Role of Serotonin in the Pathophysiology of Depression: Focus on the Serotonin Transporter

Michael J. Owens¹ and Charles B. Nemeroff

Considerable evidence has accrued in the last two decades to support the hypothesis that alterations in serotonergic neuronal function in the central nervous system occur in patients with major depression. These findings include the following: (a) reduced cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin (5-HT) in drug-free depressed patients; (b) reduced concentrations of 5-HT and 5-HIAA in postmortem brain tissue of depressed and (or) suicidal patients; (c) decreased plasma tryptophan concentrations in depressed patients and a profound relapse in remitted depressed patients who have responded to a serotonergic antidepressant when brain tryptophan availability is reduced; (d) in general, all clinically efficacious antidepressants augment 5-HT neurotransmission following chronic treatment; (e) clinically efficacious antidepressant action by all inhibitors of 5-HT uptake; (f) increases in the density of 5-HT₂ binding sites in postmortem brain tissue of depressed patients and suicide victims, as well as in platelets of drug-free depressed patients; (g) decreased number of 5-HT transporter (detected with [³H]imipramine or [³H]paroxetine) binding sites in postmortem brain tissue of suicide victims and depressed patients and in platelets of drug-free depressed patients. In our studies, this reduction in platelet 5-HT transporter binding is not due to prior antidepressant treatment or hypercortisolemia and is not observed in mania, Alzheimer disease, schizophrenia, panic disorder, fibromyalgia, or atypical depression. In a pilot study, this deficit predicted treatment response to an experimental antidepressant. These findings support the hypothesis that alterations in 5-HT neurons play a role in the pathophysiology of depression.

Indexing Terms: mood disorders/depression/suicide/antidepressants/monoamines/receptor binding/platelets/neuroactive drugs

Initially designated "enteramine" in 1946 because of its isolation from enterochromaffin cells of the gastrointestinal mucosa as well as other tissues (e.g., amphibian skin and octopus salivary glands), through its chemical characterization and complete synthesis in 1948 and 1951, respectively, serotonin (5-hydroxytryptamine; 5-HT) has been of considerable interest to psychiatrists and pharmacologists. Soon after its chemical identification, the structural similarities between serotonin and LSD (lysergic acid diethylamide) led to the logical speculation that substances related to 5-HT might cause mental aberrations. Coincidentally, physicians working in sanitariums for tubercular patients noted that iproniazid, an antitubercular drug (and an inhibitor of monoamine oxidase (MAO)), improved mood in many individuals. Moreover, in the early 1950s it became evident that reserpine, an antihypertensive agent that depletes monoamine stores, including 5-HT, frequently produced depression as an unwanted side effect. At that time it was still unknown as to whether 5-HT was endogenous to the brain. Both bioassay and spectrophotofluorometric methods developed in the 1950s soon revealed that 5-HT was indeed enriched in certain areas of mammalian brain. However, the ground-breaking histofluorescence studies of Dahlstrom and Fuxe in the mid-1960s, using the Falk–Hillarp method, enabled visualization of monoamine-containing pathways within the central nervous system (CNS). This arguably marked the beginning of modern neuropsychopharmacology; thus, the hypothesis that alterations in 5-HT neurotransmission are of importance in the pathophysiology and treatment of psychiatric illnesses was promulgated nearly 30 years ago.

The current resurgence of interest in the role of 5-HT in psychiatry in the last 5–10 years is probably due to three related factors. First, as described here, there is a very substantial database supporting the view that 5-HT-containing neural systems are altered in depressed patients. Second, extraordinary progress has been made recently, both in the cloning of 5-HT receptor subtypes and in the synthesis of potent and relatively selective agonists and antagonists at these 5-HT receptor subtypes. These compounds are invaluable tools in the study of the regulation of 5-HT neural systems. Third, the synthesis and development of several highly selective 5-HT uptake inhibitors have allowed studies that have demonstrated them all to be effective antidepressant agents. These compounds are as efficacious as the tricyclic antidepressants but possess significantly less potential for nuisance (sedation and dry mouth) and potentially dangerous (orthostatic hypotension and cardiovascular) side effects.

The vast majority of CNS serotonergic nerve terminals originate in neuronal cell bodies of the raphe nuclei (dorsal and median) in the brainstem. These serotonergic perikarya project in a topographic fashion to neuroanatomically discrete areas, resulting in a diffuse, but heterogeneous, innervation throughout the brain (1) (Fig. 1).

