Key Words: antidepressants, mechanism of action, SNRI, SSRI, venlafaxine, tricyclic antidepressants, monoamine oxidase inhibitors

Mechanism of Action of Antidepressants

By Francesc Artigas, PhD, David J. Nutt, MD, PhD, and Richard Shelton, MD

ABSTRACT *~ A wide range of effective drugs is available for the treatment of major depression. The discovery of these agents has not always been the result of rational drug design. Tricyclic antidepressants formed the mainstay of treatment until the 1990s, and selective serotonin reuptake inhibitors (SSRIs) have dominated treatment over the last decade. However, the poor tolerability associated with tricyclic antidepressants and concerns about the efficacy of SSRIs has led to the search for alternative agents. Attention has focused on those drugs that affect norepinephrine and/or serotonin systems, with the recent introduction of a number of agents, including venlafaxine, milnacipran, nefazodone, mirtazapine, and reboxetine. Venlafaxine, which is the first in a new class of drugs known as serotonin and norepinephrine reuptake inhibitors, may be associated with an earlier onset of action and higher remission rates than SSRIs. It is hoped that the development of drugs with multiple sites of action will translate into improved clinical efficacy in the treatment of depression.* Psychopharmacology Bulletin. *2002;36(Suppl 2):123-132*

Introduction

Most of our understanding about the pathophysiology of depression has resulted from the elucidation of the mechanism of action of antidepressant drugs. However, the discovery of these agents has largely been serendipitous and the exact etiology of depression remains elusive. The first agents to be introduced in the 1950s included tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs [Figure 1]). The antidepressant efficacy of TCAs, which formed the cornerstone of treatment until the 1990s, is based on their ability to modulate norepinephrine and serotonin (5-HT) synaptic transmission to differing extents.[1,2] In particular, clomipramine, which inhibits the reuptake of 5-HT directly and norepinephrine through its demethylated metabolite, has proven

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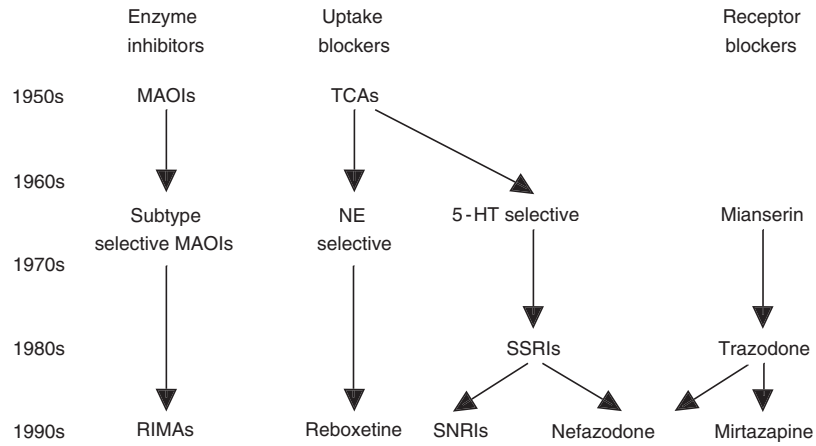
more effective than selective serotonin reuptake inhibitors (SSRIs) in severe depression.[3,4] However, while these nonselective agents are effective antidepressants, their usefulness has been limited by the anticholinergic and cardiovascular adverse events associated with them. MAOIs are associated with the potential for hypertension and hazardous food and drug interactions, and, consequently, are not widely used.[5] The poor tolerability and risk profile associated with these antidepressants has led to the search for more selective agents.

Although much of the interest in the early development of antidepressant drugs was on the norepinephrine system, by the 1980s, attention focused on the importance of the serotonergic system in the pathophysiology and treatment of depression. This led to the introduction in the 1980s of SSRIs, which have dominated the treatment of depression for the past 10 years. Since SSRIs demonstrate little or no affinity for α-adrenoceptors, muscarinic cholinergic, or histamine receptors, they are largely devoid of the adverse effects typically associated with TCAs.[6] However, the ability of several agents in this class to inhibit the cytochrome P450 2D6 enzyme increases the potential for drug-drug interactions.[7] Although SSRIs have been widely used for the treatment of affective disorders, they are associated with a relatively slow onset of action,[8] and concerns remain about their clinical efficacy in severe depression.[3,4,9,10]

