The Role of Serotonin in Schizophrenia

by Avraham Bleich, Serena-Lynn Brown, Rene Kahn, and Herman M. van Praag

Abstract

Studies examining serotonin (5-hydroxytryptamine; 5HT) in schizophrenia show variable and inconsistent findings, which might reflect the heterogeneity of the disease. When these studies are reviewed in the light of Crow's "two-syndrome" paradigm of schizophrenia, a new trend emerges. It appears that 5HT findings may be related to certain features of Type II schizophrenia such as negative symptoms, degenerative brain changes, and chronicity in the following manner: (1) $5HT_2$ antagonists, which have recently become available, have been shown to have an antipsychotic effect, particularly on the negative symptom cluster. (2) Decreased levels of 5-hydroxyindoleacetic acid in cerebrospinal fluid have been found to be correlated with cortical atrophy or ventricular enlargement in schizophrenic patients. (3) A subgroup of chronic schizophrenic patients has been shown to have elevated levels of platelet or whole blood 5HT. We propose, then, that 5HT dysfunction might be related to Type II, or negative syndrome, schizophrenia, and that the nature of this dysfunction might involve 5HT postsynaptic receptor hypersensitivity. We further suggest that the pharmacotherapy of schizophrenia should include a 5HT-blocking component, as well as a dopamine-blocking component, and we propose that future research should address the role of selective 5HT receptor hypersensitivity in schizophrenia.

This article proposes a reexamination of the role of serotonin (5-hydroxytryptamine; 5HT) in schizophrenia based on recent work, both psychopharmacological and biological, in this disorder. We first review the bases of the monoaminergic (primarily dopaminergic and serotonergic) theories of schizophrenia, after which we focus on central 5HT measures (post-mortem brain studies, cerebrospinal fluid (CSF) metabolite studies, and neuroendocrine challenge measures), peripheral 5HT measures (platelet and whole blood 5HT levels, platelet 5HT uptake, and platelet ^{3}H-imipramine binding), and treatment studies using 5HT precursors, 5HT-depleting agents, and 5HT antagonists.

The Dopamine Hypothesis of Schizophrenia

Biological research on the pathogenesis of schizophrenia has been dominated by the dopamine (DA) hypothesis for more than two decades. Originally, proponents of this hypothesis proposed that schizophrenia might be related to a primary disturbance of DA transmission or metabolism resulting in an increase in dopaminergic function (van Praag 1967; Meltzer and Stahl 1976; Snyder 1976). Evidence for this hypothesis included the following facts: (1) Antipsychotic (neuroleptic) drugs had been shown to be DA antagonists, with antipsychotic potency directly correlated with DA receptor binding and blockade (Miller et al. 1974; Meltzer and Stahl 1976). (2) Clinical similarities were observed between amphetamine psychosis and paranoid schizophrenia, and it was shown that amphetamines caused the release of presynaptic DA and norepinephrine, and that neuroleptics could attenuate the

Reprint requests should be sent to Dr. S.L. Brown, Department of Psychiatry, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10561.

acute symptoms of amphetamine psychosis (Snyder 1973; Angrist et al. 1974) (3) Recent work using positron emission tomography has shown increased binding of (^{3}N-(^{11}C)methyl)spiperone to DA D_2 receptors in the caudate nuclei of both neuroleptic-treated an untreated schizophrenics, thus suggesting an increase in DA receptor number in this disease that is unrelated to neuroleptic treatment (Wong et al. 1986)

As psychopharmacological techniques have become more sophisticated, it has been shown that certain neuroleptics (e.g., chlorpromazine, thioridazine, and clozapine) have a high affinity for serotonergic as well as dopaminergic receptors (Reynolds et al. 1983; Altar et al. 1986). In addition, it has become increasingly recognized that treatment of schizophrenia with neuroleptics is only partially effective. While conventional neuroleptics diminish the psychotic, productive symptoms of schizophrenia, negative symptomatology is hardly affected. Therefore, questions have been raised about the role of dopaminergic versus other transmitter mechanisms in the pathogenesis of schizophrenia, and about whether different subsets of schizophrenic symptomatology might be under the influence of different receptor systems.

Crow's Hypothesis: A Dopaminergic and a Nondopaminergic Form of Schizophrenia?