In the CNS, 5-HT is believed to act predominantly as
an inhibitory neurotransmitter. The availability of tryptophan, the amino acid precursor of 5-HT, is the rate-limiting step in its synthesis. Tryptophan is transported from blood to brain by a carrier-mediated transport system, taken up by serotonergic nerve terminals and converted by tryptophan hydroxylase to 5-hydroxytryptophan (5-HTP), a short-lived intermediate. 5-HTP is then rapidly converted to 5-HT by the action of a relatively nonspecific L-aromatic acid decarboxylase. At least seven distinct serotonergic receptor subtypes have been identified and cloned. This has, to say the least, added considerable complexity to our understanding of serotonergic neurotransmission. After release from presynaptic 5-HT-containing terminals, 5-HT present in the synapse is inactivated by uptake into the presynaptic terminal by the 5-HT transporter. Once taken up into the presynaptic terminal, 5-HT may be degraded by MAO to 5-hydroxyindoleacetic acid (5-HIAA), its major metabolite, or it can be repackaged into secretory vesicles by the vesicular monoamine transporter. For a more comprehensive review of 5-HT neurobiology, see Aghajanian et al. (2) or Cooper et al. (3).

Reduced Concentrations of 5-HT and 5-HIAA

In a seminal study, Asberg et al. (4, 5) reported a bimodal distribution of 5-HIAA concentrations in the CSF of 68 depressed patients. Although some of the depressed patients had CSF 5-HIAA concentrations similar to those of normal controls, a large group (40%) of patients had significantly lower levels. Moreover, these latter patients were significantly more likely to have attempted suicide. In light of results obtained from a variety of different experimental techniques, reductions in CSF concentrations of monoamine metabolites are generally believed to reflect reduced neuronal activity (neuronal release). Long-term longitudinal studies (6) in depressed patients have noted similar reductions in CSF 5-HIAA in those patients most likely to attempt suicide. In addition to studies of CSF 5-HIAA, several studies have also demonstrated significant reduction of 5-HT concentrations in whole brain, hypothalamus, and amygdala in postmortem tissue from depressed patients or suicide victims. Comprehensive reviews of this area can be found in van Praag (7), Gibbons and Davis (8), and Meltzer and Lowy (9).

Tryptophan Depletion

It has long been known that reserpine and p-chlorophenylalanine (which reduces brain concentrations of 5-HT) may precipitate depression. Because tryptophan hydroxylase is not ordinarily saturated by its substrate, changes in plasma or brain tryptophan concentrations could lead to corresponding alterations in the ability of neurons to produce 5-HT. Interestingly, 50% of studies report significantly lower concentrations of free tryptophan in plasma in depressed patients (9-11).

Recently, strong evidence indicating the need for 5-HT neuronal integrity in antidepressant response was provided by studies of experimentally induced tryptophan depletion by administration of a special diet, in depressed patients (12). Abrupt reductions in the availability of tryptophan in the brain precipitated a rapid clinical relapse in remitted depressed patients within hours after ingestion of the diet. In this study, patients were treated with a low-tryptophan diet supplemented with high doses of neutral amino acids. Neutral amino acids, via competition with endogenous tryptophan for carrier-mediated brain uptake, add further to the presumed reduction of brain 5-HT induced by dietary tryptophan depletion. When challenged with this diet, remitted depressed patients receiving serotonergic antidepressants (e.g., imipramine, fluoxetine, fluvoxamine) promptly relapsed. When tryptophan supplementation was provided, the patients promptendly became euthymic. These findings suggest that acute alterations in brain 5-HT availability may significantly alter mood, and that the integrity of serotonergic neuronal activity is a prerequisite for continued therapeutic response to certain antidepressant drugs.

