Available online at www.sciencedirect.com

SCIENCE DIRECT®

European Journal of Pharmacology 500 (2004) 371–384

www.elsevier.com/locate/ejphar

Review

The role of monoamines in the actions of established and "novel" antidepressant agents: a critical review

Mark J. Millan*

Psychopharmacology Department, IdR Servier, 125 Chemin de Ronde, Croissy/Seine, Paris 78290, France

Accepted 1 July 2004
Available online 17 August 2004

Abstract

Monoaminergic pathways are highly responsive to aversive stimuli and play a crucial role in the control of affect, cognition, endocrine secretion, chronobiotic rhythms, appetite, and motor function, all of which are profoundly disrupted in depressive states. Accordingly, a perturbation of monoaminergic transmission is implicated in the aetiology of depressive disorders, and all clinically available antidepressants increase corticolimbic availability of monoamines. However, their limited efficacy, delayed onset of action, and undesirable side effects underlie ongoing efforts to identify improved therapeutic agents. Sequencing the human genome has raised the hope not only of better symptomatic control of depression, but even of the prevention or cure of depressive states. In the pursuit of these goals, there is currently a tendency to focus on selective ligands of "novel" nonmonoaminergic targets. However, certain classes of novel agent (such as neurokinin$_1$ receptor antagonists) indirectly modulate the activity of monoaminergic networks. Others may act "downstream" of them, converging onto common cellular substrates controlling gene expression, synaptic plasticity, and neurogenesis. Further, by analogy to the broad-based actions of currently employed drugs, multitarget agents may be better adapted than selective agents to the management of depression—a complex disorder with hereditary, developmental, and environmental origins. It is, thus, important to continue the creative exploration of clinically validated and innovative monoaminergic strategies within a multitarget framework. In this light, drugs combining monoaminergic and nonmonoaminergic mechanisms of action may be of particular interest. The present article provides a critical overview of monoaminergic strategies for the treatment of depressive states, both established and under development, and discusses interactions of novel "nonmonoaminergic" antidepressants with monoaminergic mechanisms.

Keywords: Depression; Antidepressant; Monoamine; Neurogenesis; SSRI; Tricyclic; Dopamine

Contents

* Tel.: +33 1 55 72 24 25; fax: +33 1 55 72 24 70.
E-mail address: mark.millan@fr.netgrs.com.

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.07.038

1. The need for improved management of depressive states

Major depression is a serious and incapacitating disorder with a heavy social burden and a substantial lifetime risk (Greenberg et al., 2003). It is common in the elderly and is increasingly recognized in young adults, adolescents, and children. Proactive and sustained antidepressant treatment is essential to achieve optimal remission and to avoid the (considerable) danger of relapse (Zajecka, 2003). However, despite their improved safety profiles as compared to first-generation drugs, such as imipramine, even agents such as the selective (5-HT) serotonin reuptake inhibitor (SSRI), fluoxetine, offer little advantage in terms of efficacy. There remains, thus, a pressing need for more effective antidepressants that do not require several weeks of administration prior to full expression of clinical efficacy (Fig. 1) (Tamminga et al., 2002; Blier, 2003). Furthermore, there is a need to reduce undesirable side effects, such as sexual dysfunction, insomnia, and weight gain, which compromise patient compliance and curtail drug efficacy (Vida and Cooper, 1999; Montgomery et al., 2002).

2. Key issues for novel antidepressants: genomics, multitarget strategies, and monoamines

In the development of improved antidepressants, three fundamental and interrelated issues must be addressed.

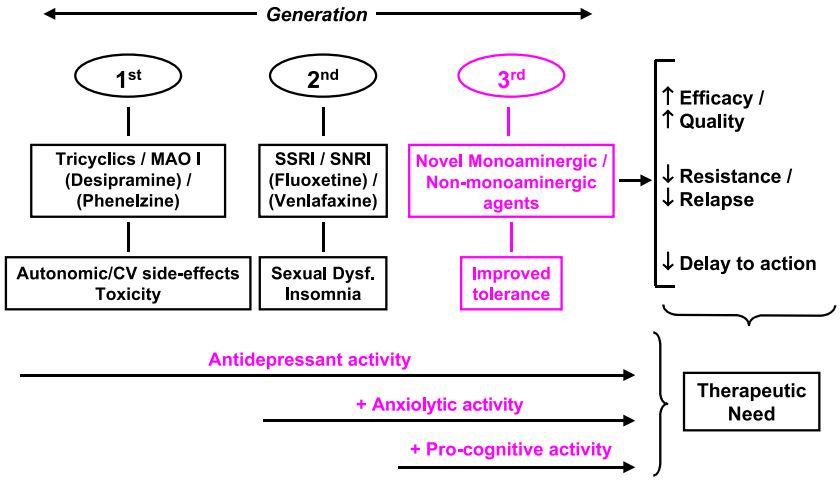


Fig. 1. Chronology of the development of antidepressant agents and their principle characteristics. Second-generation antidepressants are safer than first-generation agents, permitting widespread use in the treatment of depressive (and anxious) states, although cognitive symptoms remain poorly controlled. There remains a need for well-tolerated and more rapidly acting antidepressant agents of improved efficacy. MAOI=monoamine oxidase inhibitor.

First, what will be the impact of the human genome? It is improbable that any single gene ineluctably triggers depression—a multifactorial disease with genetic, developmental, and environmental origins (Hong and Tsai, 2003; Manji et al., 2003; Wong and Licinio, 2004). Nevertheless, patients may express (a) gene(s) rendering them vulnerable to other genetic (epistatic), developmental (neonatal), and/or environmental (life events) factors. Further, irrespective of the genetic bases of depressive states, the human genome may yield hitherto unknown targets allowing for their improved symptomatic control and their prevention in susceptible individuals displaying genetic, endocrine, or neurological markers (Lerer and Macciardi, 2002; Wong and Licinio, 2004). Second, in exploiting the human genome, should we concentrate on selective agents—the current tendency as concerns innovative gene-derived targets? Or should we focus on agents with multiple mechanisms of action in view of the complex aetiology of depression and the operationally multitarget nature of all existing drugs (see below)? Third, should we renounce monoamines as targets, despite their pivotal role in the control of mood, the response to stress, and, as amply validated clinically, the management of depression? Rather, as argued herein, there remains substantial scope for directly and indirectly harnessing monoaminergic networks for the improved control of depressive states. Thus, innovative monoaminergic, nonmonoaminergic, and combined strategies will all be of importance in the search for better antidepressant agents. In discussing the above issues, general principles are emphasised and the focus is firmly on drug classes for which—at least limited—clinical information is available.

3. Monoaminergic strategies for the improvement of depressive states

3.1. The importance of restoring and reequilibrating monoaminergic transmission

The notion that perturbed monoaminergic transmission is causally implicated in depressive states has been enshrined in the literature for decades (Manji et al., 2003). It might be contended that definitive proof for this hypothesis is still unavailable, and that the precise nature of defects remains to be clarified. This is perfectly true, yet no one would seriously challenge the importance of monoamines to affective disorders. In addition to a vast body of experimental data, monoamine depletion studies in patients have unambiguously demonstrated the importance of functionally competent monoaminergic pathways for combating depressive states, and all currently available treatments of depression restore the compromised activity of corticolimbic monoaminergic pathways (Delgado, 2000; Millan et al., 2000b; Pacher et al., 2001).

3.2. Chronic exposure to antidepressants triggers adaptive "plastic charges": novel targets for antidepressant agents?

Although rapid benefits with augmentation strategies, intravenous administration of tricyclics, sleep deprivation, and electroconvulsive therapy suggest that an extensive (3–4 weeks) delay to therapeutic efficacy may not be unavoidable, it is still controversial whether drugs can achieve a rapid and sustained relief of depressive states (Tamminga et al., 2002; Wong and Licinio, 2004). This temporal mismatch between the rapid elevations in extracellular levels of monoamine induced by antidepressant agents (hours) and their slow onset of action (weeks) reflects the initiation of plastic events including: alterations in receptor density and intracellular signalling, changes in synaptic transmission, modification of neuronal architecture, and neurogenesis (Manji et al., 2003). Intriguingly, in addition to ligands that interact with monoaminergic neurones per se, these "downstream" cellular mechanisms have themselves become targets (both directly and via other convergent pathways) for the treatment of depression. The following mediators have been implicated in the ability of antidepressants to enhance neuronal resilience and proliferation, and to counter deleterious changes in neuronal integrity provoked by chronic stress or excessive glucocorticoid secretion: neurotrophins (such as brain-derived neurotrophic factor), effector immediate early genes (like *Arc*), transcription factors (such as cAMP-responsive element binding), and antiapoptoptic proteins (such as bcl-2) (Jacobs et al., 2000; McEwen, 2000; Donati and Rasenick, 2003; Nguyen and Woo, 2003; Pei et al., 2003). Accordingly, in addition to neurochemical/electrophysiological parameters of antidepressant action (increases in monoaminergic transmission) and behavioural paradigms, cellular models of receptor/G-protein coupling and neuronal plasticity have become important in the characterization of novel antidepressants. Today, then, an interdisciplinary strategy is indispensable (Fig. 2).