Recently, Crow (1980*a*, 1980*b*) proposed that schizophrenia can be divided into two syndromal dimensions. Type I syndrome consists of primarily positive symptoms, with a predominance of hallucinations, delusions, thought disorder, and bizarre behavior. This syndrome is thought to reflect an increase in dopaminergic function and to respond well to neuroleptics. Type II syndrome consists of primarily negative symptoms (e.g., social and emotional withdrawal, apathy and loss of drive, restricted and blunted affective responsivity, narrowing of ideation, and poverty of speech) This syndrome is thought to be associated with structural abnormalities in the brain (cortical atrophy or ventricular enlargement), chronic course, and a limited response to neuroleptics

The sizable heuristic value of Crow's hypothesis is related to its comprehensiveness. On the other hand, such a far-ranging theory is vulnerable to many problems in verifying its various components and exploring the interrelationships between them. For example, the relationship between enlarged ventricles and negative symptoms, proposed by Crow (1980*a*, 1980*b*) and by others (Andreasen et al 1982, Pearlson et al 1984), does not appear to be as clearcut as initially hypothesized (Weinberger 1984; Losonczy et al. 1986*a*). In fact, recently Crow et al (1986) proposed that the temporal lobe should be explored as the potential primary site of structural brain abnormalities in schizophrenic patients on the basis of recent data from post-mortem brain studies conducted by Crow's group.

From a clinical point of view, the concept of negative symptomatology requires much clarification Recently, Carpenter et al. (1985) discussed ambiguities in this concept. After emphasizing the fact that there are several differing lists purporting to define negative symptoms, these authors provide their own definition of primary negative symptoms, or deficit symptoms, which they consider to be core features of the disease, and differentiate these from secondary negative symptoms. Secondary negative symptoms can derive from other psychopathological components of the disease process such as depression or emotional and social withdrawal due to psychotic decompensation. Negative symptoms could also be associated with neuroleptic-induced side effects (e g., akinesia and sedation) or prolonged exposure to an understimulating environment (e.g , chronic institutionalization)

These different components of such a putative negative symptom complex might be the target for various psychopharmacological interventions, and might explain how various different psychopharmacological agents, sometimes with opposing actions (e.g., neuroleptics, amphetamines, L-dopa, propranolol, alprazolam, and monoamine oxidase inhibitors) have been reported to ameliorate negative symptoms. (Carpenter et al. 1985; Meltzer et al. 1986; Bucci 1987)

Even with the problems cited above, Crow's two syndrome hypothesis has important implications for the crucial issue of heterogeneity in schizophrenia. Several recent studies with new selective and/or potent 5HT antagonists have suggested their efficacy in schizophrenia, especially in the negative syndrome (Ceulemans et al 1985*a*, 1985*b*, Gelders et al 1985*a*, 1985*b*). Therefore, particularly in view of the lack of complete efficacy of DA antagonists in this syndrome, it seems that Crow's two-syndrome paradigm might provide a valuable new way of reexamining the possible role of serotonin in schizophrenia

The 5HT Hypothesis of Schizophrenia

Serotonergic theories of schizophrenia originated several decades ago with the observation that the hallucinogenic drug LSD was peripheral 5HT antagonist. This led Gaddum (1954) and Woolley and Shaw (1954) to suggest that schizophrenia might be related to a deficiency of 5HT.

Other investigators proposed a "transmethylation" theory of schizophrenia, speculating that normally occurring biogenic amines, including certain indoleamines, might be converted to methylated amines with hallucinogenic properties that might account for some forms of schizophrenia (Kaplan et al. 1974; Gillin et al. 1976*a*).

This theory, however, has fallen from favor over time, as no differences have been found in the concentration of these methylated indoleamines in the urine (Carpenter et al. 1975; Gillin et al. 1976*a*), whole blood and plasma (Axelsson and Nordgren 1974; Lipinski et al. 1974), and CSF (Corbett et al. 1978) of schizophrenic patients in comparison to normal controls. In addition, the type of psychosis induced by transmethylated indoleamines and other hallucinogens, such as LSD, involves primarily perceptual disturbances and expresses only one narrow dimension of schizophrenic psychopathology (Szara 1967; Snyder 1972), thereby putting the very foundation of the transmethylation theory in question.

Nevertheless, new data have emerged on the possible involvement of 5HT in schizophrenia, justifying the reexamination of the role of 5HT in this psychiatric disorder.

Central 5HT Measures

Post-Mortem Studies. Progress in the direct assessment of the possible involvement of abnormalities in the 5HT system has been limited because the only direct means of assaying central 5HT function in schizophrenia has been the analysis of levels of its primary metabolite 5-hydroxyindoleacetic acid (5HIAA) and its precursor tryptophan, all reflecting 5HT metabolism and therefore considered to be presynaptic parameters. Postsynaptic parameters are reflected by the measurement of 5HT (generally $5HT_2$) receptor density in postmortem brain samples of schizophrenic patients.

