Strategies for producing faster acting antidepressants

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Existing antidepressant treatments exhibit limited efficacy and a slow onset of action. Several neurobiological adaptive mechanisms might delay the clinical effects of antidepressants, whose therapeutic action is primarily triggered by an increase of serotonergic and noradrenergic neurotransmission. Here, we review several potential mechanisms that could be useful to increase the speed of current antidepressant drugs, such as additional blockade of aminergic autoreceptors or antagonism of certain postsynaptic (5-HT_{2A}, 5-HT_{2C}) receptors. The potential use of strategies not based on monoaminergic transmission, such as CRF and NK_1 receptor antagonists, or more novel strategies, based on glutamatergic or GABAergic transmission or on intracellular messengers, are also reviewed.

Regardless of chemical structure, pharmacokinetic properties and molecular or cellular target in the brain, all antidepressant drugs need to be administered for weeks to produce a significant clinical improvement (e.g. 50% reduction of severity). This lag is considered to be necessary for certain brain adaptive processes to occur, which are the neurobiological substrate of the clinical improvement [1–4]. Indeed, a crucial question in attempting to develop faster-acting antidepressant drugs is whether such an action is feasible; in other words, whether the clinical latency is representative of a neurobiological limitation or if it simply reflects the limitations of current standard treatments. Indeed, there is evidence that some antidepressant drugs, such as the tricyclic drug clomipramine, might have a greater efficacy/speed than the selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (SSRIs), at least in depressed inpatients [5–7]. Also, some non-standard treatments, such as sleep deprivation or electroconvulsive therapy (ECT), exert their effects more rapidly than drugs that block the reuptake of 5-HT and/or noradrenaline (NA), which represent >90% of all treatments. Moreover, marked circadian mood changes occur in some patients (e.g. melancholia). Altogether, these observations suggest that antidepressant treatments have not yet reached their maximum speed of action and that further research on new targets is likely to result in the discovery of drugs having a faster onset of action.

Given the uneven distribution of neurotransmitters, neuromodulators and their receptors in the brain, an important question to address is: what are the brain areas where drug effects are required? The array of depressive symptoms suggests the involvement of different brain areas: anhedonia (nucleus accumbens), fear and anxiety (amygdaloid complex), depressed mood (limbic system), cognitive impairment (prefrontal cortex) and somatic symptoms, such as changes in hormonal secretion, appetite, sexual drive, sleep, and so on (hypothalamus). Do antidepressants act on all these brain areas at once or do they affect primarily a brain area where a primary dysfunction occurs, which later triggers a cascade of

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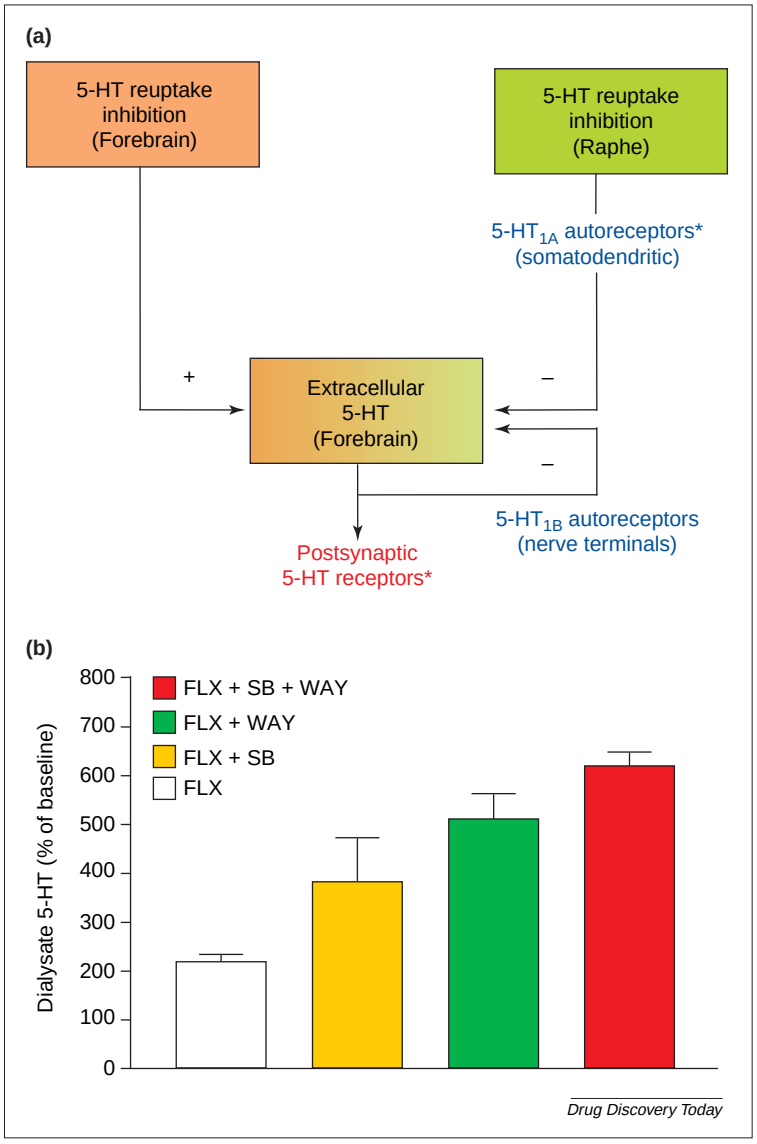