However, one may remain skeptical as to whether such intracellular signals represent genuine clinical targets. Generalized induction of bcl-2 could well be tumerogenic (as suggested by studies of mice overexpressing bcl-2), and cAMP-responsive element binding fulfils many contrasting roles (exerting either a positive or negative influence upon mood dependent on the structure in which it is induced) (Newton et al., 2002); despite the existence of region-specific isoforms of phosphodiesterase (which enhance cAMP-responsive element binding activation), inhibitors are poorly tolerated (O'Donnell and Zhang, 2004). Moreover, the prospect of inducing brain-derived neurotrophic factor expression throughout the entire organism raises serious safety concerns. There remains, thus, the necessity for "vectorization"—directing drugs specifically to structures where these signals require modulation, such as the hippocampus or parietal cortex, and other mood-related corticolimbic circuits. This is, of course, precisely what

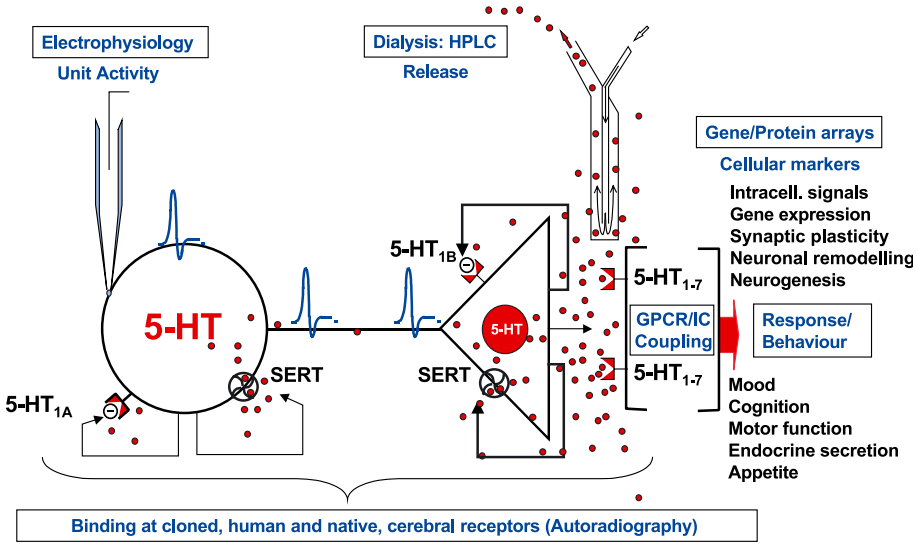


Fig. 2. Schematic representation of an interdisciplinary approach to characterisation of antidepressant agents. GPCR=G-protein-coupled receptor; IC=ion channel.

monoaminergic antidepressants achieve. Nevertheless, other concepts could be elaborated, either upstream of monoamines, or in parallel and converging onto specific populations of corticolimbic neurones.

3.3. Contrasting mechanisms of action of clinically used antidepressant agents

Irreversible monoamine oxidase (MAO) inhibitors block mitochondrial enzymes for monoamine degradation. They are effective antidepressants, but poorly tolerated. Further, more recently described, reversible inhibitors with superior safety margins have made little inroad into the hegemony of monoamine reuptake inhibitors (Schatzberg, 2002). Amongst these, "tricyclics," such as imipramine, exert therapeutic actions by joint inhibition of 5-HT and noradrenaline reuptake, although auxiliary 5-$HT_{2A/2C}$ receptor blockade may also favourably influence mood (Sanchez and Hyttel, 1999; Tamminga et al., 2002). Unfortunately, their indiscriminate multitarget profiles, which extend to antagonism of α_1-adrenoceptors, muscarinic receptors, and histaminergic receptors, as well as cardiac ion channels, underlies their poor tolerance (Schatzberg, 2002). Although SSRIs provoke their own spectrum of side effects (sexual dysfunction, nervousness at the onset of treatment, nausea, and insomnia), they are indubitably safer than tricyclics and MAO inhibitors (Vida and Cooper, 1999; Montgomery et al., 2002). Accordingly, they are universally employed for the long-term control of depressive—as well as anxious and impulsive—states (Millan, 2003; Shorter and Tyrer, 2003). This notion of comorbidity, which is shown in Fig. 3, also reflects current awareness that, like other major psychiatric disorders, depression cannot be simplistically ascribed to the dysfunction of any one monoamine; rather, it reflects a complex disruption of the overall operation of monoaminergic networks (see below).

SSRIs are not more efficacious than tricyclics (Anderson, 2000). Paradoxically, then, despite the original insistence on their selectivity, this was subsequently perceived as a handicap leading to the development of mixed serotonin/noradrenaline reuptake inhibitors (SNRIs), exemplified by venlafaxine, which lacks the unwanted receptor interactions of tricyclics. Further, although venlafaxine shares the side effects of SSRIs, it may be more efficacious and more rapidly active, and it mimics their utility in the management of anxious states (Millan et al., 2000b, 2001a; Blier, 2003; Davidson et al., 2003). It is interesting that the selective noradrenaline reuptake inhibitor, reboxetine, is likewise an effective antidepressant agent in view of evidence for a heterogeneity of depressive states with differential involvement of adrenergic and serotonergic deficits (Delgado, 2000; Millan et al., 2000b). Further, the distinctive clinical profile of reboxetine has been accentuated as regards facilitation of social integration (Millan et al., 2001a,b; Andreoli et al., 2002). Bupropion has been forwarded as a selective dopamine reuptake inhibitor, but it is rapidly converted into a metabolite that blocks noradrenaline reuptake (Ascher et al., 1995). Consequently, bupropion displays a neurochemical profile similar to reboxetine (Sanchez and Hyttel, 1999; Millan et al., 2000b, 2001a).

Trazodone and its descendant, nefazodone, are weak inhibitors of 5-HT reuptake and possess antagonist properties at 5-$HT_{2A/2C}$ receptors (Davis et al., 1997; Sanchez and Hyttel, 1999; Leysen, 2004). This profile is interesting inasmuch as there is clear evidence that postsynaptic 5-$HT_{2A/2C}$ receptor blockade enhances cortical release of dopamine and noradrenaline. Further, this action is associated with moderation of the anxiety, hypophagia, sexual dysfunction, and insomnia elicited by inhibition of 5-HT reuptake (Millan et al., 2000b; Montgomery et al., 2002; Di Matteo and Esposito, 2003; Millan, 2003). Indeed, the relative lack of sexual dysfunction and sleep loss has been emphasized for

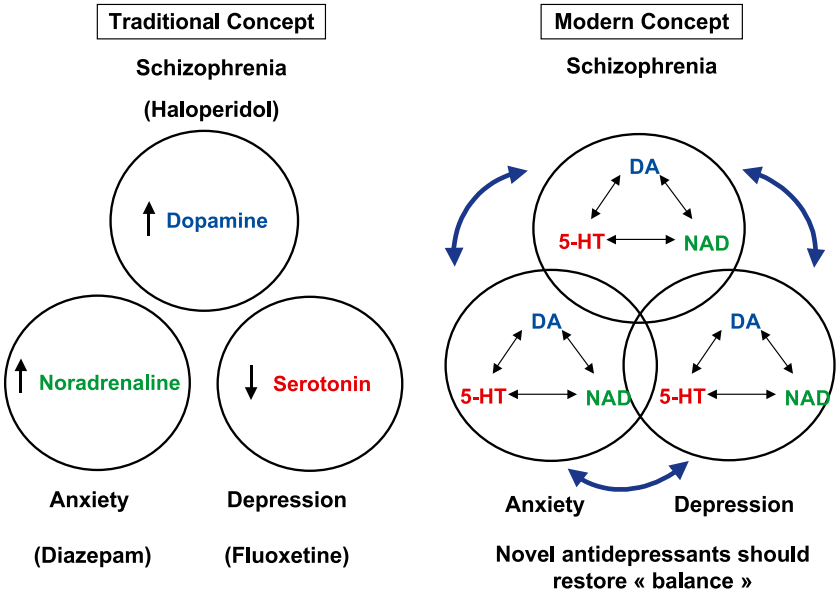


Fig. 3. Depressive states are often comorbid with other psychiatric disorders, all of which involve complex alterations in monoaminergic transmission. Attribution of disorders to unitary changes in the activity of one monoamine is a simplification in view of complex patterns of changes in monoaminergic transmission and equilibrium in depressive and other psychiatric states.

nefazodone (Davis et al., 1997; Schatzberg, 2002). However, this characteristic partly reflects potent antihistaminergic (H_1 receptor antagonist) properties, which, in common with α_1-adrenoceptor blockade, provoke somnolence and sedation (Leysen, 2004). These generally undesirable side effects, together with metabolic instability, compromise the clinical utility of nefazodone (Davis et al., 1997). Nevertheless, the pertinence of 5-$HT_{2A/2C}$ receptor blockade is underlined by two tetracyclic agents, mianserin, and its derivative, mirtazapine (Kasper, 1995; Millan et al., 2000a,b; Blier, 2003). The latter, which is devoid of affinity for reuptake sites, blocks α_2-adrenoceptors, which share the inhibitory influence of 5-HT_{2C} sites upon corticolimbic adrenergic (and dopaminergic) projections (Di Matteo and Esposito, 2003). Further, 5-HT_{2C} and α_2-adrenoceptor antagonist properties improve sexual function (Montgomery et al., 2002). Despite the originality of mirtazapine, it is regrettable that the term "NaSSA," in allusion to an ostensibly serotonergic mechanism of action, has proliferated throughout the literature (Kasper, 1995). Indeed, recent studies failed to confirm that mirtazapine liberates 5-HT, although corroborating its enhancement of noradrenaline and dopamine release (Millan et al., 2000a,b; Devoto et al., 2004b). A drawback of mirtazapine is antagonism at H_1 sites, underlying somnolence, and obesity.