Only a few studies of this kind have been done, and the limited data are difficult to interpret because of differences in type of control group, cause of death, drug-free interval before death, age, food intake, time elapsing between death and autopsy, regions of brain sampled, dissection techniques, and laboratory techniques in the different studies.

Crow et al. (1979) found increased 5HT in the putamen of nine chronic schizophrenic patients (medication histories not completely known) as compared to normal controls who died of similar causes. Farley et al. (1980) reported increases in both 5HT and 5HIAA in the globus pallidus and nucleus accumbens, and increases in 5HT alone in the medial olfactory area as well as the lateral hypothalamus of chronic paranoid schizophrenics as compared to normal controls. Korpi et al. (1986) investigated 30 chronic schizophrenic patients with or without suicide as a cause of death, compared to normal controls without psychiatric or neurological disorders. They found that 5HT concentrations were significantly elevated in the basal ganglia and that 5HIAA concentrations were significantly elevated in the occipital cortex in schizophrenic patients as compared to normal controls. No differences were reported in 5HT concentration in the hypothalamus between schizophrenic patients who committed suicide and those who did not.

However, Winblåd et al. (1979) found the opposite: that is, decreased mean 5HT levels in hypothalamus, medulla oblongata, and hippocampus of post-mortem brain specimens of 12 schizophrenic patients who had been on neuroleptics at the time of death and half of whom had previously been lobotomized. Joseph et al. (1979), however, could not demonstrate any significant difference in 5HT, 5HIAA, or tryptophan concentrations in the putamen, hippocampus, or temporal cortex from 15 individuals retrospectively diagnosed as schizophrenic, both on and off neuroleptics, as compared to normal control specimens taken from a general hospital morgue.

Post-mortem studies of cortical $5HT_2$ receptor binding in schizophrenic brain specimens have generally used two radioligands, ^{3}H-LSD and ^{3}H-ketanserin. Bennett et al. (1979) found reduced binding of ^{3}H-LSD in frontal cortex from 21 schizophrenic patients, some of whom had been heavily treated with neuroleptics before death. On the other hand, Whitaker et al. (1981) could not demonstrate any change in ^{3}H-LSD binding in the frontal cortex of 13 chronic schizophrenic patients as compared to normal controls. Moreover, they reported that for five of these schizophrenic patients who had

Table 1. Cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA): Schizophrenic patients vs. controls

Investigators	Number of schizophrenic subjects	Condition	CSF 5HIAA
Ashcroft et al. (1966)	7	Unmedicated, baseline[1]	Low
Bowers et al. (1969)	7	Unmedicated, baseline[1]	Low
Persson & Roos (1969)	40	Medicated, baseline[1]	NS[2]
Rimón et al. (1971)	22	Unmedicated, baseline[1]	NS[2]
Bowers (1974)	17	Unmedicated, postprobenecid	NS[2]
Post et al. (1975)	17	Unmedicated, postprobenecid	NS[2]
Gattaz et al. (1982)	28	Unmedicated, baseline[1]	Low
Nybäck et al. (1983)	26	Unmedicated, baseline[1]	NS[2]
Potkin et al. (1983)	24	Unmedicated, baseline[1]	NS[2]

[1]Without probenecid
[2]NS = No significant differences between groups

been drug free for 1 year before death, there was a significant increase in cortical ^{3}H-LSD binding compared to normal controls.

Mita et al. (1986) found a decrease in ^{3}H-ketanserin binding sites in the prefrontal cortex of nine schizophrenic patients, with no differences shown between neuroleptic-treated and untreated individuals. However, Reynolds et al. (1983) demonstrated no significant differences in ^{3}H-ketanserin binding in the frontal cortex of 11 schizophrenic patients (medication history unknown) as compared to controls.

In conclusion, it appears that post-mortem brain studies of schizophrenic patients, while providing one of the few means of assessing 5HT function in the brain directly (via examining 5HT, 5HIAA, and tryptophan concentrations as well as 5HT postsynaptic receptor binding parameters), have unfortunately yielded inconsistent and contradictory results, in all probability due to reasons cited above.

CSF Studies. A common strategy for investigating central 5HT metabolism in humans is measurement of the 5HT metabolite 5HIAA in CSF. Investigators have traditionally measured either baseline CSF 5HIAA directly or after administration of probenecid, which inhibits the transport of 5HIAA from the central nervous system (CNS), including the CSF, to the periphery. Probenecid-induced 5HIAA accumulation in the CSF is considered to be a crude indicator of 5HT metabolism in the CNS, and thus to reflect presynaptic 5HT parameters.