Neuropharmacological Consequences of Antidepressant Treatment

Although the "final common pathway" of antidepressant mechanism of action remains unknown, neurochemical and electrophysiological studies in laboratory animals suggest that virtually every known antidepressant drug and electroconvulsive shock (ECS) treatment functionally increases serotonergic neurotransmission during long-term treatment (Table 1). De Montigny and Blier have pioneered this research for the past decade. De Montigny and Aghajanian (13) first reported that

Fig. 1. Summary diagram of the primate serotonergic system: The main nuclei are shaded; the fiber pathways are shown as broken lines.
AC, anterior commissure; AM, amygdaloid nucleus; CB, cortical bundle; CC, corpus callosum; Cer, cerebellum; CQ, corpus quadrigemina; CSM, centralis superior nucleus, pars mediales; CSuI, central sulcus; DG, dentate gyrus; DR, dorsal raphe; F, fornix; FCtx, frontal cortex; H, habenula; Hipp, hippocampus; i, layer i; IC, internal capsule; IO, inferior olive nucleus; IV, layer iv; LC, locus ceruleus; MB, mammillary body; MFB, medial forebrain bundle; OB, olfactory bulb; P, pons; RM, raphe magnus; RO, raphe obscurus; RP, raphe pallidus; S, septum; SM, stria media; T, thalamus; TCtx, temporal cortex; VAPP, ventro amygdalofugal pathway; VR, raphe ventriculic. Reprinted from ref. 7 with permission.
tricyclic antidepressant treatment increases forebrain neuronal responsivity to 5-HT. Similar conclusions were reached regarding ECS treatment (14). These electrophysiological models also suggest that lithium may exert its well-documented ability to convert antidepressant nonresponders to responders via augmentation of serotonergic neurotransmission (15). These findings have been extended by this group to indicate that tricyclic antidepressants, MAO inhibitors, 5-HT-uptake inhibitors, ECS, lithium, and 5-HT_{1A} agonists augment serotonergic neurotransmission in the hippocampus in a temporal sequence similar to that of the clinical treatment response. The hippocampus was chosen for these studies because it allows for relatively easy and consistent electrophysiological investigation of a known serotonergic pathway. This does not necessarily imply that the hippocampus is the site where increased serotonergic neurotransmission underlies the antidepressant action. It is likely that similar increases in serotonergic neurotransmission are found in other limbic or cortical regions. As reviewed by this group (16), tricyclic antidepressants and ECS enhance 5-HT neurotransmission by increasing the sensitivity of postsynaptic 5-HT_{1A} receptors, whereas selective 5-HT-uptake inhibitors produce this effect by reducing the function of terminal and dendritic 5-HT autoreceptors, thereby increasing the amount of 5-HT released per neuronal depolarization. These studies also suggest the potential use of different classes of antidepressant drugs to act at different sites simultaneously to achieve synergistic effects in enhancing serotonergic neurotransmission.

5-HT-uptake Inhibitors Are Antidepressants

Several new 5-HT-uptake inhibitors have been developed for treatment of depression: fluoxetine, sertraline, and paroxetine, which are available in the US, and other agents available in other countries and under investigation in the US such as fluvoxamine, citalopram, and litoxetine. Thus far, all of the 5-HT-uptake inhibitors are effective in treating depression and have equal efficacy with the tricyclic antidepressants, except perhaps in severe melancholic inpatients, although this is still debatable.

Changes in 5-HT_{2} Receptors

Several investigators have reported an increased density of postsynaptic 5-HT_{2} receptor binding sites in the frontal cortices from depressed suicide victims (17–19) and unmedicated depressed patients (20). Moreover, Yates et al. (20) noted that depressed patients who died while euthymic showed a marked reduction in 5-HT_{2} receptor binding, even when compared with controls. This upregulation of cortical 5-HT_{2} receptors in depression could be interpreted as an adaptive response to reduced synaptic 5-HT.

As will be discussed below, the human platelet, for a number of reasons, has been studied as a model for the serotonergic neuron. Several investigators have measured the number of 5-HT_{2} receptors on human platelets. The results, in general, tend to resemble those reported in brain tissue. Biegon et al. (21–23), Arora and Meltzer (24), and Pandey et al. (25) have observed increases in platelet 5-HT_{2} binding-site density in depressed individuals. Moreover, the changes appear to be state-dependent, in that 5-HT_{2} binding-site density decreased to control values only in those patients who showed clinical improvement.

