]. Thus, in order to correctly treat depression and achieve remission it would be fundamental to rapidly identify the correct treatment otption.

Current guidelines advise against combination treatment has been commonly mainly due to the enhanced risk of medication interactions and poor tolerability. Whereas, the use of antidepressant combinations with additive mechanisms of action may represent a useful strategy before augmenting with medications of different classes [13 14]. Interestingly, combining different pharmacological actions affecting multiple monoamine targets is associated with greater efficacy [14]: this reinforces the notion that is may be possible to further improve the outcomes of depression by integrating novel pharmacological agents with different mechanisms of action.

Novel molecular targets of antidepressant drugs: neurotrophins and intracellular pathways

The neurotrophic hypothesis of depression. Neurotrophic factors play a fundamental role in neuronal development, growth, survival as well as neuroplasticity [15-19]. Whereas, chronic stress is associated with a significant reduction in hippocampal neurotrophins levels and volume, as is commonly observed in depression [20]. These and other findings support the neurotrophic hypothesis of depression, postulating that the long-term effects of stress/depression are mediated by a deficiency of neurotrophins [21]. According to this hypothesis, altered neurotrophic signaling is viewed as one of the most relevant factors in the pathophysiology of major depression. Consistently, the latency of antidepressant action is explained with that of neuroplasticity, which is usually occurs after 3-4 weeks of treatment with traditional antidepressant drugs [15 22 23].

Hippocampal neurogenesis is regulated by several neurotrophic factors such as brain-derived-neurotrophic factors (BDNF), insulin-like growth factor I (IGF-I), and vascular endothelium growth factor (VEGF-B) [24-27]. Chronic mild stress has been reported to be associated in animal models with a general reduction of neurogenesis together with reduced hippocampal BDNF levels. Importantly, antidepressant drugs may reverse stress-induced changes and enhance neurogenesis by normalizing BDNF levels [28-30]. Indeed, by inhibiting 5-HT2A/2C receptor, these molecules are able to reverse stress-induced downregulation of BDNF mRNA in the hippocampus leading to adaptations of synaptic strength that may mediate either some short- and long-term behavioral effects of these compounds [31].

Hippocampal neurogenesis may be also enhanced by VEGF [32] as observed by the decline of immature neurons in VEGF-B knockout mice [33]. Kiuchi et al. [34] suggested that VEGF Flk-1 (a Receptor for VEGF) signaling plays a crucial role in ameliorating the adult hippocampal cell proliferation together with the survival of newly hippocampal neurons promoted by antidepressants. Interestingly, after silencing of hippocampal VEGF [35] or using antagonists for its receptor Flk-1 [34], VEGF antidepressant-like properties are interrupted and it has been reported that markers of newborn neurons as doublecortin were drastically reduced. Both electroconvulsive therapy (ECT) [36] and some antidepressant medications are associated with the up-regulation of VEGF, and even the local VEGF administration increases hippocampal neurogenesis. Peripheral administration of IGF, a liver-secreted peptide under the control of growth hormone (GH), was reported to increase hippocampal cell proliferation, enhance exercise-induced increases in neurogenesis [37], and exert antidepressant behavioral effects as well [27 38]. Hoshaw and colleagues [39] reported that central administration of IGF-I is associated with prolonged antidepressant-like activity in the modified rat forced swim test (FST) model. The authors postulated that the behavioral effects of IGF-I were similar to those of BDNF, suggesting that neurotrophins may

be an effective target for the development of novel antidepressant agents. Furthermore, Malberg et al. [40] reported that medications inhibiting binding proteins for IGF-1 (thus, increasing the effects of free IGF-1), may produce both antidepressant-like or anxiolytic effects in mice. Overall, targeting VEGF [34] and IGF [41 42] has yielded interesting results and a new therapeutic strategy to develop innovative antidepressant agents. Other neurotrophic factors such as fibroblast growth factor-2 and nerve growth factor have also been proposed to enhance adult neurogenesis and may serve as novel potential therapeutic targets for the treatment of MDD. However, further studies are required to establish the clinical efficacy and tolerability of neurotrophic agents, and whether their effects are uniquely due to their impact on neuroplasticity [43].

The Cyclic Adenosine Monophosphate Pathway (CAMP) is an important intracellular cascade which is involved in the pathophysiology of major affective disorders; therefore, its components have been generally identified as possible targets for antidepressant agents [44]. Notably, antidepressant-like effects have been provoked in animals by suppressing cAMP degradation with rolipram, or directly injecting cAMP [45 46]. The PKA is activated by cAMP: consequently its activity is increased after chronic treatment with antidepressants [47]. Once PKA is activated, it phosphorylates CREB, the involvement of which in the pathophysiology of major depression is well known. A close interaction between the cAMP cascade and VEGF expression has been suggested by Lee and colleagues [35]; relevantly, antidepressant treatment has been associated with increased VEGF levels [35]. Both BDNF and VEGF genes have been reported to be regulated by CREB [48-51]; CREB, in particular, is a crucial regulator of BDNF synthesis and is virtually involved in most aspects of neuroplasticity [52 53].

Antidepressant medications may not only enhance the phosphorylation of CREB but also the Ca2 +/ calmodulin-dependent protein kinase II [54 55]. Interestingly, chronic treatment with agomelatine has been reported to normalize hippocampal levels of phosphorylated p-CREB, mGlu2/3, and mGlu5 metabotropic glutamate receptors that are involved in the pathophysiology of major depression [56]. It is important to note that some antidepressant drugs such as tianeptine are able to restore stress-induced changes of the transcription factor c-fos, which is considered one of the fundamental markers of the biochemical activity [57 58].

Notably, a novel target for antidepressants activity has been identified in the exchange protein directly activated by cAMP (EPAC) as supported from experimental data emerged from postmortem samples in the hippocampus of depressed individuals [59]. EPAC is able to regulate the release of glutamate in central neurons, but the specific effects of this regulation is still unclear. There are two isoforms of EPAC proteins (EPAC1 and EPAC2), each having multiple domains, with one or two cAMP regulatory binding motifs, respectively [60 61]. EPAC1 and/or EPAC2 proteins are expressed throughout the brain development, particularly in the hippocampus, striatum, and prefrontal cortex formation [45 62]. Dwivedi and colleagues [59] reported that Rap-1, one of the major substrates of PKA, was significantly reduced in the prefrontal cortex and hippocampus of depressed subjects who died by suicide whereas protein level of only Epac-2 was significantly increased in the prefrontal cortex and hippocampus of these individuals.

This differential regulation of Rap-1 and EPAC and their possible involvement in the pathophysiology of depression suggest that these molecules may be considered novel potential targets for antidepressant treatment.

Wnt/ß-Catenin pathway. Several intracellular processes such as neural differentiation [63], hippocampal formation [64 65], dendritic morphogenesis [66 67], axon guidance [68 69], synapse formation [70], spatial learning [71], and memory, including long-term potentiation (LTP), seem to be regulated by the Wnt/ß-catenin pathway activity [44]. Depressed patients and young subjects who died by suicide showed impairments of Wnt/ß glycogen synthase kinase-3beta (GSK-3ß) signaling as well as a significant decrease of ß-catenin expression in the prefrontal cortex. Interestingly, antidepressant medications and mood stablizers such as valproate, lithium, and antipsychotic drugs have been reported to control both GSK-3 ß and ß-catenin expression [72-78]. These compounds may induce antidepressant-like effects or reduce anxiety by inhibiting GSK-3ß, thus enhancing brain ßcatenin levels [74 79-82]. GSK-3ß knock-in mice demonstrated impairment of cell proliferation throughout the subgranular zone (SGZ) of the dentate gyrus, a significant reduction of VEGF levels, and impaired neurogenesis in response to antidepressant drugs [83]. The antidepressant-induced ß-catenin increase has been observed in the SGZ of the dentate gyrus, both in membrane and nuclear fractions [76 84]. However, there might be a complex interaction between the GSK-3 ß-catenin pathway and other neurotransmitters which are implicated at complex levels in the pathophysiology of MDD.

As recently suggested by Pilar-Cuéllar and colleagues [44], the pharmacological modulation of the Wnt/ßcatenin pathway will presumably represent one of the most innovative mechanisms for the treatment of neuropsychiatric disorders in the next future (e.g. by block of GSK-3).

mTOR pathway. Rapamycin (TOR) genes are members of the phosphoinositol kinase-related kinase (PIKK) family of kinases [85]. mTOR-signaling pathway is involved in intracellular processes such as synaptic plasticity, memory retention, and modulation of neuronal repair after injury [44]. mTOR-signaling pathway can exist in two complexes – complex 1 (mTORC1) and complex 2 (mTORC2), depending on the presence of regulatory-associated protein of mTOR or rapamycin independent companion of mTOR, respectively [86,87]. In neurons, mTORC1 is switched on by phosphorylation in response to various neurotrophins such as BDNF. It has been suggested that the mTOR pathway is crucial for the regulation of synaptic plasticity [88]. Reductions of synaptic proteins and impairment of mTOR signaling were observed in the prefrontal cortex of depressed individuals [89] demonstrating its important role in the pathogenesis of MDD. Existing evidence [90-92] reported that mTOR, which is phosphorylated by Akt and extracellular-regulated kinase (ERK), enables the translation of synaptic protein by activating p70S6 kinase (S6K) and inhibiting 4E-BPs, the inhibitory 4E binding proteins. It is important to mention that the mTOR-signaling pathway is activated after the acute administration of different NMDA receptor antagonists such as ketamine [92], Ro 25-6981 [93], MK-801 [94], or antagonists of the group II metabotropic glutamate receptors (mGlu2/3) such as MGS0039 and LY341495. All these compounds are characterized by rapid antidepressant effects [95 96]. Some authors [92 97] suggested that the ketamine-induced synaptogenesis appears to be consequent to the blocking of NMDA receptors at rest, resulting in the translation of rapid dendritic proteins and BDNF. Ketamine rapidly activates the mTOR pathway, enhances synapse formation, increases spine synapses density in the prefrontal cortex of rats [93 98], but also increases BDNF expression in the hippocampus [99] leading to rapid antidepressant-like effects in humans [100 101] and rats [93]. The role of mTORC1 in the efficacy of ketamine was demonstrated by studies showing that pretreatment with a selective mTORC1 inhibitor such as rapamycin is able to drastically reduce the behavioral effects of ketamine [93 96]. In addition, the mTOR inhibition by rapamycin blocks ketamine-induced synaptogenesis [93]. However, mTORC2 is also supposed to play a role in ketamine antidepressant effect as it activates Akt and is involved in the organization of the actin cytoskeleton [102]. Moreover, scopolamine (for more details see below), a muscarinic receptor antagonist able to induce rapid antidepressant effects, also augments mTORC1 and leads to enhanced synaptogenesis in the prefrontal cortex [103]. Interestingly, electroconvulsive treatment has been suggested to activate the mTOR pathway inducing a VEGF enhancement [104].