FIGURE 1

(a) The selective serotonin reuptake inhibitors (SSRIs) exert two opposite effects on the extracellular 5-HT concentration in forebrain synapses, which result from the effect of the drug on two distinct anatomical sites. On the one hand, an increase in 5-HT results from blockade of the 5-HT transporter in nerve terminals. On the other hand, the excess 5-HT produced in the raphé by the SSRI activates inhibitory 5-HT_{1A} autoreceptors, which reduces cell firing and terminal 5-HT release. A similar negative feedback mechanism also occurs at terminal level through the activation of 5-HT_{1B} autoreceptors. **(b)** Autoreceptor antagonists potentiate the effects of SSRIs. Microdialysis studies show that blockade of 5-HT_{1A} and/or 5-HT_{1B} receptors with selective antagonists (0.3 mg kg^{-1} s.c. WAY100635 and 4 mg kg^{-1} i.p. SB224289, respectively) potentiates the effects of the administration of the SSRI fluoxetine (FLX) (10 mg kg^{-1} i.p.) on extracellular 5-HT in frontal cortex. Figure redrawn, with permission, from reference [14].

changes in these other areas? In this regard, anatomical or functional abnormalities have been reported in the hippocampus and prefrontal cortex of depressed patients [8,9]. Both of these areas could have a key role in triggering secondary changes in other brain structures due to their central position in many brain circuits.

In the absence of such information, current research often proceeds through a step-by-step improvement of standard drugs or by empirically trying new potential targets. Here, we focus on several of these strategies that are potentially useful to obtain faster, and possibly more effective, antidepressant responses.

Treatments based on dual reuptake inhibition

As outlined previously, most antidepressant drugs inhibit 5-HT and/or NA reuptake. There is evidence suggesting that dual reuptake blockers, such as the tricyclic clomipramine or the selective 5-HT/NA reuptake inhibitor (SNRI) venlafaxine, are more rapid and/or efficacious than SSRIs [5,6,10,11]. Another drug (duloxetine), with the ability to selectively block 5-HT and NA transporters, has also been approved for the treatment of depression in the USA and Europe. Hence, dual-action drugs could represent an advance over SSRIs, yet they do not appear to meet the requirements of a fast-acting antidepressant.

