Alterations in central noradrenergic and serotonergic function have been implicated in the pathophysiology of depression and in the mechanism of action of antidepressant drugs. Evidence is emerging, based on changes in norepinephrine and serotonin metabolism in the central nervous system (CNS), that supports the concept that there may be subtypes of depressed patients: some with primary disturbances in serotonin function and others with primary disturbances in catecholamine function. Patients therefore may have differential responses to norepinephrine and serotonin reuptake inhibitors.

The development of a new, selective norepinephrine reuptake inhibitor (selective NRI) without the side effects (anticholinergic, antihistaminergic, and cardiovascular) of the relatively norepinephrine-selective tricyclic antidepressant drugs (TCAs) would be a major addition to our armamentarium of drugs to treat depression. Such a compound, reboxetine, has been developed and is the first in its class of agents—a selective NRI. Thus, reboxetine could have the same impact on the treatment of depression as the serotonin selective reuptake inhibitors (SSRIs) have had because of their positive side effect profile when compared with the TCAs.

In this article, evidence suggesting that there are subsets of patients with differential responses to antidepressants is presented, and the use of neuroimaging and depletion paradigms are described. In time, such probes may be used to identify patients who might respond preferentially to the SSRIs or to new selective NRIs, for example, reboxetine.

**SEROTONIN DYSFUNCTION IN DEPRESSION**

Abnormalities of transmitter regulation may be located either presynaptically or postsynaptically and may involve transmitter precursors, or postreceptor second and third messengers. Serotonin precursor availability, synthesis,
and storage are all important factors. Early work, such as that of Coppen et al. (1973), suggested that plasma levels of the essential amino acid tryptophan, the key precursor of serotonin, were reduced in depressed patients.

The role of 5-HT$_{1A}$ and 5-HT$_{1B}$ autoreceptors may be of importance in the understanding of depression and its treatment. Recently this has been the subject of novel clinical investigations to determine whether the 5-HT$_{1A}$ antagonist pindolol, or 5-HT$_{1A}$ antagonists in combination with an SSRI, hasten the antidepressant response. Some studies, but not all, have reported that coadministration of pindolol enhances the therapeutic efficacy and shortens the onset of action of SSRIs in depressed patients.

In general, the available data support the concept that there is an abnormality in presynaptic serotonin function in depression. In part, this is reflected by the following observations: there is a blunted prolactin response to the serotonin precursor tryptophan, and a reduced prolactin response to the releasing agent fenfluramine. Results with the available neuroendocrine probes of postsynaptic function, for example, the serotonin agonist m-chlorophenylpiperazine (mCPP), have suggested that the functioning of postsynaptic serotonergic receptors responsive to mCPP is relatively intact in depression.

**Role of Serotonin Transporters**

The reuptake of serotonin by membrane transporters has been implicated in various forms of depression, and it is these transporters that are the site of action for the SSRIs. It has been known for some time that levels of serotonin transporters in platelets are reduced in depression. Assuming these changes in platelet transporters reflect similar changes in the brain, platelet serotonin transporter levels have been taken to be a biochemical index of depression. Postmortem studies in depressed patients have also demonstrated reduced transporter levels in some key brain regions. Until recently, however, there have been no studies investigating abnormalities in the living brain of depressed patients. The availability of ligands that bind to the transporter now allows this hypothesis to be tested.

In a recently completed single photon emission computerized tomography (SPECT) scanning study, the radiotracer $\beta$-CIT was used to study the serotonin transporter in depression. $^{[123]}$I $\beta$-CIT binds with high affinity to the serotonin transporter in the midbrain and the dopamine transporter in the striatum. In an initial group of 15 depressed patients, there was a robust reduction in the levels of the transporter to below that in healthy subjects in almost all patients (Malison RT, Price LH, Berman R, et al, unpublished observations). This result is consistent with reduced transporter levels as determined in platelets. This method may allow the identification of patients who will be particularly responsive to serotonin reuptake inhibitor drugs.

The same ligand can be used to identify whether or not a putative antidepressant drug binds to the serotonin transporter at clinically relevant doses. When a patient is medication-free, the ligand binds to the serotonin transporter in the midbrain and to the dopamine transporter in the striatum. After 1 week of treatment with the SSRI paroxetine, there was reduced ligand binding in the midbrain, as it had been displaced by the paroxetine. In contrast, in the striatum, paroxetine had no effect on the binding of the ligand to the dopamine transporter (Malison RT, Charney DS, Innis R, unpublished observations, June 1997).