The Serotonin Transporter

The primary means by which serotonergic neurons terminate neurotransmission is through the concurrent uptake of one molecule of 5-HT plus one Na⁺ ion via the 5-HT transporter molecule. This effectively reduces synaptic cleft concentrations of 5-HT to amounts not capable of maintaining postsynaptic activation. Because both tricyclic antidepressants and the newer 5-HT-selective reuptake inhibitors bind to the 5-HT transporter and inhibit 5-HT uptake, the importance of understanding the biochemical characteristics of the transporter has long been appreciated. The recent cloning of both the rat and human 5-HT transporter should provide invaluable knowledge on antidepressant drug and transporter molecule interactions, and possibly lead to the design and synthesis of novel antidepressant medications. Additionally, study of the 5-HT transporter in depression has already provided insight into the pathophysiology of the disease (see below), and further scrutiny with molecular biological techniques may very well provide additional information on 5-HT neuronal alterations in depression.

Blakely and Berson (26) have recently recounted the cloning of the 5-HT transporter. Briefly, detailed molecular studies of the transporter required the availability of an abundance of highly purified transporter protein or a cDNA that could be used in cell expression studies. Until that time, only the relatively abundant γ-aminobutyric acid (GABA) and glutamate transporter proteins had been purified in functional form. Knowledge of
the protein sequence of the GABA transporter allowed for the isolation of the cDNA that encoded the GABA transporter. The sequence analysis of this molecule revealed a lack of homology with other transport molecules, e.g., the intestinal Na+/glucose transporter and the Escherichia coli Na+/proline carrier. Thus, despite hopes that cloning of the GABA transporter might provide additional probes for identification of monoamine transporters, progress awaited the isolation and identification of another transporter gene. This was accomplished after the isolation of a cDNA encoding the norepinephrine transporter. Sequence analysis of the GABA and norepinephrine transporters showed remarkable homology, given the clear pharmacological differences between the two transporters. Specific regions within, or adjacent to, the deduced 12 membrane-spanning regions were even more highly conserved and thus provided sites from which oligonucleotide probes could be synthesized to identify related cDNAs that might encode other transporters, including the 5-HT transporter. Shortly thereafter, Blakely et al. (27) and Hoffman et al. (28) simultaneously reported the cloning of 5-HT transporters in rat brain and RBL (a peripheral cell line), respectively.

As shown in Fig. 2, the cDNAs encode proteins that are predicted to have 12 hydrophobic membrane-spanning regions. This topology is shared with other classes of carrier molecules, including the Na+/glucose transporter, the multidrug-resistance gene product, and prokaryotic "nutritional" transporters such as the Na+/glycerol or Na+/proline carrier noted above (29). Although these molecules do not display significant homology to the 5-HT transporter, the neurotransmitter transporters (5-HT, norepinephrine, dopamine, GABA, etc.) all show significant homology with each other. Furthermore, the close relationship between the GABA transporter/norepinephrine transporter homologs suggests that they may have all evolved from a single precursor transporter.

The amino acid sequence conservation among the neurotransmitter transporters is most striking within the hydrophobic membrane-spanning regions (Fig. 2). All of these transporters exhibit glycosylation sites on the extracellular loop between transmembrane domains 3 and 4. Additionally, all exhibit potential phosphorylation sites on the intracellular portions of the molecule, suggesting the potential for posttranslational regulation. Although the potential for subtypes of serotonin transporters exists, the fact that independent laboratories cloned identical molecules from brain and a peripheral cell line suggests that a single type is most abundant. More recently, cDNAs encoding human 5-HT transporters have been isolated by Blakely's group (30) and others (31, 32) and localized to chromosome 17. The predicted sequence of the human 5-HT transporter shows 92% homology with the rat transporter. Leach et al. (32) have confirmed that the human brain and platelet 5-HT transporter are identical. Although it appears that a single gene is responsible for expression of the transporter, Ramamoorthy et al. (30) observed multiple hybridizing mRNAs in human placenta and lung, suggesting the possibility of alternative processing and production of several different mRNAs such as that observed with the dopamine D2 receptor.

Prior to the molecular cloning of the 5-HT transporter, biochemical studies were undertaken with radiolabeled 5-HT-uptake inhibitors or 5-HT itself. The specificity of many of the selective uptake inhibitors was also exploited for anatomical mapping and regulation studies of serotonergic nerve terminals. As noted earlier, two systems act in series to terminate the action of 5-HT. The 5-HT transporter removes 5-HT from the synaptic cleft and returns it into the cell, where it is either metabolized by MAO or sequestered into secretory vesicles by the vesicular transporter.