Autoreceptor antagonists

Serotonergic neurones are endowed with two sets of autoreceptors, located in the somatodendritic level in the midbrain raphé nuclei (5-HT_{1A}) and in 5-HT axons (5-$HT_{1B/1D}$) in projection areas. The activation of 5-HT_{1A} autoreceptors by 5-HT or selective agonists suppresses cell firing and impulse-dependent 5-HT release, whereas 5-HT_{1B} receptors control 5-HT synthesis and release at terminal level. The increase of extracellular 5-HT produced by reuptake blockade activates 5-HT_{1A} receptors in the midbrain raphé, suppressing cell firing and terminal release [2,12], an effect that attenuates the extracellular 5-HT increase produced by reuptake blockade. 5-HT_{1B} autoreceptors exert a similar negative feedback at a local level (Figure 1). Following repeated administration of SSRIs, 5-HT_{1A} receptors desensitize, which enables 5-HT neurones to recover cell firing [2] and leads to an increase in extracellular 5-HT, to a level higher than seen after single treatment [13]. The blockade of these negative feedback mechanisms with 5-HT_{1A} and/or 5-HT_{1B} receptor antagonists potentiates the 5-HT increase produced by SSRIs and, therefore, might serve to accelerate the clinical effects of SSRIs (for reviews, see [3,14]).

The lack of selective 5-HT_{1A} receptor antagonists that are available for human use dictated that this strategy be investigated using the β-adrenoceptor/5-HT_{1A} (partial) antagonist pindolol [14,15]. The results of 15 placebo-controlled clinical trials and several open-label studies using pindolol have been reported [14]. A recent meta-analysis has indicated that pindolol significantly hastens the effect of SSRIs within the first two weeks of treatment [16]. However, although pindolol has been shown to partially occupy 5-HT_{1A} receptors in the human brain at clinical doses [17], drawing a firm conclusion that its effects are solely due to interaction with 5-HT_{1A} receptors is not possible because of its complex pharmacology. Other studies have found an even lower occupancy [18]. However, agonists and partial agonists of the 5-HT_{1A}

receptor poorly displace the antagonist ligand used in these studies ([^{11}C]WAY-100635), therefore, the actual receptor occupancy exerted by pindolol is controversial, although there is a general agreement that clinical doses used so far could be suboptimal [14,17,18].

A similar negative feedback also occurs in noradrenergic neurones, involving α_2-adrenoceptors. Thus, α_2-adrenoceptor antagonists have been used to potentiate the effects of NA reuptake inhibitors at the experimental level [19].

The studies outline here open the way to the development of dual-action drugs (e.g. SSRI + 5-HT$_{1A}$ receptor antagonist) and of add-on strategies based on the addition of autoreceptor antagonists to SSRIs/SNRIs. A few 5-HT$_{1A}$ receptor antagonists have been developed for human use, such as NAD-299 (robalzotan) or DU-125530, which show high occupancies of 5-HT$_{1A}$ receptors [20,21], although they have not been tested in add-on strategies. Regarding dual-action drugs, efforts have recently started to be productive. Lilly and Wyeth have reported on series of compounds with high affinity for the 5-HT transporter and the 5-HT$_{1A}$ receptor, where they appear to act as antagonists [22,23], in contrast to previous dual-action drugs, such as EMD-68843 or VN-2222, which display partial agonist effects at 5-HT$_{1A}$ receptors [24,25].

Possible role of 5-HT$_{2A/2C}$ receptors in the augmentation of antidepressant response

Several open-label and double blind placebo-controlled studies show that some antidepressants (e.g. mirtazapine and mianserin) and atypical antipsychotics could augment the clinical response to SSRIs in treatment-resistant patients (for review, see [26]). Often, these responses have been observed shortly after administration of these drugs, which suggests that addition of the second drug induces rapid antidepressant changes. One common characteristic of mirtazapine, mianserin and the atypical antipsychotics is their ability to occupy 5-HT$_{2A}$ receptors at the doses used [26]. Various histological techniques reveal the presence of 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors in cortical areas of the human brain [27,28]. It is controversial to speculate whether depressive symptoms might be associated with changes in the cortical density of 5-HT$_{2A}$ receptors [29]. Also, conflicting results have been reported after antidepressant treatments because SSRIs appear to increase [30], and tricyclic drugs appear to decrease [31], binding of ligand to the 5-HT$_{2A}$ receptor. Likewise, many antidepressants down-regulate 5-HT$_{2A}$ receptors after repeated treatment [32]. Altogether, we would suggest that this supports a role for 5-HT$_{2A}$ receptors in antidepressant drug action. The selective blockade of these receptors, by acute administration of M100907, augments the antidepressant effect of SSRIs in the DRL 72-s schedule, a task related to prefrontal cortex function. This effect does not involve a presynaptic potentiation of the 5-HT release produced by the SSRI, which suggests that the improvement in executive functions arises from the blockade of postsynaptic 5-HT$_{2A}$ receptors [33]. A NIH–sponsored controlled trial was designed to examine the ability of M100907 to improve the action of citalopram (see www.clinicaltrials.gov) but the outcome of this study is not yet available.

