Expert Opinion

1. Introduction
2. The need for newer antidepressants
3. Animal models used to screen antidepressant molecules and their limitations
4. Revisiting dopamine in major depression: the concept of 'triple reuptake inhibitors'
5. Triple reuptake inhibitors (SNDRIs)
6. L-arginine-nitric oxide-cyclic guanosine monophosphate pathway modulators
7. Sigma-1 receptor modulato
8. Neurosteroids
9. Agomelatine
10. Glutamatergic modulators
11. 5-HT$_6$ serotonin receptor modulators
12. 5-HT$_7$ serotonin receptor modulators
13. Other approaches
14. Conclusion
15. Expert opinion

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Current investigational drugs for major depression

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Background: The World Health Organization (WHO) report has predicted that major depression will become a key cause of illness-induced disability by the year 2020, second only to ischemic heart diseases. *Objectives/methods*: Although a large number of antidepressant drugs (from monoamine oxidase inhibitors and tricyclic antidepressants to dual reuptake inhibitors) are available for treatment of the disease, approximately 30% of patients failed to respond to this therapy. Therefore, the search for newer or novel drug targets for the treatment of major depression continues. Some of these targets include dopamine, triple reuptake inhibition, L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway, sigma-1 receptors, neurosteroids, melatonin, glutamate, 5HT$_6$, 5HT$_7$ serotonin receptor antagonists, β-3 adrenoceptor antagonist, vasopressin V(Ib) receptor antagonists, NK2 tachykinin receptor antagonists, glucocorticoid receptor antagonists and corticotropin-releasing factor-1 receptor antagonists, as well as herbal antidepressant drugs. The present review attempts to discuss the status of some of these novel approaches and the drugs that are under investigation for the treatment of major depression. An attempt is also made to review the status of three indigenous plant-derived drugs, berberine, curcumin and rutin, as novel and safe future herbal antidepressants. *Results/conclusion*: There is an exciting future in the discovery of novel targets and target-specific agents for the management of major depression.

Keywords: antidepressants, herbal drugs, major depression, novel targets

Expert Opin. Investig. Drugs (2009) ***18****(6):767-788*

1. Introduction

Major depression represents one of the most common and proliferating health problems worldwide [1,2]. With increasing longevity, its prevalence is estimated to be 15 – 20 % [3-5]. It is speculated that approximately 340 million people worldwide suffer from major depressive disorder [6] and nearly 35 – 40% of suicides are considered to be related to major depression as an underlying cause [7]. At one time it was commonly considered as a progressive neurodegenerative disorder (commonly observed in elderly people), but in recent years it is increasingly observed in young adults, adolescent and even in children [8]. Major depression, particularly in lower age groups, if untreated can affect the performance and learning, social interactions and development of normal peer relationships, self-esteem and life skill acquisition during adulthood, as well as leading to antisocial activities like substance abuse, disruptive behavior, violence and aggression, criminal activity, and even suicidal ideations later in life [9]. Major depression is more commonly seen among women than men (in all age groups) [9]. In spite of the large number of drugs available for the management of the disease, there has been a continuous search for newer and target-specific drugs to better manage the disease. The present review discusses the status of these developments.

10.1517/13543780902880850 © 2009 Informa UK Ltd ISSN 1354-3784

2. The need for newer antidepressants

Although a large number of antidepressant drugs are commercially available for the treatment of major depression, the search for alternative targets and specific drugs is a continuous effort, for the following reasons.

- The presently available blockbuster drugs like imipramine (Tofranil® [Novartis, Basel, Switzerland]; tricyclic antidepressant), fluoxetine (Prozac® [Eli Lilly, IN, USA]; selective serotonin reuptake inhibitor), citalopram (Celexa® [H. Lundeback, IL, USA]; selective serotonin reuptake inhibitor) and venlafaxine (Effexor® [Wyeth, Madison, New Zealand]; dual reuptake inhibitor of norepinephrine and serotonin) have been in use for many years. However, approximately 30% of depressed patients do not respond fully to the drug therapy and the remaining 70% do not achieve complete remission [10,11]. A 10-year follow-up study to determine the number of well versus unwell days in patients on antidepressant drugs [12] has shown that they spent three-quarters of the decade in euthymia and the remaining quarter in subthreshold or threshold major depression [12].
- Currently available antidepressant drugs show clinical response after a lag period of 2 – 4 weeks. Therefore, there is a need to develop drugs with a faster onset of action [13].
- Currently used antidepressants have several adverse drug reactions as well as drug–drug interactions, besides other actions. For example, tricyclic antidepressant drugs are associated with a plethora of side effects that include antimuscarinic, α_1-adrenergic, and histaminergic actions [14]. Similarly, monoamine oxidase inhibitors are known to produce 'cheese reaction' when administered with dairy products [15].

Figure 1 depicts the development of antidepressants and the available new targets for the treatment of major depression. These new drug targets are discussed below.

3. Animal models used to screen antidepressant molecules and their limitations

Out of all the animal models, forced swim test (FST) and tail-suspension test (TST) are commonly employed to screen antidepressant drugs. The FST is credited for having good predictive validity for detecting antidepressant activity [16,17]. The test also has been used to investigate the mechanism of action of antidepressant drugs [18-20]. The FST relatively is highly selective for antidepressants as compared to other classes of central nervous system drugs [21]. For example, the benzodiazepines are not active in FST [21], with the exception of alprazolam, the only benzodiazepine to exhibit antidepressant-like effects [22]. However, psychomotor stimulants like amphetamines reduce the immobility period in FST and are probably not effective as antidepressants. Because of this pattern, additional testing for locomotor activity along with FST is generally advocated, although drugs that decrease immobility time in the FST and also simultaneously increase the locomotor activity, such as bupropion and GBR12909, may still have antidepressant activity [23]. Genetic factors and strain variation also influence immobility profile in FST [24-27]. The Swiss strain of mice has been found to be highly sensitive to detect serotonin and/or noradrenaline-mediated behaviors [28]. DBA/2 inbred mice do not show any specific immobility profiles in FST [28]. The DBA/2 strain have high levels of dopamine, noradrenaline and serotonin contents in the brain and as such do not show despair behavior [28].

In TST, mice are suspended by their tails for a defined period of time and their immobility is assessed. The model has been validated across a broad range of antidepressants [29]. Despite the apparent conceptual similarity with the FST, behavior in the TST may have a different neurochemical basis [26,30]. A major advantage of TST is that it is simple, inexpensive and allows for automation. A major drawback of TST is that its application is limited to strains that do not climb their tail [31]. Moreover, neither FST nor TST reflect the slow onset of antidepressant action as is observed in clinics. Therefore, whether these tests (or others) will predict true antidepressant efficacy for novel mechanisms remains to be seen.

4. Revisiting dopamine in major depression: the concept of 'triple reuptake inhibitors'

Dopaminergic neurons are known to innervate brain areas associated with behavioral and physiological functions that are altered in major depression (e.g., the cortex, limbic structures, and the pituitary gland). These brain areas are involved in cognition and modulation of behaviors linked with motivation and reward [32]. Disruption of these behaviors may lead to anhedonia (decreased pleasure), social isolation, and psychomotor retardation or agitation and other behavioral symptoms that are the core psychopathologies of major depression [33]. Various evidence has implicated the involvement of the dopaminergic system in the pathophysiology of major depression [34]. A lower density of radioligand binding to the dopamine transporter was observed in the basal and central nuclei of the amygdala from subjects diagnosed with major depression [33]. Homovanillic acid (HVA), a metabolite of dopamine, is found to be decreased in patients suffering from major depression, suggesting that a decrease in dopamine turnover is associated with the pathophysiology of major depression [34] (**Figure 2**). Recently, it has been found that the HVA/5-hydroxyindolacetic acid (metabolite of serotonin) (HVA/5-HIAA) ratios are reduced in cerebrospinal fluid of depressed patients who committed suicide due to major depression [36].

Animal studies have shown that lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area produced depression-like behavior in rats [37]. It is being suggested that that the HVA/5-HIAA ratio may be a biomarker of suicidal intent [36]. In one of the studies conducted in our laboratory, it has been suggested that bupropion (Wellbutrin®[Sun Pharmaceuticals,

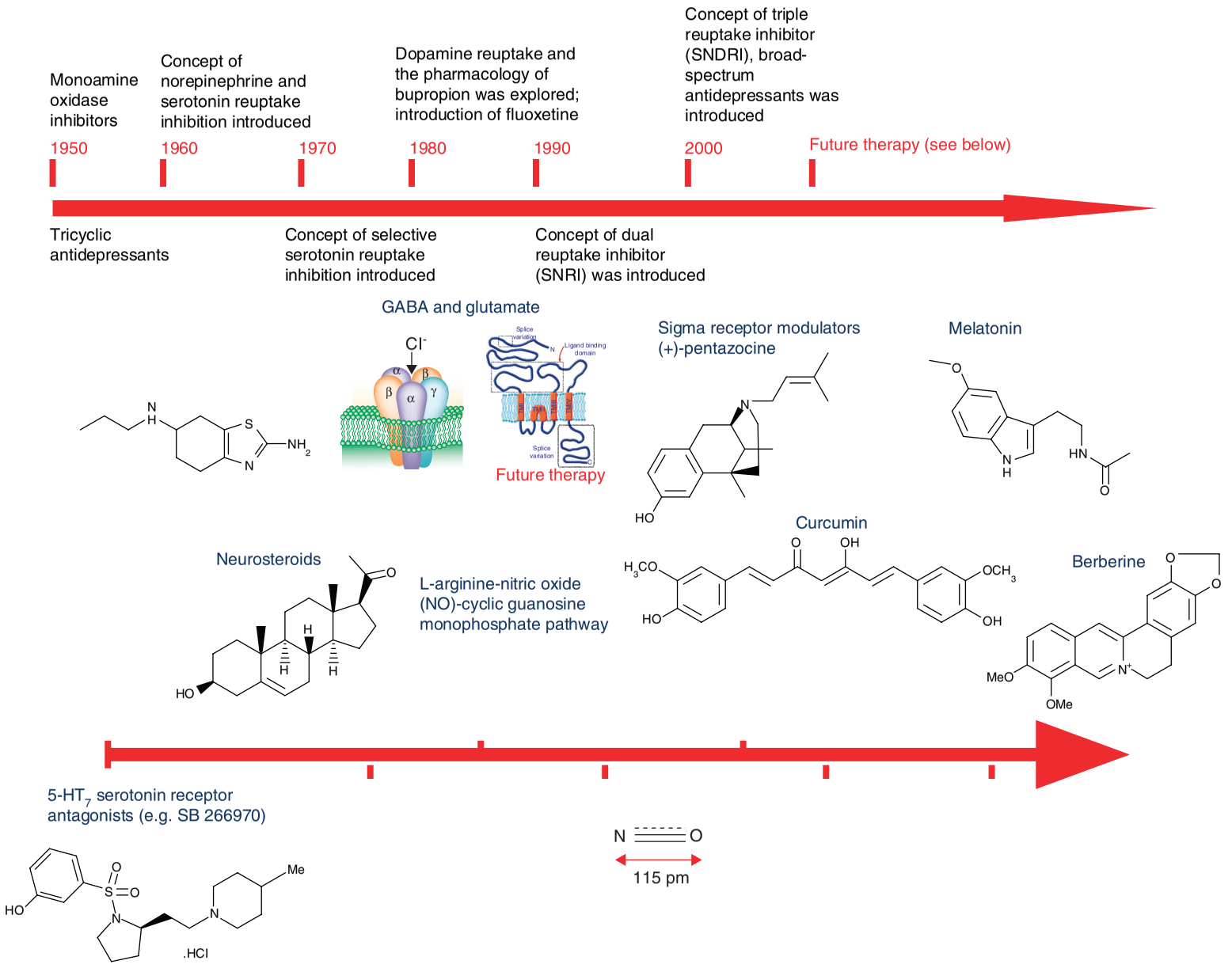

Figure 1. Historical development of antidepressants and novel drug targets that are under investigation for the treatment of depression.

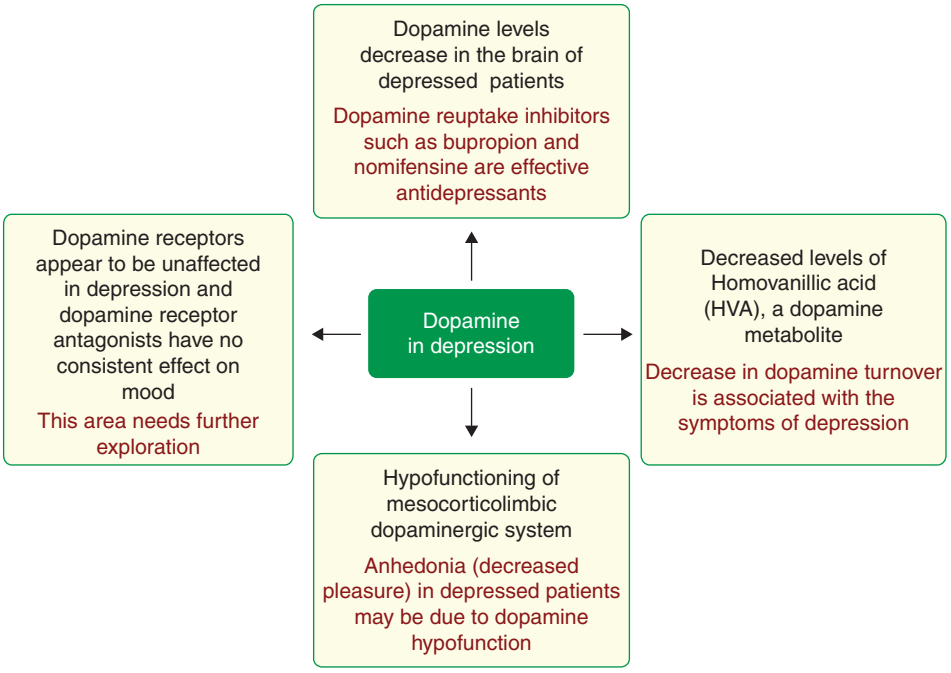

Figure 2. Summary of the role of dopamine in depression.