In conclusion, the modulation of mTOR is a novel target for alternative therapeutic strategies for patients suffering from psychiatric disorders, in particular MDD [105].

The inflammatory hypothesis of depression: antidepressant effects of anti-inflammatory compounds

Immune alterations are considered among the most relevant mechanisms involved in the pathophysiology of depression. Several lines of evidence has led to develop the inflammatory hypothesis of depression. First, a wealth of studies showed that serum levels of proinflammatory cytokines such as IL-1, IL6, and TNF-α are abnormally increased among depressed individuals [106 107]. Furthermore, increases of pro-inflammatory cytokines seem to be linked with the occurrence of depressive-like symptoms such as sickness behavior, fatigue, lethargy, appetite loss [108]. Whereas, Infliximab, or Etanercept administration, by neutralizing TNFα and IL-1 are also associated with antidepressant effects [44 109-112]. To further demonstrate this assumption, the repression of the purinergic 2X7 (P2X7) receptor, that activates the IL-1 release, is also associated with antidepressant effects [111].

However, it is still unclear whether proinflammatory cytokines may play a role in neuronal atrophy, although preliminary data seem to support this assumption [113]. Chronic stress reduces plasmatic BDNF levels in the hippocampal dentate gyrus and increases IL-1β, IL-6, tumor necrosis factor (TNFα). Stress hormones such as cortisol, corticotropin-releasing-hormone (CRH), and adrenocorticotropic hormone (ACTH) levels contribute to cognitive impairment observed after chronic stress exposure [114]. Peripheral inflammation increases proinflammatory cytokines in the CNS that, on in turn, may control neurotransmission [115], neurotransmitter metabolism [116 117] and neurogenesis in the CNS [118 119] (for more details see) [120]. Importantly, selective serotonin reuptake inhibitors are linked with a balance of plasmatic inflammatory cytokine levels [121] while treatment-resistant depressed patients

have increased plasmatic cytokine levels compared to remitted patients [122 123]. Lastly, a higher incidence of depression among patients with chronic inflammatory diseases further supports the inflammatory hypothesis of depression [124].

Interestingly, brain expression of IDO (an enzyme that converts tryptophan into kynurenine and quinolinic acid in microglia or kynurenic acid in astrocytes) is normally low but can be significantly induced by inflammatory cytokines. Lipopolysaccharide (LPS) administration induces depression-like effects in rodents, likely via NMDA receptor agonism by quinolinic acid (IDO-dependent) [125]. IDO activation is associated with a depletion of the precursor for serotonin by increasing the degradation of tryptophan [125 126]. Microglia is activated under stress, resulting in proinflammatory state (reviewed in) [127]. Conversely, chronic stress commonly reduces both the number and size of microglia, particularly in the hippocampus [128]. Furthermore, neurogenesis in the hippocampal dentate gyrus has been reported to be significantly impaired after long-term inflammatory nociception. Significant activators of the nociception-like neurokinin 1 (NK-1) receptor and BDNF in the limbic areas have been closely associated with MDD. Interestingly, imipramine inhibits pain- and stress-evoked down-regulation of hippocampal NK-1 receptor and BDNF gene expression in rats [129]. Thus, antidepressant medications seem to block those changes, which were induced in gene expression, contributing to long-term nociceptive sensory plasticity both in the spinal cord and limbic regions implicated in mood regulation.

It has been suggested that NK-1 receptor antagonists may exert relevant anxyolitic, antidepressant, and neuroprotective effects in the CNS representing promising drugs [130]. Preliminary evidence suggests that antidepressant drugs may successfully interact with immune inflammatory signaling pathways [131]. For instance, a significant reduction of LPS-induced pro-inflammatory cytokines such as TNF-α and IL-6 and cytokine induced depressive-like behavior has been reported with antidepressant drugs use [132 133].

According to animal studies, desipramine administration has been associated with increased IL-1β mRNA levels in rat hypothalamus [134], while a significant up-regulation of phospholipase A2 (PLA2)-mediated arachidonic acid turnover has been observed after chronic antidepressant treatment in the rodent brain [135 136]. It is also important to note that resistance to commonly used antidepressants has been linked with higher levels of IL-6 and C Reactive Protein (CRP) [137 138].

Adjunctive treatment with celecoxib, a selective COX-2 inhibitor, enhanced the therapeutic efficacy of reboxetine (a noradrenergic reuptake inhibitor) in subjects with MDD [139 140]. Thus, adjunctive treatment with antiinflammatory compounds may enhance the potential of traditional antidepressant drugs. Mendlewicz and colleagues [141] found higher remission rates among MDD subjects who were previously nonresponsive to fluoxetine alone when acetylsalicylic acid (aspirin), a COX-1 inhibitor, was added to treatment. In MDD patients, adjunctive long-chain omega-3 fatty acids were associated with higher therapeutic efficacy of fluoxetine [142] and citalopram [143], respectively. Moreover, Peet and Horrobin [144] reported a significant reduction of MDD symptom severity in depressed patients who were refractory to conventional antidepressant medications.

Overall, abnormally elevated immune-inflammatory signaling represents a pathogenic mechanism contributing to mood dysregulation in MDD; therefore, altered inflammatory pathways need to be carefully considered as new targets for novel antidepressant treatments.

Other potential therapeutic targets for the development of novel antidepressants in the serotonergic system?

Serotonin or 5-hydroxytryptamine (5-HT) may be generally found in the serotonergic neurons of the raphe nuclei and their axonal projections [145]. Serotonergic transmission regulates a wide range of behaviors like mood, memory, sleep, appetite, aggression, and thermoregulation. Notably, serotonin is also involved in the modulation of hippocampal neurogenesis which is known to be abnormally impaired in both chronic stress and MDD. Administration of selective 5-HT1A and 5-HT2C receptor agonists was able to increase the number of newly formed neurons in the hippocampal dentate gyrus and/or olfactory bulb. Furthermore, stimulation of 5-HT1A and -2B receptors resulted in enhanced neurogenesis combined with antidepressant-like activity in the animal model. In order to identify novel therapeutic targets, an alternative antidepressant approach would consist in the administration of selective 5-HT1A or 5-HT2C receptor agonists that have shown specific anxiolytic/antidepressant properties based on animal models [146-148]. In addition, it has been proposed that the stimulation of postsynaptic 5-HT1A receptors in the corticolimbic brain regions is related with antidepressant effects

whereas the activation of presynaptic 5-HT1A receptors is linked with a higher propensity to major affective disorders, reduced response to antidepressants, and suicidal behavior. Chronic antidepressant treatment is linked with a desensitization of presynaptic 5-HT1A receptors drastically reducing the negative feedback related with these receptors [149]. Moreover, the combination of 5HT2C antagonism with MT1 and MT2 melatonergic agonism (e.g., the mechanism of action of agomelatine) was shown to be effective in the treatment of MDD [150]. Overall, 5-HT1A or 5-HT2C receptor agonists may provide an interesting alternative target for the treatment of MDD and need to be further implemented in the next future.

Dopaminergic and norepinephrinergic systems are highly involved in hippocampal neurogenesis. Dopamine reduction has been reported to abnormally reduce hippocampal cell proliferation [151] as demonstrated after quinpirole administration, which was associated with subgranular zone proliferation provoked by D2 receptor stimulation [152], as well as following D3 receptor knockout or inhibition [153]. According to Guiard et al. [154], the effect of dopamine on hippocampal neurogenesis is indirectly mediated by 5-HT, norepinephrine, and other neurotransmitters suggesting the complex interaction between monoaminergic systems at this level. Norepinephrine might influence hippocampal neurogenesis, considering the extensive noradrenergic innervation of the adult hippocampus. Importantly, the norepinephrine depletion was found to weaken the proliferation, but not survival/differentiation of adult hippocampal granule cell progenitors [155]. Given this context, the authors suggested that the hippocampal precursors of neurogenesis might be modified through the α- adrenergic receptor activity [156 157] although their functioning still remained unclear [158]. Alpha-2-adrenoceptors are identified as presumed targets in the development of rapid acting antidepressants [8]. Various studies demonstrated increased α2-adrenoceptor expression as well as binding and functional actions within limbic brain areas in both patients with major depression and animal models of depression [159-162]. Chronic antidepressant treatment has been found to down-regulate and desensitize α2-adrenoreceptors, therefore proposed to mediate the therapeutic delay of antidepressant medications [163 164]. Antidepressant drugs with α2-adrenoceptor antagonist properties, such as mirtazapine, are associated with more rapid behavioral effects, alone or in combination with other traditional antidepressants[165,166]. Interestingly, the co-administration of α2-adrenoceptor antagonist yohimbine with fluoxetine [167] or the tricyclic antidepressant imipramine [168] hastens the antidepressant response in patients with MDD. Therefore, antagonism of the α2-adrenoceptor may be identified as a prospective target in the development of antidepressant monotherapy or combined antidepressant treatment [169].