3.4. General properties of antidepressants: broad-based increases in monoamine levels

Several general conclusions may be drawn from the above. First, all clinically available antidepressants directly harness monoaminegic mechanisms in that they interact with enzymes for catabolism, transporters for reuptake, or receptors expressing their actions. Second, all operatively behave as multitarget agents, either stricto senso, in the case of, for example, SNRIs or mirtazapine, and/or in terms of their broad reinforcement of corticolimbic monoaminergic transmission. SSRIs are a false exception since, in principle, 5-HT can recruit all 14 classes of postsynaptic 5-HT receptor. By analogy, reboxetine indirectly recruits all classes of postsynaptic α-adrenoceptors and β-adrenoceptors. "Alternative" treatments, such as electroconvulsive therapy, also exert a pervasive influence upon monoaminergic transmission in diverse corticolimbic structures (Tamminga et al., 2002). These broad-based actions are commensurate with the widespread perturbation of monoaminergic networks (and other modulators) in depressive states. Indeed, the involvement of monoamines in depressive states cannot be subsumed by a simplistic formula of "insufficient release." Rather, they are implicated in a complex region and receptor-dependent manner. Accordingly, there is a need for antidepressant strategies, which reestablish the perturbed equilibrium amongst corticolimbic monoaminergic pathways (Fig. 4).

4. Innovative monoaminergic strategies for improving treatment of depression

4.1. The search for novel monoaminergic agents: uncertainties and difficulties

Of several interrelated problems hindering research into novel treatments for depression, the most fundamental is our

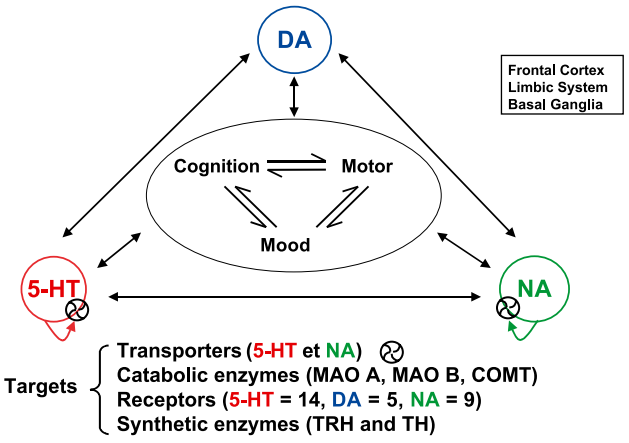


Fig. 4. Corticolimbic monoaminergic mechanisms control mood, cognition, and motor behaviour—functions profoundly disrupted in depressive states. For restoration of perturbed monoaminergic transmission and homeostasis, a multiplicity of targets is available. TRH=tryptophan hydroxylase; TH=tyrosine hydroxylase; COMT=catechol-*O*-methyltransferase; MAO=monoamine oxidase.

ignorance of the identity(ies) of postsynaptic receptor(s) mediating the actions of antidepressant agents. For SSRIs, a potential role of 5-HT_{1A} receptors has been evoked, but experimental data are contradictory. Further, while 5-HT_{1A} receptor agonists show antidepressant actions in rodents, their clinical profiles are less robust (Lucki et al., 1994; Naughton et al., 2000; Mayorga et al., 2001; Bymaster et al., 2003). A more consistent case has been made for a role of 5-HT_{1B} receptors in the actions of SSRIs, but, on the contrary, antidepressant effects of 5-HT_{1B} antagonists have been reported in rodents and there is no clinical support for this hypothesis (Mayorga et al., 2001; Hudzik et al., 2003). Despite claims for an involvement of 5-HT_{2C} receptors, this is incompatible with antagonist properties of many antidepressants at these sites and their progressive down-regulation upon long-term exposure to SSRIs (Naughton et al., 2000). As concerns noradrenaline, despite a surprising claim for a "protective" role of α_{2A}-adrenoceptors in depression, more likely candidates are β_1-adrenoceptors (and β_2-adrenoceptors), possibly in conjunction with α_1-adrenoceptors (Schramm et al., 2001; Stone et al., 2003; Zhang et al., 2003). Clearly more research is needed into this critical issue, although it must be emphasized that stimulation of any one receptor can hardly mimic the multireceptorial actions of 5-HT, noradrenaline, or dopamine. Further, the implication of specific receptor types will depend upon several factors, including the deficit under study (e.g., neural atrophy vs. anhedonia) and the central nervous system region concerned (e.g., hippocampus vs. cortex). A second and related problem is our ignorance of the precise pathophysiological significance of specific classes of monoamine receptor. Third, compounding these problems, experimental models for characterization of tricyclics and SSRIs may be inappropriate to the detection of novel monoaminergic mechanisms of antidepressant activity (Cryan et al., 2002).

4.2. Novel monoaminergic strategies for treating depression

4.2.1. Enzymes of synthesis, catabolic routes, and novel approaches to transporters

Potential antidepressants have been described (such as vindeburnol), which induce tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis (Schmitt et al., 1993). Detection of a brain-specific form of tryptophan hydroxylase raises the possibility of its induction for selective enhancement of central vs. peripheral generation of 5-HT (Walker et al., 2003). In addition to MAO, catecholamines are metabolised by catechol-*O*-methyltransferase, which may also be a target for novel antidepressants. Disparities between the in vivo vs. in vitro actions of SSRIs may reflect poorly understood actions at 5-HT transporter isoforms differentially distributed between various cerebral regions (Kitayama and Dohi, 2003). Such isoforms provide a potential target for novel reuptake inhibitors. The operation of monoaminergic transporters may also be controllable via drugs recognising their sites of interaction with protein kinases and other postsynaptic proteins (Torres et al., 2003).

4.2.2. Multiple classes of 5-HT receptor as novel targets

Of the 14 classes of 5-HT receptor known, only one (the 5-HT_{1A} site) has been systematically evaluated in the clinic. Despite positive data with partial agonists such as gepirone (Bymaster et al., 2003), recent interest has gravitated towards 5-HT_{1A} antagonists, such as robalzaton, on the grounds that they may increase 5-HT release by blocking inhibitory autoreceptors (Sorbera et al., 1999; Naughton et al., 2000; Bymaster et al., 2003). However, evidence that 5-HT_{1A} autoreceptors tonically decrease 5-HT release is poor. Further, antagonists also block postsynaptic 5-HT_{1A} sites, which may mediate antidepressant actions (vide supra), and initial clinical data are not encouraging (Ybema, 2003). For similar reasons, despite evidence for antidepressant actions of 5-HT_{1B} antagonists in rodent models (Hudzik et al., 2003), it is hard to be optimistic for their clinical fate. Perhaps, combined 5-$HT_{1A/1B/1D}$ antagonists will fare better (Bymaster et al., 2003). Curiously, despite powerful arguments for the utility of 5-HT_{2C} receptor blockade in the management of depression (Naughton et al., 2000; Millan et al., 2003), clinical data for selective 5-HT_{2C} antagonists are not available (Leysen, 2004). 5-HT_3 and 5-HT_4 receptors offer no obvious leads, but corticolimbic 5-HT_5 and 5-HT_6 receptors justify additional study in view of intriguing hints for a role in the control of mood (Millan, 2003; Nelson, 2004; Woolley et al., 2004). 5-HT_7 receptors are of interest for several reasons. They are concentrated in corticolimbic structures; suprachiasmatic populations participate in the control of circadian rhythms; chronic administration of antidepressants downregulates hypothalamic 5-HT_7 sites, although their expression is elevated in cortical astrocytes; 5-HT_7 knockout mice show an antidepressant-like profile;

and (like antidepressants) 5-HT_7 antagonists reduce latency to rapid eye movement (REM) sleep (Thomas and Hagan, 2004). However, no evidence for antidepressant actions of 5-HT_7 antagonists in experimental models (or man) has been provided (Thomas and Hagan, 2004).

4.2.3. α-Adrenoceptors and β-adrenoceptors

There is compelling evidence for a role of α_1-adrenoceptors in the actions of antidepressant agents. Thus, blockade of α_1-adrenoceptors mimics depressive states, which, like chronic stress, are associated with α_1-adrenoceptor desensitisation (Stone et al., 2003). In contrast, chronic antidepressants and electroconvulsive therapy enhance the density and functional activity of α_1-adrenoceptors in structures such as frontal cortex and hippocampus: therein, α_1-adrenoceptors couple to intracellular signals controlling synaptic plasticity (Stone et al., 2003). Although a role of α_{1A}-adrenoceptors has been proposed (Nalepa et al., 2002), the α_{1B}-adrenoceptor subtype is principally involved, in line with its high density in corticolimbic structures and regions containing serotonergic and dopaminergic perikarya (Blendy et al., 1990; Millan, 2003; Stone et al., 2003). If cardiovascular effects could be constrained, α_{1B}-adrenoceptors could represent targets for novel antidepressant agents.

Chronic antidepressant treatment gradually downregulates α_2-adrenoceptor autoreceptors. This adaptive effect is related to their delay to onset of action and underpins the utility of antagonist properties at α_2-adrenoceptor sites for hastening therapeutic properties (Millan et al., 2000b; Payne et al., 2002). As regards autoreceptors, the α_{2A}-adrenoceptor subtype predominates over α_{2C}-adrenoceptors and its levels are elevated both in depressed patients and by long-term stress (Flügge et al., 2003; Ordway et al., 2003). Curiously, knockout studies suggest that mice lacking α_{2C}-adrenoceptors but not α_{2A}-adrenoceptors show an antidepressant profile (Sallinen et al., 1998; Schramm et al., 2001). Irrespective of the precise role of α_{2C}-adrenoceptor vs. α_{2A}-adrenoceptor subtypes, since antagonists that fail to discriminate them are poor antidepressants (Nutt and Pinder, 1996), there is a case for clinical evaluation of both classes of subtype-selective antagonist.