Mumbai, India], a dopamine reuptake inhibitor with some noradrenergic activity via enhancing the levels of dopamine in brain [38]) possessed antidepressant-like effects (**Figure 3**) [39]. However, in clinics the antidepressant activity of bupropion is still controversial. While it was effective in a 70-year-old female patient suffering from resistant depression [38], it produced a major depression-like state in another set of patients [40]. It is often classified as an atypical antidepressant, as bupropion was also demonstrated to selectively inhibit the firing rates of noradrenergic cells in the locus coeruleus (at doses significantly lower than those which inhibit the activity of midbrain dopaminergic cells or dorsal raphe serotonergic cells) [41].

Nomifensine is another antidepressant having dopamine- and norepinephrine-inhibiting properties with little effect on serotonin reuptake mechanism [42]. Various dopamine D_3-preferring (D_2/D_3) dopamine receptor agonists such as pramipexole [43] have been reported to show therapeutic efficacy in major depression. The pharmacokinetic profile has been shown in **Table 1**. Dopamine D_3 receptors are mainly located in the limbic area of the brain, and are therefore speculated to play an important role in the pathophysiology of major depression. It has been proposed that the 2 allele of the dopamine receptor D_3 gene seems to be associated with unipolar depression [44].

In one of the studies using mice, we have reported the antidepressant profile of ropinirole (Requip® [GlaxoSmithKline, PA, USA]), a D_2/D_3 dopamine receptor agonist in both FSTs and TSTs [45]. It exhibited an S-shaped curve in its antidepressant-like activity. Further, the antidepressant action was blocked by haloperidol (Haldol®), a D_2 dopamine receptor blocker, and sulpiride, a D_2/D_3 dopamine receptor antagonist, suggesting the involvement of dopamine receptors in its antidepressant action. When neurochemical analysis was done, surprisingly, it was found that the administration of ropinirole did not affect dopamine levels in the brain but resulted in increased levels of serotonin in the whole brain preparation (**Figure 4**) [45]. It was hypothesized that serotonergic stimulation of the prefrontal cortex [46], or the nucleus accumbens [47], potently releases dopamine.

The increase of dopamine release in the prefrontal and frontal cortex by 5-HT_{1A} serotonin agonists has also been demonstrated [48]. Lejeune and Millan demonstrated that the selective activation of $5HT_{1A}$ postsynaptic receptors also elicits an increase in ventral tegmental area dopaminergic output [48]. However, the exact mechanisms of ropinirole-induced serotonin release and its relationship with dopamine needs further exploration. The use of ropinirole in clinics is limited, as it produced transient hallucination [49]. Similarly, pramipexole (Mirapex® [Boehringer Ingelheim, Ingelheim, Germany]), a D_2/D_3 dopamine receptor agonist, piribedil, a dopamine receptor agonist [50] and oxcarbazepine, a keto-analogue of carbamazepine (Tegretol®, an antiepileptic drug) have also been shown to possess antidepressant-like effects in animal models of despair, possibly by modulating the dopaminergic neurotransmission [51].

It is therefore, reasonable to assume that antidepressant medications that increase all the three monoamines (norepinephrine, serotonin and dopamine), such as a 'triple monoamine reuptake inhibitor', may offer an additional advantage in the treatment of major depression over a single-site agent. Therefore, the simultaneous targeting of all three monoaminergic systems may be advantageous.

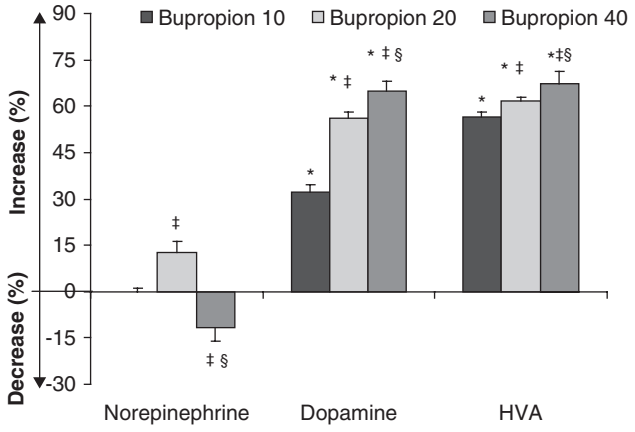

Figure 3. Effect of bupropion (10, 20 and 40 mg/kg i.p.) on the biogenic amines levels in the mice brain homogenates. Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's test (n = 6 – 8) [39].

*$p < 0.05$ compared with vehicle-treated group.

‡$p < 0.05$ compared with bupropion (10 mg/kg, i.p.)-treated group.

§$p < 0.05$ compared with bupropion (20 mg/kg, i.p.)-treated group.

Table 1. Pharmacokinetic parameters of ropinirole and pramipexole dopamine receptor agonist.

Parameters	Ropinirole	Pramipexole
Oral bioavailability	55%	> 90%
Time to peak action	1 – 2 h	2 h
Volume of distribution	7.5 l/kg	500 l/kg
Plasma proteins bounding	40%	15%
Elimination half-life	6 h	8 – 12 h
Available tablets	0.25 – 5 mg	0.125 – 1.5 mg

5. Triple reuptake inhibitors (SNDRIs)

Recently, the concept of triple reuptake inhibition has been introduced [52,53]. Two major molecules belonging to this category are GlaxoSmithKline's lead candidate, NS2359, and Merck's triple reuptake inhibitor DOV216303 [54,55] racemic compound (expected to be launched in 2011). It is anticipated that these molecules will have better efficacy and safety profiles compared with those of existing antidepressants; more interestingly, the lag period of 2 – 4 weeks with conventional antidepressants may be overcome by the use of these inhibitors [53]. GlaxoSmithKline also has the rights to launch NS2359 for the treatment of attention deficit hyperactivity disorder (ADHD), a psychiatric disorder characterized by disturbances in attention, hyperactivity and impulsiveness [56]. NS2359 is known to induce a significant improvement of cognitive function, as this molecule also alters the cholinergic neurotransmission in the brain. DOV216303 is active in mouse FSTs and tetrabenazine-induced ptosis [55]. In a recent clinical study, DOV216303 was found to be safe and well tolerated both at single doses of ≤ 100 mg and multiple doses of ≤ 100 mg/day for 10 days [57]. Chronic, but not acute, treatment with DOV216303 (20 mg/kg) is known to normalize olfactory bulbectomy-induced hyperactivity in the open field test, the effect being similar to that of imipramine (20 mg/kg) [54]. Interestingly, these doses of DOV216303 had no effect on sexual behavior at any time point [54]. Regarding the pharmaco-kinetics of DOV 216303, it is known to be rapidly absorbed (plasma T_{max} of 0.7 – 1.2 h and $t_{½}$ of 3.3 – 4.4 h) [57]. Another molecule, DOV21947, which is the enantiomeric form of DOV216303, is also effective in FSTs in rats [58]. Another triple reuptake inhibitor, DOV102677, enhanced the extracellular levels of dopamine, serotonin, and norepinephrine in the prefrontal cortex and levels of dopamine and serotonin in the nucleus accumbens, along with reducing their metabolites in both regions [59].

Some of the other triple reuptake inhibitors under investigation include PRC 200-SS, AMRI CNS-1 and AMRI CNS-2. Tesofensine (NS-2330) is another triple reuptake inhibitor developed by NeuroSearch that has an added advantage of long duration acting drug with a $t_{½}$ of approximately 8 days [60]. This molecule is also known to increase the mRNA expression of brain-derived neurotrophic factor and promotes hippocampal neurogenesis. However, due to inadequate inhibition of dopamine reuptake, tesofensine failed to provide clinical benefit as monotherapy in early Parkinson's disease [61]. Another triple reuptake inhibitor in Phase I clinical trials is the Sepracor molecule SEP225289 [62]. PRC200-SS, a new triple reuptake inhibitor synthesized by the Mayo Clinic and currently in preclinical studies, is known to potently bind to the human serotonin, norepinephrine, and dopamine transporters with Kd values of 2.3, 0.63, and 18 nM, respectively [63]. Similarly, JNJ-7925476 is a triple reuptake inhibitor synthesized by Johnson & Johnson; it is under preclinical development [64]. One of the triple reuptake inhibitors from Bristol-Myers Squibb is also in Phase I clinical trials for the treatment of major depression.

It is interesting to note that SNRIs (dual reuptake inhibitors of serotonin and norepinephrine) such as venlafaxine and sibutramine are also known to weakly inhibit the reuptake of dopamine at high doses, and so while these drugs are selective for the serotonin and noradrenaline transporters at usual doses, they can act as SNDRIs when taken at doses above the normal therapeutic range.

6. L-arginine-nitric oxide-cyclic guanosine monophosphate pathway modulators

The nitric oxide pathway has recently been demonstrated to play a major role in the action of various antidepressants [40,45,65,66]. Nitric oxide, a gaseous molecule, is formed from L-arginine by a reaction catalyzed by the enzyme nitric oxide synthase

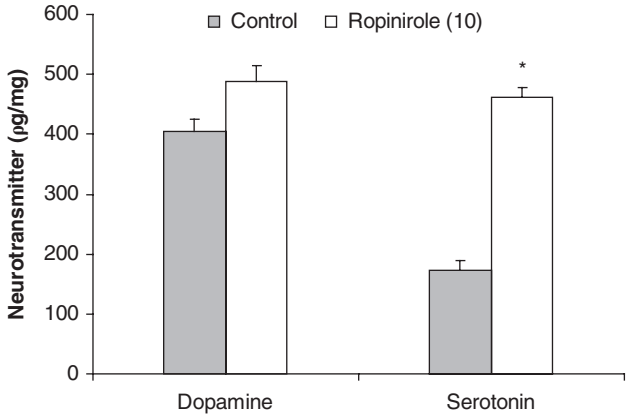

Figure 4. Effect of ropinirole (10 mg/kg, i.p.) on the alteration in neurotransmitter levels in the mouse whole brain. Ropinirole (10 mg/kg, i.p.) was administered 30 min before sacrificing the animals. Data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's test. [45].
*$p < 0.05$ compared with vehicle-treated group.

(NOS) enzyme. Three isoforms of nitric oxide synthase enzyme have been identified: neuronal nitric oxide synthase (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) [65]. Various NOS inhibitors have been demonstrated to have antidepressant-like action in animal models of despair. In some of the studies carried out in our laboratory, the involvement of this pathway in the antidepressant-like action of venlafaxine [65], bupropion [40], and berberine (an isoquinoline alkaloid obtained from *Berberis aristata*) [67,68] have been demonstrated. This pathway is also involved in mediating the antidepressant-like action of adenosine [69], memantine [70], zinc [71], tramadol [72], and others.

It is known that nitric oxide activates soluble guanylate cyclase, which further converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), as shown in **Figure 5**.

It is known that excessive production of cGMP may produce a depression-like state, while reduced levels of cGMP can produce the opposite (i.e., have an antidepressant-like action) [73]. cGMP can be decreased either by inhibiting the soluble guanylate cyclase (e.g., using methylene blue) or by decreasing the production of nitric oxide (by inhibiting NOS enzyme). cGMP is further degraded into guanosine monophosphate (GMP) with the help of enzyme phosphodiesterase. Therefore, inhibiting phosphodiesterase enzyme by using various inhibitors (such as sildenafil) may increase the levels of cGMP and in turn produce depression-like phases. This pathway may be further explored in elucidating the mechanism of action of various antidepressant drugs. However, nitric oxide is known to produce dual effects. Both L-arginine (a precursor of nitric oxide) and N(G)-nitro-L-arginine (L-NNA, a NOS inhibitor) display antidepressant-like activity in FSTs [74]. Various nitric oxide modulators could be the future drugs for the treatment of major depression.

7. Sigma-1 receptor modulators

Sigma receptors are non-opioid, non-phencyclidine intracellular receptors that have been explored as novel targets for antidepressant drugs. This receptor system was initially categorized as a subtype of opioid receptors in the 1970s [75]. However, due to a lack of sensitivity to naltrexone (selective antagonist of opioid receptors), these receptors are now categorized as distinct from the opioid class [76]. The sigma receptor binding sites have been identified in various regions of brain with its abundance in hippocampus, hypothalamus and substantia nigra, the brain areas related to motor, endocrine and memory functions [77,78]. Selective serotonin reuptake inhibitors like fluvoxamine (Luvox® [Solvay Pharmaceuticals, Bruselles, Belgium]) have been reported to possess higher affinity for sigma-1 receptors [79], while tricyclic antidepressants appear to have moderate affinity [80].

A recent positron emission tomography (PET) study demonstrated that a single oral administration of fluvoxamine occupies sigma-1 receptors in the human brain [81]. Other evidence has shown that sigma-1 receptor agonists have antidepressant-like action in various animal models of despair [82]. In some of the studies carried out in our laboratory, the involvement of sigma-1 receptors in the antidepressant action of venlafaxine [83], bupropion [84], berberine [68] and neurosteroids [85] has been extensively demonstrated. (+)-Pentazocine, an agonist of sigma receptors, enhanced the antidepressant-like effect of neurosteroids (dehydroepiandrosterone sulfate and pregnenolone sulfate), whereas prior administration of progesterone, rimcazole and BD-1047 reversed the antidepressant-like effect of these neurosteroids. It is suggested that neurosteroids (dehydroepiandrosterone and pregnenolone sulfate) may have sigma-1 receptor-modulatory action [85].

Sigma-1 receptor activation tonically inhibits the K^+ channel activity, as these receptors are closely associated with these channel function [86]. Earlier studies have shown inhibition of different types of potassium channels to produce antidepressant-like effects in mice [87,88]. Sigma-1 receptors are also associated with regulation of the activity of NMDA receptor channels [89]. Inhibition of K^+ channels by sigma-1 receptors indirectly induces the functioning of NMDA receptor channels. The activation of sigma-1 receptors by (+)-pentazocine potentiated NMDA receptor responses and associated long-term potentiation by inhibiting a small Ca^{2+}-activated K^+ current [90]. All these actions seem to lead to higher excitation states of neurons [91]. Therefore, if NMDA activity is increased, it may lead to neuronal cell death and further major depression. However, on the other hand, this activation may contribute to the proper functioning of active ion channels and the ensuing signal transduction that are a prerequisite for the physiological functions of neurons, for example neurotransmitter release.