Similarly to antidepressants, cannabinoids may also reduce anxiety and depressive symptoms in the short term [32 170]. Chronic antidepressant treatment with SSRIs and tricyclics was reported to alter the expression of cannabinoid (CB1) receptors and endocannabinoid levels (EC) in brain regions involved in the pathophysiology of mood and anxiety symptoms [59 74 171-174]. Genetic or pharmacological manipulations of both CB1 and CB2 or enzymes involved in the endocannabinoid metabolism also regulates hippocampal neurogenesis: thus, disruption of endocannabinoid signaling could be involved in the reduction of hippocampal neurogenesis induced by chronic stress. Notably, cannabinoids can also impact on serotonergic neurotransmission and serotonin 1A and 2A/2C receptors expression [175 176]. A better understanding of this complex interaction may contribute to the development of new targets in the treatment of mood and anxiety disorders [177].

It is now becoming evident that the normalization of hippocampal neurogenesis caused by antidepressants may be associated with the glucocorticoid hormones [7 178-180]. Fitzsimons et al. [181] reported that antiglucocorticoids might revert depressive symptoms by promoting neurogenesis in the ventral hippocampus. Mice that are heterozygous for glucocorticoid receptor (GR) showed a depression-related phenotype, that is, elevated learned helplessness on the behavioral level and neuroendocrine alterations with HPA axis overdrive. Moreover, they had abnormally impaired BDNF levels and altered neurogenesis further repressed by restraint stress [182]. Traditional antidepressants are known to modulate GR activity [7 183 184] as they might affect neuroplasticity through their potential to modulate both BDNF and 5-HT, potentially influencing HPA axis, which is subsequently able to affect hippocampal neurogenesis and neuronal functioning [185]. Moreover, the antidepressant effects of chronic fluoxetine treatment were described to be linked to the maturation of newborn neurons together with the HPA axis inhibition [186]. The down-regulation of hippocampal neurogenesis may affect HPA axis functions observed in chronic stress or depressed patients [186 187]. In addition, the normalization of stress related HPA axis abnormalities following pharmacological inhibition of the orexinergic system was con-

nected with antidepressant effects [188]. Thus, another potential class of medications with antidepressant action could be anti-glucocorticoid treatments which are reported to diminish stress-induced depressive symptoms by increasing neurogenesis [189].

Estrogens (the estrogen receptors (ER) α and β) might regulate synaptogenesis and dendrite length, also activating intracellular signaling pathways that control the formation of synapse, and cause antidepressant effects in behavioral models of depression [190 191]. Clinical studies reported the neuroprotective effects of estrogens against cognitive decline during normal aging but also Alzheimer's symptoms, whereas laboratory evidence provided insight into the mechanisms through which estrogens may induce changes in brain neuroplasticity. Specifically, electrophysiological studies suggested that estrogens are able to promote changes in synaptic plasticity within the central nervous system. New selective estrogen ligands showed an advantageous potential reversing the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression [192 193].

As a whole, the 17β-estradiol-mediated neuroprotection has been characterized by initial studies but there is an urgent need to elucidate the impact of estrogens on different signaling pathways involved in the regulation of cell survival and death.

Vilazodone, vortioxetine, brexpiprazole (OPC-34712), and amitifadine

Vilazodone acts by inhibiting serotonin reuptake and by partial agonism of 5-HT1A receptors [194]. It has been approved as antidepressant by the US Food and Drug Administration in 2011. Importantly, 5-HT1A partial agonism has been associated with the improvement of depressive, anxiety [195], and aggressive [196] symptoms. According to clinical studies, vilazodone at 40 mg daily dose is associated with a significant antidepressant response as demonstrated by the improvements at the MADRS and HAMD-17 total scores after one week of treatment [197] and a significantly higher response rate than placebo at week 8 based on MADRS total score [198]. Vilazodone has demonstrated a good tolerability profile similar to that observed with SSRIs with diarrhoea, nausea, and somnolence [198] as the most relevant treatment-emergent adverse events.

Similarly, vortioxetine acts as a partial agonist at the 5-HT1A receptor, and a SERT, HT3, and 5-HT7 inhibitor [199]. It has been recently approved in Italy for the treatment of major depression. The antagonistic effects on 5-HT7 receptors of this drug are associated with improvements of sleep, circadian rhythms, and mood. Based on preclinical studies, vortioxetine has been associated with a more pronounced and rapid recovery of 5-HT neuronal firing when compared with other SSRIs. When compared with placebo, vortioxetine was associated with significant improvements from baseline to week 6 in the mean change of MADRS total score in a sample of 429 patients with severe MDD. Alvarez and colleagues [200] reported significant and earlier improvements vs. placebo according to HAMD-24 total scores for both 5 and 10 mg daily doses of this medication from week 1 (when compared with venlafaxine from week 2). A better tolerability profile when compared with that of 225 mg venlafaxine was also observed [200].

Brexpiprazole (OPC-34712) is a novel promising medication for the treatment of MDD, with similar structural characteristics and pharmacological properties to aripiprazole. Brexpiprazole has a broader activity across multiple monoamine systems, reduced partial agonism on D2 receptors, and enhanced affinity for 5-HT1A, 5-HT2A and 5-HT7 receptors. It has been proposed as an adjunctive treatment in MDD. Relative to placebo, brexpiprazole as adjunctive treatment has been associated with significant improvements on MADRS total score in patients with insufficient response to other antidepressants.

Furthermore, amitifadine (DOV 21,947)/DOV-216,303 amitifadine (previously DOV 21,947) and DOV 216,303 (a racemic mixture of which amitifadine is one of the enantiomers) are other two interesting molecules currently under development to treat MDD. Both are serotonin-NE-dopamine reuptake inhibitors and promising therapeutic options, although prior trials on other triple-reuptake inhibitors such as SEP225289 (Sepracor Inc., 2009) and GSK372475 had yielded conflicting results [201]. However, amitifadine is a serotonin preferring triple-reuptake inhibitor with lower affinity for the dopamine transporters, differently from SEP225289 and GSK372475. Such differences in the relative affinities for the three transporters may explain the improvements in pharmacology, tolerability, and efficacy observed in the earliest studies for these novel compounds. Amitifadine has been associated with markedly and persistently increases in extracellular concentrations of serotonin, noradrenaline, and dopamine in the prefrontal cortex [202]. Time-dependent significant reductions in HAMD scores were observed both with DOV 216,303 and citalopram [203]. Based on a post-hoc analyses,

amitifadine was reported to be particularly effective for anhedonia and did not exert significant sexual side-effects or other serious adverse events over 6 weeks [204].

Rapid acting antidepressant effects: the potential of glutamatergic compounds

Modern antidepressant medications may work by reversing neuroplasticity impairments associated with chronic stress and MDD and restoring the abnormal changes observed in specific neural circuits [48 52 54 205]. Although conventional antidepressants predominantly modulate norepinephrine, dopamine, and/or 5-HT systems [206], the interest towards glutamatergic system is growing in terms of importance [43]. It is well established that the majority of molecular and biological impairments of neuroplasticity are associated with the cytotoxic action of glutamate. For instance, the antidepressant-mediated inhibition of stress-induced morphological changes in both the hippocampus and amygdala is dependent on glutamatergic transmission [207]. In addition, according to animal models stress-induced morphological changes in the hippocampus are reversed by pharmacological manipulation of glutamatergic system [207 208].

Importantly, a critical role of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors activation in inducing morphological changes associated with neuroplasticity such as reduction of dendritic length and branching, spine density, and hippocampal volume has been suggested by multiple evidence [209 210]. NMDA receptors are composed by two major subunits, NR1 and NR2 as functional NMDA receptors are tetramers and are comprised of two NR1 subunits and two NR2 subunits. NR2b subtype may be commonly found in extrasynaptic locations and has been explored as a new target for blocking glutamate excitoxicity damage [211]. NR2b antagonists may show antidepressant effects exerting antidepressant-like activity similarly to ketamine (for more details see below) but without exerting significant adverse effects [192 193]. The structural remodeling of neurons leading to reversible modifications such as reduced neurogenesis, neuronal shrinkage and decreased growth may be, at least partially, mediated by glutamate if present at certain concentrations as well as by glucocorticoids levels [212]. The inhibition of glutamate release by NMDA receptors may prevent this structural remodeling [213 214].

Both antidepressants and electroconvulsive shock therapy can reverse glutamate impairment, particularly in the anterior cingulated cortex of subjects with MDD [215]. The antidepressant tianeptine has been reported to prevent the retraction of hippocampal CA3 pyramidal neurons apical dendrites together with increasing granule cell proliferation [49]. Differently from fluoxetine, tianeptine prevents an excessive release of glutamate in the basolateral nucleus of the amygdala. NMDA receptor antagonists such as ketamine have been associated with rapid antidepressant action in TRD patients [100 216]. Ketamine may be considered as safe and well-tolerated in the short-term period for nonpsychotic depressed patients when administered at a subanesthetic dose of 0.5 mg/kg over 40 minutes as well [217]. Duncan et al. [218] reported that ketamine represent a novel and promising option to treat both MDD and TRD patients according to its earlier efficacy. It wa shown to drastically reduce depressive symptoms within the first 5 days in contrast with the delayed action of currently available antidepressant medications, requiring 4 to 6 weeks. Ketamine seems also effective in reducing suicidality among TRD patients according to its rapid onset of action on core depressive symptoms, as well as hopelessness [219]. It was suggested that (S)-ketamine is approximately 4 times more active than its (R)-enantiomer given its better pharmacokinetic properties and higher tolerability [219 220]. (S)-ketamine has also been reported to induce less psychomimetic adverse effects such as dissociation and hallucinations relative to (R)- enantiomer. Several studies showed that rapid-acting antidepressants are able to enhance glutamate transmission, mTORC1 signaling as well as synaptogenesis [103 192 193] but other relevant mechanisms need to be mentioned. The rapid induction of neuroplasticity is supposed to be one of the main mechanism underlying the antidepressant effect of ketamine [221]. Duman et al. [98] focused on the additional activity of ketamine to rapidly reverse both behavioral and neuronal changes associated with chronic stress presumably due to the stimulation of BDNF signaling. Unfortunately, ketamine has important psychotomimetic effects that may seriously limit its utility and require additional studies.

