Possible Neurobiological Mechanisms Underlying Faster Onset of Antidepressant Action

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All antidepressant drugs have a delayed onset of action. There is, however, evidence that some agents may attenuate depressive symptoms more rapidly than others. The present review examines the mechanisms by which selective serotonin reuptake inhibitors, the dual 5-HT norepinephrine reuptake inhibitor venlafaxine, and the α_2-adrenoceptor antagonist mirtazapine alter 5-HT and/or norepinephrine neurotransmission. Particular attention is given to the time course with which these effects manifest themselves in relation to the possibility that these 3 types of drugs may act more rapidly, or exert a greater antidepressant action, than other agents. Based on the effects of antidepressant drugs presently available, strategies to accelerate or augment the antidepressant response are described, some of which have already been examined in patients. *(J Clin Psychiatry 2001;62[suppl 4]:7–11)*

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Most antidepressant drugs act primarily through the inactivation processes for monoamines. They either block the reuptake of serotonin, norepinephrine (Figure 1), or dopamine or inhibit monoamine oxidase, which catabolizes serotonin, norepinephrine, and dopamine. The administration of these drugs rapidly (within hours at most) leads to inhibition of the above-mentioned monoaminergic neuronal processes in the brain. Nevertheless, their onset of therapeutic action in major depression requires sustained administration for at least 1 to 2 weeks.

Before addressing the possible links between the therapeutic response in major depression and the almost immediate biochemical effects of antidepressant drugs, it is crucial to determine which monoamine(s) is/are important in mediating the clinical benefits of the different types of drugs used in the treatment of unipolar affective disorder. This question has been addressed by studying depressed patients who exhibited significant improvement with various types of antidepressant drugs and then determining whether they would relapse following either a dietary depletion of tryptophan, the amino acid precursor of serotonin, or the administration of a catecholamine synthesis inhibitor, α-methyl-*p*-tyrosine (AMPT). It was observed that 5 hours after ingesting a mixture of amino acids lacking tryptophan, several patients who had responded to a selective serotonin reuptake inhibitor (SSRI) presented a clear relapse of their depressive symptomatology that strikingly resembled the clinical features of their illness prior to treatment.[1,2] This resurgence of symptoms most likely resulted from a decreased availability of serotonin, since plasma tryptophan and brain serotonin synthesis are both decreased by about 90% in such a time frame.[3] In sharp contrast, patients who had improved using the selective norepinephrine reuptake inhibitor desipramine did not relapse when submitted to this dietary depletion of tryptophan.[2] Such patients did, however, get worse when they underwent the norepinephrine-dopamine depletion using AMPT. Conversely, the latter synthesis inhibitor did not alter the condition of the depressed patients who had responded to the SSRI fluoxetine.[4] These results are quite convincing, not only because of their clarity but also because they were carried out under double-blind conditions. The control condition for the dietary depletion consisted of giving an amino acid mixture containing tryptophan, which tastes and looks exactly the same as the one lacking tryptophan, and that for the catecholamine depletion consisted of giving 50 mg of diphenhydramine, which is as sedating as AMPT. Nevertheless, it would be interesting to ascertain the reliability of the latter results using the newly developed catecholamine dietary depletion paradigm.[5] With respect to the basis for the response obtained with monoamine oxidase inhibitors, fewer patients underwent these depletion strategies, but they generally showed a relapse following the serotonin depletion.[6] These results unambiguously point toward an enhanced brain availability of one or more monoamines at least for maintaining an antidepressant response. The following sections will address how the various types of antidepressant drugs achieve this enhanced synaptic availability of neurotransmitter.

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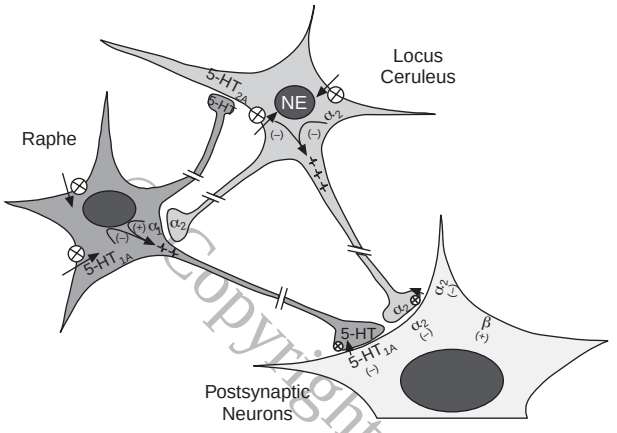
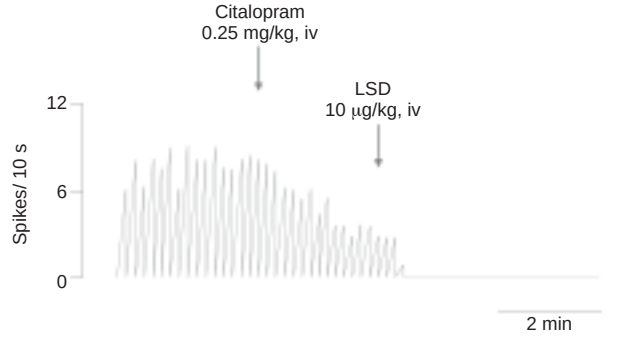
Figure 1. Reciprocal Interactions Between Dorsal Raphe Serotonin (5-HT) Neurons and Norepinephrine (NE) Neurons in the Midbrain With Respective Projections Throughout the Brain[a]