**Abnormalities in Serotonin Transporter Gene Promoter**

The platelet and brain imaging data outlined above are supported by the recent observations of Lesch and colleagues, which indicate that there may be an abnormality in the promoter aspects of the serotonin transporter gene in patients with anxiety and depressive symptoms. Transcription of the human serotonin transporter gene was found to be modulated by a common polymorphism in its upstream region. In particular, the occurrence of the short allele variant reduces the transcriptional efficiency of the serotonin transporter gene promoter, resulting in decreased serotonin transporter expression and serotonin uptake in test systems. The presence of the short allele variant may relate to anxiety and depressive symptomatology as there appears to be an increased occurrence of this short allele in patients with unipolar depression.

**Tryptophan Depletion Studies**

A further approach to the study of serotonin function is the use of a tryptophan-free amino acid drink, which acutely reduces plasma levels of tryptophan, the serotonin precursor, to approximately 10% to 20% of baseline levels within 5 to 7 hours. Rapid tryptophan depletion in this manner reduces the availability of serotonin and allows the determination of the impact of reduced serotonin in the brain on mood.

The impact of lowering brain serotonin in patients with a past history of depression, but who are in remission, has been studied. Moreno and Delgado have presented data from healthy subjects showing that there was no major change in mood when serotonin levels were lowered (Moreno F, Delgado P, manuscript submitted). However, in patients in remission an exacerbation of depressive symptomatology suggesting a trait disturbance in serotonin function was observed. This work has recently been confirmed by Smith and colleagues.

Interestingly, it seems that there is a gender difference in response to tryptophan depletion; even in normal subjects, the impact of lowering brain serotonin is greater in females than in males. Nishizawa and colleagues have also investigated changes in serotonin synthesis in response to tryptophan depletion using PET imaging with...
C-α-methyl-tryptophan. They found baseline serotonin synthesis was lower in healthy females than in healthy males. It is possible that these findings may relate to the increased vulnerability of female patients to depression.

To summarize, there is a large body of data indicating a role for serotonin dysfunction in depression, at least in particular subgroups of patients. The use of probes such as those described above may allow the identification of subsets of depressed patients that might respond preferentially to either SSRIs or selective NRIs.

**NOREPINEPHRINE DYSFUNCTION IN DEPRESSION**

An important body of literature suggests a role for norepinephrine in patients with depression. These findings include alterations in platelet α2-adrenergic receptor binding, decreased cyclic AMP responses to β-adrenergic agonists, increased β-adrenergic receptors in the brains of suicide victims, and decreased growth hormone responses to clonidine and other catecholamine agonists.

**Catecholamine Depletion Studies**

As a corollary to the studies where serotonin depletion was achieved using the tryptophan-free amino acid drink, the effects of reducing brain catecholamines by the administration of α-methylparatyrosine (AMPT) have also been studied. These studies test the hypothesis that changes in neurotransmission through the catecholamine system may underlie the therapeutic response to norepinephrine uptake inhibitors. AMPT blocks tyrosine hydroxylase, the enzyme critical for the synthesis of norepinephrine and dopamine, resulting in a rapid depletion of both catecholamines. AMPT has very little effect on mood in normal subjects, but when given to depressed patients in remission, AMPT produced a return of depressive symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D) (Berman R, Charney DS, unpublished observations, March 1998). This response is in contrast to that seen with the active control treatment, diphenhydramine, and in some patients was quite robust.

My group has recently begun a study to determine whether or not a given individual will be sensitive to both catecholamine and serotonin depletion or whether there are particular subtypes of patients that respond preferentially to only one intervention. Of the first few subjects for which data are available, 4 subjects were catecholamine-depleted; 3 of the 4 experienced a robust increase in depressive symptoms, and, of those 3 patients, 1 also experienced an increase in depressive symptoms when serotonin was lowered (D.S.C. unpublished data, March 1998). Although in its early stages, this technique may help to determine whether or not there are relative subtypes of depressed patients in relation to catecholamines and serotonin.