Upon chronic treatment, many antidepressants downregulate β_1-adrenoceptors, while agonists at β_1-adrenoceptors (and β_2-adrenoceptors) facilitate noradrenaline release in frontal cortex and display antidepressant properties in rodents (Gobert and Millan, 1999; Vetulani and Nalepa, 2000; Zhang et al., 2003). Interestingly, antidepressant actions of β_1-adrenoceptor agonists involve sites in the hippocampus wherein their positive coupling to adenylyl cyclase recruits transcription factors such as cAMP-responsive element binding (Zhang et al., 2003). Antidepressants that raise noradrenaline levels also likely act via β_1-adrenoceptors to induce factors controlling synaptic plasticity (Crissman and O'Donnell, 2002). Despite these observations, concerns of cardiovascular side effects discourage the development of β-adrenoceptor agonists as antidepressant (or procognitive) agents.

4.2.4. The importance of dopaminergic mechanisms: novel modes of exploitation

A dysfunction of mesolimbic and mesocortical dopaminergic pathways is primarily implicated in the melancholic and cognitive features of depression, respectively (Millan et al., 2000a,b; Naranjo et al., 2001; Lehr, 2002). Interestingly, a common trait of antidepressants is an enhancement in extracellular levels of dopamine in the frontal cortex, exerted by two basic mechanisms: (1) blockade of cortical noradrenaline transporters, which—since they greatly outnumber dopamine transporters in this region—are responsible for taking up dopamine (Millan et al., 2000b; Devoto et al., 2004a); and (2) blockade of α_2-adrenoceptors and 5-HT_{2C} receptors, which tonically inhibit mesocortical vs. subcortical dopaminergic projections (Millan et al., 2000b; Devoto et al., 2004a,b). Although antidepressants do not, in general, enhance dopamine release in nucleus accumbens, they "strengthen" dopaminergic signalling and elicit adaptive changes in mesolimbic D_2/D_3 receptors: clarification of underlying mechanisms could lead to more effective treatment of anhedonia (Vetulani and Nalepa, 2000). Surprisingly, despite the abuse potential of agents that (like psychostimulants) interact with dopamine transporters, several drugs that inhibit dopamine as well as 5-HT and noradrenaline reuptake are under development (e.g., derivatives of the antiobesity agent, sibutramine) (Bymaster et al., 2003). D_2/D_3 receptor agonists, such as pramipexole, reveal marked antidepressant actions in rodents and in humans both alone and in association with SSRIs, but clinical efficacy at well-tolerated doses remains to be proven (Corrigan et al., 2000; Vetulani and Nalepa, 2000). Dopamine D_2/D_3 receptor agonists act by stimulation of D2 sites (Millan et al., 2004a,b). An alternative approach may be D3 receptor antagonists since, in models of mood, motor function, and cognition, they exert actions opposite to dopamine D2 receptor antagonists that aggravate depressive states (Joyce, 2001). Finally, blockade of inhibitory D2 autoreceptors, which enhances dopamine levels in the nucleus accumbens and frontal cortex, may be involved in antidepressant properties of the antipsychotic, amisulpride (Cassano and Jori, 2002).

4.2.5. Multitarget agents: associating monoamine uptake with actions at postsynaptic sites

The mixed 5-HT reuptake inhibitors/5-HT_2 antagonists, trazodone and nefazodone, both present significant drawbacks (see above) and there remains considerable scope for discovery of improved agents in this class. Supporting this contention, combination of the SSRI, fluoxetine, with olanzapine, an antipsychotic with 5-$HT_{2A/2C}$ antagonist properties, synergistically reinforces corticolimbic monoaminergic transmission in rats and was more effective than fluoxetine in treatment-resistant patients (Shelton et al., 2001; Bymaster et al., 2003).

Drugs interacting with several classes of postsynaptic monoaminergic receptor may possess complementary mechanisms of antidepressant action, auxiliary anxiolytic properties and, possibly, improved tolerance relative to "selective" agents. Examples include sunepitron (a 5-HT_{1A} receptor agonist/α_2-adrenoceptor antagonist) (Rollema et al., 1996), roxindole (a 5-HT_{1A} receptor agonist/dopamine D2 receptor agonist) (Gründer et al.), and flibanserine (a mixed 5-HT_{1A} receptor agonist/5-$HT_{2A/2C}$ antagonist) (Millan et al., 1992; Borsini et al., 2002). Furthermore, it would be of interest to obtain drugs that mimic the mixed 5-HT_2/α_2-adrenoceptor antagonist profile of mirtazapine (Millan et al., 2000a,b), but lack antihistaminergic properties.

4.2.6. Multitarget agents: associating monoamine reuptake with autoreceptor blockade

Blockade of 5-HT_{1A} (cell body) or 5-HT_{1B} (terminal) autoreceptors enhances elevations in extracellular levels of 5-HT provoked by SSRIs (Millan et al., 2000b). Further, the weak 5-HT_{1A} partial agonist, pindolol, accelerates the actions of SSRIs in a subpopulation of patients (Perez et al., 2001; Blier, 2003). These findings have triggered an intensive search for drugs with cojoint 5-HT_{1A} antagonist or 5-HT_{1B} antagonist/SSRI properties, and clinical data are eagerly awaited (Mitchell et al., 2001). One criticism of this concept is that it may just be equivalent to increasing the dose of SSRI—or worse if postsynaptic 5-HT_{1A} and/or 5-HT_{1B} receptors mediate antidepressant properties of 5-HT (Naughton et al., 2000; Mayorga et al., 2001). Furthermore, it has been questioned whether clinical benefits of pindolol genuinely reflect 5-HT_{1A} autoreceptor blockade (Gobert and Millan 1999; Kinney et al., 2000; Blier, 2003). Pindolol is actually a partial agonist at 5-HT_{1A} sites, and a mixed SSRI/5-HT_{1A} partial agonist, vilazodone, displayed a promising preclinical profile but was recently abandoned (Bartoszyk et al., 1997).

An alternative approach to reinforcing actions of reuptake inhibitors—not subject to the above criticisms—is association with α_2-adrenoceptor blockade. Such agents may prove to be efficacious and rapid antidepressants since activation of α_2-adrenoceptors inhibitory to monoamine release breaks the actions of reuptake inhibitors (Millan et al., 2003; Payne et al., 2002). Moreover, α_2-adrenoceptor antagonist/5-HT noradrenaline reuptake inhibitors (Cordi et al., 2001) may improve sexual function and cognitive–attentional performance (Nutt and Pinder, 1996; Montgomery et al., 2002).

5. The role of monoamines in the actions of "nonmonoaminergic" antidepressant agents

5.1. General considerations

A fundamental question awaiting clinical resolution is whether antidepressant efficacy can be achieved by drugs that do not directly recruit monoaminergic mechanisms. If one conceives of this question as embracing mechanisms that indirectly harness monoaminergic mechanisms by actions either upstream of (afferent to) or downstream of (efferent to) monoaminergic neurones, then the answer is almost certainly yes (Fig. 5). There may also exist therapeutically relevant targets entirely independent of monoaminergic networks, although one might be less optimistic as regards their clinical fate. In any case, for all "novel" classes of antidepressants and their targets, it would appear wise to examine interactions with monoaminergic networks. For innovative agents that harness monoaminergic mechanisms, such as tachykinin neurokinin $(NK)_1$ receptor antagonists (below), their participation should not a priori be construed either as a disadvantage or as an advantage. However, the question inevitably arises as to how their clinical profiles compare to those of conventional monoaminergic antidepressants. This issue of monoaminergic involvement is also crucial to gene array and other approaches for identification of novel targets. Are potential targets affected by known classes of monoaminergic antidepressants intrinsically attractive (validated) or unattractive (just more of the same)? Perhaps such strategies should focus on proteins known to control mood states but unaffected by currently available monoaminergic antidepressants.

5.2. Brain-derived neurotrophic factor

Chronic stress and antidepressant treatment reduce and enhance the synthesis of brain-derived neurotrophic factor, respectively—actions related to their parallel suppression and induction of neurogenesis. Moreover, the progressive induction of brain-derived neurotrophic factor and the enhancement of neurogenesis may be causally related to the onset of antidepressant activity (Malberg and Duman, 2003; Manji et al., 2003; Santarelli et al., 2003). Via activation of Trk_B receptors, brain-derived neurotrophic factor displays antidepressant properties in rodents: this action is related to its stimulation of serotonergic pathways and nicely illustrates the reciprocal relationship between factors controlling cellular plasticity and monoaminergic pathways (Shirayama et al., 2002; Millan, 2003).

5.3. Ionotropic glutamate receptors

The complex pattern of mutual interactions amongst glutamatergic and monoaminergic networks plays a crucial role in the control of mood and cognition (Skolnick et al., 2001; Millan, 2003; Zarate et al., 2003), and excessive corticolimbic glutamate release upon chronic exposure to stress may contribute to the genesis of depressive states (Millan, 2003; Reagan et al., 2004). In this regard, most studies have focussed on detrimental *N*-methyl-D-aspartate receptor (NMDA)-mediated alterations in the structure of

hippocampal neurones (Skolnick et al., 2001; Manji et al., 2003) (Fig. 5). However, it is unclear whether interference with such processes is involved in rapid antidepressant actions of NMDA receptor antagonists in rodents, exerted both alone and in synergy with SSRIs (Skolnick et al., 2001; Rogoz et al., 2002; Padovan and Guimaraes, 2004). Rather, they may involve the disinhibition of corticolimbic monoaminergic pathways (Millan et al., 2000b). Both these neurochemical effects and antidepressant actions in behavioural models are more pronounced for open channel blockers (such as ketamine) than recognition site antagonists, consistent with a causal relationship. Similarly, antidepressant actions of ketamine in man (Berman et al., 2000) may involve monoaminergic mechanisms. (Propsychotic properties of ketamine should, not, however, be neglected.)