More direct evidence of the otential antidepressant properties of sigma ligands have been reported from the studies

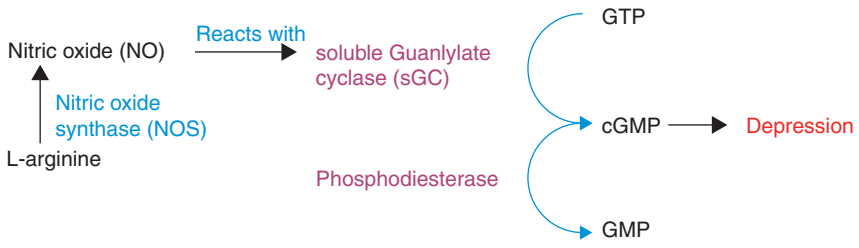

Figure 5. L-Arginine-nitric oxide-cGMP pathway and involvement in depression.

involving SA-4503, (+)- pentazocine, DTG, JO-1784 and SKF-10047, all sigma agonists that have been shown to dose-dependently decrease the immobility period in mice subjected to FSTs [92,93]. These drugs are under trial for their therapeutic use in major depression.

8. Neurosteroids

Neurosteroids are steroidal hormones that are synthesized in the central nervous system either *de novo* from cholesterol or from steroid hormone precursors; they are involved in a wide variety of psychopathological processes [94]. Several neurosteroids have been shown to be formed *de novo* in mammalian brain via classical steroid metabolic pathways [95,96]. It is suggested that neurosteroids are biosynthesized during embryogenesis and the development of the nervous system.

These neurosteroids are known to modulate mainly $GABA_A$ receptors, but also calcium channels, NMDA, sigma, and glycine receptors, respectively [94]. Non-conjugated metabolites of progesterone such as allopregnanolone are potent positive modulators of $GABA_A$ receptors. They open ion channels for Cl^- and are known to possess analgesic, hypnotic, anxiolytic and anticonvulsant effects. By contrast, neurosteroids such as dehydroepiandrosterone and its sulfate are negative modulators of $GABA_A$ receptors acting as excitants and proconvulsants. They are able to positively modulate NMDA receptors and open Ca^{2+} ion channels [94].

Neurosteroids are shown to have antidepressant actions [97]. A recent clinical study has demonstrated the antidepressant activity of fluoxetine and fluvoxamine: both selective serotonin reuptake inhibitors are correlated with an ability to increase the brain and cerebrospinal fluid content of allopregnanolone, a potent positive allosteric modulator of gamma-aminobutyric acid, at $GABA_A$ receptors [98]. Similarly, it was found that fluoxetine and norfluoxetine are active in improving the behavior of socially isolated mice at a dose that does not affect serotonin neurotransmission, the mechanism being through upregulation of neurosteroid contents in the brain [98]. In a preclinical investigation, the neurosteroid allopregnanolone (3α-hydroxy-5α-pregnan-20-one) was observed to have antidepressant-like activity in mouse FSTs [99]. This action is potentiated by the additional administration of muscimol and blocked by bicuculline, suggesting the involvement of GABAergic neurotransmission in its antidepressant-like action [99]. It has been found out that the $GABA_A$ receptor containing delta subunit is essential for the enhanced activity of neurosteroids [100]. The δ-subunit containing $GABA_A$ receptors are found exclusively at extrasynaptic sites, and these receptors can be activated by GABA overspill in the molecular layer [101]. Neuroactive steroids are known to specifically enhance a tonic inhibitory conductance in central neurons that is mediated by extrasynaptic δ subunit-containing $GABA_A$ receptors further leads to decreases in neuronal excitability [102].

THIP (4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridine-3-ol, Gaboxadol) is a selective $GABA_A$ receptor agonist, acting *in vitro* with high potency and efficacy at the extrasynaptic $GABA_A$ delta-containing receptors [103]. Similar to these findings, it has been shown that neurosteroids such as 5alpha-pregnan-3alpha-ol, 20-one and ganaxolone positively modulate the firing activity of dorsal raphe nucleus serotonergic neurons in female rats [104]. It has been revealed that testosterone and 17-β estradiol increased the firing activity of serotonergic neurons in both male and female rats [104]. A similar study from our laboratory has demonstrated the antidepressant-like activity of 17-β estradiol in mice. It was shown that it is the β-isomer of estradiol (not the α-isomer) that is active in both FSTs and TSTs, and this involves monoaminergic neurotransmission [66]. Neurosteroids may find clinical applications in the treatment of postpartum depression. It has been found that a large increase in progesterone-derived neurosteroids during pregnancy and their precipitous decline at parturition may lead to depression in females; this can be corrected by the administration of neurosteroids such as gaboxadol [105].

Analysis of the cerebrospinal fluid levels of neuroactive steroids in healthy volunteers suffering from major depression revealed that pregnenolone is decreased in subjects with affective illness, particularly during episodes of severe depression [106]. Administration of dehydroepiandrosterone to the patients suffering from Alzheimer's disease resulted in improvement in mood, energy, confidence, interest and activity levels. Interestingly, both pregnenolone and dehydroepiandrosterone are negative modulators of $GABA_A$ receptors [94], yet they possessed antidepressant activity. In one recent study, it has been proposed that reduced dehydroepiandrosterone may

be associated with the early onset of depressive behavior [107]. In another study, it has been suggested that progesterone may enhance the serotonin-stimulated gene expression of brain-derived neurotrophic factor, which is considered to contribute to the survival, regeneration, and plasticity of neuronal cells in the brain, hence leading to the improvement of mood disorders and other symptoms in depressive patients [108].

The cross-talk between antidepressant-like effects of neurosteroids and sigma-1 receptor modulation is the topic of debate, suggesting a role for central sigma receptors in the antidepressant-like effects of neurosteroids (discussed below). In our previous studies, moderate doses of dehydroepiandrosterone sulfate or pregnenolone sulfate displayed an antidepressant-like effect in the FST, which is sensitive to NE-100, a putative sigma-1 receptor antagonist, or progesterone, a neurosteroid sigma receptor antagonist [109]. Recently, in another study, we have also elucidated the role of sigma receptor modulation in the antidepressant action of pregnenolone sulfate and dehydroepiandrosterone sulfate in the TST in mice. Pregnenolone sulfate and dehydroepiandrosterone sulfate both displayed antidepressant-like activity in TSTs (**Figures 6** and 7). It was concluded that the antidepressant activity of pregnenolone sulfate and dehydroepiandrosterone sulfate is antagonized by prior treatment with progesterone (a neurosteroid sigma receptor antagonist), rimcazole (sigma receptor antagonist) and, more interestingly, with BD-1047 (a novel specific sigma-1 receptor antagonist) [85].

More importantly, neurosteroids are shown to have antidepressant activity in FSTs, possibly by modulating the sigma-1 receptors [110]. Sigma-1 receptor agonists are known to enhance the firing rates of serotonergic neurons in the dorsal raphe nucleus area of the brain [111]. Sigma receptors may rapidly modulate the NMDA receptor-mediated transmission in the hippocampus, and potentially other forebrain regions, which in turn would lead to modulation of serotonergic neurotransmission in the dorsal raphe nucleus [112]. Also, although many studies have suggested the therapeutic relevance of neuroactive steroids in neuropsychiatric diseases, including major depression, there are currently no neuroactive steroids used in clinical practice. Examining the clinical use of these neuroactive steroids in the treatment of major depression may be warranted.

9. Agomelatine

Circadian rhythms are considered an important factor in the etiology, expression and treatment of major depression [113]. It has been observed that most patients suffering from major depression have more severe symptoms during the daytime, compared with the night hours. Therefore, it is speculated that there is some chronobiology involved in the major depression symptomology. Melatonin, a chronobiotic agent, is considered to be nature's most versatile biological signal [114]. It is a hormone secreted by the rudimentary pineal gland present in the brain that is involved in the regulation of circadian rhythm. Melatonin is known to interact with different neurotransmitter systems via its two major receptors, MT_1 and MT_2. These G-protein-coupled receptors are expressed in various parts of the central nervous system (suprachiasmatic nuclei, hippocampus, cerebellar cortex, prefrontal cortex, basal ganglia, substantia nigra, ventral tegmental area, nucleus accumbens and retinal horizontal, amacrine and ganglion cells) and in peripheral organs (blood vessels, mammary gland, gastrointestinal tract, liver, kidney and bladder, ovary, testis, prostate, skin and immune system) [115]. Melatonin is known to modulate the serotonergic system in the body and alters the circadian phase-setting, sexual behavior, sleep-wake cycle and neuroendocrine effects [116]. Similarly, melatonin is known to influence dopaminergic, GABAergic, opioidergic system and cholinergic systems in the body [116].

Alterations in melatonin receptor expression as well as changes in endogenous melatonin production have been shown in circadian rhythm sleep disorders, Alzheimer's and Parkinson's diseases, glaucoma, depressive disorder, breast and prostate cancer, hepatoma and melanoma [116]. In one preclinical study, melatonin has been shown to possess antidepressant-like activity in FSTs. Melatonin is known to enhance the antidepressant-like effect of imipramine in the FST [117]. Similarly, melatonin is also known to be effective in mouse TSTs through modulation of NMDA receptors and the L-arginine-nitric oxide pathway [118]. In one of the studies carried out in our laboratory, it has been demonstrated that melatonin has antidepressant action in chronic FST-induced despair behavior by an action involving peripheral benzodiazepine receptors [119].

Agomelatine (a synthetic analog of the hormone melatonin), a compound with agonistic properties at MT_1 and MT_2 receptors and antagonistic properties at the 5-HT_{2C} serotonin receptor, is a novel agent that is under late-stage development as a potential antidepressant [120-122]. In one study carried out by Millan and colleagues, agomelatine was found to be antagonist at 5-HT_{2B} and 5-HT_{2C} receptors. It has been speculated that blockade of 5-HT_{2C} serotonin receptors reinforces frontocortical adrenergic and dopaminergic transmission, and thus shows antidepressant action [123]. It has no measurable affinity to any other known receptor. In one of the double-blind randomized clinical studies using 25 mg/day of agomelatine in a large patient population (238 patients), agomelatine was significantly more efficacious than placebo, with an agomelatine/placebo difference of 3.44 ($p < 0.001$) using the Hamilton Depression Rating Scale (HAMD) final total score [124]. Agomelatine is an efficacious, safe antidepressant but does not possess any major efficacy advantages when compared with other antidepressant drugs [124]. The most common adverse effects reported with agomelatine use are headache, nasopharyngitis, and gastrointestinal complaints, effects that are also observed with conventional antidepressants [125]. Agomelatine is expected to be available on the market by the year 2009.

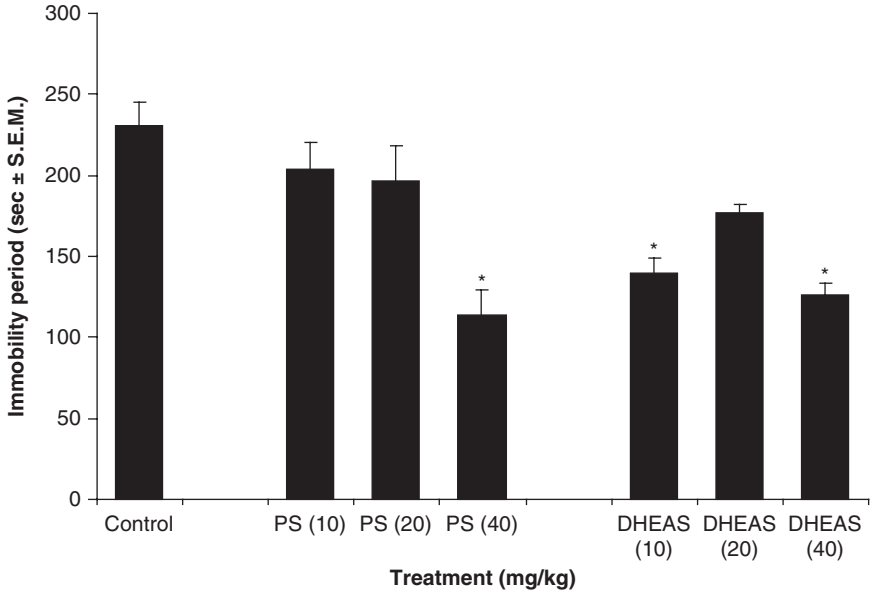

Figure 6. Effects of neurosteroid dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate (PS) on the immobility period during the 6-min tail suspension test in mice. DHEAS (10 – 40 mg/kg, s.c.) or PS (10 – 40 mg/kg, s.c.) was administered 30 min before the swimming test. Values are expressed as mean ± SEM (n = 6 animals per group). Data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's test. [85].
*$p < 0.05$ compared with vehicle-treated group.

10. Glutamatergic modulators

Glutamate, a major excitatory neurotransmitter in the brain, may be a promising target for a novel antidepressant therapy [126]. Glutamate acts by stimulation of two distinct groups of receptors: ionotropic glutamate receptors (including NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor [AMPA] and kainate receptors), which are coupled to ion channels, and metabotropic glutamate receptors (mGluRs), a family of G-protein-coupled receptors [126]. The mGluRs are additionally divided into three groups according to their sequence homology, effector coupling and agonist selectivity. Group I mGluRs (mGlu 1 and mGlu 5) are coupled to the phosphatidylinositol hydrolysis/Ca^{2+} signal transduction pathway, while group II (mGluR2 and mGluR3) and group III mGluRs (mGluR4, mGluR6, mGluR7, mGluR8) are both coupled in an inhibitory manner to the adenylyl cyclase signal transduction pathway [127].

In 1990, Trullas and Skolnick provided the first evidence that the NMDA subtype of glutamate receptors may be involved in the pathophysiology of major depression. It was observed that NMDA receptor antagonists – 2-aminophosphoheptanoic acid (competitive NMDA receptor antagonist) or MK-801 (non-competitive NMDA receptor antagonist) – reduce the immobility period of mice in the FST [128]. MK-801 has been thoroughly investigated in various animal models of depression and was effective in FSTs in rats [129] and mice [130,71], as well as TSTs in mice [118,131], foot-shock-induced fighting behavior in chronically stressed rats [132], chronic mild stress model of depression [133] and the olfactory bulbectomy model of depression [134], respectively.