[a]The crossed circles with arrows represent the high-affinity reuptake transporters for 5-HT and NE. The plus and minus signs in parentheses indicate the excitatory and the inhibitory action, respectively, of the various subtypes of receptors. There is, as yet, no direct evidence that 5-HT_{2A} receptors are located on the cell body of NE neurons, but the activation of this receptor subtype, using systemic administration of a 5-HT_{2A} agonist, suppresses their firing activity. This is also the subtype of 5-HT receptor through which 5-HT exerts an inhibitory tone on NE neuron activity.

Figure 2. Integrated Firing Rate Histogram of a Serotonin (5-HT) Neuron Obtained From the Nucleus Raphe Dorsalis of an Anesthetized Rat[a]

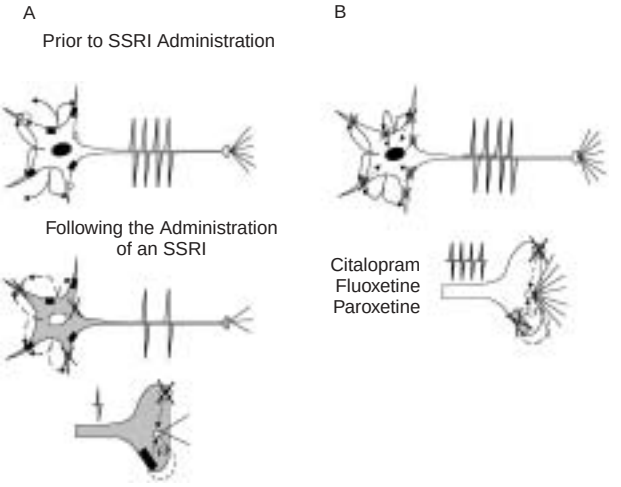


[a]Reprinted, with permission, from Chaput et al.[10] The histogram shows the inhibitory effect of an intravenous injection of the selective 5-HT reuptake inhibitor citalopram. The subsequent injection of LSD (lysergic acid diethylamide), a 5-HT autoreceptor agonist, was used as a verification of the 5-HT nature of the neuron recorded.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Positron emission tomography and functional magnetic resonance spectroscopy studies have now clearly demonstrated that SSRIs rapidly penetrate into and accumulate in the human brain.[7,8] Systemic injection of an SSRI rapidly

Figure 3. The Effect of Selective Serotonin (5-HT) Reuptake Inhibitors (SSRIs) on the Firing Activity and Release of 5-HT[a]



[a]The squares on the cell body represent the 5-HT_{1A} autoreceptors, which normally exert an inhibitory action on firing activity, represented on the axon by peaks and troughs (i.e., action potentials). The crosses over the circles represent the blockade of the 5-HT transporters by the reuptake inhibitors. These drugs produce a decrease in firing rates and release of 5-HT. The total amount of 5-HT at the level of the terminals is, however, not decreased because the transporters are blocked and the terminal 5-HT_{1B} autoreceptor, represented by a square, compensates for the decreased firing in A. In B, prolonged administration of the SSRIs listed produces a desensitization of the 5-HT_{1A} autoreceptors (represented by an X over them), which permits a normalization of the firing rate. This treatment desensitizes the terminal 5-HT_{1B} autoreceptor as well, which ultimately produces a net increase in 5-HT release.

suppresses the firing activity of serotonin neurons in the brain of laboratory animals as a result of blocking the high-affinity serotonin reuptake transporter on the cell body of serotonin neurons (Figure 2).[9,10] This results in an excess activation of serotonin-1A (5-HT_{1A}) autoreceptors, opening potassium channels and thereby producing a hyperpolarization of the intracellular medium. This slows the pacemaker activity of serotonin neurons.[11] Since the release of serotonin from axon terminals throughout the brain is directly proportional to the firing rate of serotonin neurons, the synaptic availability of serotonin in projection areas cannot be markedly enhanced following acute administration of an SSRI.[12] Indeed, although reuptake is blocked in these nerve terminal regions, the electrical impulse flow is significantly diminished (Figure 3A).