The search has continued for newer agents with the hope of finding drugs with higher efficacy and a more rapid onset of action. Compelling evidence to support the involvement of both norepinephrine and 5-HT

FIGURE 1

THE EVOLUTION OF ANTIDEPRESSANTS OVER THE LAST 50 YEARS



MAOIs=monoamine oxidase inhibitors; TCAs=tricyclic antidepressants; NE=norepinephrine; 5-HT=serotonin; SSRIs=selective serotonin reuptake inhibitors; RIMAs=reversible inhibitors of monoamine oxidase; SNRIs=serotonin norepinephrine reuptake inhibitors.

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in the etiology of depression[11,12] has led to the recent introduction of a range of antidepressants including venlafaxine, nefazodone, mirtazapine, and reboxetine.[13] Venlafaxine is the first in a new class of drugs known as serotonin-norepinephrine reuptake inhibitors (SNRIs). Nefazodone is a potent 5-HT_2 receptor antagonist, but also inhibits 5-HT and norepinephrine reuptake to a limited extent. Mirtazapine enhances noradrenergic and serotonergic transmission by blocking presynaptic α_2-adrenoceptors, as well as 5-HT_2 and 5-HT_3 receptors, and reboxetine is an selective norepinephrine reuptake inhibitor.

This article outlines the main modes of action of antidepressants. It focuses particularly on SSRIs and SNRIs, their effects on the 5-HT and norepinephrine reuptake systems, and how inhibition of transmitter uptake can impact their onset of action and antidepressant efficacy.

Mode of Action of Antidepressants

The evolution of antidepressants, such as SSRIs and SNRIs, and our understanding of their mechanisms of action have helped to establish the notion that 5-HT and norepinephrine play a significant role in the pathophysiology of depression.[14] Indeed, patients with severe depression appear to benefit from agents that modulate the transmission of both neurotransmitters.[3,4,10]

Although 5-HT and norepinephrine have independent actions, they should not be considered in isolation, as the two systems are in fact intimately connected in the central nervous system.[15] Noradrenergic projections arising from the locus coeruleus are linked with serotonergic projections from the dorsal and median raphe nuclei in the brainstem, and activate the same intracellular signaling pathways (Nemeroff, pages 6-23).[16] On the other hand, both systems project to virtually all forebrain areas in parallel and share intracellular effector systems in their postsynaptic targets.

A single, simple mechanism of action for all antidepressants has not been identified, and is unlikely given the complex and heterogeneous nature of the disorder.[17] At present, three main routes are employed in order to restore monoamine balance: reuptake inhibition, receptor blockade, and inhibition of enzymes that degrade monoamines, particularly monoamine oxidase (Figure 2).[2] The effect of each of these mechanisms of action is to increase the concentration of the monoamines 5-HT and norepinephrine at their postsynaptic receptors. Since little is known about the actual receptor subtypes or intracellular effector systems (eg, second and third messengers, transcription factors) involved in the relief of depression, most treatments rely on presynaptic modulation of the activity of monoamine (5-HT, norepinephrine) neurotransmitter systems.