The molecules, which are capable of reducing neurotransmission at the NMDA receptors complex, might represent a new class of antidepressant drugs. However, these drugs are often associated with an adverse side-effect profile, which limits their use in psychiatry. These drugs are known to produce psychomimetic effects and neurodegeneration that further leads to disturbed motor performances. Further, their higher doses may lead to cognitive decline, ataxia and muscle relaxation [135]. However, the newly discovered NMDA receptor antagonist, memantine, has been shown to have promising antidepressant-like effects in preclinical studies and is free of the adverse effects that are typical of high-affinity NMDA receptor blockers [136]. However, in one of the clinical studies, memantine failed to display any antidepressant-like activity [137]. The study was a double-blind, placebo-controlled study carried on 32 subjects with major depression [137].

Ketamine (ketamine hydrochloride), another NMDA receptor antagonist, was found to possess antidepressant activity in clinical situations. Ketamine is known to exhibit a significant reduction in HAMD scores after 40 min of its infusion (0.5 mg/kg), and can be beneficial to patients not responding to conventional antidepressant therapy [138,139]. It has been demonstrated that acute administration of ketamine elicits antidepressant-like effects in rats by enhancing

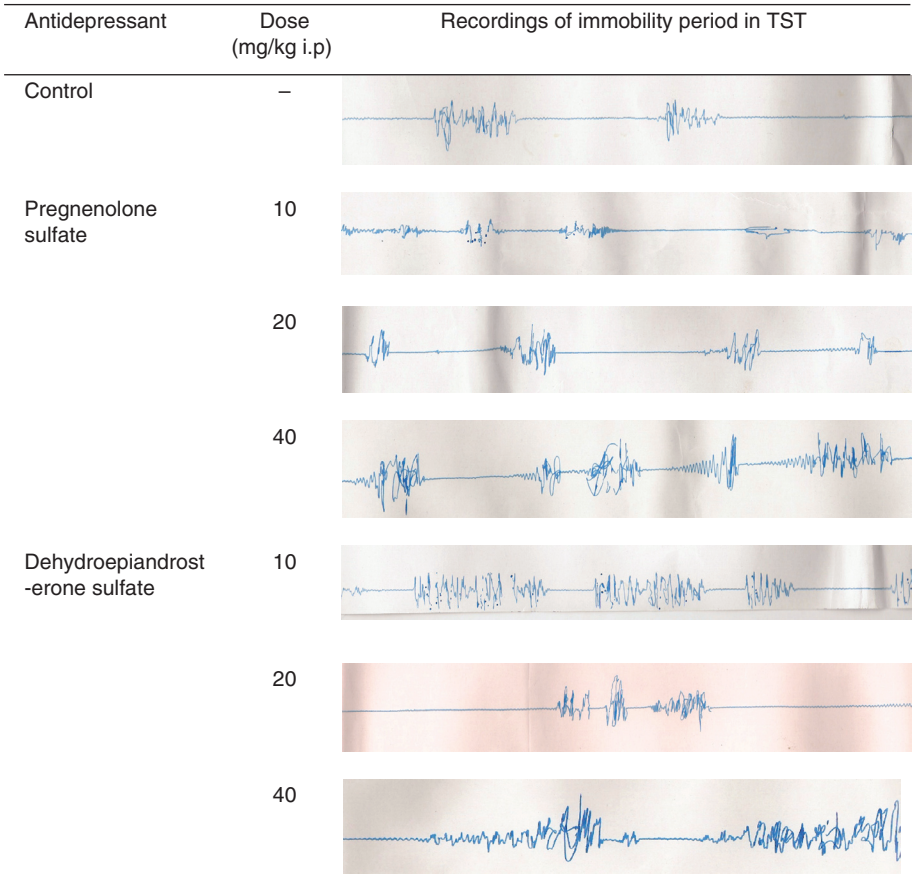

Figure 7. Representative recordings of tail-suspension test of pregnenolone sulfate and dehydroepiandrosterone sulfate.

hippocampal brain-derived neurotrophic factor protein levels [140]. However, by contrast, it has been shown that ketamine neither produces antidepressant-like effects in rodents nor does it display antidepressant-like behavioral or neurochemical effects after chronic treatment [141]. Other antiglutamatergic agents, such as lamotrigine (Lamictal® [GlaxoSmithKline, PA, USA], through blockade of voltage-sensitivity sodium channels and stabilization of the neuronal membrane), have demonstrated potential antidepressant efficacy and may be useful in the treatment of resistant depression [142,143]. The antidepressant property of folic acid is also dependent on the inhibition of NMDA receptors [144].

A reduction in NMDA receptor reactivity has been also been found after chronic treatment with both classic and atypical antidepressants. In 1999, Skolnick proposed that brain-derived neurotrophic factor (BDNF) may be the mediator linking the action of conventional antidepressants and attenuation of NMDA receptor function [145]. As discussed previously, it is known that chronic treatment with antidepressants causes an increase in the expression of BDNF mRNA [146]. Further, BDNF was shown to decrease NMDA receptor function, thus producing an effect similar to that produced by NMDA receptor antagonists [147].

Contrary to this, AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor potentiators are known to have antidepressant-like action [148,149]. It has been found that mice with deletion of the main AMPA receptor subunit GluR-A represent a depression model, and display various behavioral and neurochemical features of human major depression. Also, chronic treatment with LY-451646, an AMPA receptor potentiator, increases cell proliferation in the adult rat hippocampus [150]. Further, AMPA receptor activation has been shown to increase the expression of BDNF [145]. It has been suggested that ketamine, a NMDA receptor antagonist, might exert rapid antidepressant-like effects by enhancing AMPA relative to NMDA receptors in critical neuronal circuits [151].

More recent studies have indicated that antagonists of group I mGluRs (mGluR1 and mGluR5) produce antidepressant-like effects in behavioral tests in rodents [152,153]. Antagonists of mGluR5, MPEP (2-methyl-6-[phenylethynyl]-pyridine) reduced the immobility period in TSTs in mice without affecting locomotor activity [134]. Moreover, repeated MPEP administration reversed the olfactory bulbectomy-induced behavioral deficits, similar to the classic antidepressant desipramine [154]. The mechanism behind the

antidepressant-like effect of group I mGluR antagonists may be connected with their ability to reduce NMDA receptor activity, which was observed in several brain areas [152].

Similarly, group II mGluR antagonists MGS-0039 and LY-341495 dose-dependently reduced the immobility time of mice in TSTs [155]. It has been demonstrated that repeated administration of MGS-0039 increases cell proliferation in the adult mouse hippocampus [156].

Little is known about the potential antidepressant activity of group III mGluRs ligands, as they are not systemically active drugs. ACPT-1, a group III mGluR agonist, as well as RS-PPG, a mGluR8 agonist, produced a dose-dependent decrease in the immobility time of rats in FSTs [157]. However, the exact mechanisms of glutamatergic neurotransmission have to be explored in major depression.

11. 5-HT_6 serotonin receptor modulators

Dysfunction in the serotonergic system is a well-established theory explaining the pathophysiology of major depression. The effect of serotonin is known to be mediated through serotonin receptors, of which at least 13 molecular subtypes have been identified. These include three major receptor families such as $5HT_{1A}$, $5HT_{2A/C}$, and 5 HT_3, respectively [158]. These receptors are present both at pre- and postsynaptic sites, in addition to their location on serotonergic nerve-cell bodies.

5-HT_6 receptors are mainly located in the limbic areas of the brain, and are therefore known to play an imperative role in the pathophysiology of major depression. The molecular mechanism is not clear; however, it is hypothesized to act by activating the extracellular signal-regulated kinase1/2 via Fyn-dependent pathway [159]. It has been demonstrated that SB-399885 (N-[3,5-dichloro-2-(methoxy)phenyl]-4-(methoxy)-3-(1-piperazinyl)benzenesulfonamide), a 5-HT_6 receptor antagonist, is effective in FSTs. The effect, comparable to that of imipramine, is independent of any lack of motor coordination in mice and rats as tested in the rotarod test [160]. Similarly, SB-258585, another selective 5-HT_6 receptor antagonist, when administered intrahippocampally to rats, is known to be active in the FST [161]. Interestingly, 5-HT_6 receptor antagonists also act as cognitive enhancers [162]; this property may be beneficial for depressed patients. 5-HT_6 receptors are also known to play an important role in the mechanism of various antidepressants, particularly selective serotonin reuptake inhibitors. It has been demonstrated that SB271046, a 5-HT_6 receptor antagonist, significantly counteracted the stimulatory actions of fluoxetine on cortical c-fos mRNA, phospho-Ser845-GluR1, and in the tail suspension antidepressant assay, whereas it had no effect on these parameters by itself [163].

12. 5-HT_7 serotonin receptor modulators

Recently, the 5-HT_7 serotonin receptor has been known to play an important role in the pathophysiology of major depression, and the antagonists of these receptors are known to possess antidepressant action [164]. It is also known that the administration of selective serotonin reuptake inhibitors downregulates 5-HT_7 serotonin receptors, suggesting its crucial role. Studies have shown that 5-HT_7 serotonin receptor knockout mice display antidepressant-like behaviors. It has been demonstrated that (2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]-pyrrolidine (SB269970), a potent and selective 5-HT_7 serotonin receptor antagonist, is known to decrease the immobility time in FSTs. It has further been demonstrated that SB269970 (0.3, 1 and 3 µg) showed an anticonflict effect in a conflict drinking model which was weaker than that of diazepam (40 µg), whereas the same compound at doses of 3 and 10 µg had marked antidepressant-like action comparable to that of imipramine (0.1 µg) [165]. Further, SB269970 also enhanced the antidepressant-like action of some of the standard agents such as imipramine, desipramine, citalopram or moclobemide [165].

Similarly, one study has explored the sleep-promoting ability of 5-HT_7 serotonin receptors antagonists. It has been demonstrated that SB-269970 and SB-656104-A, 5-HT_7 serotonin receptor antagonists, increased the latency to rapid eye movement (REM) sleep and reduced the amount of time spent in it; therefore, blockade of 5-HT_7 receptors may provide a novel therapy to alleviate sleep disturbances associated with major depression [166]. In rats, SB-269970 is known to potentiate the citalopram-induced increase in REM latency and the decreased duration of REM sleep [167]. The mechanism of action of these antagonists as an antidepressants are not clear; however, it is expected that 5-HT_7 serotonin receptors also affect neuronal activity.

It has been observed that AS-19, a 5-HT_7 serotonin receptor agonist, inhibits the firing activity of dorsal raphe serotonergic neurons, the action being antagonized by SB-269970, a 5-HT_7 serotonin receptor antagonist. Similarly, 5-HT_7 receptor antagonists promote the hippocampal neurogenesis [168] and can also be considered a promising target for the treatment of obsessive-compulsive disorder [169].

13. Other approaches

13.1 Beta-3 adrenoceptor agonists

Besides β-1 and β-2, β-3 receptors are also known to contribute to the pathophysiology of major depression. The mechanism is yet not clear; however, it has been hypothesized that β-3 adrenoceptor activation results in an increase in the brain tryptophan content, which in turn leads to an elevation of brain serotonin synthesis [170]. It has been demonstrated that amibegron (SR-58611A), a selective β-3 receptor agonist, has antidepressant-like effects and significantly reduced immobility in Flinders Sensitive Line (FSL) rats [171]. In another study, SR-58611A proved active in FSTs; the effect was comparable to that of clomipramine, a tricyclic antidepressant. The molecule also prevented excessive grooming in a novel environment (novelty-induced grooming test),

which is consistent with an anxiolytic-like effect. The antidepressant action of SR-58611A is sensitive to SR-59230A, a β-3 receptor antagonist [170]. Similarly, SR-58611A has also demonstrated marked anxiolytic-like effects in animal models [172]. Therefore, it is speculated that stimulation of the β-3 adrenoceptor may prove to be a novel treatment strategy for anxiety and depressive disorders.

13.2 Vasopressin V(1b) receptor antagonist

It has been shown that vasopressin possesses the ability to potentiate the stimulatory effect of corticotropin releasing factor and thus is critical for adaptation of the HPA axis during stress [173]. Vasopressin V(1b) receptor s are located in the limbic region of the brain, thus playing an important role in the control of emotional processes [174]. These receptors are also located in the lateral septum, the amygdala, the bed nucleus of the stria terminalis, the hippocampal formation, and in several cortical areas. Vasopressin V(1b) receptor antagonists are known to possess antidepressant activity [175]. In one of the studies, SSR-149415 ((2S, 4R)-1-[5-chloro-1-[(2,4-dizzmethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2, 3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidinecarboxamide), a non-peptide vasopressin V(1b) receptor antagonist, reversed the hyperactivity in olfactory bulbectomized Wistar rats; the effect was persistent even 7 days after cessation of treatment [176].

It has been demonstrated that chronic treatment of SSR-149415 is required to observe the antidepressant effect in olfactory bulbectomy. Similarly, SSR-149415 produced anxiolytic-like activity in models involving traumatic stress exposure, such as the social defeat paradigm and the defense test battery [174]. SSR-149415 also increased the time spent in social interaction in FSL rats [177]. It has been shown that V1b receptors located in the lateral septum participate in the antidepressant- but not the anxiolytic-like action of SSR-149415 in rats [175]. SSR-149415 is known to block the release of adrenocorticotrophic releasing hormone, noradrenaline release and hyperthermic responses following various stress exposures [173]. Further, the molecule is safe and devoid of any adverse effects on motor activity, sedation, memory or cognitive functions and produces no tachyphylaxis when administered repeatedly [178].

13.3 NK2 tachykinin receptor antagonists

The mammalian tachykinins (substance P, neurokinin A and neurokinin B) act as neurotransmitters and neuromodulators by acting on NK_1, NK_2, and NK_3 receptors, respectively. It has been demonstrated that NK_1, NK_2 and NK_3 receptor antagonists have antidepressant-like activity. MK-869 (aprepitant), a NK_1 receptor antagonist, has been investigated for its antidepressant effect in clinics, but the results were disappointing and further clinical development was suspended on this molecule. NK_1 knockout mice have also been developed [179]. One study demonstrated that saredutant (a NK_2 receptor antagonist) and osanetant (a NK_3 receptor antagonist) produced anxiolytic-like effects in the gerbil social interaction test. Interestingly, the effect was similar to that obtained with the vasopressin 1b receptor antagonist SSR-149415 [180]. SR-48968, a selective non-peptide NK_2 receptor antagonist, is known to decrease flight reactions, risk assessment behavior, defensive biting and escape attempts [181]. SR-48968, a NK_2 receptor antagonist, is known to increase the expression of the cyclic adenosine monophosphate response-element binding protein mRNA in the rat hippocampus after repeated but not acute administration [182]. In one of the studies, treatment of rats with saredutant exhibited more active behavior in the FST after previous exposure to stressors [183].