In some brain areas, the synaptic availability of serotonin must nevertheless be enhanced, because some side effects, such as nausea, occur rapidly. The latter side effect could be due to an excess activation of postsynaptic 5-HT_3 receptors.[13] Such receptors desensitize within a few days in vivo, which would explain why this side effect commonly disappears within 1 to 2 weeks in patients receiving an SSRI.[14] Similarly, the 5-HT_{1A} autoreceptors desensitize within about 2 weeks during sustained administration of an

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SSRI. This desensitization allows a recovery of the normal firing activity of serotonin neurons in the sustained presence of reuptake blockade (Figure 3B).

The time course of the latter events is congruent with the onset of the beneficial actions of SSRIs in major depression. In the case of SSRIs, however, another neuronal element would contribute to enhancing serotonin synaptic availability throughout the brain: the desensitization of the terminal serotonin autoreceptor, which is of the 5-HT_{1B} subtype. This receptor normally exerts a negative feedback influence on serotonin release. When this action is lifted as a result of a desensitization of this receptor, more serotonin can be released in the synaptic cleft for each action potential reaching the serotonin terminals.[15]

If these events truly underlie the delayed onset of action of SSRIs in major depression, then bypassing the 5-HT_{1A} autoreceptor desensitization step should significantly accelerate the occurrence of the therapeutic response. This bypassing could be achieved theoretically by concurrently giving an SSRI and a 5-HT_{1A} autoreceptor antagonist. Pindolol, which antagonizes both β-adrenoceptors and 5-HT_{1A} autoreceptors but does not block all postsynaptic 5-HT_{1A} receptors,[16] was used to verify this hypothesis.

In 6 of 8 placebo-controlled studies, pindolol has accelerated the therapeutic effects of SSRIs, mostly in nonresistant patients (Table 1).[17–24] The time necessary to obtain a 50% improvement with an SSRI plus pindolol in these studies was shorter than that needed with an SSRI plus placebo by a few days to more than 2 weeks. Taking into consideration the large proportion of recent drug trials failing to separate active drugs from placebo, together with the fact that these pindolol-SSRI trials were truly double-blind since the side effect profile of pindolol is really indistinguishable from placebo, it is remarkable that pindolol produced such an acceleration. One factor that would tend to weaken the beneficial profile of pindolol is the observation that it is not very effective in cases of treatment-resistant depression.[25,26] Nevertheless, these clinical trials suggest that it is possible to obtain a more rapid onset of antidepressant action in some patients.

Table 1. Reported Data on the Possibility That Pindolol Accelerates Antidepressant Drugs

Placebo-Controlled Study	N	Acceleration (rapid onset)	Augmentation (greater efficacy)
Maes et al, 1996[17]	33	–	+
Perez et al, 1997[18]	111	+	+
Tome et al, 1997[19]	80	+	–
Berman et al, 1997[20]	43	–	–
Bordet et al, 1998[21]	100	+	–
Zanardi et al, 1997[22]	63	+	+
Zanardi et al, 1998[23]	72	+	–
Maes et al, 1999[24]	21	+	+

NOREPINEPHRINE AND DUAL REUPTAKE INHIBITORS

As seen for the rapid action of SSRIs to suppress serotonin neuronal firing, the selective norepinephrine reuptake inhibitor desipramine produces a rapid inhibition of the firing rate of norepinephrine neurons. This phenomenon is believed to be due to an excess activation of the cell body α_2-adrenoceptors in the locus ceruleus.[27] In contrast to serotonin neurons, however, norepinephrine neurons do not regain their normal firing activity with treatment prolongation,[28] because α_2-adrenergic autoreceptors do not become desensitized following sustained norepinephrine reuptake blockade.[29] Nevertheless, given that norepinephrine depletion does result in a reversal of the antidepressant response achieved with desipramine,[4] this tricyclic drug must somehow enhance norepinephrine neurotransmission following long-term administration. Such increased norepinephrine neurotransmission may be achieved in 2 ways. It was observed that, following long-term desipramine treatment, the α_2-adrenergic autoreceptors on norepinephrine terminals present an attenuated capacity to decrease norepinephrine release using a frequency of stimulation of 5 Hz, i.e., a rate mimicking the basal firing activity of locus ceruleus neurons during active waking.[29] The same desipramine treatment has also been reported to enhance the responsiveness of postsynaptic α-adrenoceptors in a time-dependent manner in various brain structures that may be involved in mediating some aspects of the antidepressant response, such as the facial motor nucleus, the thalamus, and the amygdala.[30,31] It will be interesting to assess whether the nontricyclic selective norepinephrine reuptake blocker reboxetine produces the same alterations as desipramine. Nevertheless, these alterations that result in an enhancement of norepinephrine neurotransmission are time dependent and possess a long time constant.