Data from studies examining CSF 5HIAA in schizophrenic patients compared to control subjects have been inconsistent. Several studies (Ashcroft et al. 1966, Bowers et al. 1969; Gattaz et al. 1982) have demonstrated decreased CSF 5HIAA levels in schizophrenic patients. However, the majority of investigators have not been able to demonstrate any differences in CSF 5HIAA in schizophrenic patients compared to controls (Persson and Roos 1969; Rimón et al. 1971; Bowers 1974; Post et al. 1975, Nyback et al. 1983; Potkin et al. 1983). Table 1 summarizes data on CSF 5HIAA findings in schizophrenic patients versus controls.

More recently, CSF 5HIAA concentration in schizophrenia has been linked to specific identifying characteristics. When schizophrenic patients are divided into two subpopulations, those with brain atrophy (increased sulcal width and/or enlarged brain ventricles, also expressed as an increase in ventricle-to-brain ratio, or VBR) and those without brain atrophy, a new trend emerges.

Three groups of investigators (Nybäck et al. 1983; Potkin et al. 1983; Losonczy et al. 1986*b*) have reported that schizophrenic patients with brain atrophy show decreased CSF 5HIAA as compared both to schizophrenic patients without brain atrophy and to normal controls. The total number of patients involved in these studies was 67; patients were drug free at the time of the studies and both baseline (Nybäck et al. 1983; Potkin et al. 1983) and postprobenecid CSF 5HIAA (Losonczy et al. 1986*a*, 1986*b*) were measured.

It should be noted, however, that the DA metabolite homovanillic acid (HVA) has also been shown

to be decreased in the same population of schizophrenic patients, those with enlarged ventricles. Interestingly, CSF 5HIAA correlates with CSF HVA significantly, and both correlate negatively with VBR. One possible explanation for such a correlation between these metabolites might involve a similar transport mechanism from the CSF (van Kammen et al. 1986).

Another subdivision within the group of schizophrenic patients involves those who have attempted suicide versus those who have never attempted suicide. Van Praag (1983), Ninan et al. (1984), and Banki et al. (1984) all have shown a correlation between low CSF 5HIAA and suicidal behavior, especially recent suicide attempts, in schizophrenic patients. However, Roy et al. (1985) could not replicate this finding. Interestingly, Levy et al. (1984) found that an increased VBR in chronic schizophrenic patients is significantly associated with a history of suicide attempts. Therefore, suicidality might be another possible factor linking decreased central 5HT metabolism and Type II schizophrenia.

Van Kammen et al. (1986) have recently presented data from seven studies including more than 100 schizophrenic patients suggesting that CSF 5HIAA concentration is not altered during neuroleptic treatment. This is somewhat surprising in view of the fact that neuroleptics might affect the serotonergic system both presynaptically and postsynaptically by inhibiting 5HT uptake (Arora and Meltzer 1983) and by blocking 5HT receptors (Reynolds et al. 1983; Altar et al. 1986).

Finally, a few additional studies have shown an association between increased CSF 5HIAA and family history of schizophrenia (Sedvall and Wode-Helgodt 1980), and the schizophrenic symptom of "mannerisms and posturing" (King et al. 1985) within the schizophrenic population. The meaning of these data is unclear as yet. Table 2 summarizes data on CSF 5HIAA differences between schizophrenic subgroups.

The following conclusions can be drawn: (1) Cortical atrophy and ventricular enlargement in schizophrenic patients are significantly associated with decreased CSF 5HIAA levels. These data are consistent across all three studies

Table 2. Cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5HIAA) in schizophrenia: Subgroup differences

Investigators	Number of schizophrenic subjects	Condition	CSF 5HIAA
Sedvall & Wode-Helgodt (1980)	36	Unmedicated, baseline[1]	High in schizophrenic patients with family history of schizophrenia
Nyback et al. (1983)	26	Unmedicated, baseline[1]	Low in schizophrenic patients with cortical atrophy or ventricular enlargement
Potkin et al. (1983)	24	Unmedicated, baseline[1]	Low in schizophrenic patients with cortical atrophy or ventricular enlargement
van Praag (1983)	20	Unmedicated, postprobenecid	Low in schizophrenic patients with history of suicide attempts
Ninan et al. (1984)	16	Unmedicated, baseline[1]	Low in schizophrenic patients with history of suicide attempts
Banki et al. (1984)	15	Unmedicated, baseline[1]	Low in schizophrenic patients with history of suicide attempts
Roy et al. (1985)	54	Unmedicated, baseline[1]	No significant difference between suicidal and nonsuicidal schizophrenic patients
King et al. (1985)	21	Unmedicated, baseline[1]	High in schizophrenic patients with abnormal motor behavior
Losonczy et al. (1986)	28	Unmedicated, postprobenecid	Low in schizophrenic patients with cortical atrophy or ventricular enlargement

[1]Without probenecid.

completed at this time. (2) The association between decreased CSF 5HIAA and suicidal behavior, already demonstrated in depression (van Praag 1986), has also been found in schizophrenia. (3) Neuroleptic treatment does not appear to affect CSF 5HIAA levels.