13.4 Glucocorticoid receptor antagonists

The hypothalamic region of the brain is known to play an important role in producing various neurovegetative symptoms in major depression, including too much or too little sleep, appetite, and energy, as well as a loss of interest in sex and other pleasurable activities [184]. Excessive activation of the HPA axis has been demonstrated in individuals suffering from major depression [185]. Activation of this axis may lead to increased release of glucocorticoids such as cortisol, which may damage hippocampal neurons and produce cognitive impairment in depressed patients (**Figure 8**). Glucocorticoid such as dexamethasone is known to prevent brain-derived neurotrophic factor-mediated maturation of synaptic function in developing hippocampal neurons [186]. Therefore, it is hypothesized that glucocorticoid receptor antagonists have antidepressant properties.

In one study, subchronic treatment with RU-43044, a glucocorticoid receptor antagonist, decreased the immobility period in the FST in chronic corticosterone-treated and isolation-reared mice, but not in the control mice. It is necessary to mention that chronic corticosterone administration and isolation rearing increases the depressive-like behavior in a glucocorticoid receptor-dependent manner [187]. Further, glucocorticoid receptor antagonists are also known to improve insomnia in the depressed condition [188]. In conclusion, glucocorticoid antagonists may be of use for treatment-resistant major depression.

13.5 Corticotropin releasing factor-1 (CRF-1) receptor antagonists

Corticotropin-releasing factor (CRF) is known to play a crucial role in the proper functioning of the stress response system through its actions on its receptors, CRF receptor 1 (CRF_1) and CRF receptor 2 (CRF_2) [189]. It has been demonstrated that there is hyperstimulation of CRF_1 receptors in the pathophysiologies of major depression and anxiety [189]. CRF_1 receptor antagonists have become the novel target in the treatment of major depression. Therefore, CRF_1 antagonists are being developed for the treatment of affective disorders. Chronic administration with antalarmin, a CRF_1 receptor antagonist, led to an improvement of chronic mild stress-induced decrease of physical state, body weight gain and blunted emotional response in the light/dark test [190]. In the FST, CP-154,526 shows a different profile in mice and rats.

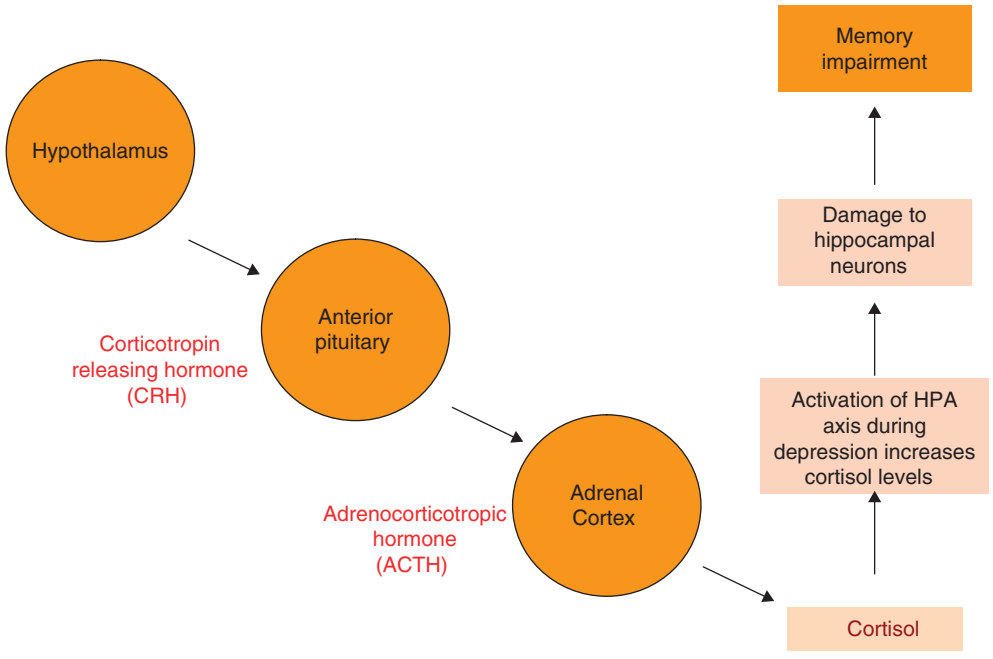

Figure 8. Hypothalamic-pituitary-adrenal (HPA) axis and participation in depression symptomology.

Interestingly, the compound was active in rat FST but inactive in mouse models [191].

In another study, 1-[8-(2,4-dichlorophenyl)-2-methylquinolin-4-yl]-1,2,3,6-tetrahydropyridine-4-carboxamide benzenesulfonate (R-278995/CRA-0450), a CRF_1 receptor antagonist, showed dose-dependent antidepressant-like effects in the rat learned helplessness paradigm and the olfactory bulbectomy model. However, the compound was inactive in mouse FSTs [192]. R-121919, another CRF_1 receptor antagonist, is known to dose-dependently attenuate the swim stress-induced anxiogenic-like behavior in the elevated plus-maze model of anxiety [193].

NBI-30775/R-121919 has a clinical profile comparable to that of the antidepressant paroxetine [185]. DMP-696 and DMP-904, a non-peptidergic CRF_1 receptor antagonist known to exhibit > 1000-fold selectivity for CRF_1 over CRF_2 receptors, were effective as anxiolytic agents; however, the compounds were found to be ineffective in the learned helplessness paradigm task [194]. In one clinical study, R-121919 was found to be effective in treating 20 depressed patients [195]. However, in another study, CRF_1 receptor antagonist failed to display any antidepressant effect [196].

Similar to CRF_1, CRF_2 has been found to play a major role in the pathophysiology of major depression. It has been demonstrated that CRF_2 knockout mice display increased hippocampal levels of activated (phosphorylated) mitogen-activated protein kinase (MAPK)/ERK kinase (MEK), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and ribosomal protein S6 kinases 1 (RSK1), the effect being reversed by CRF_2 receptor antagonists [189]. However, further confirmatory studies are required to establish the use of CRF_1 receptor antagonists in major depression.

13.6 Berberine

Berberine, an isoquinoline alkaloid obtained from an array of plants, has been used in the Indian and Chinese system of medicines as an antimicrobial, stomachic, bitter tonic and in the treatment of oriental sores. Some of the plant sources of berberine include the roots, rhizomes, and stem bark of *Hydrastis canadensis* (goldenseal; Ranunculaceae), *Coptis chinensis* (coptis or goldenthread; Ranunculaceae), *Berberis aquifolium* (Oregon grape; Berberidaceae), *Berberis vulgaris* (barberry; Berberidaceae), *Berberis aristata* (tree turmeric; Berberidaceae), and *Berberis thunbergii* (red barberry; Berberidaceae). Recent evidence supports the antidepressant-like action of berberine [67,68]. In our laboratory, we have demonstrated that berberine is active in FSTs and TSTs [67,68].

It has been demonstrated that berberine modulates the monoaminergic neurotransmission in the brain. Berberine enhanced the antidepressant activity of various typical antidepressants: imipramine (tricyclic antidepressant), fluoxetine (selective serotonin reuptake inhibitor), venlafaxine (dual reuptake inhibitor of serotonin and norepinephrine), and bupropion (dopamine reuptake inhibitor). Berberine also reversed the depression-like syndrome induced by reserpine in animals [67]. It was found that berberine (both acute and chronic administration) modulates the brain levels of norepinephrine, serotonin and dopamine; thus, it may be categorized as triple reuptake inhibitor.

Following its acute administration in mice, berberine (5 mg/kg, i.p.) resulted in increased levels of norepinephrine (31%), serotonin (47%) and dopamine (31%) in the whole brain [67]. Chronic administration of berberine (5 mg/kg, i.p.) for 15 days significantly increased the levels of norepinephrine

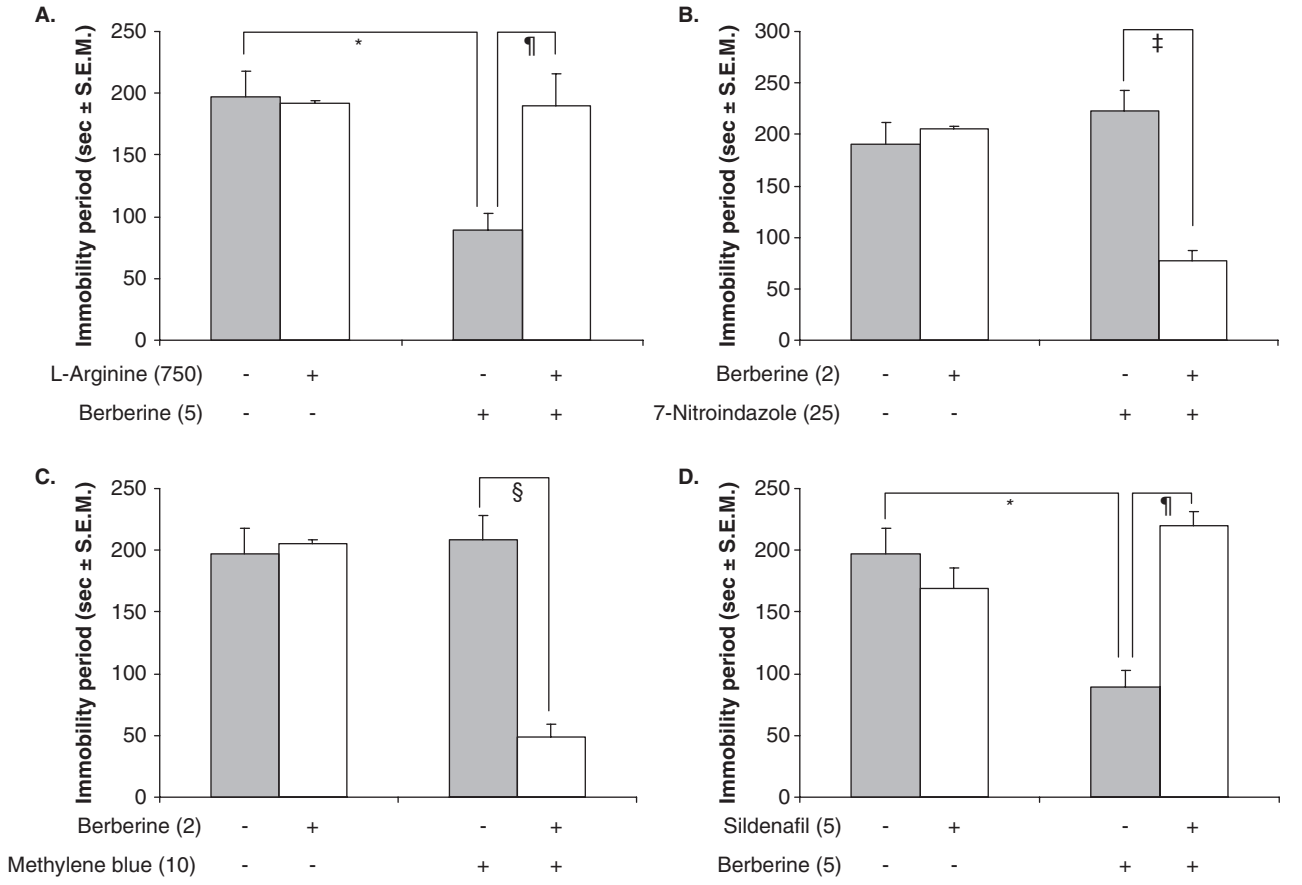

Figure 9. Effect of berberine and its modification by (A) L-Arginine (750 mg/kg, i.p.), **(B)** 7-nitroindazole (25 mg/kg, i.p.), **(C)** Methylene blue (10 mg/kg, i.p.), **(D)** Sildenafil (5 mg/kg, i.p.) on the mean immobility period in mouse forced swim test. The values are expressed as mean ± S.E.M. (n = 6 – 8). Data were analysed by two-way analysis of variance (ANOVA) followed by Dunnett's test.

*$p < 0.05$ compared with respective vehicle-treated group.

‡$p < 0.05$ compared with 7-nitroindazole (25 mg/kg, i.p.)-treated group.

§$p < 0.05$ compared with methylene blue (10 mg/kg, i.p.)-treated group.

¶$p < 0.05$ compared with berberine (5 mg/kg ,i.p.)-treated group [67].

(29%) and serotonin (19%), as well as dopamine (52%). At a higher dose (10 mg/kg, i.p.), there was no change in the norepinephrine (12%) levels, but a significant increase in the serotonin (53%) and dopamine (31%) levels was found [68]. Also, the monoamine oxidase-A inhibiting property of berberine is known in the literature.

Our further extensive studies have demonstrated the involvement of the nitric oxide pathway in the antidepressant-like action of berberine chloride [67]. The antidepressant-like effect of berberine in FSTs was prevented by pretreatment with L-arginine (750 mg/kg, i.p.) or sildenafil (5 mg/kg, i.p.) (**Figure 9**). By contrast, pretreatment of mice with 7-nitroindazole (7-NI) (25 mg/kg, i.p.) or methylene blue (10 mg/kg, i.p.) potentiated the effect of berberine (2 mg/kg, i.p.) in the FSTs (**Figure 9**). Similarly, the role of sigma-1 receptors in the antidepressant-like action of berberine was demonstrated [68]. Pretreatment of mice with (+)-pentazocine, a high-affinity sigma-1 receptor agonist, produced synergism with a subeffective dose of berberine. Pretreatment with various sigma receptor antagonists – progesterone, rimcazole and N-[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine (BD-1047) – reversed the anti-immobility effects of berberine.

Various studies have demonstrated that berberine is a safe drug when used within therapeutic doses. Berberine lacks any genotoxic, cytotoxic or mutagenic activity, which supports its clinical use in a wide variety of situations in humans.