Memantine is another N-methyl-D-aspartate receptor (NMDAR) antagonist, a dimethyl derivative of amantadine. It showed good tolerability [222] and demonstrated preliminary hints of antidepressant efficacy based on animal models of depression [223]. Moryl and colleagues [224]. More specifically, memantine may be associated with antidepressant-like activity by reducing immobility time in the forced swim test. There are

also evidence suggesting that combining memantine with traditional antidepressants may be effective in the treatment of MDD. The enhanced antidepressant action may be observed only when fluoxetine was administered with memantine indicating that the combined effect of traditional antidepressants and NMDA antagonists is necessary to induce any antidepressant effects [225].

Finally, the non-selective muscarinic (M) receptor antagonist scopolamine has been also associated with a rapid antidepressant-like effect [75 226]. Scopolamine inhibits all five receptors located at pre- and postsynaptic sites and it is associated with modulation of both cholinergic and glutamatergic transmissions. It was suggested that postsynaptic M1 receptors can regulate long-term synaptic depression (LTD) through the induced AMPA/NMDA receptors internalization [227]. The inhibition of these receptors induced by scopolamine is associated with enhancing synaptic plasticity and synaptogenesis suggesting that this medication may determine the inhibition of muscarinic activation of GABA firing as well as the dis-inhibition of glutamate release [192].

The possible role of miRNAS

Finally, a further alternative antidepressant strategy needs to be reported. MicroRNAs (miRNAs), which regulate gene expression by targeting the three prime untranslated region (3′-UTR) of genes, have been demonstrated to play a significant role in neurogenesis [228], thus they may need to be considered as new targets in the treatment of major neuropsychiatric conditions [216 229 230]. Exploring miRNAs effects may help to develop new molecular strategies aimed at modulating the expression of certain genes with an interesting potential in the antidepressant field [231]. To date, more studies are still required to thoroughly explore the specific role of miRNAs in depression-related disorders as well as investigate detailed information about the possible use of miRNAs as new therapeutic targets for antidepressant activity.

Conclusion

The present review examined the main novelties in the field of antidepressant pharmacology, by including a brief overview of novel agents and potential innovative molecular targets with their implications and future perspectives. Over the last 20 years, the theoretical landscape has radically changed: the classic serotonergic view of depression has been integrated with substantial knowledge on other monoamines and specific intracellular signaling pathways. In addition to 5-HT, dopaminergic and norepinephrinergic systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival, while neuroplasticity is now recognized as a crucial factor in the pathogenesis of depression. Furthermore, several intracellular pathways (e.g., cyclic adenosine monophosphate pathway, Wnt/ß-Catenin Pathway, and mTOR pathway) may function as final common mechanisms for these systems. Thus, the direct modulation of intracellular pathways represents an exciting perspective for novel treatment strategies in MDD.

Current models of depression have recognized a prominent role also to other pathophysiological mechanisms, such as neuro-inflammation and chronic stress, which constitute the basis for further advancement in the field of psychopharmacology. Immune/inflammatory abnormalities have been also hypothesized to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of MDD. Indeed, part of the clinical efficacy of current antidepressant medications may already work by reducing immune inflammatory signaling pathways; thus, altered inflammatory pathways need to be carefully considered as novel alternative targets for developing novel antidepressant treatments. Estrogen ligands are an additional endocrine target, currently in the early phase of development. Selective agonists have been proposed to reverse the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression. Similarly, molecules that target the cannabinoid system may also reduce anxiety and depressive symptoms and are potential targets for novel antidepressants.

Glutamate transmission is already targeted by novel antidepressants. Drugs targeting specific glutamate receptors have been already marketed after demonstration of their efficacy [4]. The noncompetitive NMDA receptor antagonist ketamine has been identified as one the most intriguing therapeutic option for patients with MDD and TRD. Ketamine is associated with a rapid and prolonged glutamate burst stimulating the BDNF-mTORC1 cascade, and leads to increased synaptic connections in specific brain areas such as the prefrontal cortex [232]. The acute synaptogenic action of ketamine is rapid and is not associated with excitoxicity. However, future studies are required to test long-term clinical efficacy in both MDD and TRD.

The efficacy of scopolamine, a muscarinic agent, largely depends on glutamate transmission, and also showed rapid effects.

Despite these exciting perspectives in the field of antidepressant drug discovery, clinicians continue to be challenged by the need to manage MDD while addressing several unmet needs in terms of tolerability, efficacy and long-term acceptability. Thus, further studies are urgently needed to translate preliminary evidence into tangible advances for our patients.

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Take home messages for psychiatric care

- Over the last 20 years, the classic serotonergic view of depression has been significantly integrated with substantial knowledge related to the contribution of other monoamines and specific intracellular signaling pathways
- In addition to 5-HT, dopaminergic and norepinephrinergic systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival. Modern antidepressant drugs such as ketamine may act by reversing neuroplasticity impairments and enhance synaptogenesis
- Immune/inflammatory abnormalities have been suggested to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of major depression

References

1 Kessler RC, Berglund P, Demler O, et al. *The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R).* JAMA 2003;289:3095-105.

2 Greenberg PE, Kessler RC, Birnbaum HG, et al. *The economic burden of depression in the United States: how did it change between 1990 and 2000?* J Clin Psychiatry 2003;64:1465-75.

3 Simon GE. *Social and economic burden of mood disorders.* Biol Psychiatry 2003;54:208-15.

4 Serafini G, Pompili M, Innamorati M, et al. *Pharmacological properties of glutamatergic drugs targeting NMDA receptors and their application in major depression.* Curr Pharm Des 2013;19:1898-922.

5 Nierenberg AA, Husain MM, Trivedi MH, et al. *Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report.* Psychol Med 2010;40:41–50.

6 Trivedi MH, Rush AJ, Wisniewski SR, et al. *Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice.* Am J Psychiatry 2006;163:28-40.

7 Anacker C, Zunszain PA, Cattaneo A, et al. *Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor.* Mol Psychiatry 2011;16:738-50.

8 Blier P. *The pharmacology of putative early-onset antidepressant strategies.* Eur Neuropsychopharmacol 2003;13:57-66.

9 Rosenzweig-Lipson S, Dunlop J, Marquis KL. *5-HT2C receptor agonists as an innovative approach for psychiatric disorders.* Drug News Perspect 2007;20:565-71.

10 Girardi P, Pompili M, Innamorati M, et al. *Duloxetine in acute major depression: review of comparisons to placebo and standard antidepressants using dissimilar methods.* Hum Psychopharmacol Clin Exp 2009;24:177–90.

11 Richelson E. *Multi-modality: a new approach for the treatment of major depressive disorder.* Int J Neuropsychopharmacol 2013;16:1433–42.

12 Bull SA, Hunkeler EM, Lee JY, et al. *Discontinuing or switching selective serotonin-reuptake inhibitors.* Ann Pharmacother 2002;36:578–84.

13 Dodd S, Horgan D, Malhi GS, Berk M. *To combine or not to combine? A literature review of antidepressant combination therapy.* J Affect Disord 2005;89:1–11.

14 Stahl SM. *Enhancing outcomes from major depression: using antidepressant combination therapies with multifunctional pharmacologic mechanisms from the initiation of treatment.* CNS Spectr 2010;15:79–94.

15 Schmidt HD, Duman RS. *The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior.* Behav Pharmacol 2007;18:391-418.

16 Thoenen H. *Neurotrophins and neuronal plasticity.* Science 1995;270:593-8.

17 Lindvall O, Kokaia Z, Bengzon J, Elmér E, Kokaia M. *Neurotrophins and brain insults.* Trends Neurosci 1994;17:490-6.

18 Lindsay RM, Wiegand SJ, Altar CA, DiStefano PS. *Neurotrophic factors: from molecule to man.* Trends Neurosci 1994;17:182-90.

19 Lo DC. *Neurotrophic factors and synaptic plasticity.* Neuron 1995;15:979-81.

20 Lee KJ, Kim SJ, Kim SW, et al. *Chronic mild stress decreases survival, but not proliferation, of newborn cells in adult rat hippocampus.* Exp Mol Med 2006;38:44-54.

21 Duman RS, Heninger GR, Nestler EJ. A *molecular and cellular theory of depression.* Arch Gen Psychiatry 1997;54:597-606.

22 Castrén E, Võikar V, Rantamäki T. *Role of neurotrophic factors in depression.* Curr Opin Pharmacol 2007;7:18-21.

23 Duman RS. *Role of neurotrophic factors in the etiology and treatment of mood disorders.* Neuromolecular Med 2004;5:11-25.

24 Hayley S, Litteljohn D. *Neuroplasticity and the next wave of antidepressant strategies.* Front Cell Neurosci 2013;7:218.

25 Kozisek ME, Middlemas D, Bylund DB. *Brain-derived neurotrophic factor and its receptor tropomyosin-related kinase B in the mechanism of action of antidepressant therapies.* Pharmacol Ther 2008;117:30-51.

[26] Jin K, Zhu Y, Sun Y, et al. *Vascular endothelial growth factor (VEGF) stimulates neurogenesis in vitro and in vivo.* Proc Natl Acad Sci USA 2002;99:11946-50.