The 5-HT$_{2C}$ receptor also warrants consideration in the development of novel antidepressant therapies. Using *in vivo* microdialysis, it has been reported that 5-HT$_{2C}$ receptor-selective antagonists (SB242084 and RS102221), potentiate the elevation in extracellular 5-HT concentration elicited by SSRIs. These observations are in accordance with the fact that fluoxetine increases cortical extracellular 5-HT levels more in 5-HT$_{2C}$ receptor knockout mice, than in wild-type mice [34].

Enhancement of central 5-HT system function has been associated with antidepressant action, as indicated by the widespread use of SSRIs. In addition, dysfunction in the catecholamine systems (noradrenaline and dopamine) is likely to have some role in the etiology of depression. Hence, the combination of atypical antipsychotic agents synergistically potentiated the effect of fluoxetine on the cortical extracellular concentrations of catecholamines, an effect that could also contribute to the aforementioned effects of these drugs in clinical trials [35].

5-HT$_7$ receptors

The affinity of clinically effective antidepressant drugs for the 5-HT$_7$ receptor [36], and the finding that chronic administration of antidepressant drugs down-regulates 5-HT$_7$-mediated responses and receptor binding in limbic areas [37,38], form the basis for a possible involvement of this receptor in depressive states and antidepressant response. Furthermore, the presence of the 5-HT$_7$ receptor gene transcripts and protein in midbrain, hypothalamic, cortical and limbic areas [39,40] suggests a potential role in learning and memory, as well as in affective behaviour. For this reason, it is tempting to speculate that this receptor might have some role in some forms of depression. However, it is unknown whether the expression of the 5-HT$_7$ receptor is altered in the brain of depressed individuals.

NK$_1$ receptor antagonists

NK$_1$ receptor antagonists constitute a new drug class, although a clear-cut therapeutic outcome has not prevailed so far. Substance P (SP) is the preferred endogenous agonist for NK$_1$ receptors. The connection between SP and depression is based on several preclinical and clinical observations.

- First, the administration of SP or SP agonists evokes a stress response in animals [41] that can be prevented by NK$_1$ receptor antagonists [42].
- Second, there is a colocalization of SP with brain serotonergic and noradrenergic systems known to be involved in the regulation of mood [43,44].
- Third, the expression of NK$_1$ receptors occurs in brain areas that are involved in the control of emotional and stress responses, such as the amygdala, habenula, hippocampus, frontal cortex, raphé nuclei and locus coeruleus [45,46]

- Fourth, a decreased biosynthesis of SP in rat forebrain appears to be a common trait of various chronic antidepressant treatments [47], although these treatments do not appear to alter the expression of NK_1 receptors [48].
- Finally, two clinical studies have evidenced that the NK_1 receptor antagonists MK-869 and L-759274 possess antidepressant properties [49,50]. MK-869 was as effective as SSRIs, but with a better side-effect profile, notably for nausea and sexual dysfunction. Unfortunately, subsequent studies showed that these compounds did not separate from placebo, in contrast to an active comparator. The obvious interpretation of these findings is that NK_1 receptor antagonists have weaker antidepressant efficacy than SSRIs. Therefore, their development for depression was discontinued, although several drug companies have NK_1 receptor antagonists in their pipelines.