13.7 Curcumin

Curcumin is the principal curcuminoid of the popular Indian curry spice, turmeric (*Curcuma longa*, Zingiberaceae), and has been found to be useful in almost all bodily disease, including its recently explored use in neurodegenerative and neuropsychiatric disorders. There is considerable evidence, including findings from our laboratory, to support the antidepressant-like activity of curcumin [197,198], which can be potentiated by the concomitant administration of fluoxetine, venlafaxine, or

bupropion [197]. However, no significant change in the anti-immobility effect of imipramine and desipramine was observed [197]. When alterations in brain levels of monoamines were checked following curcumin administration, it was observed that it increased serotonin as well as dopamine levels (at higher doses), without affecting norepinephrine levels [197]. Biochemically, this herbal molecule is also known to inhibit the monoamine oxidase enzymes (both MAO-A and MAO-B, higher doses) in mice [196].

When administered along with curcumin (20 and 40 mg/kg, i.p.), the bioavailability-enhancing agent piperine (2.5 mg/kg, i.p.), obtained from *Piper nigrum* Linn and *Piper longum* Linn, resulted in enhanced antidepressant-like action and increased brain penetration [197]. In another study, the involvement of 5-HT_1 and 5 HT_2 serotonin receptors was elucidated in the antidepressant-like action of curcumin. It was found out that p-chloro-phenylalanine (PCPA), a tryptophan hydroxylase (rate-limiting enzyme for the synthesis of serotonin) inhibitor, blocked the antidepressant-like effect of curcumin in FSTs [198].

Moreover, pretreatment of pindolol (10 mg/kg, i.p., a β-adrenoceptor blocker/5-$HT_{1A/1B}$ receptor antagonist), 4-(2′-methoxy-phenyl)-1-[2′-(n-2′′-pyridinyl)-p-iodobenzamino-]ethyl-piperazine (p-MPPI, 1 mg/kg, s.c., a selective 5-HT_{1A} receptor antagonist), or 1-(2-(1-pyrrolyl)-phenoxy)-3-isopropylamino-2-propanol (isamoltane, 2.5 mg/kg, i.p., a 5-HT_{1B} receptor antagonist) were found to prevent the effect of curcumin (10 mg/kg) in FSTs [198]. In contrast, curcumin produced synergism when administered concomitantly with (+)-8-hydroxy-2-(di-n-propylamino)tetralin, (8-OH-DPAT, a 5-HT_{1A} receptor agonist), anpirtoline (0.25 mg/kg, i.p., a 5-HT_{1B} receptor agonist) or ritanserin (4 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist), but not with ketanserin (5 mg/kg, i.p., a 5-$HT_{2A/2C}$ receptor antagonist with higher affinity to 5-HT_{2A} receptor) or R(-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, 1 mg/kg, i.p., a 5-HT_{2A} receptor agonist) [199].

Curcumin is also known to reverse olfactory bulbectomy-induced major depression [200]. It has been observed that olfactory bulbectomized animals display low levels of serotonin (5-HT), noradrenaline (NA) and high levels of 5-hydroxyindoleacetic acid (5-HIAA, metabolite of serotonin) and 4-dihydroxyphenylacetic acid (DOPAC, metabolite of dopamine) that were completely reversed by administration of curcumin [200]. It has been shown that curcumin displays antidepressant-like action by enhancing the action of BDNF and increasing its TrkB receptor activity [201].

In another recent study carried out in our laboratory, curcumin was found to be active in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes [198]. Therefore, curcumin may be developed as a novel drug for the treatment of major depression.

13.8 Rutin

Hypericum perforatum is considered to be a 'modern' herbal antidepressant and rutin is one of the active constituents present in this plant extract. It is hypothesized that rutin is essential in demonstrating the antidepressant activity of *Hypericum perforatum* extracts in the FST [202]. Rutin alone is known to possess antidepressant-like activity [203]. The compound is known to reduce immobility time in the TST, but not in the FST, without altering locomotor activity. It has been shown that there is an involvement of the serotonergic and noradrenergic systems in its antidepressant-like activity [203].

14. Conclusion

Based on the considerable progress that has been made over the past two decades in opur understanding of the disease pathophysiology and development of newer target-specific drugs, it is hoped that newer strategies in the management of major depression will emerge sooner than expected. It is hoped that new drugs will be developed that have a faster onset of action, better efficacy and fewer long-term side effects.

15. Expert opinion

In spite of the availability of a large number of antidepressant agents, the treatment of major depression continues to be a challenge for clinicians. It has been hypothesized that major depression is multifactorial in nature, and no single gene is associated with its pathophysiology. The initial lag period of 2 – 4 weeks in onset, and the side effects, of currently used antidepressant activity are limiting factors. There are no appropriate animal model(s) to mimic the human condition of clinical major depression in which to test newer drug candidates. The value of FST and TST, the two behavioral paradigms commonly used in the testing of antidepressant drugs, is limited by inter-laboratory variations, and their predictive validity is very low: some drugs active in these models are not antidepressants in clinical situations.

There is an urgent need to develop newer and more sensitive animal models and *in vitro* testing procedures to screen newer antidepressant compounds in order to identify lead molecules for clinical trials in major depression. The new molecule so discovered should have quick onset of action and an improved therapeutic profile, with fewer drug–drug interactions and relatively few side effects resulting from long-term use. Herbal drugs could prove to be an alternative source of therapy, both as main-line treatment and as adjunctives.

The newer targets enumerated above need to be explored in detail with adequately designed clinical trials to identify their role in major depression. The whole area of management of major depression, though challenging, offers a great opportunity for future studies.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Wong ML, Licinio J. Research and treatment approaches to depression. Nat Rev Neurosci 2001;2:343-51
2. Wong ML, Licinio J. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. Nat Rev Drug Discov 2004;3:136-51
3. Artigas F, Romero L, de Montigny C, et al. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT1A antagonists. Trends Neurosci 1996;19:378-83
4. Greist JH, Mundt JC, Kobak K. Factors contributing to failed trials of new agents: can technology prevent some problems? J Clin Psychiatry 2002;63:8-13
5. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-105
6. Kessler RC, Mcgonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19
7. Vijayakumar L. Suicide and mental disorders in Asia. Int Rev Psychiatry 2005;17:109-14
8. Millan MJ. The role of monoamines in the actions of established and 'novel' antidepressant agents: a critical review. Eur J Pharmacol 2004;500:371-84
   - • **The present review discuses about the monoaminergic approach in exploring new targets in mental depression.**
9. Sadock BJ, Sadock VA. Classification of mental disorders. In:. Kaplan & Sadock (Eds), Comprehensive textbook of Psychiatry. Lippincott Williams & Wilkins, Philadelphia, USA 2000. p. 1125-45
10. Holtzheimer PE 3rd, Nemeroff CB. Advances in the treatment of depression. NeuroRx 2006;3:42-56
    - • **The article describes the novel drug approaches in major depression.**
11. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179-200
12. Furukawa TA, Yoshimura R, Harai H, et al. How many well vs. unwell days can you expect over 10 years, once you become depressed? Acta Psychiatr Scand 2009;119:290-7
13. Nierenberg AA. Do some antidepressants work faster than others? J Clin Psychiatry 2001;15:22-5
14. Schatzberg AF. Pharmacological principles of antidepressant efficacy. Hum Psychopharmacol 2002;17:S17-22
15. Youdim MB, Weinstock M. Therapeutic applications of selective and non-selective inhibitors of monoamine oxidase A and B that do not cause significant tyramine potentiation. Neurotoxicology 2004;25:243-50
16. Kulkarni SK, Parale MP. Despair behavior: a tool in experimental psychopharmacology. A review. Method Find Exp Clin Pharmacol 1986;8:741-44
    - • **The review briefly explains the various behavioral paradigms of despair.**
17. Borsini F, Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity? Psychopharmacology (Berl) 1988;94:147-60
    - • **The article discusses the limitations of FST as an animal model to explore new antidepressant drugs.**
18. Borsini F. Role of the serotonergic system in the forced swimming test. Neurosci Biobehav Rev 1995;19:377-95
19. Redrobe JP, Bourin M, Colombel MC, et al. Psychopharmacological profile of the selective serotonin reuptake inhibitor, paroxetine: implication of noradrenergic and serotonergic mechanisms. J Psychopharmacol 1998;12:348-55
20. Redrobe JP, Bourin M. Partial role of 5-HT2 and 5-HT3 receptors in the activity of antidepressants in the mouse forced swimming test. Eur J Pharmacol 1997;325:129-35
21. Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev 2005;29:547-69
22. Flugy A, Gagliano M, Cannizzaro C, et al. Antidepressant and anxiolytic effects of alprazolam versus the conventional antidepressant desipramine and the anxiolytic diazepam in the forced swim test in rats. Eur J Pharmacol 1992;214:233-38
23. Hemby SE, Lucki I, Gatto G, et al. Potential antidepressant effects of novel tropane compounds, selective for serotonin or dopamine transporters. J Pharmacol Exp Ther 1997;282:727-33
24. Porsolt RD, Anton G, Blavet N, et al. Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol 1978;47:379-91
25. Tadano T, Abe Y, Morikawa Y, et al. Relationship between learning behaviour and genetic factor on immobility shown during forced swimming test. Nihon Shinkei Seishin Yakurigaku Zasshi 1997;3:129-35
26. Bai F, Li X, Clay M, et al. Intra- and interstrain differences in models of behavioral despair. Pharmacol Biochem Behav 2001;70:187-92
27. Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. Psychopharmacology 2001;155:315-22
28. David DJ, Renard CE, Jolliet P, et al. Antidepressant-like effects in various mice strains in the forced swimming test. Psychopharmacology 2003;166:373-82
29. Steru L, Chermat R, Thierry B, et al. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology 1985;85:367-70
30. Renard CE, Dailly E, David DJ, et al. Monoamine metabolism changes following the mouse forced swimming test but not the tail suspension test. Fundam Clin Pharmacol 2003;17:449-55
31. Deussing JM. Animal models of depression drug discovery today. Disease Models 2006;3:375-83
32. Creese I, Chen A. Selective D-1 dopamine receptor increase following chronic treatment with SCH 23390. Eur J Pharmacol 1985;109:127-28
33. Klimek V, Schenck JE, Han H, et al. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. Biol Psychiatry 2002;52:740-48
34. Nemeroff CB. Fostering foster care outcomes: quality of intervention matters in overcoming early adversity. Arch Gen Psychiatry 2008;65:623-24

35. Lambert G, Johansson M, Agren H, et al. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. Arch Gen Psychiatry 2000;57:787-93

36. Jokinen J, Nordstrom AL, Nordstrom P. The relationship between CSF HVA/5-HIAA ratio and suicide intent in suicide attempters. Arch Suicide Res 2007;11:187-92

37. Winter C, von Rumohr A, Mundt A, et al. Lesions of dopaminergic neurons in the substantia nigra pars compacta and in the ventral tegmental area enhance depressive-like behavior in rats. Behav Brain Res 2007;184:133-41

38. Leentjens AF, Verhey FR, Vreeling FW. Successful treatment of depression in a Parkinson disease patient with bupropion. Ned Tijdschr Geneeskd 2000;144:2157-59

39. Dhir A, Kulkarni SK. Involvement of nitric oxide (NO) signaling pathway in the antidepressant action of bupropion, a dopamine reuptake inhibitor. Eur J Pharmacol 2007c;568:177-85

•• **The article demonstrated the involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the pathophysiology of major depression.**

40. Grandas F, López-Manzanares L. Bupropion-induced parkinsonism. Mov Disord 2007;22:1830-31

41. Cooper BR, Wang CM, Cox RF, et al. Evidence that the acute behavioral and electrophysiological effects of bupropion (Wellbutrin) are mediated by a noradrenergic mechanism. Neuropsychopharmacology 1994;11:133-41

•• **The manuscript explains the antidepressant activity of dopaminergic modulators.**

42. Kinney JL. Nomifensine maleate: a new second-generation antidepressant. Clin Pharm 1985;4:625-36

43. Lemke MR, Brecht HM, Koester J, et al. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. J Neurol Sci 2006;248:266-70

44. Dikeos DG, Papadimitriou GN, Avramopoulos D, et al. Association between the dopamine D3 receptor gene locus (DRD3) and unipolar affective disorder. Psychiatr Genet 1999;9:189-95

45. Dhir A, Kulkarni SK. Involvement of dopamine (DA)/serotonin (5-HT)/sigma (sigma) receptor modulation in mediating the antidepressant action of ropinirole hydrochloride, a D2/D3 dopamine receptor agonist. Brain Res Bull 2007;74:58-65

•• **The article explores the interaction between dopaminergic and serotoninergic system.**

46. Chen J, Paredes W, Van Praag HM, et al. Presynaptic dopamine release is enhanced by 5-HT3 receptor activation in medial prefrontal cortex of freely moving rats. Synapse 1992;10:264-66

47. Parsons LH, Justice JB. Perfusate serotonin increases extracellular dopamine in the nucleus accumbens of the rat as measured by in vivo microdialysis. Brain Res 1993;606:195-99

48. Lejeune F, Millan MJ. Induction of burst firing in ventral tegmental area dopaminergic neurons by activation of serotonin (5-HT)1A receptors: WAY 100,635-reversible actions of the highly selective ligands, flesinoxan and S 15535. Synapse 1998;30:172-80

49. Pae CU, Marks DM, Han C, et al. A case of transient hallucination with ropinirole augmentation antidepressant in a patient with treatment-resistant depression: is there differential effect of ropinirole dose on developing psychotic symptom? Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1087-88

50. Brocco M, Dekeyne A, Papp M, et al. Antidepressant-like properties of the anti-Parkinson agent, piribedil, in rodents: mediation by dopamine D2 receptors. Behav Pharmacol 2006;17:559-72

51. Joca SR, Skalisz LL, Beijamini V, et al. The antidepressive-like effect of oxcarbazepine: possible role of dopaminergic neurotransmission. Eur Neuropsychopharmacol 2000;10:223-28

52. Chen Z, Skolnick P. Triple uptake inhibitors: therapeutic potential in depression and beyond. Expert Opin Investig Drugs 2007;16:1365-77

• **The article reviews the action of "Triple Reuptake Inhibitors" as future antidepressant drugs.**