[27] Aberg MA, Aberg ND, Hedbäcker H, Oscarsson J, Eriksson PS. *Peripheral infusion of IGF-I selectively induces neurogenesis in the adult rat hippocampus.* J Neurosci 2000;20:2896-903.

[28] Hanson ND, Owens MJ, Nemeroff CB. *Depression, antidepressants, and neurogenesis: a critical reappraisal.* Neuropsychopharmacology 2011;36:2589-602.

[29] Gersner R, Toth E, Isserles M, Zangen A. *Site-specific antidepressant effects of repeated subconvulsive electrical stimulation: potential role of brain-derived neurotrophic factor.* Biol Psychiatry 2010;67:125-32.

[30] Czubak A, Nowakowska E, Kus K, et al. *Influences of chronic venlafaxine, olanzapine and nicotine on the hippocampal and cortical concentrations of brain-derived neurotrophic factor (BDNF).* Pharmacol Rep 2009;61:1017-23.

[31] Vaidya VA, Marek GJ, Aghajanian GK, Duman RS. 5-*HT2A receptor-mediated regulation of brainderived neurotrophic factor mRNA in the hippocampus and the neocortex.* J Neurosci 1997;17:2785-95.

[32] Jin K, Xie L, Kim SH, et al. *Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice.* Mol Pharmacol 2004;66:204-8.

[33] Sun Y, Jin K, Childs JT, et al. *Vascular endothelial growth factor-B (VEGFB) stimulates neurogenesis: evidence from knockout mice and growth factor administration.* Dev Biol 2006;289:329-35.

[34] Kiuchi T, Lee H, Mikami T. *Regular exercise cures depression-like behavior via VEGF-Flk-1 signaling in chronically stressed mice.* Neuroscience 2012;207:208-17.

[35] Lee JS, Jang DJ, Lee N, et al. *Induction of neuronal vascular endothelial growth factor expression by cAMP in the dentate gyrus of the hippocampus is required for antidepressant-like behaviors.* J Neurosci 2009;29:8493-505.

[36] Warner-Schmidt JL, Madsen TM, Duman RS. *Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation.* Eur J Neurosci 2008;27(6):1485-93.

[37] Trejo JL, Carro E, Torres-Aleman I. *Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus.* J Neurosci 2001;21: 1628-34.

[38] Duman CH, Schlesinger L, Terwilliger R, et al. *Peripheral insulin-like growth factor-I produces antidepressant-like behavior and contributes to the effect of exercise.* Behav Brain Res 2009;198:366-71.

[39] Hoshaw BA, Evans JC, Mueller B, Valentino RJ, Lucki I. *Social competition in rats: cell proliferation and behavior.* Behav Brain Res 2006;175:343-51.

[40] Malberg JE, Platt B, Rizzo SJ, et al. *Increasing the levels of insulin-like growth factor-I by an IGF binding protein inhibitor produces anxiolytic and antidepressant-like effects.* Neuropsychopharmacology 2007;32:2360-8.

[41] Schechter LE, Ring RH, Beyer CE, et al. *Innovative approaches for the development of antidepressant drugs: current and future strategies.* NeuroRx 2005;2:590-611.

[42] Glasper ER, Llorens-Martin MV, Leuner B, Gould E, Trejo JL. *Blockade of insulin-like growth factor-I has complex effects on structural plasticity in the hippocampus.* Hippocampus 2010;20: 706-12.

[43] Serafini G, Hayley S, Pompili M, et al. *Hippocampal neurogenesis, neurotrophic factors and depression: possible therapeutic targets?* CNS Neurol Disord Drug Targets 2014a;13:1708-21.

[44] Pilar-Cuéllar F, Vidal R, Díaz A, et al. *Neural Plasticity and Proliferation in the Generation of Antidepressant Effects: Hippocampal Implication.* Neural Plast 2013;2013;537265.

[45] Zhang CL, Katoh M, Shibasaki T, et al. *The cAMP sensor Epac2 is a direct target of antidiabetic sulfonylurea drugs.* Science 2009a;325(5940):607-10.

[46] Zhang HT. Cyclic *AMP-specific phosphodiesterase-4 as a target for the development of antidepressant drugs.* Curr Pharm Des 2009b;15:1688-98.

[47] Nestler EJ, Terwilliger RZ, Duman RS. *Chronic antidepressant administration alters the subcellular distribution of cyclic AMP-dependent protein kinase in rat frontal cortex.* J Neurochem 1989;53:1644-7.

[48] Duman RS, Malberg J, Thome J. *Neural plasticity to stress and antidepressant treatment.* Biol Psychiatry 1999;46:1181-91.

[49] Malberg JE, Eisch AJ, Nestler EJ, Duman RS. *Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus.* J Neurosci 2000;20:9104-10.

[50] Nibuya M, Nestler EJ, Duman RS. *Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus.* J Neurosci 1996;16:2365-72.

[51] Perera TD, Park S, Nemirovskaya Y. *Cognitive role of neurogenesis in depression and antidepressant treatment.* Neuroscientist 2008;14:326-38.

[52] Pittenger C, Duman RS. *Stress, depression, and neuroplasticity: a convergence of mechanisms.* Neuropsychopharmacology 2008;33:88-109.

[53] DSa C, Duman RS. *Antidepressants and neuroplasticity.* Bipolar Disord 2002;4:183-94.

[54] Manji HK, Duman RS. *Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics.* Psychopharmacol Bull 2001;35:5-49.

[55] Popoli M, Vocaturo C, Perez J, Smeraldi E, Racagni G. *Presynaptic Ca2+/calmodulin-dependent protein kinase II: autophosphorylation and activity increase in the hippocampus after long-term blockade of serotonin reuptake.* Mol Pharmacol 1995;48:623-9.

[56] Morley-Fletcher S, Mairesse J, Soumier A, et al. *Chronic agomelatine treatment corrects behavioral, cellular, and biochemical abnormalities induced by prenatal stress in rats.* Psychopharmacology (Berl) 2011;217:301-13.

[57] Beck KD, Powell-Braxton L, Widmer HR, Valverde J, Hefti F. *Igf1 gene disruption results in reduced brain size, CNS hypomyelination, and loss of hippocampal granule and striatal parvalbumincontaining neurons.* Neuron 1995;14:717-30.

[58] Duncan GE, Knapp DJ, Johnson KB, Breese GR. *Functional classification of antidepressants based on antagonism of swim stress-induced fos-like immunoreactivity.* J Pharmacol Exp Ther 1996;277:1076-89.

[59] Dwivedi Y, Mondal AC, Rizavi HS, et al. *Differential and brain region-specific regulation of Rap-1 and Epac in depressed suicide victims.* Arch Gen Psychiatry 2006;63:639-48.

[60] Kawasaki H, Springett GM, Mochizuki N, et al. *A family of cAMP-binding proteins that directly activate Rap1.* Science 1998;282:2275-9.

[61] Rehmann H, Prakash B, Wolf E, et al. *Structure and regulation of the cAMP-binding domains of Epac2.* Nat Struct Biol 2003;10:26-32.

[62] Yang Y, Shu X, Liu D, et al. *EPAC null mutation impairs learning and social interactions via aberrant regulation of miR-124 and Zif268 translation.* Neuron 2012;73:774-88.

[63] Ciani L, Salinas PC. *WNTs in the vertebrate nervous system: from patterning to neuronal connectivity.* Nat Rev Neurosci 2005;6:351-62.

[64] Galceran J, Miyashita-Lin EM, Devaney E, Rubenstein JL, Grosschedl R. *Hippocampus development and generation of dentate gyrus granule cells is regulated by LEF1.* Development 2000;127:469-82.

[65] Zhou CJ, Zhao C, Pleasure SJ. *Wnt signaling mutants have decreased dentate granule cell production and radial glial scaffolding abnormalities.* J Neurosci 2004;24:121-6.

[66] Yu X, Malenka RC. *Beta-catenin is critical for dendritic morphogenesis*. Nat Neurosci 2003;6:1169-77.

[67] Gao X, Arlotta P, Macklis JD, Chen J. *Conditional knockout of beta-catenin in postnatal-born dentate gyrus granule neurons results in dendritic malformation.* J Neurosci 2007;27:14317-25.

[68] Zaghetto AA, Paina S, Mantero S, et al. *Activation of the Wnt-beta catenin pathway in a cell population on the surface of the forebrain is essential for the establishment of olfactory axon connections.* J Neurosci 2007;27:9757-68.

[69] Purro SA, Ciani L, Hoyos-Flight M, et al. *Wnt regulates axon behavior through changes in microtubule growth directionality: a new role for adenomatous polyposis coli.* J Neurosci 2008;28:8644-54.

[70] Bamji SX, Shimazu K, Kimes N, et al. *Role of beta-catenin in synaptic vesicle localization and presynaptic assembly.* Neuron 2003;40:719-31.

[71] Hernández F, Borrell J, Guaza C, Avila J, Lucas JJ. *Spatial learning deficit in transgenic mice that conditionally over-express GSK-3beta in the brain but do not form tau filaments.* J Neurochem 2002;83:1529-33.

[72] Li X, Zhu W, Roh MS, Friedman AB, Rosborough K, Jope RS. *In vivo regulation of glycogen synthase kinase-3beta (GSK-3beta) by serotonergic activity in mouse brain.* Neuropsychopharmacology 2004;29:1426-31.

[73] Liu R, Dang W, Jianting M, et al. *Citalopram alleviates chronic stress induced depression-like behaviors in rats by activating GSK3*β *signaling in dorsal hippocampus.* Brain Res 2012;1467:10-7.

[74] Beaulieu JM, Zhang X, Rodriguiz RM, et al. *Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency.* Proc Natl Acad Sci USA 2008;105:1333-8.

[75] Pascual-Brazo J, Castro E, Díaz A, et al. *Modulation of neuroplasticity pathways and antidepressantlike behavioural responses following the short-term (3 and 7 days) administration of the 5-HT$_4$ receptor agonist RS67333.* Int J Neuropsychopharmacol 2012;15:631-43.