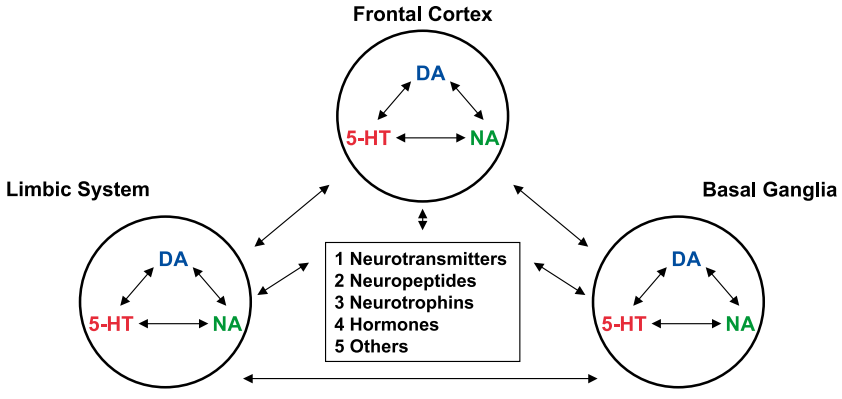
Stimulation of ionotropic α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) sites by allosteric modulators ("AMPAkines") elicits antidepressant effects, alone and in synergy with SSRIs (Grove et al., 2000; Li et al., 2003). AMPAkines also induce brain-derived neurotrophic factor synthesis and neurogenesis (Mackowiak et al., 2002; Bai et al, 2003). AMPAkines do not enhance monoamine release but—supporting an interplay with serotonergic networks—AMPA receptors mediate the immediate early gene expression elicited by 5-HT release, while 5-HT promotes AMPA receptor phosphorylation (Svenningsson et al., 2002; Pei et al., 2004).

5.4. NK_1, NK_2, and NK_3 receptor antagonists

Both tachykinin NK_1 receptor antagonists and NK_1 receptor knockout mice display reduced stress sensitivity, anxiolytic- and antidepressant-like profiles, and enhanced brain-derived neurotrophic factor synthesis (Maubach et al., 1999; Rupniak, 2002; van der Hart et al., 2002; Millan, 2003; Morcuende et al., 2003). Further, in a high-profile article documenting the effectiveness of aprepitant 2(*R*)-[1(*R*)-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3(*S*)-(4-fluorophenyl)-4-morpholinyl)methyl]-2,4-dihydro3*H*-1,2,4-tria-zol-3-one] (MK869) in major depression, it was proclaimed that tachykinin NK_1 receptor antagonists offer an entirely original mechanism of antidepressant activity independent of monoamines (see Maubach et al., 1999). However, it is now known that tachykinin NK_1 receptor antagonists: (1) activate adrenergic and dopaminergic pathways innervating the hippocampus and frontal cortex; and (2) upon long-term administration, potentiate serotonergic transmission (Millan et al., 2001b; Lejeune et al., 2002; Millan, 2003). Perhaps as a consequence of these indirect monoaminergic effects, the efficacy and delay to action of tachykinin NK_1 receptor antagonists do not differ markedly from monoamine reuptake inhibitors—although the significance of their lesser impact upon sexual function should not be underestimated (Maubach et al., 1999). The clinical fate of tachykinin NK_1 receptor antagonists is unclear. There is also interest in NK_2 and NK_3 receptor antagonists as potential antidepressants, and both NK_2 and NK_3 receptors display a complex pattern of interactions with monoaminergic pathways (Raffa, 1998; Panocka et al., 2001; Steinberg et al., 2001; Léger et al., 2002; Millan 2003).

5.5. Corticotropin-releasing factor (CRF) and glucorticoid receptor antagonists

While mice overexpressing CRF elicit enhanced stress sensitivity, depression, and anxiety, mice genetically



1	Glutamate	AMPAkines	Phase I/II
2	Substance P	NK_1 Antags	Phase II/III
	CRF	CRF_1 Antags	Phase I
3	BDNF	Modulators	Preclinical
4	Melatonin	MT_1/MT_2 Ago	Phase II/III
5	$Sigma_1$	« Antagonists »	Phase II

Fig. 5. Many other mediators interact with monoamines in the expression of their influence upon mood and depressive states. Several examples are given: *N*-methyl-D-aspartate (NMDA), brain-derived neurotrophic factor (BDNF); corticotrophin-releasing factor (CRF), and neurokinin (NK).

deprived of CRF_1 receptors (and CRF_1 receptor antagonists) display an opposite antidepressant- and anxiolytic-like profile in models with a high stress quotient (Reul and Holsboer, 2002; Millan, 2003). In a small, open-label trial, depressive symptoms were moderated by the selective CRF_1 receptor antagonist, 3-[6-(dimethylamino)-4-methyl-pyrid-3-yl]-2,5-dimethyl-*N*,*N*-dipropyl-pyrazolo[2,3-a]pyrimidin-7-amine (R121919) (Zobel et al., 2000). Notably, CRF_1 receptor antagonists indirectly enhance the activity of serotonergic pathways (Reul and Holsboer, 2002; Millan, 2003) although they do not, in contrast to tachykinin NK_1 receptor antagonists, activate dopaminergic input to the cortex and may inhibit the activity of adrenergic neurones (Millan et al., 2001a,b; Lejeune et al., 2002). It will be interesting to see how the differential interactions of CRF_1 receptor antagonists vs. tachykinin NK_1 receptor antagonists with monoaminergic pathways are translated into (contrasting?) clinical actions. CRF_2 receptors likewise modulate the activity of serotonergic neurones under conditions of stress, but studies with antagonists, antisense probes, and genetically modified mice have yielded a conflicting picture of their relevance to mood and depressive states (Hammack et al., 2003; Millan, 2003).

It is unclear as to what extent antidepressant actions of CRF_1 receptor antagonists involve suppression of excessive and persistent corticosteroid release in response to chronic stress. In any case, high levels of glucocorticoids are generally associated with a negative influence upon mood, as well as deleterious structural changes in the hippocampus, perhaps via reduced brain-derived neurotrophic factor synthesis, excessive glutamate release, and/or reduced neuronal glucose uptake (Manji et al., 2003). In line with these findings, there are reports of antidepressant actions of glucocorticoid synthesis inhibitors and antagonists (Belanoff et al., 2001; Reus and Wolkowitz, 2001; Hoyberg et al., 2002). Cerebral glucocorticoid receptors exert a complex pattern of reciprocal interactions with monoamines, suggesting an involvement of monoaminergic mechanisms in the influence of glucocorticoids upon mood and depressive states (Gold and Chrousos, 2002, Millan, 2003).

5.6. σ_1 Ligands

Owing to difficulties in detecting a genuine receptor and the absence of an endogenous ligand, σ_1 sites have long been the "pariah" of central nervous system pharmacology. In fact, neurosteroids interact with σ_1 sites that (in the endoplasmic reticulum) control intracellular levels of Ca^{2+}: this action may be related to their antidepressant properties (Maurice et al., 2001; Urani et al., 2002; Millan, 2003). Nevertheless, questions remain concerning the role of σ_1 sites as compared to direct actions at monoaminergic receptors in antidepressant properties of several "selective" σ_1 ligands under clinical development (Tottori et al., 2001; Millan, 2003).

6. Mixed monoaminergic/nonmonoaminergic agents

One attractive multitarget strategy is to "build into" a monoaminergic profile associated with antidepressant properties, complementary actions affording improved tolerance, enhanced efficacy, and/or broader therapeutic range. This would be analogous to the reduced extrapyramidal impact and greater therapeutic efficacy of antipsychotic agents possessing serotonergic—in addition to D2 antagonist—properties. Several examples may be given. First, the fusion of tachykinin NK_1 antagonist and 5-HT reuptake-inhibiting properties may yield agents that synergistically restore monoaminergic transmission and rapidly express antidepressant (and anxiolytic) actions (Millan, 2003; Guiard et al., 2004). Drugs displaying such dual activity have been described (Ryckmans et al., 2002). Second, the association of NMDA antagonist and 5-HT reuptake-inhibiting properties has been shown to additively elicit antidepressant actions in rodents, suggesting the possibility of their combination into a single agent (Rogoz et al., 2002). Third, inhibitors of phosphodiesterases would potentiate antidepressant effects of drugs acting via the cAMP-triggered recruitment of cAMP-responsive element binding and brain-derived neurotrophic factor (Zhang et al., 2002; O'Donnell and Zhang, 2004). Fourth, to conclude with a clinically validated concept, the novel agent, agomelatine, possesses a distinctive profile of antidepressant activity, with improved sleep quality and wake–sleep rhythmicity in the absence of sexual dysfunction. This profile reflects its unique combination of melatonin ("$MT_{1/2}$") receptor agonist and $5\text{-}HT_{2C}$ antagonist properties (Lôo et al., 2002; Millan et al., 2003, 2004a). Many other permutations could be forwarded. Arguably, the most appropriate vehicle for clinical exploitation of the modulatory role of many novel nonmonoaminergic targets in the treatment of depression may be incorporation into such rationally designed multitarget agents (Bymaster et al., 2003; Wong and Licinio, 2004).