Reuptake Inhibition

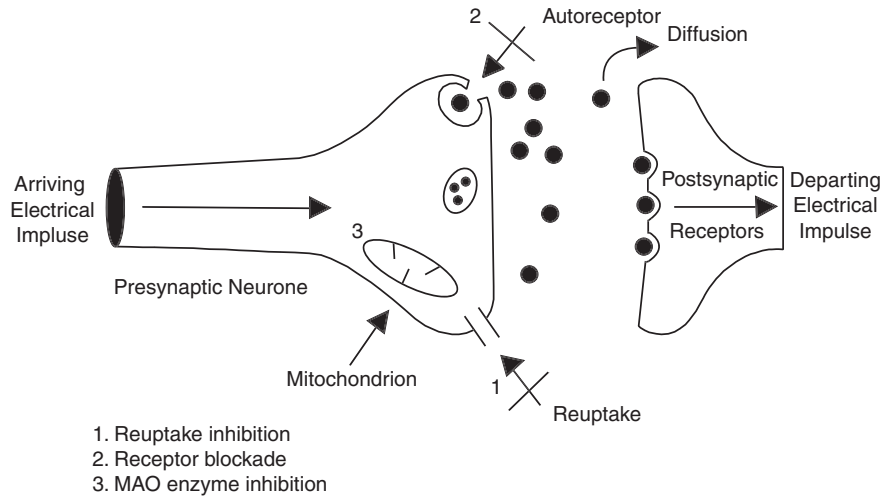
The mode of action of the majority of antidepressants involves inhibiting the transporters responsible for the uptake of monoamines, namely reuptake inhibition. When an action potential arrives at the nerve ending, it results in the release of a neurotransmitter into the synaptic cleft, where it binds to its pre- and postsynaptic receptors. In the normal state, the excess neurotransmitter (the available transmitter that is not bound to a postsynaptic receptor) is actively transported back into the nerve terminal after binding to a large 12-transmembrane domain protein, where it is stored in vesicles for release during subsequent nerve impulses. This mechanism terminates the action of the monoamine in the synapse.

Acute inhibition of the transporter that pumps the neurotransmitter back into the nerve terminal can significantly enhance neurotransmission.[2] This approach to increasing the effectiveness of a transmitter is thought to be the mechanism of action of the vast majority of antidepressants that are currently available. However, this simplistic model of enhancing transmitter function is not without its conceptual limitations. Chronic/long-term administration of drugs may result in compensatory mechanisms that

FIGURE 2

THE THREE MAIN MODES OF ACTION OF ANTIDEPRESSANTS

Uptake blockers and MAO inhibitors act by interfering with the main mechanism of inactivation of amine neurotransmitter, reuptake, and enzymatic degradation. Autoreceptor antagonists prevent self-inhibitory effects on nerve terminals of 5-HT or norepinephrine neurons. Postsynaptic receptor antagonists block the actions of neurotransmitters at selective receptors, thus changing the balance between excitatory and inhibitory inputs onto postsynaptic cells.



MAO=monoamine oxidase.

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modulate their efficacy. Blockade of neurotransmitter uptake may lead to homeostatic compensatory changes in sensitivity (desensitization) and/or density (receptor downregulation) of postsynaptic receptors, resulting from an increase in synaptic concentration of transmitters. Chronic inhibition of 5-HT reuptake may lead to the downregulation of postsynaptic receptors, resulting from continual high concentrations of 5-HT at the receptor.[17] Although not well understood, the downregulation of postsynaptic receptors could contribute to the loss of therapeutic effect (tachyphylaxis) observed with some antidepressants.[18]

Autoreceptor Blockade

In addition to the postsynaptic effects, neurotransmitters also bind to presynaptic receptors that inhibit their own release, thereby limiting synaptic levels. For 5-HT, the presynaptic (somatodendritic) 5-HT_{1A} autoreceptor inhibits 5-HT release by reducing the rate of neuronal firing.[19,20] However, chronic exposure to increased levels of 5-HT eventually produces desensitization of the 5-HT_{1A} autoreceptor, resulting in a subsequent enhancement of 5-HT release from serotonergic terminals.[21,22] The delay in onset of action ascribed to SSRIs is thought to be associated, in part, with the compensatory activation of 5-HT_{1A} autoreceptors in the raphe nuclei and time taken for receptor downregulation to take place. Moreover, presynaptic 5-$HT_{1B/D}$ receptors that are present in nerve terminals also contribute to the self-regulation of serotonergic activity. Chronic treatment with some antidepressant drugs has also been reported to cause downregulation of 5-$HT_{1B/D}$ receptors.[22]

The α_2-adrenoceptor is the autoreceptor that modulates the release of norepinephrine from noradrenergic nerve endings.[2] Similar to the relationship between the 5-HT_{1A} autoreceptor and 5-HT, stimulation of the α_2-adrenoceptor inhibits further release of norepinephrine. Chronic drug treatment produces a gradual attenuation of this feedback inhibitory mechanism, possibly as a result of desensitization of the α_2-autoreceptor.[23,24] Furthermore, recent studies have demonstrated the downregulation of nerve terminal α_2-autoreceptors.[25] Likewise, reboxetine elicites a functional desensitization of α_2-autoreceptors.[26] However, since not all antidepressants cause functional desensitization of the somatodendritic α_2-autoreceptor, it is difficult to assign a significance of this phenomenon to antidepressant efficacy.[27]