[76] Mostany R, Valdizán EM, Pazos A. *A role for nuclear beta-catenin in SNRI antidepressant-induced hippocampal cell proliferation.* Neuropharmacology 2008;55:18-26.

[77] Chen G, Huang LD, Jiang YM, Manji HK. *The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3.* J Neurochem 1999;72:1327-30.

[78] Gould TD, Chen G, Manji HK. *In vivo evidence in the brain for lithium inhibition of glycogen synthase kinase-3.* Neuropsychopharmacology 2004;29:32-8.

[79] Kaidanovich-Beilin O, Milman A, Weizman A, Pick CG, Eldar-Finkelman H. *Rapid antidepressivelike activity of specific glycogen synthase kinase-3 inhibitor and its effect on beta-catenin in mouse hippocampus.* Biol Psychiatry 2004;55:781-4.

[80] OBrien WT, Harper AD, Jové F, et al. *Glycogen synthase kinase-3beta haploinsufficiency mimics the behavioral and molecular effects of lithium.* J Neurosci 2004;24:6791-8.

[81] Latapy C, Rioux V, Guitton MJ, Beaulieu JM. *Selective deletion of forebrain glycogen synthase kinase 3*β *reveals a central role in serotonin-sensitive anxiety and social behaviour.* Philos Trans R Soc Lond B Biol Sci 2012;367:2460-74.

[82] Gould TD, Einat H, ODonnell KC, et al. *Beta-catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors.* Neuropsychopharmacology 2007;32:2173-83.

[83] Eom TY, Jope RS. *Blocked inhibitory serine-phosphorylation of glycogen synthase kinase-3alpha/beta impairs in vivo neural precursor cell proliferation.* Biol Psychiatry 2009;66:494-502.

[84] Madsen TM, Newton SS, Eaton ME, Russell DS, Duman RS. *Chronic electroconvulsive seizure upregulates beta-catenin expression in rat hippocampus: role in adult neurogenesis.* Biol Psychiatry 2003;54:1006-14.

[85] Kunz J, Henriquez R, Schneider U, et al. *Target of rapamycin in yeast, TOR2, is an essential phosphatidylinositol kinase homolog required for G1 progression.* Cell 1993;73:585-96.

[86] Sengupta S, Peterson TR, Sabatini DM. *Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress.* Mol Cell 2010;40:310-22.

[87] Sarbassov DD, Ali SM, Sengupta S, et al. *Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB.* Mol Cell 2006;22:159-68.

[88] Dwyer JM, Duman RS. *Activation of mammalian target of rapamycin and synaptogenesis: role in the actions of rapid-acting antidepressants.* Biol Psychiatry 2013;73:1189-98.

[89] Jernigan CS, Goswami DB, Austin MC, et al. *The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder.* Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1774-9.

[90] Hoeffer CA, Klann E. *mTOR signaling: at the crossroads of plasticity, memory and disease*. Trends Neurosci 2010;33:67-75.

[91] Livingstone M, Atas E, Meller A, Sonenberg N. *Mechanisms governing the control of mRNA translation.* Phys Biol 2010;7:021001.

[92] Zunszain PA, Horowitz MA, Cattaneo A, Lupi MM, Pariante CM. *Ketamine: synaptogenesis, immunomodulation and glycogen synthase kinase-3 as underlying mechanisms of its antidepressant properties.* Mol Psychiatry 2013;18:1236-41.

[93] Li N, Lee B, Liu RJ, et al. *mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists.* Science 2010;329:959-64.

[94] Yoon SC, Seo MS, Kim SH, et al. *The effect of MK-801 on mTOR/p70S6K and translation-related proteins in rat frontal cortex.* Neurosci Lett 2008;434:23-8.

[95] Maeng S, Zarate CA Jr, Du J, et al. *Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors.* Biol Psychiatry 2008;63:349-52.

[96] Koike H, Iijima M, Chaki S. *Involvement of the mammalian target of rapamycin signaling in the antidepressant-like effect of group II metabotropic glutamate receptor antagonists.* Neuropharmacology 2011;61(8):1419-23.

[97] Takei N, Inamura N, Kawamura M, et al. *Brain-derived neurotrophic factor induces mammalian target of rapamycin-dependent local activation of translation machinery and protein synthesis in neuronal dendrites.* J Neurosci 2004;24:9760-9.

[98] Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. *Signaling pathways underlying the rapid antidepressant actions of ketamine.* Neuropharmacology 2012;62:35-41.

[99] Yang C, Hu YM, Zhou ZQ, Zhang GF, Yang JJ. *Acute administration of ketamine in rats increases hippocampal BDNF and mTOR levels during forced swimming test.* Ups J Med Sci 2013;118:3-8.

[100] Zarate CA Jr, Singh JB, Carlson PJ, et al. *A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression.* Arch Gen Psychiatry 2006a;63:856-64.

[101] Zarate CA Jr, Singh JB, Quiroz JA, et al. *A double-blind, placebo-controlled study of memantine in the treatment of major depression.* Am J Psychiatry 2006b;163:153-5.

[102] Sarbassov DD, Ali SM, Kim DH, et al. *Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton.* Curr Biol 2004;14:1296-302.

[103] Voleti B, Navarria A, Liu RJ, et al. *Scopolamine rapidly increases mTORC1 signaling, synaptogenesis, and antidepressant behavioral responses.* Biol Psychiatry 2013;74:742-9.

[104] Elfving B, Wegener G. *Electroconvulsive seizures stimulate the vegf pathway via mTORC1.* Synapse 2012;66:340-5.

[105] Dwyer JM, Lepack AE, Duman RS. *mTOR activation is required for the antidepressant effects of mGluR$_2$/$_3$ blockade.* Int J Neuropsychopharmacol 2012;15:429-34.

[106] Dowlati Y, Herrmann N, Swardfager W, et al. *A meta-analysis of cytokines in major depression.* Biol Psychiatry 2010;67:446-57.

[107] Howren MB, Lamkin DM, Suls J. *Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis.* Psychosom Med 2009;71:171-86.

[108] Schiepers OJ, Wichers MC, Maes M. *Cytokines and major depression.* Prog Neuropsychopharmacol Biol Psychiatry 2005;29:201-17.

[109] Krishnan V, Han M-H, Graham DL, et al. *Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions.* Cell 2007;131:391-404.

[110] Raison CL, Rutherford RE, Woolwine BJ, et al. *A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers.* JAMA Psychiatry 2013;70:31-41.

[111] Iwata M, Ota KT, Duman RS. *The inflammasome: pathways linking psychological stress, depression, and systemic illnesses.* Brain Behav Immun 2013;31:105-14.

[112] Koo JW, Duman RS. *IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress.* Proc Natl Acad Sci USA 2008;105:751-6.

[113] Paolicelli RC, Bolasco G, Pagani F, et al. *Synaptic pruning by microglia is necessary for normal brain development.* Science 2011;333:1456-8.

[114] Li S, Wang C, Wang W, Dong H, Hou P, Tang Y. *Chronic mild stress impairs cognition in mice: from brain homeostasis to behavior.* Life Sci 2008;82:934-42.

[115] Szelényi J. *Cytokines and the central nervous system.* Brain Res Bull 2001;54:329-38.

[116] Myint AM, Kim YK. *Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression.* Med Hypotheses 2003;61:519-25.

[117] Dunn AJ. *Effects of cytokines and infections on brain neurochemistry.* Clin Neurosci Res 2006;6: 52-68.

[118] Russo I, Amornphimoltham P, Weigert R, Barlati S, Bosetti F. *Cyclooxygenase-1 is involved in the inhibition of hippocampal neurogenesis after lipopolysaccharide-induced neuroinflammation.* Cell Cycle 2011;10:2568-73.

[119] Eyre H, Baune BT. *Neuroplastic changes in depression: a role for the immune system.* Psychoneuroendocrinology 2012;37:1397-416.

[120] Haase J, Brown E. *Integrating the monoamine, neurotrophin and cytokine hypotheses of depressiona central role for the serotonin transporter?* Pharmacol Ther 2015;147:1-11.

[121] Hannestad J, DellaGioia N, Bloch M. *The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis.* Neuropsychopharmacology 2011;36:2452-9.

[122] OBrien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. *Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy.* J Psychiatr Res 2007;41:326-31.

[123] Yoshimura R, Hori H, Ikenouchi-Sugita A, et al. *Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression.* Prog Neuropsychopharmacol Biol Psychiatry 2009;33(4):722-6.

[124] Loftis JM, Huckans M, Morasco BJ. *Neuroimmune mechanisms of cytokine-induced depression: current theories and novel treatment strategies.* Neurobiol Dis 2010;37:519-33.

[125] OConnor JC, Lawson MA, André C, et al. *Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice.* Mol Psychiatry 2009;14:511-22.

[126] Dantzer R, OConnor JC, Lawson MA, Kelley KW. *Inflammation-associated depression: from serotonin to kynurenine.* Psychoneuroendocrinology 2011;36:426-36.

[127] Walker AK, Budac DP, Bisulco S, et al. *NMDA receptor blockade by ketamine abrogates lipopolysaccharide-induced depressive-like behavior in C57BL/6J mice.* Neuropsychopharmacology 2013;38:1609-16.

[128] Kreisel T, Frank MG, Licht T, et al. *Dynamic microglial alterations underlie stress-induced depressive-like behavior and suppressed neurogenesis.* Mol Psychiatry 2014;19:699-709.

[129] Duric V, McCarson KE. *Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression.* J Pain 2006;7:544-55.

[130] Muñoz M, Coveñas R. *NK-1 receptor antagonists: a new paradigm in pharmacological therapy.* Curr Med Chem 2011;18:1820-31.