7. Conclusions

Monoaminergic pathways fulfil a crucial role in the control of mood, motor behaviour, endocrine secretion, cognition, and chronobiotic rhythms—functions profoundly disturbed in depressive states. Further, there is substantial evidence that a disruption of monoaminergic transmission contributes to depressive disorders and, at least for the next decade, antidepressants that reinforce the activity of monoaminergic networks are likely to remain the cornerstone of drug treatment for depression. However, they exploit but a subset of potential targets and there remains considerable scope for the creative exploitation of monoaminergic mechanisms in the improved treatment of depressive states. It would, therefore, be foolhardy to abandon monoaminergic targets in favour of nonmonoaminergic (and clinically nonvalidated) targets in the search for better antidepressant

agents. Although many concepts are under evaluation, the "proof of the pudding" is always therapeutic efficacy and, as emphasized above, there is frustratingly little clinical feedback for the many promising monoaminergic hypotheses under consideration. Inextricably linked with the issue of "monoaminergic or nonmonoaminergic" is the question of "selective" or (to quote a recent review advocating multireceptorial antipsychotics) "selectively nonselective" drugs (Roth et al., 2004). Rather than obsessively seeking highly selective agents, a more appropriate strategy for this multifactorial disorder may be development of drugs at a chosen constellation of receptors. This axiom applies equally to monoaminergic and nonmonoaminergic approaches, while drugs possessing a mixed mechanism of action hold particular therapeutic promise. Irrespective of the mechanism of drug action, whether monoaminergic and/or nonmonoaminergic, selective or multitarget, genome-derived or other, success will ultimately depend upon rigorous experimental evaluation of hypotheses, thorough preclinical characterisation of drugs, and, imaginative, target-adapted, and well-controlled clinical trials.

Acknowledgements

T. Sharp is thanked for helpful comments, M. Soubeyran for secretarial assistance, and J.-M. Rivet for graphics.

References

Anderson, I.M., 2000. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J. Affect. Disord. 58, 19–36.

Andreoli, V., Caillard, V., Deo, R.S., Rybakowski, J.K., Versiani, M., 2002. Reboxetine, a new noradrenaline selective antidepressant, is at least as effective as fluoxetine in the treatment of depression. J. Clin. Psychiatry 22, 393–399.

Ascher, J.A., Cole, J.O., Colin, J.N., Feighner, J.P., Ferris, R.M., Fibiger, H.C., Golden, R.N., Martin, P., Potter, W.Z., Richelson, E., 1995. Bupropion: a review of its mechanism of antidepressant activity. J. Clin. Psychiatry 56, 395–401.

Bai, F., Bergeron, M., Nelson, D.L., 2003. Chronic α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid receptor potentiator (LY451646) increases cell proliferation in adult rat hippocampus. Neuropharmacology 44, 1013–1121.

Bartoszyk, G.D., Hegenbart, R., Ziegler, H., 1997. EMD 68843, a serotonin reuptake inhibitor with presynaptic 5-HT_{1A} receptor agonistic properties. Eur. J. Pharmacol. 464, 127–133.

Belanoff, J.K., Flores, B.H., Kalezhan, M., Sund, B., Schatzberg, A.F., 2001. Rapid reversal of psychotic depression using mifepristone. J. Clin. Psychopharmacol. 21, 516–521.

Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depression. Biol. Psychiatry 47, 351–354.

Blendy, J.A., Grimm, L.J., Perry, D.C., West-Jonsrud, L., Kellar, K.J., 1990. Electroconvulsive shock differentially increases binding to α_1 adrenergic receptor subtypes in discrete regions of rat brain. J. Neurosci. 10, 2580–2586.

Blier, P., 2003. The pharmacology of putative early-onset antidepressant strategies. Eur. NeuroPsychopharmacol. 13, 57–66.

Borsini, F., Evans, K., Jason, K., Rohde, F., Alexander, B., Pollentier, S., 2002. Pharmacology of flibanserin. CNS Drug Rev. 8, 117.

Bymaster, F.P., McNamara, R.K., Tran, P.V., 2003. New approaches to developing antidepressants by enhancing monoaminergic transmission. Expert Opin. Investig. Drugs 12, 531–543.

Cassano, G.B., Jori, M.C., 2002. Efficacy and safety of amisulpride 50 mg versus paroxetine 20 mg in major depression: a randomized, double-blind, parallel group study. Int. Clin. Psychopharmacol. 17, 27–32.

Cordi, A.A., Berque-Bestel, I., Persigand, T., Lacoste, J.-M., Newman-Tancredi, A., Audinot, V., Millan, M.J., 2001. Potential antidepressants displayed combined alpha$_{(2)}$-adrenoceptor antagonist and monoamine uptake inhibitor properties. J. Med. Chem. 44, 787–805.

Corrigan, M.H., Denahan, A.Q., Wright, C.E., Ragual, R.J., Evans, D.L., 2000. Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress. Anxiety 11, 58–65.

Crissman, A.M., O'Donnell, J.M., 2002. Effects of antidepressants in rats trained to discriminative centrally administered isoproterenol. J. Pharmacol. Exp. Ther. 302, 606–611.

Cryan, J.F., Markou, A., Lucki, I., 2002. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol. Sci. 23, 238–245.

Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am. J. Psychiatry 160, 64–75.

Davis, R., Whittington, R., Bryson, H.M., 1997. Nefazodone. A review of its pharmacology and clinical efficacy in the management of major depression. Drugs 53, 608–636.

Delgado, P.L., 2000. Depression: the case for monoamine deficiency. J. Clin. Psychiatry 61, 7–11.

Devoto, P., Flore, G., Pira, L., Longu, G., Gessa, G.L., 2004a. Alpha$_2$-adrenoceptor mediated co-release of dopamine and noradrenaline from noradrenergic neurons in the cerebral cortex. J. Neurochem. 88, 1003–1009.

Devoto, P., Flore, G., Pira, L., Longu, G., Gessa, G.L., 2004b. Mirtazapine-induced co-release of dopamine and noradrenaline from noradrenergic neurons in the medial prefrontal and occipital cortex. Eur. J. Pharmacol. 487, 105–1110.

Di Matteo, V., Esposito, E., 2003. Serotonin control of dopaminergic neurotransmission: focus on 5-HT_2 receptors. Curr. Neuropharmacol. 1, 153–164.

Donati, R.J., Rasenick, M.M., 2003. G-protein signalling and the molecular basis of antidepressant action. Life Sci. 73, 1–17.

Flügge, G., Van Kampen, M., Meyer, H., Fuchs, E., 2003. α_{2A} and α_{2C}-adrenoceptor regulation in the brain: α_{2A} changes persist after chronic stress. Eur. J. Neurosci. 17, 917–928.

Gobert, A., Millan, M.J., 1999. Modulation of dialysate levels of dopamine, noradrenaline, and 5-HT in frontal cortex of freely-moving rats by (−)-pindolol alone and in association with 5-HT reuptake inhibitors: comparative roles of β-adrenergic, 5-HT_{1A}, and 5-HT_{1B} receptors. Neuropsychopharmacology 21, 268–284.

Gold, P.W., Chrousos, G.P., 2002. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs. low CRH/NE states. Mol. Psychiatry 7, 254–275.

Greenberg, P.E., Kessler, R.C., Birnbaum, H.G., Leong, S.A., Lowe, S.W., Berglund, P.A., Corey-Lisle, P.K., 2003. The economic burden of depression in the United States: how did it change between 1990 and 2000? J. Clin. Psychiatry 64, 1465–1475.

Grove, S.J.A., Rogers, G.A., Zhang, M.Q., 2000. Positive modulators of the α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid receptor. Expert Opin. Ther. Pat. 10, 1539–1548.

Gründer, G., Wetzel, H., Hammes, E., Benkert, O., Roxindole, a dopamine autoreceptor agonist, in the treatment of major depression. Psychopharmacology. 111, 123–126.

Guiard, B.P., Przybylski, C., Guilloux, J.-P., Seif, I., Froger, N., De Felipe, C., Hunt, S.P., Lanfumey, L., Gardier, A.M., 2004. Blockade of substance P (neurokinin$_1$) receptors enhances extracellular serotonin

when combined with a selective serotonin reuptake inhibitor: an in vivo microdialysis study in mice. J. Neurochem. 89, 54–63.

Hammack, S.E., Schmid, M.J., LoPresti, M., Der-Avakian, A., Pellymounter, M.A., Foster, A.C., Watkins, L.R., Maier, S.F., 2003. Corticotropin releasing hormone type 2 receptors in dorsal raphe nucleus mediate the behavioural consequences of stress. J. Neurosci. 23, 1019–1025.

Hoyberg, O.J., Wik, G., Mehtonen, O.P., Peeters, B.W.M.M., Sennef, C., 2002. Org 34517, a selective glucocortical receptor antagonist with potent antidepressant activity. First clinical results. Int. J. Neuropsychopharmacol. 5, p. 3.E.044.

Hong, C.-J., Tsai, S.-J., 2003. Genomic approaches to depression. Curr. Pharmacogen. 1, 67–74.

Hudzik, T.J., Yanek, M., Porrey, T., Evenden, J., Paronis, C., Mastrangelo, M., Ryan, C., Ross, S., Stenfors, S., 2003. Behavioral pharmacology of AR-A000002, a novel, selective 5-hydroxytryptamine(1_B) antagonist. J. Pharmacol. Exp. Ther. 304, 1072.

Jacobs, B.L., Praag, H., Gage, F.H., 2000. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol. Psychiatry 5, 262–269.

Joyce, J.N., 2001. Dopamine D_3 receptors as a therapeutic target for antipsychotic and antiparkinsonian drugs. Pharmacol. Ther. 90, 231–259.

Kasper, S., 1995. Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. Int. Clin. Psychopharmacol. 10, 25–35.

Kinney, G.G., Taber, M.T., Gribkoff, V.K., 2000. The augmentation hypothesis for improvement of antidepressant therapy. Mol. Neurobiol. 21, 137–154.

Kitayama, S., Dohi, T., 2003. Norepinephrine transporter splice variants and their interaction with substrates and blockers. Eur. J. Pharmacol. 479, 65–70.

Léger, L., Gay, N., Cespuglio, R., 2002. Neurokinin NK_1- and NK_3-immunoreactive neurones in serotonergic cell groups in the rat brain. Neurosci. Lett. 323, 146–150.