Challenge Studies

A recently developed strategy for studying the functional state of central monoaminergic systems is the neuroendocrine challenge paradigm. In peripheral blood, release of hormones known to be under monoaminergic (in this case serotonergic) control, such as cortisol, prolactin, and growth hormone, is measured after stimulation or inhibition of 5HT receptors with either 5HT agonists or antagonists. The magnitude of the hormonal response is a measure of the responsiveness of the 5HT system In a hypersensitive system, 5HT agonists will induce an augmented release of the aforementioned hormones In a hypoactive system, the reverse is expected to occur If 5HT antagonists are used, opposite results are anticipated (Murphy et al 1986).

So far only two 5HT challenge studies, investigating prolactin and growth hormone (GH) response in schizophrenic patients during neuro leptic treatment, have been published Cowen et al. (1985) found higher prolactin peaks and diminished GH response in schizophrenic patients as compared with normal controls after administration of 6-10 g of intravenous tryptophan. Hoshino et al (1985) administered a single oral dose of 3 mg/kg of 5-hydroxytryptophan (5HTP), the immediate precursor of 5HT, and found increased blood 5HT and inconsistent results for prolactin and GH levels both at baseline and post-5HTP in schizophrenic patients.

The variable and inconsistent results of these studies probably relate to the effect of neuroleptic treatment and the very small number of patients studied It should also be noted that neither tryptophan nor 5HTP stimulates the 5HT receptor directly; rather, both compounds cause indirect stimulation by increasing 5HT synthesis and availability. In addition, both of these 5HT precursors also have major effects on dopaminergic and noradrenergic systems (to be discussed below).

The challenge paradigm appears to be a valid one, provided the 5HT challenger is selective. As such drugs are now evolving, van Praag et al. (1987*a*, 1987*b*) have suggested that this paradigm should be used more extensively to study the serotonergic system in medication-free patients.

Platelet Studies

Over the last decade, the human blood platelet, which is a neuroectodermal derivative, has emerged as a peripheral model for the study of the transport, storage, metabolism, and release of 5HT by serotonergic nerve endings (Sneddon 1973; Stahl 1977) Because of biochemical and morphological similarities between blood platelets and CNS 5HT synaptosomes, and because of data suggesting that virtually all 5HT in blood is associated with the platelets (Yuwiler et al 1981), platelets have been widely used as a minimally invasive means of studying 5HT in the CNS

Platelet and Whole Blood 5HT Levels. There have been a number of studies of platelet or whole blood 5HT levels. Eight groups of investigators, having studied approximately 200 chronic schizophrenic patients, found elevated platelet or whole blood 5HT levels in schizophrenic patients as compared with normal controls (Todrick et al. 1960; Torre et al. 1970; Garelis et al 1975; DeLisi et al. 1981; Freedman et al 1981; Jackman et al. 1983; Stahl et al. 1983; King et al. 1985). The increased platelet 5HT levels were not found to be an artifact of age, sex, or medication (DeLisi et al 1981; Jackman et al. 1983; Stahl et al. 1983).

However, several other researchers failed to find increased blood or platelet 5HT levels in schizophrenic patients (Feldstein et al 1959; Joseph et al. 1977; Kolakowska and Molyneux 1987)

DeLisi et al. (1981) found that high 5HT levels in blood were significantly correlated with specific computed tomographic (CT) abnormalities (enlargement of cerebral ventricles, cortical atrophy, or both) in patients with chronic schizophrenia This finding could not be confirmed by Jackman et al. (1983) In other studies increased whole blood and platelet 5HT levels were found to be correlated with the diagnosis of chronic undifferentiated and paranoid schizophrenia (Freedman et al 1981), auditory hallucinations (Jackman et al 1983), and abnormal motor behavior in chronic schizophrenic patients (King et al. 1985) Table 3 summarizes data on platelet and whole blood 5HT in schizophrenic patients versus controls

5HT concentration in platelets is influenced by several factors including synthesis, uptake, storage, catabolism, and release of 5HT Platelets do not synthesize 5HT; rather, it is synthesized by ente-

rochromaffin cells in the intestine and is then taken up by platelets through active and passive processes (Sneddon 1973). The elevated platelet 5HT concentrations found in chronic schizophrenic patients cannot be explained by an abnormality in platelet 5HT uptake, storage, or release (Jackman et al. 1983; Stahl et al. 1983).