[131] Castanon N, Leonard BE, Neveu PJ, Yirmiya R. *Effects of antidepressants on cytokine production and actions.* Brain Behav Immun 2002;16:569-74.

[132] Kenis G, Maes M. *Effects of antidepressants on the production of cytokines.* Int J Neuropsychopharmacol 2002;5:401-12.

[133] Yirmiya R, Pollak Y, Barak O, et al. *Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents.* Neuropsychopharmacology 2001;24:531-44.

[134] Porterfield VM, Zimomra ZR, Caldwell EA, et al. *Rat strain differences in restraint stress-induced brain cytokines.* Neuroscience 2011;188:48-54.

[135] Lee HJ, Rao JS, Chang L, Rapoport SI, Kim HW. *Chronic imipramine but not bupropion increases arachidonic acid signaling in rat brain: is this related to switching in bipolar disorder?* Mol Psychiatry 2010;15:602-14.

[136] Lee HJ, Rao JS, Ertley RN, et al. *Chronic fluoxetine increases cytosolic phospholipase A(2) activity and arachidonic acid turnover in brain phospholipids of the unanesthetized rat.* Psychopharmacology (Berl) 2007;190:103-15.

[137] Sluzewska A, Sobieska M, Rybakowski JK. *Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression.* Neuropsychobiology 1997;35:123-7.

[138] Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. *Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression.* Cytokine 1997;9:853-8.

[139] Müller N, Schwarz MJ, Dehning S, et al. *The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine.* Mol Psychiatry 2006;11:680-4.

[140] Musil R, Schwarz MJ, Riedel M, et al. *Elevated macrophage migration inhibitory factor and decreased transforming growth factor-β levels in major depressionno influence of celecoxib treatment.* J Affect Disord 2011;134:217-25.

[141] Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. *Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study.* Int Clin Psychopharmacol 2006;21:227-31.

[142] Jazayeri S, Tehrani-Doost M, Keshavarz SA, et al. *Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder.* Aust N Z J Psychiatry 2008;42:192-8.

[143] Gertsik L, Poland RE, Bresee C, Rapaport MH. *Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder.* J Clin Psychopharmacol 2012;32:61-4.

[144] Peet M, Horrobin DF. *A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs.* Arch Gen Psychiatry 2002;59:913-9.

[145] Hornung JP. *The human raphe nuclei and the serotonergic system.* J Chem Neuroanat 2003;26: 331-43.

[146] Carr GV, Lucki I. *The role of serotonin receptor subtypes in treating depression: a review of animal studies.* Psychopharmacology (Berl) 2011;213:265-87.

[147] De Vry J. *5-HT1A receptor agonists: recent developments and controversial issues.* Psychopharmacology (Berl) 1995;121:1-26.

[148] Rosenzweig-Lipson S, Beyer CE, Hughes ZA, et al. Differentiating antidepressants of the future: efficacy and safety. Pharmacol Ther 2007;113:134–53.

[149] Celada P, Puig MV, Artigas F. *Serotonin modulation of cortical neurons and networks.* Front Integr Nuerosci 2013;7:25.

[150] Pompili M, Serafini G, Innamorati M, et al. *Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review.* World J Biol Psychiatry 2013;14:412-31.

[151] Höglinger GU, Rizk P, Muriel MP, et al. *Dopamine depletion impairs precursor cell proliferation in Parkinson disease.* Nat Neurosci 2004;7:726-35.

[152] Yang P, Arnold SA, Habas A, Hetman M, Hagg T. *Ciliary neurotrophic factor mediates dopamine D2 receptor-induced CNS neurogenesis in adult mice.* J Neurosci 2008;28:2231-41.

[153] Egeland M, Zhang X, Millan MJ, Mocaer E, Svenningsson P. *Pharmacological or genetic blockade of the dopamine D3 receptor increases cell proliferation in the hippocampus of adult mice.* J Neurochem 2012;123:811-23.

[154] Guiard BP, El Mansari M, Merali Z, Blier P. *Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions.* Int J Neuropsychopharmacol 2008;11:625-39.

[155] Kulkarni VA, Jha S, Vaidya VA. *Depletion of norepinephrine decreases the proliferation, but does not influence the survival and differentiation, of granule cell progenitors in the adult rat hippocampus.* Eur J Neurosci 2002;16:2008-12.

[156] Jhaveri DJ, Mackay EW, Hamlin AS, et al. *Norepinephrine directly activates adult hippocampal precursors via beta3-adrenergic receptors.* J Neurosci 2010;30:2795-806.

[157] Masuda T, Nakagawa S, Boku S, et al. *Noradrenaline increases neural precursor cells derived from adult rat dentate gyrus through β2 receptor.* Prog Neuropsychopharmacol Biol Psychiatry 2012;36:44-51.

[158] Rizk P, Salazar J, Raisman-Vozari R, et al. *The alpha2-adrenoceptor antagonist dexefaroxan enhances hippocampal neurogenesis by increasing the survival and differentiation of new granule cells.* Neuropsychopharmacology 2006;31:1146-57.

[159] Escribá PV, Ozaita A, García-Sevilla JA. *Increased mRNA expression of alpha2A-adrenoceptors, serotonin receptors and mu-opioid receptors in the brains of suicide victims.* Neuropsychopharmacology 2004;29:1512-21.

[160] Flügge G, Van Kampen M, Mijnster MJ. *Perturbations in brain monoamine systems during stress.* Cell Tissue Res 2004;315:1-14.

[161] Rivero G, Gabilondo AM, García-Sevilla JA, et al. *Increased α2- and β1-adrenoceptor densities in postmortem brain of subjects with depression: differential effect of antidepressant treatment.* J Affect Disord 2014;167:343-50.

[162] Valdizán EM, Díez-Alarcia R, González-Maeso J, et al. *α-Adrenoceptor functionality in postmortem frontal cortex of depressed suicide victims.* Biol Psychiatry 2010;68:869-72.

[163] Invernizzi RW, Garattini S. *Role of presynaptic alpha2-adrenoceptors in antidepressant action: recent findings from microdialysis studies.* Prog Neuropsychopharmacol Biol Psychiatry 2004;28:819-27.

[164] Subhash MN, Nagaraja MR, Sharada S, Vinod KY. *Cortical alpha-adrenoceptor downregulation by tricyclic antidepressants in the rat brain.* Neurochem Int 2003;43:603-9.

[165] Carpenter LL, Yasmin S, Price LH. *A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine.* Biol Psychiatry 2002;51:183-8.

[166] Quitkin FM, Taylor BP, Kremer C. *Does mirtazapine have a more rapid onset than SSRIs?* J Clin Psychiatry 2001;62:358-61.

[167] Sanacora G, Berman RM, Cappiello A, et al. *Addition of the alpha2-antagonist yohimbine to fluoxetine: effects on rate of antidepressant response.* Neuropsychopharmacology 2004;29:1166-71.

[168] Yanpallewar SU, Fernandes K, Marathe SV, et al. *Alpha2-adrenoceptor blockade accelerates the neurogenic, neurotrophic, and behavioral effects of chronic antidepressant treatment.* J Neurosci 2010;30:1096-109.

[169] Husain BF, Nanavaty IN, Marathe SV, Rajendran R, Vaidya VA. *Hippocampal transcriptional and neurogenic changes evoked by combination yohimbine and imipramine treatment.* Prog Neuropsychopharmacol Biol Psychiatry 2015;61:1-9.

[170] Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. *Endocannabinoid system and mood disorders: priming a target for new therapies.* Pharmacol Ther 2013;138:18-37.

[171] Wallace TL, Stellitano KE, Neve RL, Duman RS. *Effects of cyclic adenosine monophosphate response element binding protein overexpression in the basolateral amygdala on behavioral models of depression and anxiety.* Biol Psychiatry 2004;56:151-60.

[172] Hill MN, Carrier EJ, McLaughlin RJ, et al. *Regional alterations in the endocannabinoid system in an animal model of depression: effects of concurrent antidepressant treatment.* J Neurochem 2008a;106:2322-36.

[173] Hill MN, Ho WS, Hillard CJ, Gorzalka BB. *Differential effects of the antidepressants tranylcypromine and fluoxetine on limbic cannabinoid receptor binding and endocannabinoid contents.* J Neural Transm (Vienna) 2008b;115:1673-9.

[174] Mato S, Vidal R, Castro E, et al. *Long-term fluoxetine treatment modulates cannabinoid type 1 receptor-mediated inhibition of adenylyl cyclase in the rat prefrontal cortex through 5-hydroxytryptamine 1A receptor-dependent mechanisms.* Mol Pharmacol 2010;77:424-34.

[175] Bambico FR, Nguyen NT, Katz N, Gobbi G. *Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission.* Neurobiol Dis 2010;37:641-55.

[176] Cassano T, Gaetani S, Macheda T, et al. *Evaluation of the emotional phenotype and serotonergic neurotransmission of fatty acid amide hydrolase-deficient mice.* Psychopharmacology (Berl) 2011;214:465-76.