Lehr, E., 2002. Potential antidepressant properties of pramipexole detected in locomotor and operant behavioural investigation in mice. Psychopharmacology 163, 495–500.

Lejeune, F., Gobert, A., Millan, M.J., 2002. The selective neurokinin $(NK)_1$ antagonist, GR205,171, stereospecifically enhances mesocortical dopaminergic transmission in the rat: a combined dialysis and electrophysiological study. Brain Res. 935, 134–139.

Lerer, B., Macciardi, F., 2002. Pharmacogenetics of antidepressant and mood-stabilizing drugs: a review of candidate-gene studies and future research directions. Int. J. Neuropsychopharmacol. 8, 255–275.

Leysen, J.E., 2004. 5-HT_2 receptors. Curr. Drug Targets 3, 11–26.

Li, X., Witkin, J.M., Need, A.B., Skolnick, P., 2003. Enhancement of antidepressant potency by a potentiator of α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid receptors. Cell. Mol. Neurobiol. 23, 419–430.

Lôo, H., Hale, A., D'haenen, H., 2002. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder. A placebo controlled dose range study. Int. Clin. Psychopharmacol. 17, 239–247.

Lucki, I., Singh, A., Kreiss, D.S., 1994. Antidepressant-like behavioral effects of serotonin receptor agonists. Neurosci. Biobehav. Rev. 18, 85–95.

Mackowiak, M., O'Neill, M., Hicks, M., Bleakman, D., Skolnick, P., 2002. An α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid receptor potentiator modulates hippocampal expression of brain-derived neurotrophic factor. Neuropharmacology 43, 1–10.

Malberg, J.E., Duman, R.S., 2003. Cell proliferation in adult hippocampus is decreased by inescapable stress: reversal by fluoxetine treatment. Neuropsychopharmacology 28, 1562–1571.

Manji, H.K., Quiroz, J.A., Sporn, J., Payne, J.L., Denicoff, K., Gray, N.A., Zarate, C.A., Charney, D.S., 2003. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol. Psychiatry 53, 707–742.

Maubach, K.A., Rupniak, N.M.J., Kramer, M.S., Hill, R.G., 1999. Novel strategies for pharmacotherapy of depression. Curr. Opin. Chem. Biol. 3, 481–488.

Maurice, T., Urani, A., Phan, V.-L., Romieu, P., 2001. The interaction between neuroactive steroids and the $sigma_1$ receptors: function, behavioral consequences and therapeutic opportunities. Brain Res. Rev. 37, 116–132.

Mayorga, A.J., Dalvi, A., Page, M.E., Zimov-Levinson, S., Hen, R., Lucki, I., 2001. Antidepressant-like behavioral effects in 5-hydroxytryptamine$_{1A}$ and 5-hydroxytryptamine$_{1B}$ receptor mutant mice. J. Pharmacol. Exp. Ther. 298, 1101–1107.

McEwen, B.S., 2000. Effects of adverse experiences for brain structure and function. Biol. Psychiatry 48, 721–731.

Millan, M.J., 2003. The neurobiology and control of anxious states. Prog. Neurobiol. 70, 83–244.

Millan, M.J., Canton, H., Lavielle, G., 1992. Targeting multiple serotonin receptors: 5-HT_{1A} agonists/5-$HT_{1C/2}$ antagonists as therapeutic agents. Drug News Perspect. 5, 397–406.

Millan, M.J., Gobert, A., Rivet, J.-M., Adhumeau-Auclair, A., Cussac, D., Newman-Tancredi, A., Dekeyne, A., Nicolas, J.-P., Lejeune, F., 2000a. Mirtazapine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of α_2 and 5-HT_{2C} receptors: a comparison with citalopram. Eur. J. Neurosci. 12, 1079–1095.

Millan, M.J., Lejeune, F., Gobert, A., 2000b. Reciprocal autoreceptor and heteroceptor control of serotonergic, dopaminergic and adrenergic transmission in frontal cortex: a review, and relevance to the actions of antidepressant agents. J. Psychopharmacol. 14, 114–138.

Millan, M.J., Gobert, A., Lejeune, F., Newman-Tancredi, A., Rivet, J.-M., Auclair, A., Peglion, J.-L., 2001a. S33005, a novel ligand at both serotonin and norepinephrine transporters: I. Receptor binding, electrophysiological, and neurochemical profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine. J. Pharmacol. Exp. Ther. 298, 565–580.

Millan, M.J., Lejeune, F., De Nanteuil, G., Gobert, A., 2001b. Selective blockade of neurokinin $(NK)_1$ receptors facilitates the activity of adrenergic pathways projecting to frontal cortex and dorsal hippocampus in rats. J. Neurochem. 76, 1949–1954.

Millan, M.J., Gobert, A., Lejeune, F., Dekeyne, A., Newman-Tancredi, A., Pasteau, V., Rivet, J.-M., Cussac, D., 2003. The novel melatonin agonist, agomelatine (S20098), is an antagonist at 5-hydroxytryptamine$_{2C}$ receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. J. Pharmacol. Exp. Ther. 306, 954–964.

Millan, M.J., Brocco, M., Gobert, A., Dekeyne, A., 2004a. Anxiolytic properties of agomelatine, and antidepressant with melatoninergic and serotonergic properties: role of 5-HT_{2C} receptor blockade. Psychopharmacology (in press).

Millan, M.J., Brocco, M., Papp, M., Serres, F., Drieu la Rochelle, C., Sharp, T., Peglion, J.-P., Dekeyne, A., 2004b. S32504, a novel naphtoxazine agonist at dopamine D_3/D_2 receptors: III. Actions in models of potential antidepressive and anxiolytic activity in comparison to ropinirole. J. Pharmacol. Exp. Ther. 309, 162–175.

Mitchell, S.N., Greenslade, R.G., Cooper, J., 2001. LY393558, a 5-hydroxytryptamine reuptake inhibitor and 5-HT($_{1B}$/$_{1D}$) receptor antagonist: effects on extracellular levels of 5-hydroxytryptamine in the guinea pig and rat. Eur. J. Pharmacol. 432, 19–27.

Montgomery, S.A., Baldwin, D.S., Riley, A., 2002. Antidepressant medications: a review of the evidence for drug-induced sexual dysfunction. J. Affect. Disord. 69, 119–140.

Morcuende, S., Gadd, C.A., Peters, M., Moss, A., Harris, E.A., Sheasby, A., Fisher, A.S., De Felipe, C., Mantyh, P.W., Rupniak, N.M.J., Glese, K.P., Hunt, S.P., 2003. Increased neurogenesis and BDNF in neurokinin$_{-1}$ receptor gene knockout mice. Eur. J. Neurosci. 18, 1828–1836.

Nalepa, I., Kreiner, G., Kowalska, M., Sanak, M., Zelek-Molik, A., Vetulani, J., 2002. Repeated imipramine and electroconvulsive shock

increase α_{1A}-adrenoceptor mRNA level in rat prefrontal cortex. Eur. J. Pharmacol. 444, 151–159.

Naranjo, C.A., Tremblay, L.K., Busto, U.E., 2001. The role of the brain reward system in depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25, 781–823.

Naughton, M., Mulrooney, J.B., Leonard, B.E., 2000. A review of the role of serotonin receptors in psychiatric disorders. Hum. Psychopharm. Clin. Exp. 15, 397–415.

Nelson, D.L., 2004. 5-HT_5 receptors. Curr. Drug Targets 3, 53–58.

Newton, S.S., Thome, J., Wallace, T.L., Shirayama, Y., Schlesinger, L., Sakai, N., Chen, J., Neve, R., Nestler, E.J., Duman, R.S., 2002. Inhibition of cAMP or dynorphin in the nucleus accumbens produces an antidepressant-like effect. J. Neurosci. 24, 10883–10890.

Nguyen, P.V., Woo, N.H., 2003. Regulation of hippocampal synaptic plasticity by cyclic AMP-dependent protein kinases. Prog. Neurobiol. 71, 401–437.

Nutt, D.J., Pinder, R.M., 1996. α_2-Adrenoceptors and depression. J. Psychopharmacol. 10, 35–42.

O'Donnell, J.M., Zhang, H.-T., 2004. Antidepressant effects of inhibitors of cAMP phosphodiesterase (PDE4). Trends Pharmacol. Sci. 25, 158–163.

Ordway, G.A., Schenk, J., Stockmeier, C.A., May, W., Klimek, V., 2003. Elevated agonist binding to α_2-adrenoceptors in locus coeruleus in depression. Biol. Psychiatry 53, 315–323.

Pacher, P., Kohegyi, E., Kecskemeti, V., Furst, S., 2001. Current trends in the development of new antidepressants. Curr. Med. Chem. 8, 89–100.

Padovan, C.M., Guimaraes, F.S., 2004. Antidepressant-like effects of NMDA receptor antagonists injected into the dorsal hippocampus of rats. Pharmacol. Biochem. Behav. 77, 15–19.

Panocka, I., Massi, M., Lapo, I., Swiderski, T., Kowalczyk, M., Sadowski, B., 2001. Antidepressant-type effect of the NK_3 tachykinin receptor agonist aminosenktide in mouse lines differing in endogenous opioid system activity. Peptides 22, 1037–1042.

Payne, J.L., Quiroz, J.A., Zarate, C.A., Manji, H.K., 2002. Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? Biol. Psychiatry 52, 921–926.

Pei, Q., Zetterström, T.S.C., Sprakes, M., Tordera, R., Sharp, T., 2003. Antidepressant drug treatment induces *Arc* gene expression in the rat brain. Neuroscience 121, 975–982.

Pei, Q., Tordera, R., Sprakes, M., Sharp, T., 2004. Glutamate receptor activation is involved in 5-HT_2 agonist-induced *Arc* gene expression in the rat cortex. Neuropharmacology 46, 331–339.