**POSSIBLE MECHANISMS OF ANTIDEPRESSANT DRUG ACTION**

Mechanisms by which a variety of antidepressant drugs may increase serotonin neurotransmission have been discussed by Bluer and de Montigny. Preclinical studies suggest that antidepressant drugs may block the transporter site, with chronic treatment causing a desensitization of the inhibitory autoreceptor. The net effect of these actions is increased transmission.

By using the depletion paradigms described above, results of these preclinical studies have been tested in the clinical population. In patients maintained on SSRIs and depleted of serotonin, about 70% experienced a dramatic and rapid return of their depressive symptoms. These data suggest that the integrity of the serotonin system is critical to the function of SSRIs. However, in patients in whom remission was achieved with the relatively selective NRI desipramine, depletion of serotonin had no effect relative to control. This suggests that the mechanism of action of desipramine and other NRIs does not critically involve serotonin, that is, a different mechanism may be involved. In order to determine whether the catecholamine system is critical to the maintenance of antidepressant effect with NRIs, the effects of AMPT in patients maintained on different types of antidepressants were investigated. Patients in remission maintained on desipramine experienced a return of depressive symptoms when depleted of norepinephrine. When these patients were depleted of serotonin, they did not experience a return of depressive symptoms. In contrast, in patients maintained on an SSRI and catecholamine-depleted, remission remained intact. Thus, the mechanisms by which SSRIs and NRIs act are likely to be different at least in certain aspects of their immediate pharmacologic effects. This work raises the possibility that there are different mechanisms by which an antidepressant response may be achieved, and that if there are relevant subtypes of depressed patients with abnormalities in catecholamines versus serotonin, these drugs may be differentially effective.

Another important factor is that, in general, the efficacy of these 2 classes of drugs is not different in terms of the population as a whole. This raises the possibility that both monoamine systems may have critically important effects on a third system that is more central to antidepressant efficacy. At present, such a system is unknown; however, 2 possibilities are likely: both classes of drug could have effects beyond the receptor, influencing transcription factors, growth factors, or gene expression in a common way, or, alternatively, both classes of drug may affect behaviorally active neuropeptides.

**Postsynaptic Effects**

There are at least 15 different postsynaptic serotonin receptor subtypes, and, for most of these, their functional
role has not been determined. There are also a number of postsynaptic adrenergic receptors, in particular α-subtypes and β-subtypes. Beyond the receptor level, the work of Duman and others has shown that different classes of antidepressant drugs have common effects on second messengers, in particular alterations in cyclic AMP.\(^{18-20}\) Further into the intracellular cascade, a variety of antidepressant treatments affecting norepinephrine and serotonin have common pathways involving protein kinases, transcription factors, and neurotrophic factors such as brain-derived neurotrophic factor.\(^{19,21}\)

**Behaviorally Active Neuropeptides**

Another intriguing possibility is that the primary abnormality in depression may result from an abnormality in a neuronal system, as yet undiscovered, that is highly regulated by central monoaminergic systems. In this regard, it is clear there are important functional interactions between norepinephrine and corticotropin-releasing hormone (CRH). There is a large body of preclinical and clinical evidence that suggests a role for CRH in the mediation of anxiety and depressive mood,\(^{22}\) and it is well documented that levels of CRH in cerebrospinal fluid are elevated in depression. It is also clear that norepinephrine function is altered by CRH in many ways. For example, CRH increases the firing rate of the major brain norepinephrine-containing nucleus, the locus ceruleus. A drug such as reboxetine that has a very potent and selective action on the noradrenergic system may in turn have regulatory effects on CRH that could be relevant to its antidepressant action and perhaps convey added benefit.

**SUMMARY**

There is evidence for dysfunction of both the serotonin and norepinephrine systems in depression. At the present time, it is unclear whether this is a broad monoamine disturbance that occurs within every patient or whether there are different subtypes related to these monoamine systems. New imaging and genetic and pharmacologic tools now available will help to clarify this issue and should enable the determination of the differential efficacy of the SSRIs versus selective NRIs, such as reboxetine. Thus, it may be possible to predict treatment response based on subtypes of patients.

**Drug names:** clonidine (Catapres), desipramine (Norpramin and others), diphenhydramine (Benadryl and others), paroxetine (Paxil), pindolol (Visken).

**REFERENCES**