Alternatively, the increased 5HT content of platelets could be the consequence of decreased activity of platelet monoamine oxidase (MAO), the enzyme that deaminates 5HT into 5HIAA. Although lowered MAO activity has been reported in chronic schizophrenia (Potkin et al. 1978; Stahl et al. 1983), this was refuted by others (Meltzer et al. 1982). Moreover, platelet MAO activity does not correlate with platelet 5HT concentration in chronic schizophrenia (Joseph et al. 1977; Freedman et al. 1981). Finally, increased 5HT content in platelets could be a result of increased plasma availability of the 5HT precursor tryptophan. This hypothesis appears unlikely, since the very opposite has been found; that is, tryptophan levels were shown to be lowered in the plasma of schizophrenic patients (Manowitz et al. 1973; Domino and Krause 1974; Freedman et al. 1981).

In conclusion, there appears to be fairly good agreement among investigators that chronic schizophrenic patients show elevated platelet and whole blood 5HT levels. Neither the cause nor the clinical significance of this finding is known at this time, nor is the relationship between 5HT in platelets and 5HT in synapotosomes fully understood.

Platelet 5HT Uptake. The human blood platelet possesses a high-affinity active transport system that is temperature-dependent and inhibited by ouabain (Sneddon 1969). The kinetic parameters of this transport system are V_{max}, indicating the number of carrier molecules, and K_m, a measure of the affinity of the carrier molecules for 5HT. This system has been studied in schizophrenic patients to determine whether active transport of 5HT into the platelet is associated with the increased platelet 5HT concentration that some investigators have shown in schizophrenia.

A number of studies conducted by Rotman's group (Modai et al. 1979; Rotman et al. 1979, 1980, 1982*a*, 1982*b*) have shown that 5HT uptake in platelets of schizophrenic patients is significantly reduced in comparison to normal controls. This finding was related

Table 3. Platelet or whole blood serotonin: Schizophrenic patients vs. controls

Investigators	Number of schizophrenic subjects	Medicated	Platelet or whole blood serotonin concentrations
Feldstein et al. (1959)	22	+	NS[1]
Todrick et al. (1960)	35	+	High
Garelis et al. (1975)	16	+ and -	High only in unmedicated schizophrenic patients
Joseph et al. (1977)	16	-	NS[1]
DeLisi et al. (1981)	33	+ and -	High in schizophrenic patients with cortical atrophy or ventricular enlargement
Freedman et al. (1981)	33	+	High in schizophrenic patients, particularly with chronic undifferentiated subtype
Jackman et al. (1983)	41	+ and -	High in schizophrenic patients, particularly correlated with auditory hallucinations
Stahl et al. (1983)	14	+ and -	High in schizophrenic patients
King et al. (1985)	25	-	High in schizophrenic patients, particularly correlated with cerebrospinal fluid 5-hydroxyindoleacetic acid and abnormal motor behavior
Kolakowska & Molyneux (1987)	62	+	NS[1]

[1]NS = no significant differences between groups.

to a decrease in V_{max} (Rotman et al. 1979). Some of the patients in these studies were receiving neuroleptic drugs, but the investigators claim to have found no effect of neuroleptics on 5HT uptake in in vitro studies of platelets of normal controls (Modai et al. 1979; Rotman et al. 1979). Decreased 5HT uptake by blood platelets of schizophrenic patients was reported by other investigators in studies of neuroleptic-treated patients (Wood et al. 1983), drug-free patients (Kaplan and Mann 1982), and both drug-free and neuroleptic-treated patients (Lingjaerde 1983). In contrast, these findings could not be confirmed by other investigators (Meltzer et al. 1981; Arora and Meltzer 1982, 1983; Jackman et al. 1983; Stahl et al. 1983), who found platelet uptake of 5HT in primarily drug-free schizophrenic patients to be within the same range as in normal controls, and without any significant difference in kinetic parameters (V_{max} and K_m).

Arora and Meltzer (1983) investigated the effect of chlorpromazine on platelet 5HT uptake in schizophrenic patients and normal subjects. 5HT uptake was studied before and after 2-3 weeks of treatment with chlorpromazine (200-600 mg/day). Administration of chlorpromazine was associated with a significant decrease in platelet uptake of 5HT in most subjects in both groups. Decreased platelet 5HT uptake in neuroleptic-treated chronic schizophrenic patients was also reported by Lingjaerde (1983) and by Stahl et al. (1983). Table 4 summarizes data on platelet 5HT uptake studies.