Perez, V., Puigdemont, D., Gilaberte, I., Alvarez, E., Artigas, F., 2001. Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors. J. Clin. Psychopharmacol. 21, 36–45.

Raffa, R.B., 1998. Possible roles of neurokinins in central nervous system development and neurodegenerative or other disorders. Neurosci. Biobehav. Rev. 22, 789–813.

Reagan, L.P., Rosell, D.R., Wood, G.E., Spedding, M., Munoz, C., Rothstein, J., McEwen, B.S., 2004. Chronic restraint stress up-regulates GLT-1 mRNA and protein expression in the rat hippocampus: reversal by tianeptine. PNAS 101, 2179–2184.

Reul, J.M., Holsboer, F., 2002. Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. Curr. Opin. Pharmacol. 2, 23–33.

Reus, V.I., Wolkowitz, O.M., 2001. Antiglucocorticoid drugs in the treatment of depression. Exp. Opin. Invest. 10, 1789–1796.

Rogoz, Z., Skuza, G., Maj, J., Danysz, W., 2002. Synergistic effect of uncompetitive *N*-methyl-D-aspartate receptor antagonists and antidepressant drugs in the forced swimming test in rats. Neuropharmacology 42, 1024–1030.

Rollema, H., Clarke, T., Lu, Y., Schmidt, A., Sprouse, J., 1996. Comparison of the effects of CP-93,393 and buspirone on 5-HAT and NE release: microdialysis studies in the hippocampus of freely moving rats and guinea pigs. J. Neurochem. 66, S37.

Roth, B.L., Sheffler, D.J., Kroeze, W.K., 2004. Magic shotguns vs. magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nat. Rev., Drug Discov. 3, 353–359.

Rupniak, N.M.J., 2002. Elucidating the antidepressant actions of substance P (NK_1 receptor) antagonists. Curr. Opin. Investig. Drugs 3, 257–261.

Ryckmans, T., Berton, O., Grimée, R., Kogej, T., Lamberty, Y., Pasau, P., Talaga, P., Genicot, C., 2002. Dual NK_1 antagonists–serotonin reuptake inhibitors as antidepressants. SAR and activity of benzyloxyphenthyl$_1$ piperazine derivatives. Bioorg. Med. Chem. Lett. 12, 3195–3198.

Sallinen, J., Haapalinna, A., MacDonald, E., Viitamaa, T., Lähdesmäki, J., Rybnikova, E., Pelto-Huikko, M., Kobilka, B.K., Scheinin, M., 1998. Genetic alteration of the α_2-adrenoceptor subtype C in mice affects the development of behavioral despair and stress-induced increases in plasma corticosterone levels. Mol. Psychiatry 4, 443–452.

Sanchez, C., Hyttel, J., 1999. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell. Mol. Neurobiol. 19, 467–489.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O., Belzung, C., Hen, R., 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301, 805–809.

Schatzberg, A.F., 2002. Pharmacological principles of antidepressant efficacy. Hum. Psychopharmacol. 17, S17–S22.

Schmitt, P., Reny-Palasse, V., Bourde, O., Garcia, C., Pujol, J.F., 1993. Further characterization of the long-term effect of RU24722 on tyrosine hydroxylase in the rat locus coeruleus. J. Neurochem. 61, 1423–1429.

Schramm, N.L., McDonald, M.P., Limbird, L.E., 2001. The α_{2A}-adrenergic receptor plays a protective role in mouse models of depression and anxiety. J. Neurosci. 21, 4875–4882.

Shelton, R.C., Tollefson, G.D., Tohen, M., Stahl, S., Gannon, K.S., Jacobs, T.G., Buras, W.R., Bymaster, F.P., Zhang, W., Spencer, K.A., Feldman, P.D., Meltzer, H.Y., 2001. A novel augmentation strategy for treating resistant major depression. Am. J. Psychiatry 158, 131–134.

Shirayama, Y., Chen, A.C.-H., Nakagawa, S., Russell, D.S., Duman, R.S., 2002. BDNF produces antidepressant effects in behavioural models of depression. J. Neurosci. 22, 3251–3261.

Shorter, E., Tyrer, P., 2003. Separation of anxiety and depressive disorders: blind alley in psychopharmacology and classification of disease. Br. Med. J. 327, 158–160.

Skolnick, P., Legutko, B., Li, X., Bymaster, F.P., 2001. Current perspectives on the development of non-biogenic amine-based antidepressants. Pharmacol. Res. 43, 411–443.

Sorbera, L.A., Leeson, P., Castaner, J., 1999. Robalzotan tartrate hydrate. Drugs Future 24, 740.

Steinberg, R., Alonso, R., Griebel, G., Bert, L., Jung, M., Oury-Donat, F., Poncelet, M., Gueudet, C., Desvignes, C., Le Fur, G., Soubrié, P., 2001. Selective blockade of neurokinin-$_2$ receptors produces antidepressant-like effects associated with reduced corticotropin-releasing factor function. J. Pharmacol. Exp. Ther. 299, 449–458.

Stone, E.A., Lin, Y., Rosengarten, H., Kenneth Kramer, H., Quartermain, D., 2003. Emerging evidence for a central epinephrine-innervated α_1-adrenergic system that regulates behavioral activation and is impaired in depression. Neuropsychopharmacology 28, 1387–1399.

Svenningsson, P., Tzavara, E.T., Witkin, J., Fienberg, A.A., Nomikos, G.G., Greengard, P., 2002. Involvement of striatal and extrastriatal DARPP-32 in biochemical and behavioral effects of fluoxetine (Prozac). Proc. Natl. Acad. Sci. 99, 3182–3187.

Tamminga, C.A., Nemeroff, C.B., Blakely, R.D., Brady, L., Carter, C.S., Davis, K.L., Dingledine, R., Gorman, J.M., Grigoriadis, D.E., Henderson, D.C., Innis, R.B., Killen, J., Laughren, T.P., McDonald, W.M., Murphy, G.M., Paul, S.M., Rudorfer, M.V., Sausville, E., Schatzberg, A.F., Scolnick, E.M., Suppes, T., 2002. Developing novel treatments for mood disorders: accelerating discovery. Biol. Psychiatry 52, 589–609.

Thomas, D.R., Hagan, J.J., 2004. 5-HT_7 receptors. Curr. Drug Targets 3, 81–90.

Torres, G.E., Gainetdinov, R.R., Caron, M.G., 2003. Plasma membrane monoamine transporters: structure, regulation and function. Nat. Rev., Neurosci. 4, 13–25.

Tottori, K., Miwa, T., Uwahodo, Y., Yamada, S., Nakai, M., Oshiro, Y., Kikuchi, T., Altar, C.A., 2001. Antidepressant-like responses to the combined sigma and 5-HT_{1A} receptor agonist OPC-14523. Neuropharmacology 41, 976–988.

Urani, A., Romieu, P., Portales-Casamar, E., Roman, F.J., Maurice, T., 2002. The antidepressant-like effect induced by the $sigma_1$ receptor agonist igmesine involves modulation of intracellular calcium mobilization. Psychopharmacology 163, 26–35.

Van der Hart, M.G.C., Czéh, B., De Biurrun, G., Michaelis, T., Watanabe, T., Natt, O., Frahm, J., Fuchs, E., 2002. Substance P antagonist and clomipramine prevent stress-induced alterations in cerebral metabolites, cytogenesis and hippocampal volume. Mol. Psychiatry 7, 933–941.

Vetulani, J., Nalepa, I., 2000. Antidepressants: past, present and future. Eur. J. Pharmacol. 405, 351–363.

Vida, S., Cooper, K., 1999. Precision and comparability of adverse event rates of newer antidepressants. J. Clin. Psychopharmacol. 19, 416–426.

Walker, D.J., Peter, J.U., Bashammakh, S., Hortnagl, H., Voits, M., Fink, H., Bader, M., 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science 299, 76–78.

Wong, M.-L., Licinio, J., 2004. From monoamines to genomic targets: a paradigm shift for drug discovery in depression. Nat. Rev., Neurosci. 3, 136–151.

Woolley, M.L., Marsden, C.A., Fone, K.C.F., 2004. 5-HT_6 receptors. Curr. Drug Targets 3, 59–79.

Ybema, C., 2003. Lack of anti-depressant efficacy of the selective 5-HT_{1A} receptor antagonist NAD-299. Results from an 8 week placebo and paroxetine-controlled study. Eur. Neuropsychopharmacol. 13, S189.

Zajecka, J.M., 2003. Treating depression to remission. J. Clin. Psychiatry 64, 7–12.

Zarate, C., Quiroz, J., Payne, J., Manji, H., 2003. Modulators of the glutamatergic system: implications for the development of improved therapeutics in mood disorders. Psychopharmacol. Bull. 36, 35–83.

Zhang, H.-T., Huang, Y., Jin, S.L.C., Frith, S.A., Neesha Suvarna, M.S., Conti, M., O'Donnell, J.M., 2002. Antidepressant-like profile and reduced sensitivity to Rolipram in mice deficient in the PDE4D phosphodiesterase enzyme. Neuropsychopharmacology 27, 587–595.

Zhang, H.-T., Huang, Y., O'Donnell, J.M., 2003. Antagonism of the antidepressant-like effects of clenbuterol by central administration of β-adrenergic antagonists in rats. Psychopharmacology 170, 102–107.

Zobel, A.W., Nickel, T., Künzel, H.E., Ackl, N., Sonntag, A., Ising, M., Holsboer, F., 2000. Effects of the high-affinity corticotropin-releasing hormone $receptor_1$ antagonist, R121919, in major depression: the first 20 patients treated. J. Psychiat. Res. 34, 181–717.