Biochemical and pharmacological studies have shown that the actual uptake process involves the binding of 5-HT to a recognition site within the transporter and its transport across the membrane together with a Na+ ion. A second step involves the translocation of a K+ ion across the membrane to the outside of the cell. In recent studies, it has become increasingly clear that selective uptake inhibitors such as paroxetine, citalopram, and fluoxetine bind to the same or closely overlapping site in the transporter as 5-HT itself (33–36).

A class of amphetamine derivatives, including p-chloroamphetamine, fenfluramine, and 3,4-methylenedioxyamphetamine (MDMA, "ecstasy"), causes degeneration of serotonergic nerve terminals by an as yet unknown process, but one that may require dopamine release as well. Each of these compounds releases 5-HT by a nonexocytotic process because it does not require Ca2+. Rudnick and Wall (37–39) showed in a series of elegant studies that these compounds can bind to the transporters (at least in the case of MDMA, this is at the same site as where selective uptake inhibitors bind) and catalyze the exchange of one molecule of 5-HT to the outside of the membrane for one molecule of drug to the inside. Together with uptake-blocking properties, these compounds can lead to large concentrations of synaptic 5-HT.
Given the well-known observation that treatment response to antidepressants generally requires 2 weeks or more, studies of antidepressant mechanisms of action have focused more recently on long-term adaptive changes, e.g., consistent decreases in 5-HT\textsubscript{2} and \beta-adrenergic receptor binding along with attenuated norepinephrine-stimulated cAMP responses at \beta-adrenergic receptors. Therefore, chronic drug effects on 5-HT transporter regulation have been studied by examining 5-HT uptake, antidepressant binding, and, more recently, changes in mRNA expression. In general, various monoamine transporters have been found to be much more resistant to adaptive changes than are classical pre- and postsynaptic receptors. Nevertheless, several, but not all, studies have found evidence—using either kinetic analysis of \[^{3}H\]5-HT uptake or binding of uptake inhibitors—of time-dependent regulation of the 5-HT transporter (40–42). Very recently, Leach et al. (43) directly examined expression of 5-HT transporters after chronic antidepressant treatment. They noted that the nonselective 5-HT/norepinephrine uptake inhibitor imipramine and the selective 5-HT uptake inhibitor fluoxetine both produced significant (30–40\%) reductions in 5-HT transporter mRNA concentrations in the raphe, as determined by Northern blot analysis. Similar results were also observed with the relatively selective 5-HT uptake inhibitor chlorimipramine and the norepinephrine uptake inhibitor desipramine, though these differences did not reach statistical significance. In contrast, the MAO inhibitor clorgyline and three 5-HT agonists (8-hydroxydipropylaminotetralin, m-chlorophenylpiperazine, and 1-(2,5-dimethoxy-4-iodophenyl)-2-amino- propane) were without effect. Consistent with the observed regulation at the transcriptional level is the report of cAMP regulation of 5-HT transporter expression in a human placental carcinoma cell line (44). Of additional interest to all neurobiological investigators is the finding that 5-HT transporter mRNA was also observed in frontal cortex, hippocampus, and neostriatum, areas devoid of serotonergic perikarya (43). This was not observed by Northern blot analysis of brain RNA extracts, but after the more sensitive technique of reverse transcription polymerase chain reaction followed by Southern blot analysis and sequence analysis. Although mRNA might be expected to be exclusively located in neuronal perikarya, several investigators recently have reported the selective transport and presence of mRNA and the associated protein-synthesis machinery to manufacture proteins at the synapse (45).

Stanley et al. (46), in a seminal observation, documented a reduction in the number of \[^{3}H\]imipramine-binding sites in the frontal cortex and hypothalamus of depressed suicide victims. Similarly, Perry et al. (47) reported a reduction in \[^{3}H\]imipramine-binding sites in the hippocampus and occipital cortex of patients with depressive illness. At that time, \[^{3}H\]imipramine was the ligand of choice for labeling 5-HT transporters. Leake et al. (48) recently confirmed this finding in tissue from depressed subjects by using the much more selective ligand, \[^{3}H\]citalopram. These findings further suggest an alteration in neuronal 5-HT uptake mechanisms associated with depression.