Other central adrenoceptors may also be altered in response to chronic antidepressant therapy. For example, downregulation of central β-adrenoceptors and upregulation of central α-adrenoceptors has been observed.[28] Moreover, regardless of the long-term adaptive changes in central adrenoreceptors, the clinical studies of catecholamine depletion

suggest that changes in the availability of central catecholamine levels can significantly influence the efficacy of antidepressants.[29]

Postsynaptic Receptor Blockade

An alternative mechanism of action of some antidepressants is the blockade of postsynaptic receptors. Nefazodone is a potent and relatively selective antagonist of postsynaptic 5-HT_{2A} receptors.[17] It also has moderate activity in inhibiting the reuptake of both 5-HT and norepinephrine (although inhibition of norepinephrine reuptake is thought not to contribute to its clinical efficacy). Blockade of 5-HT_{2A} receptors increase 5-HT_{1A} receptor function.[30] As observed with reuptake inhibitors, chronic treatment with nefazodone downregulates cortical 5-HT_{2A} receptors and β_1-adrenoceptors—an action that is thought to increase the activation of post-synaptic 5-HT_{1A} receptors.[17]

The α_2-adrenoceptors antagonist and 5-HT heteroreceptor blocking agent, mirtazapine, enhances the transmission of both 5-HT and norepinephrine, resulting in the tonic activation of postsynaptic 5-HT receptors.[31-33]

Monoamine Oxidase Inhibition

5-HT and norepinephrine are metabolized by mitochondrial monoamine oxidase A. Drugs that inhibit the metabolism of MAOIs produce an elevation in the extracellular (synaptic) concentrations of monoamines, such as 5-HT, norepinephrine, and dopamine, which accounts for their antidepressant activity. Following the initial increase in extracellular monoamines, adaptive mechanisms similar to those reported for SSRIs occur, such as the desensitization and/or downregulation of a variety of monoamine receptors.[22,28]

Effects of Serotonin and Norepinephrine Reuptake

At clinically relevant doses, SSRIs increase extracellular concentrations of 5-HT in the midbrain raphé nuclei.[34] However, activation of the 5-HT_{1A} autoreceptors triggers the negative-feedback loop limiting the increase in synaptic 5-HT,[34] which results in a reduced release of 5-HT by nerve terminals in the forebrain. This rapid adaptive mechanism is thought to cause a delay in the onset of clinical efficacy (Figure 3), severely limiting the SSRI-induced increase in 5-HT levels. As a result, large doses of SSRIs cause small increases of extracellular 5-HT in various areas of the forebrain.[35,36] For instance, preclinical studies have shown that the systematic administration of paroxetine and fluoxetine (3–10 mg/kg) results in limited increases (two- to threefold) of central 5-HT.[35-37] Blockade of 5-HT_{1A} autoreceptors with selective