Theoretically, the onset of action of norepinephrine reuptake blockers could be accelerated by concomitant administration of an α_2-adrenoceptor antagonist. However, if such an agent also blocks the postsynaptic α_2-adrenoceptors, such coadministration may prevent an enhancement of norepinephrine transmission in brain structures, such as the amygdala,[32] where these α_2-adrenoceptors are important in mediating the action of norepinephrine.

In the case of dual serotonin-norepinephrine reuptake blockers, one may wonder whether the simultaneous blockade of serotonin and norepinephrine reuptake may lead to a more rapid occurrence of the antidepressant response. Indeed, in many cerebral structures, both neurotransmitters exert the same physiologic effect on neuronal function. For instance, in the hippocampus, the direct application of serotonin and norepinephrine in vivo results in a suppression of firing of pyramidal neurons via 5-HT_{1A} and α_2-adrenoceptors, respectively.[33,34] High doses of venlafaxine, which block the reuptake of both serotonin and norepinephrine,[35] were reported to have a rapid onset of

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action in a placebo-controlled trial.[36] There is, however, no published active drug comparative trial to support that claim. In contrast, while venlafaxine appeared to exhibit greater efficacy in 2 SSRI-controlled trials, it did not show a more rapid onset of action.[37,38] Similarly, the combination of the SSRI fluoxetine and the tricyclic desipramine led to a greater efficacy than either drug given alone but not until the end of the 6-week trial.[39]

THE α_2-ADRENOCEPTOR ANTAGONIST MIRTAZAPINE

Mirtazapine blocks α_2-adrenoceptors on the cell body and terminals of norepinephrine neurons. The former action leads to an enhancement of the firing activity of norepinephrine neurons, while the latter contributes to enhancing norepinephrine release from norepinephrine terminals throughout the brain.[40,41] Since norepinephrine neurons also project to the raphe nuclei where serotonin neurons are located, such α_2-adrenoceptor antagonism also exerts a major influence on the function of serotonin neurons (i.e., increases their firing activity).[42] On acute administration of mirtazapine, the firing rate of serotonin neurons is increased in a transient manner.[40] Therefore, mirtazapine can be considered as an antidepressant drug with a dual mechanism of action. Furthermore, it blocks α_2-adrenergic heteroreceptors located on serotonin terminals, which, as for 5-HT_{1B} autoreceptors, exert a negative feedback influence on serotonin release.[40] In contrast with serotonin-norepinephrine reuptake blockers, mirtazapine is not as dependent on adaptive mechanisms resulting from reuptake blockade to increase serotonin and norepinephrine neurotransmission. Theoretically, it could thus exert a more rapid onset of action than drugs acting on only one neuronal system. The possibility that mirtazapine is dependent on both the serotonin and the norepinephrine system to exert its antidepressant action has recently been supported by the monoamine depletion strategies. Delgado and Moreno[43] have shown that both tryptophan depletion and AMPT administration produced a rapid reversal of the antidepressant effect produced by mirtazapine.

Using a paradigm that allows the determination of the degree of tonic activation of 5-HT_{1A} receptors in the rat hippocampus under basal conditions, mirtazapine was observed to produce an enhanced serotonin transmission after only 2 days of treatment, whereas the SSRI paroxetine was ineffective under the same conditions. After a 21-day treatment, both paroxetine and mirtazapine produced the same degree of enhancement of serotonin neurotransmission.[44] These fundamental data are thus consistent with the results of 3 clinical trials showing a significantly faster onset of action of mirtazapine when compared with SSRIs, but not a greater efficacy at the end of these studies.[45]

SUMMARY

Most antidepressant drugs are dependent on adaptive mechanisms, triggered by monoamine inactivation processes that eventually enhance synaptic transmission. Consequently, their onset of antidepressant action is dependent on a long time constant for these phenomena to occur. Soliciting more than one such mechanism may lead to a treatment strategy that has a greater efficacy, producing a larger number of responders at the end of a trial or a transformation of resistant into responsive patients. However, the latter approach has not led to treatments with a more rapid onset of action. In contrast, if the neuronal mechanisms responsible for the negative feedback actions of monoaminergic neurons are directly interfered with, then clinical evidence has been generated in favor of a more rapid onset of action. The combination of a preferential 5-HT_{1A} autoreceptor antagonist with an SSRI or a 5-HT_{1A} agonist[46] constitutes an example of one such strategy, with the caveat that it will not necessarily work in all depressed patients. Therefore, it is possible to devise antidepressant treatments with a more rapid onset of action. However, strategies that aim at too rapid an enhancement of serotonin and/or norepinephrine in a nonselective manner may be limited by intolerable side effects. In the future, a better elucidation of the signal transduction events that occur following agonist occupation of the receptor may lead to the development of treatments that provide a more rapid onset of action with fewer side effects than the pharmacotherapies currently used.

Drug names: citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), venlafaxine (Effexor).

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