In conclusion, findings in studies of 5HT platelet uptake (considered to be a presynaptic parameter) in schizophrenic patients are inconsistent. Discrepancies between the populations studied (e.g., chronicity and drug treatment), as well as variance of assay techniques, make it difficult to draw conclusions from these data As a whole, these studies suggest that neuroleptic medications probably decrease platelet 5HT uptake in schizophrenic patients.

^{3}H-Imipramine Binding Sites. Recently, high-affinity and saturable binding sites for ^{3}H-imipramine have been found on human platelets. These sites appear to be specific for tricyclic antidepressants and their active metabolites (Langer et al. 1981), and

Table 4. Platelet serotonin uptake: Schizophrenic patients vs. controls

Investigators	Number of schizophrenic subjects	Medicated	Platelet serotonin uptake
Modai et al (1979)	10	+ and -	Decreased in schizophrenic patients by 40%, V_{max} decreased
Rotman et al. (1979)	22	+ and -	Decreased uptake and V_{max} in schizophrenic patients
Meltzer et al. (1981)	17	-	NS[1]
Rotman et al. (1982*a*	22	+ and -	Decreased uptake and V_{max} in schizophrenic patients
Rotman et al. (1982*b*)	12	+	Decreased in schizophrenic patients, positive correlation with ^{3}H-imipramine binding
Arora & Meltzer (1982)	43	-	NS[1], with a trend toward decrease in schizophrenic patients
Kaplan & Mann (1982)	14	-	Decreased in schizophrenic patients, increased K_m
Arora & Meltzer (1983	19	+ and -	NS[1] with increased K_m and V_{max}, and decreased uptake after medication
Lingjaerde (1983)	42	+ and -	Decreased in schizophrenic patients; decreased V_{max} while drug free, and increased K_m with further decrease in uptake after medication
Wood et al. (1983)	14	+	Decreased in schizophrenic patients, no correlation with ^{3}H-imipramine binding
Stahl et al (1983)	14	+ and -	NS[1], 5HT uptake decreased after medication
Jackman et al. (1983)	41	+ and -	NS[1], 5HT uptake decreased after medication

[1]NS = no significant differences between groups

appear to have a functional relationship with the 5HT uptake or transport site, probably modulating inhibition of 5HT uptake (Paul et al. 1980). While Rotman et al. (1982*b*) reported decreased ^{3}H-imipramine binding and 5HT uptake in platelets of schizophrenic patients, Wood et al. (1983), Gentsch et al. (1985), Weizman et al. (1985), Weizman et al. (1987), and Kanof et al. (1987) could not find any significant difference in ^{3}H-imipramine binding between schizophrenic and normal control subjects. Thus, it seems likely that the ^{3}H-imipramine binding site is intact in schizophrenia.

Treatment Studies

If 5HT plays a role in the pathogenesis of schizophrenia, clinical treatments using selective 5HT agonists or antagonists should affect schizophrenic symptomatology and might shed some light on the nature of this relationship.

5HT Precursors.

L-Tryptophan. The amino acid L-tryptophan is the normal dietary precursor of 5HT, and its oral administration affects 5HT synthesis in and release from 5HT neurons. It can influence the synthesis of other neurotransmitters as it competes with other neutral amino acids to gain access from the blood into the brain. One of these amino acids is tyrosine, the precursor of DA and noradrenaline (NA). Therefore, when high doses of tryptophan are administered, 5HT levels in the brain increase, whereas DA and NA levels decrease (Wurtman et al. 1981; van Praag et al. 1987*b*).

Bowers (1970) administered tryptophan (up to 4 g/day for 8–12 days), combined with pyridoxin (a decarboxylase cofactor), to six schizophrenic patients and observed some tranquilizing effects. Gillin et al. (1976*b*), in a placebo-controlled study, found tryptophan (up to 20 g/day for 11–28 days), combined with pyridoxin, to be ineffective in the treatment of eight chronic schizophrenic patients. Chouinard et al. (1978) compared up to 6 g/day of tryptophan, combined with benserazide (which inhibits tryptophan pyrrolase as well as 5HT decarboxylase), with chlorpromazine, in the treatment of 16 chronic schizophrenic patients. They found tryptophan to have a slight therapeutic effect, markedly inferior to that of chlorpromazine. Morand et al. (1983), focusing on aggressive behavior among chronic schizophrenic patients, reported that up to 5 g/day of tryptophan administration improved some aggressive variables, while the overall effect varied among individual patients.