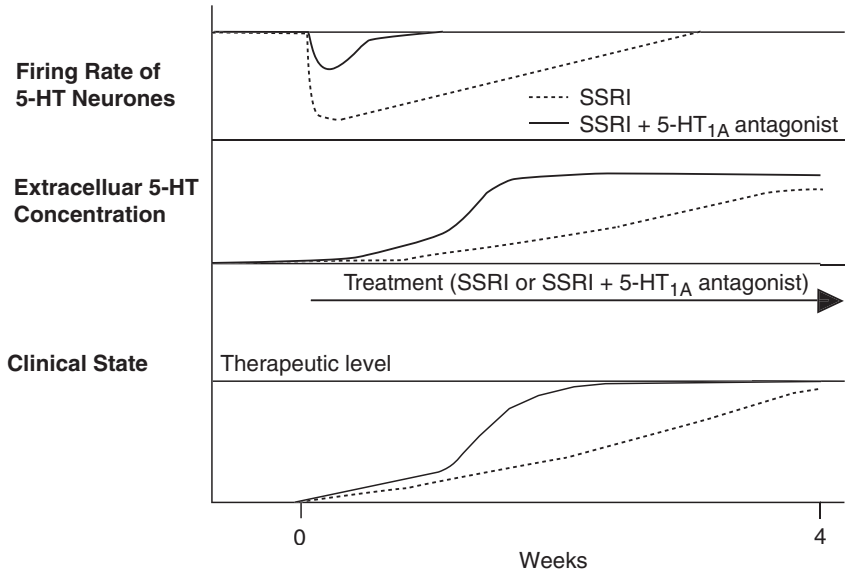
antagonists has been shown to markedly enhance the effects of SSRIs by preventing the negative feedback inhibition of 5-HT.[35] Thus, it may be possible to enhance the efficacy of SSRIs and reduce the delay in onset of action by coadministration of an agent such as pindolol or potential new and more selective antagonists that block 5-HT_{1A} autoreceptors. Results from clinical studies have demonstrated a reduction in the time to onset of antidepressant activity and rapid improvement in some treatment-resistant patients.[37]

Venlafaxine blocks the reuptake of 5-HT and norepinephrine, and may be associated with a shorter response time compared with SSRIs.[38] It is thought that venlafaxine's ability to inhibit the reuptake of both 5-HT and norepinephrine provides a possible explanation for this effect. With respect to blockade of 5-HT reuptake, venlafaxine behaves like an SSRI

FIGURE 3

SCHEMATIC REPRESENTATION OF THE ADAPTIVE CHANGES THAT OCCUR IN RESPONSE TO ANTIDEPRESSANT TREATMENT: AUGMENTATION OF SSRI ANTIDEPRESSANT RESPONSE WITH A 5-HT_{1A} RECEPTOR BLOCKER

Following treatment with an SSRI alone, the firing rate of the raphe 5-HT neurons is reduced. This impairs the release of 5-HT by nerve terminals and little or no increase in the extracellular 5-HT concentration occurs in the forebrain. In the presence of a 5-HT_{1A} autoreceptor blocker, the SSRI causes a less marked inhibition of cell firing and extracellular 5-HT levels increase as a consequence of reuptake blockade. The more rapid increase in 5-HT levels leads to a parallel, more rapid improvement of the clinical symptoms.



5-HT=serotonin; SSRI=selective serotonin reuptake inhibitor.

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and potently inhibits dorsal raphe firing through activation of 5-HT_{1A} receptors.[39] Consequently, a blunted increase in extracellular 5-HT levels takes place, unless venlafaxine is administered in combination with the 5-HT_{1A} receptor antagonist WAY100635. In this case, a clear dose-dependent increase in 5-HT occurs.[39] In contrast to its limited effect on 5-HT concentrations when given alone, venlafaxine produces a dose-dependent increase in the concentration of norepinephrine and no further increase in norepinephrine levels has been observed in the presence of WAY100635.[39]

Clinical data suggest that the response to drug treatment with venlafaxine exhibits a positive dose-response relationship[40]; this is in contrast to the response observed with increasing doses of SSRIs. As a result of this, venlafaxine can offer greater flexibility in dosing, since increasing the dose may further improve the outcome of depressive illness.[40] Similarly, preliminary findings from an open study suggest that the treatment of major depression with a combination of desipramine and fluoxetine resulted in a greater proportion of patients achieving complete symptom resolution within 4 weeks, compared with patients receiving desipramine alone.[41] Moreover, clomipramine (acting on both 5-HT and norepinephrine systems) exhibits an efficacy superior to SSRIs in severe depression.[3,4] This provides further support for the benefit of inhibiting both the norepinephrine and 5-HT systems.[41]

Conclusion

As our understanding of the pathophysiology of depression evolves, so does the range of antidepressant medications. Depression is a complex disorder and it is therefore unlikely that a single mechanism of action will be identified. However, the recent introduction of agents with multiple sites of action may translate into improvements in clinical outcome. Understanding the importance of the transmitters involved in the etiology of affective disorders and their interactions with other central transmitters and hormones will enable us to identify and develop the next generation of antidepressants. ✤

Acknowledgment

This work was supported by an educational grant from Wyeth.

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