53. Skolnick P, Basile AS. Triple reuptake inhibitors 'broad spectrum' antidepressants. CNS Neurol Disord Drug Targets 2007;6:141-49

54. Breuer ME, Chan JS, Oosting RS, et al. The triple monoaminergic reuptake inhibitor DOV 216,303 has antidepressant effects in the rat olfactory bulbectomy model and lacks sexual side effects. Eur Neuropsychopharmacol 2008;18:908-16

55. Skolnick P, Krieter P, Tizzano J, et al. Preclinical and clinical pharmacology of DOV 216,303, a 'triple' reuptake inhibitor. CNS Drug Rev 2006;12:123-34

56. Available from: http://clinicaltrials.gov/ct2/show/NCT00467428

57. Beer B, Stark J, Krieter P, et al. DOV 216,303, a 'triple' reuptake inhibitor: safety, tolerability, and pharmacokinetic profile. J Clin Pharmacol 2004;44:1360-67

58. Skolnick P, Popik P, Janowsky A. Antidepressant-like actions of DOV 21,947: a 'triple' reuptake inhibitor. Eur J Pharmacol 2003;461:99-104

59. Popik P, Krawczyk M, Golembiowska K, et al. Pharmacological profile of the 'triple' monoamine neurotransmitter uptake inhibitor, DOV 102,677. Cell Mol Neurobiol 2006;26:857-73

60. Thatte U. NS-2330 (Neurosearch). Curr Opin Investig Drugs 2001;2:1592-94

61. Hauser RA, Salin L, Juhel N, et al. Randomized trial of the triple monoamine reuptake inhibitor NS 2330 (tesofensine) in early Parkinson's disease. Mov Disord 2007;22:359-65

62. Available from: http://www.sepracor.com/products/sep225289.html

63. Liang Y, Shaw AM, Boules M, et al. Antidepressant-like pharmacological profile of a novel triple reuptake inhibitor, (1S,2S)-3-(methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS). J Pharmacol Exp Ther 2008;327:573-83

64. Aluisio L, Lord B, Barbier AJ, et al. In-vitro and in-vivo characterization of JNJ-7925476, a novel triple monoamine uptake inhibitor. Eur J Pharmacol 2008;587:141-46

65. Dhir A, Kulkarni SK. Involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of venlafaxine in mice.

Prog Neuropsychopharmacol Biol Psychiatry 2007;31:921-25

66. Dhir A, Kulkarni SK. Antidepressant-like effect of 17beta-estradiol: involvement of dopaminergic, serotonergic, and (or) sigma-1 receptor systems. Can J Physiol Pharmacol 2008;86:726-35
67. Kulkarni SK, Dhir A. Possible involvement of L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway in the antidepressant activity of berberine chloride. Eur J Pharmacol 2007;569:77-83
68. Kulkarni SK, Dhir A. On the mechanism of antidepressant-like action of berberine chloride. Eur J Pharmacol 2008;589:163-72
- **The article for the first time demonstrated the antidepressant activity of bereberine chloride.**
69. Kaster MP, Rosa AO, Santos AR, et al. Involvement of nitric oxide-cGMP pathway in the antidepressant-like effects of adenosine in the forced swimming test. Int J Neuropsychopharmacol 2005;8:601-06
70. Almeida RC, Felisbino CS, López MG, et al. Evidence for the involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of memantine in mice. Behav Brain Res 2006;168:318-22
71. Rosa AO, Lin J, Calixto JB, et al. Involvement of NMDA receptors and L-arginine-nitric oxide pathway in the antidepressant-like effects of zinc in mice. Behav Brain Res 2003;144:87-93
72. Jesse CR, Bortolatto CF, Savegnago L, et al. Involvement of l-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of tramadol in the rat forced swimming test. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1838-43
73. Heiberg IL, Wegener G, Rosenberg R. Reduction of cGMP and nitric oxide has antidepressant-like effects in the forced swimming test in rats. Behav Brain Res 2002;134:479-84
- **The article demonstrated the involvement of cyclic guanosine monophosphate in major depression.**
74. da Silva GD, Matteussi AS, dos Santos AR, et al. Evidence for dual effects of nitric oxide in the forced swimming test and in the tail suspension test in mice. Neuroreport 2000;11:3699-702
75. Martin WR, Eades CG, Thompson JA, et al. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther 1976;197:517-32
76. Vaupel DB. Naltrexone fails to antagonize the sigma effects of PCP and SKF 10,047 in the dog. Eur J Pharmacol 1983;92:269-74
77. Largent BL, Gundlach AL, Snyder SH. Pharmacological and autoradiographic discrimination of sigma and phencyclidine receptor binding sites in brain with (+)-[3H]SKF 10,047, (+)-[3H]-3-[3-hydroxyphenyl]-N-(1-propyl) piperidine and [3H]-1-[1-(2-thienyl) cyclohexyl]piperidine. J Pharmacol Exp Ther 1986;238:739-48
- **The article differentiates sigma receptors from phencyclidine receptors.**
78. Gundlach AL, Largent BL, Snyder SH. Autoradiographic localization of sigma receptor binding sites in guinea pig and rat central nervous system with (+)3H-3-(3-hydroxyphenyl)-N-(1-propyl) piperidine. J Neurosci 1986;6:1757-70
79. Narita N, Hashimoto K, Tomitaka S, et al. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol 1996;307:117-9
80. Su TP. Evidence for sigma opioid receptor: binding of [3H] SKF-10047 to etorphine-inaccessible sites in guinea-pig brain. J Pharmacol Exp Ther 1982;223:284-90
81. Ishikawa M, Ishiwata K, Ishii K, et al. High occupancy of α1 receptors in human brain after single oral administration of fluvoxamine: a positron emission study using [11C] SA4503. Biol Psychiatry 2007;62:878-83
82. Hayashi T, Su TP. An update on the development of drugs for neuropsychiatric disorders: focusing on the sigma 1 receptor ligand. Expert Opin Ther Targets 2008;12:45-58
- **The review compiles the role of sigma-1 receptor modulators in neuropsychiatric disorders.**
83. Dhir A, Kulkarni SK. Involvement of sigma-1 receptor modulation in the antidepressant action of venlafaxine. Neurosci Lett 2007;420:204-48
84. Dhir A, Kulkarni SK. Possible involvement of sigma-1 receptors in the anti-immobility action of bupropion, a dopamine reuptake inhibitor. Fundam Clin Pharmacol 2008;22:387-94
85. Dhir A, Kulkarni SK. Involvement of sigma (sigma1) receptors in modulating the anti-depressant effect of neurosteroids (dehydroepiandrosterone or pregnenolone) in mouse tail-suspension test. J Psychopharmacol 2008;22:691-96
86. Aydar E, Palmer CP, Klyachko VA, et al. The sigma receptor as a ligand-regulated auxiliary potassium channel subunit. Neuron 2002;34:399-410
87. Guo W, Todd K, Bourin M, et al. Additive effects of glyburide and antidepressants in the forced swimming test: evidence for the involvement of potassium channel blockade. Pharmacol Biochem Behav 1996;54:725-30
88. Kaster MP, Ferreira PK, Santos AR, et al. Effects of potassium channel inhibitors in the forced swimming test: possible involvement of L-arginine-nitric oxide-soluble guanylate cyclase pathway. Behav Brain Res 2005;165:204-09
89. Monnet FP, Debonnel G, Junien JL, et al. N-methyl-D-aspartate-induced neuronal activation is selectively modulated by sigma receptors. Eur J Pharmacol 1990;179:441-45
90. Martina M, Turcotte ME, Halman S, et al. The sigma-1 receptor modulates NMDA receptor synaptic transmission and plasticity via SK channels in rat hippocampus. J Physiol 2007;578:143-57
91. Hayashi T, Su TP. Regulating ankyrin dynamics: roles of sigma-1 receptors. Proc Natl Acad Sci USA 2001;98:491-96
92. Matsuno K, Kobayashi T, Tanaka MK, et al. Sigma 1 receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. Eur J Pharmacol 1996;312:267-71
93. Urani A, Romieu P, Roman FJ, et al. Enhanced antidepressant efficacy of sigma1 receptor agonists in rats after chronic intracerebroventricular infusion of beta-amyloid-(1-40) protein. Eur J Pharmacol 2004;486:151-61
94. Reddy DS, Kulkarni SK. Development of neurosteroid-based novel psychotropic drugs. Prog Med Chem 2000;37:135-75
95. Corpechot C, Synguelakis M, Talha S, et al. Pregnenolone and its sulfate ester in the rat brain. Brain Res 1983;270:119-25

96. Baulieu EE, Robel P. Neurosteroids: a new brain function? J Steroid Biochem Mol Biol 1990;37:395-403

97. Dubrovsky B. Neurosteroids, neuroactive steroids, and symptoms of affective disorders. Pharmacol Biochem Behav 2006;84:644-55

98. Pinna G, Costa E, Guidotti A. Fluoxetine and norfluoxetine stereospecifically and selectively increase brain neurosteroid content at doses that are inactive on 5-HT reuptake. Psychopharmacology (Berl) 2006;186:362-72

99. Khisti RT, Chopde CT, Jain SP. Antidepressant-like effect of the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one in mice forced swim test. Pharmacol Biochem Behav 2000;67:137-43

100. Wohlfarth KM, Bianchi MT, Macdonald RL. Enhanced neurosteroid potentiation of ternary GABAA receptors containing the δ subunit. J Neurosci 2002;22:1541-49

101. Wei W, Zhang N, Peng Z, et al. Perisynaptic localization of δ subunit-containing GABAA receptors and their activation by GABA spillover in the mouse dentate gyrus. J Neurosci 2003;23:10650-61

102. Stell BM, Brickley SG, Tang CY, et al. Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABAA receptors. Proc Natl Acad Sci USA 2003;100:14439-44

103. Winsky-Sommerer R, Vyazovskiy VV, Homanics GE, et al. The EEG effects of THIP (Gaboxadol) on sleep and waking are mediated by the GABA(A)delta-subunit-containing receptors. Eur J Neurosci 2007;25:1893-99

104. Robichaud M, Debonnel G. Allopregnanolone and ganaxolone increase the firing activity of dorsal raphe nucleus serotonergic neurons in female rats. Int J Neuropsychopharmacol 2006;9:191-200

105. Maguire J, Mody I. GABAAR plasticity during pregnancy: relevance to postpartum depression. Neuron 2008;2:207-13

106. George MS, Guidotti A, Rubinow D, et al. CSF neuroactive steroids in affective disorders: pregnenolone, progesterone and DBI. Biol Psychiatry 1994;35:775-80

•• **The article describes the effect of neurosteroids in affective disorders.**

107. Malkesman O, Shayit M, Genud R, et al. Dehydroepiandrosterone in the nucleus accumbens is associated with early onset of depressive-behavior: a study in an animal model of childhood depression. Neuroscience 2007;149:573-81

108. Morita K, Her S. Progesterone pretreatment enhances serotonin-stimulated BDNF gene expression in rat c6 glioma cells through production of 5alpha-reduced neurosteroids. J Mol Neurosci 2008;34:193-200

•• **The article demonstrates that neurosteroids increase the BDNF levels.**

109. Reddy DS, Kaur G, Kulkarni SK. Sigma (sigma1) receptor mediated anti-depressant-like effects of neurosteroids in the Porsolt forced swim test. Neuroreport 1998;9:3069-73

110. Reddy DS, Kulkarni SK. Role of GABA-A and mitochondrial diazepam binding inhibitor receptors in the anti-stress activity of neurosteroids in mice. Psychopharmacology Berl 1996;128:280-92

111. Bermack JE, Debonnel G. The role of sigma receptors in depression. J Pharmacol Sci 2005;97:317-36

• **The review demonstrates the role of sigma receptors in depression.**

112. Peyron C, Petit JM, Rampon C, et al. Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. Neuroscience 1998;82:443-68

113. Ashkenazy T, Einat H, Kronfeld-Schor N. We are in the dark here: induction of depression- and anxiety-like behaviours in the diurnal fat sand rat, by short daylight or melatonin injections. Int J Neuropsychopharmacol 2008;17:1-11

114. Pandi-Perumal SR, Srinivasan V, Cardinali DP, et al. Could agomelatine be the ideal antidepressant? Expert Rev Neurother 2006;6:1595-608

•• **The review explains the antidepressant activity of novel molecule, agomelatine.**

115. Pandi-Perumal SR, Trakht I, Srinivasan V, et al. The effect of melatonergic and non-melatonergic antidepressants on sleep: weighing the alternatives. World J Biol Psychiatry 2008;4:1-13

116. Pandi-Perumal SR, Trakht I, Srinivasan V, et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol 2008;85:335-53

117. Ergun Y, Orhan FO, Karaaslan MF. Combination therapy of imipramine and melatonin: additive antidepressant effect in mouse forced swimming test. Eur J Pharmacol 2008;591:159-63

118. Mantovani M, Pértile R, Calixto JB, et al. Melatonin exerts an antidepressant-like effect in the tail suspension test in mice: evidence for involvement of N-methyl-D-aspartate receptors and the L-arginine-nitric oxide pathway. Neurosci Lett 2003;343:1-4

119. Raghavendra V, Kaur G, Kulkarni SK. Anti-depressant action of melatonin in chronic forced swimming-induced behavioral despair in mice, role of peripheral benzodiazepine receptor modulation. Eur Neuropsychopharmacol 2000;10:473-81

120. Arendt J, Rajaratnam SM. Melatonin and its agonists: an update. Br J Psychiatry 2008;193:267-69

121. San L, Arranz B. Agomelatine: a novel mechanism of antidepressant action involving the melatonergic and the serotonergic system. Eur Psychiatry 2008;23:396-402

122. Stahl SM. Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism. Int J Neuropsychopharmacol 2007;10:575-78

123. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. Neurotherapeutics 2009;6:53-77

124. Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int J Neuropsychopharmacol 2007;10:661-73

125. Dolder CR, Nelson M, Snider M. Agomelatine treatment of major depressive disorder. Ann Pharmacother 2008;42:1822-31

126. Palucha A, Pilc A. The involvement of glutamate in the pathophysiology of depression. Drug News Perspect 2005;18:262-68

127. Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. Annu Rev Pharmacol Toxicol 1997;37:205-37