Although the antidepressant properties of NK_1 receptor antagonists were initially attributed to a unique mechanism [49], subsequent studies indicated that their therapeutic action could be associated with changes in brain monoaminergic systems (for reviews, see [51,52]). Thus, in common with other classes of antidepressants, NK_1 receptor antagonists have a delayed onset of action. However, unlike other antidepressants, the chronic administration of NK_1 receptor antagonists results in an increased firing of serotonergic neurones in the dorsal raphé nucleus [53,54]. This finding was further confirmed with NK_1 receptor knockout mice [55] and was initially attributed to a functional desensitization of $5\text{-}HT_{1A}$ autoreceptors [55,56]. This increase in 5-HT cell firing, however, was not accompanied by an enhanced release of 5-HT in the frontal cortex of NK_1 receptor knockout mice [56,57]. It is conceivable that any increase in 5-HT release could be counterbalanced by an intact 5-HT reuptake system. In accordance with this, it has been shown that NK_1 receptor antagonists potentiate the neurochemical effects of SSRIs [57], which opens up a new therapeutic approach to the treatment of depression in which NK_1 receptor antagonists could be administered in combination with 'classical' antidepressant drugs to produce a greater antidepressant response.

CRF antagonism

Abnormal hypothalamic-pituitary-adrenal (HPA) activity has been implicated in the pathophysiology of depression and anxiety disorders [58,59]. Indeed, depressed patients frequently show increased plasmatic levels of cortisol [60]. The HPA axis is mainly controlled by the neuropeptide corticotrophin-releasing factor (CRF), secreted by neurones whose cell bodies are in the paraventricular nucleus of the hypothalamus (PVN) and other brain areas. Two CRF receptor subtypes have been described: CRF_1 and CRF_2. High densities of CRF_1 receptors are found in cortico-limbic areas and in the pituitary. CRF_2 receptors are mainly peripheral, although they are also expressed in the brain.

Hypersecretion of hypothalamic CRF occurs in depressed patients and normalizes after recovery. Hence, CRF levels return towards normal values in depressed patients undergoing electroconvulsive therapy or fluoxetine [60]. In fact, a failure to normalize HPA activity usually predicts a poor clinical outcome. Evidence obtained from post-mortem brain tissue of depressed patients indicates an increase in CRF levels and CRF mRNA expression in the PVN and prefrontal cortex, and a reduction in CRF_1 receptor mRNA, probably due to chronic hyperactivity of CRF [61]. Furthermore, the HPA axis is also involved in neuroplasticity (see subsequent section). Therefore, it has been proposed that CRF antagonists, mainly of the CRF_1 subtype, might represent a novel class of antidepressant drugs.

Several synthetic CRF_1 antagonists have demonstrated antidepressant/anxiolytic activity in animal models. Mansbach *et al.* [62] reported that CP-154,526 showed acute efficacy in the learned helplessness model a test in which rats are exposed to a series of inescapable foot shocks on three consecutive days and then tested in a shock-escape procedure on the fourth day. This model presents documented sensitivity to drugs showing antidepressant activity in humans. A dose-dependent antidepressant-like effect has been demonstrated recently for other CRF_1 antagonists in several experimental paradigms, including forced swimming test, chronic mild stress and olfactory bulbectomized rats [63]. At the clinical level, an open-label trial conducted with R121919 (Janssen) in a small sample of major depressives (20 patients) showed a reduction in anxiety and depression symptoms [64]. However, the compound was dropped from subsequent studies due to hepatotoxicity. In the past few years, several pharmaceutical companies have been developing new selective CRF_1 antagonists, such as NBI-37582 (GSK), SB723620 (GSK)and CRA-1001 (Taisho). Some of these antagonists are currently undergoing clinical trials, which should provide crucial information on efficacy, speed of action and safety, which will be necessary to determine whether this class of potential antidepressants has a faster clinical response than compounds based on reuptake blockade.

In addition to the strategies outlined here, based on refinement of the 'classic' monoaminergic hypothesis of depression or on pharmacological manipulation of neuropeptide systems, novel therapeutic agents and neurobiological theories on depression have emerged in recent years, which could be potentially useful for the development faster antidepressants. Here, we will review a few of these but we will not focus on others, such as GABA-mimetic compound and cannabinoid drugs, which could also be interesting in the future.