[177] Fogaça MV, Galve-Roperh I, Guimarães FS, Campos AC. Cannabinoids, *Neurogenesis and Antidepressant Drugs: Is*

there a Link? Curr Neuropharmacol 2013;11:263-75.
[178] Dagyte G, Trentani A, Postema F, et al. *The novel antidepressant agomelatine normalizes hippocampal neuronal activity and promotes neurogenesis in chronically stressed rats.* CNS Neurosci Ther 2010;16:195-207.
[179] David DJ, Samuels BA, Rainer Q, et al. *Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression.* Neuron 2009;62:479-93.
[180] Huang GJ, Herbert J. *Stimulation of neurogenesis in the hippocampus of the adult rat by fluoxetine requires rhythmic change in corticosterone.* Biol Psychiatry 2006;59:619-24.
[181] Fitzsimons CP, van Hooijdonk LW, Morrow JA, et al. *Antiglucocorticoids, neurogenesis and depression.* Mini Rev Med Chem 2009;9:249-64.
[182] Kronenberg G, Kirste I, Inta D, et al. *Reduced hippocampal neurogenesis in the GR(+/-) genetic mouse model of depression.* Eur Arch Psychiatry Clin Neurosci 2009;259:499-504.
[183] Pariante CM, Hye A, Williamson R, et al. *The antidepressant clomipramine regulates cortisol intracellular concentrations and glucocorticoid receptor expression in fibroblasts and rat primary neurones.* Neuropsychopharmacology 2003a;28:1553-61.
[184] Pariante CM, Kim RB, Makoff A, Kerwin RW. *Antidepressant fluoxetine enhances glucocorticoid receptor function in vitro by modulating membrane steroid transporters.* Br J Pharmacol 2003b;139:1111-8.
[185] Tanti A, Belzung C. *Neurogenesis along the septo-temporal axis of the hippocampus: are depression and the action of antidepressants region-specific?* Neuroscience 2013;252:234-52.
[186] Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. *Adult hippocampal neurogenesis buffers stress responses and depressive behaviour.* Nature 2011;476:458-61.
[187] Schloesser RJ, Jimenez DV, Hardy NF, et al. *Atrophy of pyramidal neurons and increased stressinduced glutamate levels in CA3 following chronic suppression of adult neurogenesis.* Brain Struct Funct 2014;219:1139-48.
[188] Nollet M, Gaillard P, Tanti A, et al. *Neurogenesis-independent antidepressant-like effects on behavior and stress axis response of a dual orexin receptor antagonist in a rodent model of depression.* Neuropsychopharmacology 2012;37:2210-21.
[189] Hu P, Oomen C, van Dam AM, et al. *A single-day treatment with mifepristone is sufficient to normalize chronic glucocorticoid induced suppression of hippocampal cell proliferation.* PLoS One 2012;7:e46224.
[190] Hughes ZA, Liu F, Marquis K, et al. *Estrogen receptor neurobiology and its potential for translation into broad spectrum therapeutics for CNS disorders.* Curr Mol Pharmacol 2009;2:215-36.
[191] Woolley CS, McEwen BS. *Estradiol regulates hippocampal dendritic spine density via an N-methy--D-aspartate receptor-dependent mechanism.* J Neurosci 1994;14:7680-7.
[192] Duman RS, Aghajanian GK. *Neurobiology of rapid acting antidepressants: role of BDNF and GSK- 3.* Neuropsychopharmacology 2014;39:233.
[193] Duman RS. *Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections.* Dialogues Clin Neurosci 2014;16:11-27.
[194] Dawson LA, Watson JM. *Vilazodone: a 5-HT1A receptor agonist/serotonin transporter inhibitor for the treatment of affective disorders.* CNS Neurosci Ther 2009;15:107–117.
[195] Schreiber R, De Vry J. *5-HT1A receptor ligands in animal models of anxiety, impulsivity and depression: multiple mechanisms of action?* Prog Neuro-Psychopharmacol Biol Psychiatry 1993;17:87–104.
[196] de Boer SF, Koolhaas JM. *5-HT1A and 5-HT1B receptor agonists and aggression: a pharmacological challenge of the serotonin deficiency hypothesis.* Eur J Pharmacol 2005;526:125–139.
[197] Rickels K, Athanasiou M, Robinson DS, et al. *Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder : a randomized, double-blind, placebo-controlled trial.* J Clin Psychiatry 2009;70:326–333.
[198] Laughren TP, Gobburu J, Temple RJ, et al. *Vilazodone: clinical basis for the US Food and Drug Administration's approval of a new antidepressant.* J Clin Psychiatry 2011;72:1166–1173.
[199] Bang-Andersen B, Ruhland T, Jorgensen M, et al. *Discovery of 1-[2-(2,4- dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder.* J Med Chem 2011;54:3206–3221.
[200] Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. *A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder.* Int J Neuropsychopharmacol 2011;15:589–600.
[201] Learned S, Graff O, Roychowdhury S, et al. *Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder : two randomized, placebo- and active-controlled clinical trials.* J Psychopharmacol 2012;26:653–662.
[202] Golembiowska K, Kowalska M, Bymaster FP. *Effects of the triple reuptake inhibitor amitifadine on extracellular levels of monoamines in rat brain regions and on locomotor activity.* Synapse 2012;66:435–444.
[203] Skolnick P, Krieter P, Tizzano J, et al. *Preclinical and clinical pharmacology of DOV 216,303, a 'triple ' reuptake inhibitor.* CNS Drug Rev 2006;12:123–134.
[204] Tran P, Skolnick P, Czobor P, et al. *Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder : a randomized, double-blind, placebo-controlled trial.* J Psychiatr Res 2012;46:64–71.
[205] Manji HK, Moore GJ, Rajkowska G, Chen G. *Neuroplasticity and cellular resilience in mood disorders.* Mol Psychiatry 2000;5:578-93.
[206] Murrough JW, Charney DS. *Is there anything really novel on the antidepressant horizon?* Curr Psychiatry Rep 2012;14:643-9.
[207] McEwen BS, Chattarji S. *Molecular mechanisms of neuroplasticity and pharmacological implications: the example of tianeptine.* Eur Neuropsychopharmacol 2004;14:S497-502.
[208] Kasper S, McEwen BS. *Neurobiological and clinical effects of the antidepressant tianeptine.* CNS Drugs 2008;22:15-26.
[209] Fifková E, Van Harreveld A. *Long-lasting morphological changes in dendritic spines of dentate granular cells following stimulation of the entorhinal area.* J Neurocytol 1977;6:211-30.
[210] Halpain S, Hipolito A, Saffer L. *Regulation of F-actin stability in dendritic spines by glutamate and calcineurin.* J Neurosci 1998;18(23):9835-44.
[211] Sanacora G, Zarate CA, Krystal JH, Manji HK. *Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders.* Nat Rev Drug Discov 2008;7:426-37.
[212] Virgin CE Jr, Ha TP, Packan DR, et al. *Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity.* J Neurochem 1991;57:1422-8.
[213] Watanabe Y, Gould E, Daniels DC, Cameron H, McEwen BS. *Tianeptine attenuates stress-induced morphological changes in the hippocampus.* Eur J Pharmacol 1992;222:157-62.
[214] Magariños AM, McEwen BS. *Stress-induced atrophy of api-*

cal dendrites of hippocampal CA3c neurons: involvement of glucocorticoid secretion and excitatory amino acid receptors. Neuroscience 1995;69:89-98.

[215] Pfleiderer B, Michael N, Erfurth A, et al. *Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients.* Psychiatry Res 2003;122:185-92.

[216] Berman RM, Cappiello A, Anand A, et al. *Antidepressant effects of ketamine in depressed patients.* Biol Psychiatry 2000;47:351-4.

[217] Serafini G, Pompili M, Hansen KF, et al. *The involvement of microRNAs in major depression, suicidal behavior, and related disorders: a focus on miR-185 and miR-4913p.* Cell Mol Neurobiol 2014;34:17-30.

[218] Duncan WC Jr, Selter J, Brutsche N, Sarasso S, Zarate CA Jr. *Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder.* J Affect Disord 2013;145:115-9.

[219] Dowben JS, Grant JS, Keltner NL. *Ketamine as an alternative treatment for treatment-resistant depression.* Perspect Psychiatr Care 2013;49:2-4.

[220] Mion G, Villevieille T. *Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings).* CNS Neurosci Ther 2013;19:370-80.

[221] Tedesco V, Ravagnani C, Bertoglio D, Chiamulera C. *Acute ketamine-induced neuroplasticity: ribosomal protein S6 phosphorylation expression in drug addiction-related rat brain areas.* Neuroreport 2013;24:388-93.

[222] Parsons CG, Panchenko VA, Pinchenko VO, Tsyndrenko AY, Krishtal OA. *Comparative patch-clamp studies with freshly dissociated rat hippocampal and striatal neurons on the NMDA receptor antagonistic effects of amantadine and memantine.* Eur J Neurosci 1996;8:446-54.

[223] Dietrich DE, Bode L, Spannhuth CW, et al. *Amantadine in depressive patients with Borna disease virus (BDV) infection: an open trial.* Bipolar Disord 2000;2:65-70.

[224] Moryl E, Danysz W, Quack G. *Potential antidepressive properties of amantadine, memantine and bifemelane.* Pharmacol Toxicol 1993;72:394-7.

[225] Rogóz Z, Skuza G, Maj J, Danysz W. *Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats.* Neuropharmacology 2002;42:1024-30.

[226] Furey ML, Khanna A, Hoffman EM, Drevets WC. *Scopolamine produces larger antidepressant and antianxiety effects in women than in men.* Neuropsychopharmacology 2010;35:2479-88.

[227] Caruana DA, Warburton EC, Bashir ZI. *Induction of activity-dependent LTD requires muscarinic receptor activation in medial prefrontal cortex.* J Neurosci 2011;31(50):18464-78.

[228] Dwivedi Y. *Emerging role of microRNAs in major depressive disorder: diagnosis and therapeutic implications.* Dialogues Clin Neurosci 2014;16:43-61.

[229] Serafini G, Pompili M, Hansen KF, et al. *MicroRNAs: fundamental regulators of gene expression in major affective disorders and suicidal behavior?* Front Cell Neurosci 2013;7:208.

[230] Serafini G, Pompili M, Innamorati M, et al. *The role of microRNAs in synaptic plasticity, major affective disorders and suicidal behavior.* Neurosci Res 2012;73:179-90.

[231] Bortolozzi A, Celada P, Artigas F. Novel *therapeutic strategies in major depression: focus on RNAi and ketamine.* Curr Pharm Des 2014;20:3848-60.

[232] Serafini G, Howland RH, Rovedi F, et al. *The role of ketamine in treatment-resistant depression: a systematic review.* Curr Neuropharmacol 2014;12:444-61.