128. Trullas R, Skolnick P. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 1990;185:1-10

129. Maj J, Rogoz Z, Skuza G, et al. Effects of MK-801 and antidepressant drugs in the forced swimming test in rats. Eur Neuropsychopharmacol 1992;2:37-41

130. Eckeli AL, Dach F, Rodrigues AL. Acute treatments with GMP produce antidepressant-like effects in mice. Neuroreport 2000;11:1839-43

131. Panconi E, Roux J, Altenbaumer M, et al. MK-801 and enantiomers: potential antidepressants or false positives in classical screening models? Pharmacol Biochem Behav 1993;46:15-20

132. Ossowska G, Klenk-Majewska B, Szymczyk G. The effect of NMDA antagonists on footshock-induced fighting behavior in chronically stressed rats. J Physiol Pharmacol 1997;48:127-35

133. Papp M, Moryl E, Willner P. Pharmacological validation of the chronic mild stress model of depression. Eur J Pharmacol 1996;296:129-36

134. Pilc A, Kłodzinska A, Branski P, et al. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. Neuropharmacology 2002;43:181-87

135. Danysz W, Parson CG, Bersnick I, et al. Glutamate in CNS disorders. Drug News Perspect 1996;8:261-77

136. Parsons CG, Danysz W, Quack G. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist-a review of preclinical data. Neuropharmacology 1999;38:735-67

137. 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 2006;163:153-55

• **This is a clinical study demonstrating the antidepressant activity of NMDA receptor antagonists.**

138. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000;47:351-54

139. Liebrenz M, Borgeat A, Leisinger R, et al. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. Swiss Med Wkly 2007;137:234-36

•• **This study demonstrates the antidepressant activity of intravenous ketamine in patients.**

140. Garcia LS, Comim CM, Valvassori SS, et al. Acute administration of ketamine induces antidepressant-like effects in the forced swimming test and increases BDNF levels in the rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:140-44

141. Popik P, Kos T, Sowa-Kucma M, et al. Lack of persistent effects of ketamine in rodent models of depression. Psychopharmacology (Berl) 2008;198:421-30

142. Fakhoury TA, Miller JM, Hammer AE, et al. Effects of lamotrigine on mood in older adults with epilepsy and co-morbid depressive symptoms: an open-label, multicentre, prospective study. Drugs Aging 2008;25:955-62

143. Kugaya A, Sanacora G. Beyond monoamines: glutamatergic function in mood disorders. Beyond monoamines: glutamatergic function in mood disorders. CNS Spectr 2005;10:808-19

144. Brocardo Pde S, Budni J, Lobato KR, et al. Antidepressant-like effect of folic acid: involvement of NMDA receptors and L-arginine-nitric oxide-cyclic guanosine monophosphate pathway. Eur J Pharmacol 2008;598:37-42

145. Skolnick, 1999. Antidepressants for the new millennium. Eur J Pharmacol 1999;375:31-40

146. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995;15:7539-47

147. Brandoli C, Sanna A, De Bernardi MA, et al. Brain-derived neurotrophic factor and basic fibroblast growth factor downregulate NMDA receptor function in cerebellar granule cells. J Neurosci 1998;18:7953-61

148. Bleakman D, Alt A, Witkin JM. AMPA receptors in the therapeutic management of depression. CNS Neurol Disord Drug Targets 2007;6:117-26

149. Li X, Witkin JM, Need AB, et al. Enhancement of antidepressant potency by a potentiator of AMPA receptors. Cell Mol Neurobiol 2003;23:419-30

150. Bai F, Bergeron M, Nelson DL. Chronic AMPA receptor potentiator (LY451646) treatment increases cell proliferation in adult rat hippocampus. Neuropharmacology 2003;44:1013-21

151. 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

152. Pilc A, Chaki S, Nowak G, et al. Mood disorders: regulation by metabotropic glutamate receptors. Biochem Pharmacol 2008;75:997-1006

153. Witkin JM, Marek GJ, Johnson BG, et al. Metabotropic glutamate receptors in the control of mood disorders. CNS Neurol Disord Drug Targets 2007;6:87-100

154. Attucci S, Carla V, Mannaioni G, et al. Activation of type 5 metabotropic glutamate receptors enhances NMDA responses in mice cortical wedges. Br J Pharmacol 2001;132:799-806

155. Chaki S, Yoshikawa R, Hirota S, et al. MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity. Neuropharmacology 2004;46:457-67

156. Yoshimizu T, Chaki S. Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039. Biochem Biophys Res Commun 2004;315:493-96

157. Pałucha A, Tatarczynska E, Branski P, et al. Group III mGlu receptor agonists produce anxiolytic- and antidepressant-like effects after central administration in rats. Neuropharmacology 2004;46:151-59

158. Hoyer D, Martin G. 5-HT receptor classification and nomenclature: towards a harmonization with the human genome. Neuropharmacology 1997;36:419-28

159. Yun HM, Kim S, Kim HJ, et al. The novel cellular mechanism of human 5-HT6 receptor through an interaction with Fyn. J Biol Chem 2007;282:5496-505

160. Wesołowska A, Nikiforuk A. Effects of the brain-penetrant and selective 5-HT6 receptor antagonist SB-399885 in animal models of anxiety and depression. Neuropharmacology 2007;52:1274-83

161. Wesołowska A, Nikiforuk A, Stachowicz K. Anxiolytic-like and antidepressant-like effects produced by the selective 5-HT6 receptor antagonist SB-258585 after intrahippocampal administration to rats. Behav Pharmacol 2007;18:439-46

162. Mitchell ES, Neumaier JF. 5-HT6 receptors: a novel target for cognitive enhancement. Pharmacol Ther 2005;108:320-33

163. Svenningsson P, Tzavara ET, Qi H, et al. Biochemical and behavioral evidence for antidepressant-like effects of 5-HT6 receptor stimulation. J Neurosci 2007;27:4201-09

164. Wesolowska A, Nikiforuk A, Stachowicz K, et al. Effect of the selective 5-HT7 receptor antagonist SB 269970 in animal models of anxiety and depression. Neuropharmacology 2006;51:578-86

165. Wesolowska A, Tatarczynska E, Nikiforuk A, et al. Enhancement of the anti-immobility action of antidepressants by a selective 5-HT7 receptor antagonist in the forced swimming test in mice. Eur J Pharmacol 2007;555:43-7

166. Hedlund PB, Huitron-Resendiz S, Henriksen SJ, et al. 5-HT7 receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. Biol Psychiatry 2005;58:831-37

•• **The study demonstrates the antidepressant activity of $5HT_7$ serotonin receptor antagonists.**

167. Bonaventure P, Kelly L, Aluisio L, et al. Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. J Pharmacol Exp Ther 2007;321:690-98

168. Mnie-Filali O, Lambas-senas L, Zimmer L, Haddjeri N. 5-HT7 Receptor Antagonists as a New Class of Antidepressants. Drug News Perspectives 2007;20:613-8

169. Hedlund PB, Sutcliffe JG. The 5-HT7 receptor influences stereotypic behavior in a model of obsessive-compulsive disorder. Neurosci Lett 2007;414:247-51

170. Consoli D, Leggio GM, Mazzola C, et al. Behavioral effects of the beta3 adrenoceptor agonist SR58611A: is it the putative prototype of a new class of antidepressant/anxiolytic drugs? Eur J Pharmacol 2007;573:139-47

171. Overstreet DH, Stemmelin J, Griebel G. Confirmation of antidepressant potential of the selective beta3 adrenoceptor agonist amibegron in an animal model of depression. Pharmacol Biochem Behav 2008;89:623-26

172. Stemmelin J, Cohen C, Terranova JP, et al. Stimulation of the beta3-Adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. Neuropsychopharmacology 2008;33:574-87

•• **The study explains the antidepressant activity of β3 adrenoceptors agonists.**

173. Griebel G, Stemmelin J, Gal CS, et al. Non-peptide vasopressin V1b receptor antagonists as potential drugs for the treatment of stress-related disorders. Curr Pharm Des 2005;11:1549-59

174. Griebel G, Simiand J, Serradeil-Le Gal C, et al. Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci USA 2002;99:6370-75

175. Stemmelin J, Lukovic L, Salome N, et al. Evidence that the lateral septum is involved in the antidepressant-like effects of the vasopressin V1b receptor antagonist, SSR149415. Neuropsychopharmacology 2005;30:35-42

176. Breuer ME, van Gaalen MM, Wernet W, et al. SSR149415, a non-peptide vasopressin V(1b) receptor antagonist, has long-lasting antidepressant effects in the olfactory bulbectomy-induced hyperactivity depression model. Naunyn Schmiedebergs Arch Pharmacol 2009;379:101-6

177. Overstreet DH, Griebel G. Antidepressant-like effects of the vasopressin V1b receptor antagonist SSR149415 in the Flinders Sensitive Line rat. Pharmacol Biochem Behav 2005;82(1):223-7

178. Serradeil-Le Gal C, Wagnon J 3rd, Tonnerre B, et al. An overview of SSR149415, a selective nonpeptide vasopressin V(1b) receptor antagonist for the treatment of stress-related disorders. CNS Drug Rev 2005;11:53-68

179. Gardier A. Mechanism of action of antidepressant drugs: importance of genetically modified mice in the pharmacological in vivo approach. Therapie 2005;60:469-76

180. Salomé N, Stemmelin J, Cohen C, et al. Selective blockade of NK2 or NK3 receptors produces anxiolytic- and antidepressant-like effects in gerbils. Pharmacol Biochem Behav 2006;83:533-39

181. Griebel G, Perrault G, Soubrié P. Effects of SR48968, a selective non-peptide NK2 receptor antagonist on emotional processes in rodents. Psychopharmacology (Berl) 2001;158:241-51

182. Steinberg R, Alonso R, Griebel G, et al. Selective blockade of neurokinin-2 receptors produces antidepressant-like effects associated with reduced corticotropin-releasing factor function. J Pharmacol Exp Ther 2001;299:449-58

183. Micale V, Tamburella A, Leggio GM, et al. Behavioral effects of saredutant, a tachykinin NK2 receptor antagonist, in experimental models of mood disorders under basal and stress-related conditions. Pharmacol Biochem Behav 2008;90:463-69

184. Nestler EJ, Barrot M, DiLeone RJ, et al. Neurobiology of depression. Neuron 2002;34:13-25

185. Holsboer F, Ising M. Central CRH system in depression and anxiety — Evidence from clinical studies with CRH1 receptor antagonists. Eur J Pharmacol583(7):350-57

186. Kumamaru E, Numakawa T, Adachi N, et al. Glucocorticoid prevents brain-derived neurotrophic factor-mediated maturation of synaptic function in developing hippocampal neurons through reduction in the activity of mitogen-activated protein kinase. Mol Endocrinol 2008;22:546-58

187. Ago Y, Arikawa S, Yata M, et al. Antidepressant-like effects of the glucocorticoid receptor antagonist RU-43044 are associated with changes in prefrontal dopamine in mouse models of depression. Neuropharmacology 2008;55:1355-63

188. Buckley T, Duggal V, Schatzberg AF. The acute and post-discontinuation effects of a glucocorticoid receptor (GR) antagonist probe on sleep and the HPA axis in chronic insomnia: a pilot study. J Clin Sleep Med 2008;4:235-41

189. Todorovic C, Sherrin T, Pitts M, et al. Suppression of the MEK/ERK signaling pathway reverses depression-like behaviors

of CRF(2)-deficient mice. Neuropsychopharmacology 2009 (In Press)

190. Ducottet C, Griebel G, Belzung C. Effects of the selective nonpeptide corticotropin-releasing factor receptor 1 antagonist antalarmin in the chronic mild stress model of depression in mice. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:625-31

191. Hodgson RA, Higgins GA, Guthrie DH, et al. Comparison of the V1b antagonist, SSR149415, and the CRF1 antagonist, CP-154,526, in rodent models of anxiety and depression. Pharmacol Biochem Behav 2007;86:431-40

192. Chaki S, Nakazato A, Kennis L, et al. Anxiolytic- and antidepressant-like profile of a new CRF1 receptor antagonist, R278995/CRA0450. Anxiolytic- and antidepressant-like profile of a new CRF1 receptor antagonist, R278995/CRA0450. Eur J Pharmacol 2004;485:145-58

193. Heinrichs SC, De Souza EB, Schulteis G, et al. Brain penetrance, receptor occupancy and antistress in vivo efficacy of a small molecule corticotropin releasing factor type I receptor selective antagonist. Neuropsychopharmacology 2002;27:194-202

194. Li YW, Fitzgerald L, Wong H, et al. The pharmacology of DMP696 and DMP904, non-peptidergic CRF1 receptor antagonists. CNS Drug Rev 2005;11:21-52

195. Zobel AW, Nickel T, Künzel HE, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 2000;34:171-81

196. Surget A, Saxe M, Leman S, et al. Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry 2008;64:293-301

197. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. Psychopharmacology (Berl) 2008;201:435-42

• **The study explores the involvement of serotonin and dopamine in the antidepressant activity of curcumin.**

198. Bhutani MK, Bishnoi M, Kulkarni SK. Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. Pharmacol Biochem Behav 2009;92:39-43

199. Wang R, Xu Y, Wu HL, et al. The antidepressant effects of curcumin in the forced swimming test involve 5-HT1 and 5-HT2 receptors. Eur J Pharmacol 2008;578:43-50

200. Xu Y, Ku BS, Yao HY, et al. Antidepressant effects of curcumin in the forced swim test and olfactory bulbectomy models of depression in rats. Pharmacol Biochem Behav 2005;82:200-06

201. Wang R, Li YB, Li YH, et al. Curcumin protects against glutamate excitotoxicity in rat cerebral cortical neurons by increasing brain-derived neurotrophic factor level and activating TrkB. Brain Res 2008;1210:84-91

202. Nöldner M, Schötz K. Rutin is essential for the antidepressant activity of Hypericum perforatum extracts in the forced swimming test. Planta Med 2002;68:577-80

203. Machado DG, Bettio LE, Cunha MP, et al. Antidepressant-like effect of rutin isolated from the ethanolic extract from Schinus molle L. in mice: evidence for the involvement of the serotonergic and noradrenergic systems. Eur J Pharmacol 2008;587:163-68

•• **The study demonstrates the antidepressant activity of rutin.**

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