Glutamate-acting drugs

Based on the potential occurrence of glutamatergic abnormalities in major depression, several alternative drugs focusing on ionotropic glutamate receptors have

been suggested, with a special focus on the NMDA receptor. Hence, chronic treatment with clinically active antidepressants results in adaptive modifications in this receptor subtype [65], whereas antagonists acting at this receptor, such as AP7 or ACPC, induce antidepressant-like effects in animal models [66]. Eliprodil, which acts at the allosteric polyamine site of the channel, also shows antidepressant-like actions [67]. Full, direct antagonism of NMDA receptors produces severe side effects, therefore, the search has focused on drugs acting at modulatory sites of this receptor, such as the glycine site. These agents might exert their action through a modulation of glutamatergic activity, with an additional effect on hippocampal neuroplasticity (see subsequent section).

At the clinical level, a single dose of the non-competitive NMDA receptor antagonist, ketamine, induced a rapid improvement in depressed patients [68], although the potential psychotropic effects of this drug type limits its usefulness. Several preclinical and clinical studies are currently assessing the potential use of NMDA receptor-modulators. The results from these trials will enable the determination of their efficacy and safety in treating depressive disorders. Furthermore, one such study, sponsored by the NIMH, is underway (see www.clinicaltrials.gov) to evaluate the safety and efficacy of memantine, an uncompetitive NMDA blocker, recently approved for cognitive disorders.

The positive modulation of AMPA receptor-associated activity is also of recent interest in the field of antidepressant therapy [69], with some compounds in clinical development. The possible therapeutic efficacy of this approach could be related to the increase in the expression of brain-derived neurotrophic factor (BDNF) induced by these drugs (see subsequent sections).

Antiglucocorticoid agents

The functionality of the HPA axis, altered in depression, is feedback regulated by glucocorticoid receptors (GR), which are localized in the brain and the periphery. Their potential use as targets for antidepressant drugs is supported by: (a) their abnormal function in depressed patients, (b) altered behaviour in transgenic mice expressing a complementary antisense GR mRNA, and (c) increased GR expression following treatment with tricyclic antidepressants and selective NE reuptake inhibitors, but not SSRIs [58,70].

Moreover, a reduction of glucocorticoid activity might result in an improvement of depressive symptoms [71]. GR blockade could activate the HPA axis, therefore, the rationale for this strategy partially depends on the nature (primary or secondary) of the hypercortisolaemia present in depressed patients. Indeed, positive results have been reported after short-term use of mifepristone in major psychotic depression [72], but the clinical use of existing drugs is limited by their severe side effects. New compounds specifically targeting the GR are currently in development.

Neuroplasticity

The exact role of neuroplasticity in depression is still debated, particularly with regard to the temporal pattern of clinical improvement. However, mood disorders, including stress and depression, seem to be associated with an impairment of the mechanisms controlling neuroplasticity and cell survival in brain [4]. Supporting this, a reduction of the hippocampal volume in depressed patients and cortical neuronal loss has been reported [73], although such observations are not universal [74]. Conversely, chronic, but not acute antidepressant treatments and electroconvulsive shock increase neuronal proliferation in the dentate gyrus [75]. Two signaling systems appear to have a role in this response: (1) the cAMP pathway (through CREB transcription factor); and (2) activation of BDNF via TrkB receptors and the MAP kinase cascade. Hence, antidepressant treatments increase CREB expression in the hippocampus [76], while CREB overexpression in the dentate gyrus induces antidepressant effects. As hippocampal apoptosis might occur in major depression, the modulation of the CREB/BDNF/bcl-2 cascade has been proposed as a strategy for the treatment of mood disorders. Overall, there seem to be regional impairments of neuroplasticity and cellular resilience in major depression, although it remains unclear whether they are a primary etiological factor or just an epiphenomenon.