Given the inherent difficulties in obtaining postmortem brain tissue from large numbers of clinical samples, a less invasive model of the neuronal 5-HT transporter was needed. Fortunately, the platelet has been proposed, and found, to be an useful model because it shares many of the same properties as the 5-HT nerve terminal. As reviewed in detail by Pletscher (49) and Da Prada et al. (50), platelets and 5-HT neurons show many common similarities, including embryological ancestry, biochemistry, and identical 5-HT transporter sequences (32) (Table 2).

Thus, ~10 years ago Langer and colleagues (51, 52) and Paul et al. (53) reported decreased \[^{3}H\]imipramine binding in platelets from drug-free depressed patients. These results, which have subsequently been replicated in many, but not all, studies, have become one of the most reproducible findings in the biology of affective illness (54–56). In our original study (57), we found significant reductions in the density of \[^{3}H\]imipramine-binding sites in platelets of both young and middle-aged depressed patients (<50 years) and in an elderly depressed group as well, compared with age- and sex-matched controls. We have now confirmed these findings in a large study of >150 drug-free depressed patients and 100 normal controls (Fig. 3). Moreover, patients with panic disorder, mania, fibromyalgia, Alzheimer disease, and atypical depression did not exhibit any alterations in platelet \[^{3}H\]imipramine binding (Fig. 4), indicating a specificity for major depression. We have, however, noted a decrease in platelet \[^{3}H\]imipramine binding in women with premenstrual syndrome (58), a disorder that is readily treated with 5-HT uptake inhibitors.

Unlike the more recently available ligands for selective labeling of the 5-HT transporter, \[^{3}H\]imipramine also binds with high affinity to a non-Na\textsuperscript{+}-dependent site that may be unrelated to the 5-HT transporter. Therefore, more recent studies have incorporated the use of the much more selective ligands, \[^{3}H\]paroxetine or \[^{3}H\]citalopram, for use in platelet binding studies. In

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Data taken from Da Prada et al. (50) and Leach et al. (43).

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contrast to recent studies that have not found changes in platelet \[^{3}H\]paroxetine binding in depressed patients (59, 60), we observed in 28 drug-free depressed patients and 28 age-matched controls that the number of platelet binding sites for both \[^{3}H\]paroxetine and \[^{3}H\]imipramine are reduced, confirming and extending our previous results (61). Though several reports have suggested that the reduction in platelet 5-HT transporter binding may be secondary to prior antidepressant administration (62–64), we have found that depressed patients who have never received antidepressant treatment also exhibit reductions in platelet binding of \[^{3}H\]imipramine (65).

In a pilot study, we recently noted that patients who respond to a novel antidepressant exhibited at baseline the greatest decreases in platelet \[^{3}H\]imipramine binding, and that clinical recovery is associated with an increase in the number of these binding sites (66). Similarly, although low \(B_{\text{max}}\) values may persist for a considerable time after clinical improvement during and after imipramine treatment, long-term increases in \(B_{\text{max}}\) values can follow complete remission and the \(B_{\text{max}}\) values can remain high, even after imipramine has been discontinued for 4 weeks (67). These results and others (68, 69) have led to the suggestion that the apparent low density of 5-HT transporters may be a state-dependent marker of depression, though this interpretation is not universally accepted (70, 71). Indeed, whether platelet 5-HT transporters can be regulated by central or peripheral mechanisms is unclear. We have found that depletion of CNS 5-HT for periods that allow for the complete turnover of 10 generations of platelets did not alter platelet binding of \[^{3}H\]citalopram (72).

Although the studies to date are not definitive, and the mechanism(s) responsible unknown, the observation of decreased platelet and brain 5-HT transporter binding in depression is a remarkably consistent observation. Thus measurement of platelet 5-HT transporter sites may provide a “window to the brain” and potentially provide a useful, easily available laboratory “marker” to aid both in diagnosing depression and in monitoring response to pharmacotherapy. The recent advances in the molecular biology of the 5-HT transporter may allow for the characterization of the components that regulate its expression in brain and platelets (nascent mRNA can be found in the enucleate platelet). Moreover, studies could determine whether the 5-HT transporter gene itself is structurally altered in depressed subjects or their families, especially in those who exhibit the decrease in transporter binding. Clearly, the development of ligands to label the 5-HT transporter for use in functional brain-imaging studies such as positron-emission tomography or single-photon-emission computed tomography could rapidly enhance our ability to determine the specificity of these findings and to determine the anatomical areas altered in depression. Such breakthroughs seem likely in the near future.

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