From a pharmacological point of view, aminergic antidepressants have been shown to increase neurogenesis in the hippocampus, mainly due to the well-known involvement of 5-HT in neural development [77]. HPA activity also modulates cell survival in the hippocampus: sustained activity of glucocorticoids following stress results in neuronal death in this area [78]. Likewise, NMDA receptor blockade and activation of AMPA receptors positively affect neuroplasticity in the hippocampus.

Therefore, new pharmacological strategies are being designed, directed at increasing cAMP levels (see next section) or stimulating Trk receptors. Indeed, the intracerebral administration of BDNF displays antidepressant-like effects in rodents [79], although this is not a practical therapeutic approach because BDNF does not cross the blood–brain barrier. A range of small molecules has been shown to mimic the actions of neurotrophins on Trk receptors through different mechanisms [80], either directly (SB247464, the fungal metabolite L783281) or indirectly (CGS21680). Other drugs have been reported to achieve neurotrophic effects by acting downstream or independently on Trks: these include immunophilins and inhibitors of GSK-3α, drugs whose antidepressant profile has not yet been tested.

Modulation of post-receptor mechanisms: the cAMP transduction pathway

Chronic antidepressant treatment upregulates the expression of CREB, therefore, compounds that increase cAMP levels could be a valid strategy in the treatment of depression.

Phosphodiesterase-IV (PDE-IV) mediates the breakdown of cAMP: therefore, PDE-IV inhibitors could have antidepressant properties. Rolipram, a selective inhibitor of PDE-IV, showed an antidepressant pharmacological profile and increased hippocampal cell proliferation [81]. However, its development was halted due to severe adverse effects (nausea). Future developments in this field should proceed through the development of more isozyme or gene-selective inhibitors.

Concluding remarks

To date, successful attempts to improve the speed of action of antidepressants have been based on pharmacological approaches based on monoaminergic systems. This includes the combination of 5-HT reuptake blockade – which represents >80% of all antidepressant treatments on its own (e.g. SSRIs) – with (a) NE reuptake blockade (to produce SNRIs) or (b) aminergic receptor blockers, either presynaptic (pindolol) or postsynaptic, such as the atypical antipsychotics. Indeed, the complex pharmacology of the latter approaches raises questions about whether new strategies must proceed towards more selective drugs (e.g. targeting a single receptor or mechanism) or whether 'dirty drugs' are required.

When considering the different neurotransmitters, dopamine has been, in general, quite neglected, despite evidence that it has a role in core depressive symptoms (e.g. anhedonia, cognitive dysfunction) and that the antidepressant action at preclinical and clinical level can be augmented by dopamine agonists [82,83]. The main concern raised by drugs that act directly on dopamine neurones is the potential abuse risk due to enhancement of dopaminergic function in ventral striatum and related limbic areas. In fact, amineptine, an antidepressant drug that blocked dopamine uptake and had a fast onset of action, particularly on psychomotor retardation [84], had to be withdrawn from the market for this reason. However, atypical antipsychotics increase dopamine release in prefrontal cortex indirectly, by mechanisms that are still unclear but that are possibly related to the indirect activation of 5-HT_{1A} and/or blockade 5-HT_{2A} receptors [85,86]. This effect might be involved in the rapid effects of atypical antipsychotics in SSRI-resistant patients, mentioned previously.

Finally, a general problem in all antidepressant treatments is the existence of neurobiological differences among depressed patients, which have a role in treatment outcome. Hence, chronic depression could be associated with neurodegeneration in key brain areas, such as the hippocampus [8], that might impair or prevent the emergence of a rapid therapeutic response. In this regard, individual differences in the response to pindolol addition to SSRIs have been reported, with patients in early stages of the illness being more sensitive to pindolol addition than chronically ill or treatment-resistant patients (for review, see [14]). By contrast, in preclinical studies it is important to know the validity of animal models for novel antidepressants. Thus, although learned helplessness and forced swimming are of limited value in predicting activity in humans, they could represent a useful tool to define the potential antidepressant activity of drugs.

In summary, it is hoped that one or several of the aforementioned neurobiological approaches will be useful in the development of faster and, possibly, more effective antidepressant treatments that overcome the current limitations.

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