5HTP. 5-HTP is the immediate precursor of 5HT. As the enzyme 5HTP-decarboxylase is found not only in 5HT neurons, but in catecholamine (CA) neurons as well, the oral administration of 5HTP leads to the formation of 5HT not only in serotonergic neurons, but also in CA neurons, where it acts as a false transmitter, increasing CA metabolism as a compensatory mechanism. The net effect is probably an increase in CA function (van Praag et al. 1987*a*, 1987*b*). Thus, by virtue of its catecholaminergic effects, 5HTP must be categorized as a nonselective 5HT-active compound. The same is true for tryptophan in high doses.

Ten grams/day of 5HTP in combination with carbidopa, a peripheral decarboxylase inhibitor, produced some clinical improvement in 7 out of 11 chronic schizophrenic patients in a placebo-controlled study (Wyatt et al. 1972). Bigelow et al. (1979), in another placebo-controlled study, administered up to 6 g/day of 5HTP with carbidopa to 15 patients who had been withdrawn from neuroleptic medication, 7 patients who were maintained on haloperidol, and 9 patients who were maintained on chlorpromazine. Individual responses were highly variable, but the overall results suggested that 5HTP treatment in chronic schizophrenia is not effective.

5HT-Depleting Agents.

Para-chlorophenylalanine (pCPA). pCPA is an inhibitor of tryptophan hydroxylase, the enzyme involved in the first and rate-limiting step of 5HT synthesis. It is known to cause a substantial decrease in brain 5HT concentration in animals (Koe and Weissman 1966) and to decrease CSF and urine 5HIAA concentrations in humans (Cremata and Koe 1966; Goodwin and Post 1973). Casacchia et al. (1975) reported clinical improvement in three out of four acutely psychotic schizophrenic patients, during a brief open trial of pCPA up to 1.25 g/day. In a placebo-controlled study, DeLisi et al. (1982) administered up to 3 g/day of pCPA to seven chronic schizophrenic patients, demonstrating no overall improvement. The discrepancy between these two studies may have resulted from the different patient populations examined (acutely psychotic vs. chronic treatment-resistant patients). Interestingly, both studies reported a decrease in withdrawal behavior (DeLisi et al. 1982) or an increase in socialization (Casacchia et al. 1975) among these patients after treatment.

Fenfluramine. Fenfluramine is an anorectic drug. It promotes release

of 5HT and inhibits 5HT uptake, and may have direct but weak 5HT receptor agonist activity as well (Murphy et al 1986). Although these effects are 5HT agonistic, fenfluramine's net effect is considered to be a 5HT-depleting one. In animals, fenfluramine was shown to induce a decrease in brain 5HT (Clineschmidt et al. 1978), while in humans, CSF 5HIAA was reduced after 8 days of fenfluramine administration (Shoulson and Chase 1975)

Two placebo-controlled studies using fenfluramine have been conducted. Shore et al. (1985) could not demonstrate any significant benefit of fenfluramine (up to 120 mg/day for 8 weeks) in the treatment of eight chronic schizophrenic patients, though a 50 percent decrease of blood 5HT was demonstrated. Stahl et al. (1985) treated 12 chronic schizophrenic patients with fenfluramine (up to 240 mg/day for 12 weeks) and found that negative symptoms improved in some individuals within the active treatment group but not within the placebo group. However, group comparisons of active treatment versus placebo were not significant, possibly because of the small sample size

5HT Receptor Antagonists. 5HT receptors differ according to their central or peripheral location, their occurrence on neurons or other cells (e g., platelets or muscles), or their location on either presynaptic or postsynaptic 5HT nerve terminals. 5HT receptors in brain have been classified into two main types by radioligand binding: $5HT_1$ and $5HT_2$ (Leysen et al. 1978; Peroutka et al 1981). $5HT_1$ receptors have been further subclassified into various subtypes ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1C}$, $5HT_{1D}$), although our understanding of the functional importance of the various 5HT receptors and subtypes is far from complete

Methysergide Methysergide is a 5HT receptor antagonist with primarily $5HT_1$ activity (Sills et al. 1984) Gallant et al (1963) randomly administered methysergide (up to 16 mg/day), chlorpromazine (up to 800 mg/day), or placebo to a group of 40 chronic schizophrenic patients. Methysergide did not have any antipsychotic effects Mendels (1967) used oral methysergide (15 mg/day) in 14 chronic schizophrenic patients, switching after 10 days to 5 mg/day intravenous methysergide in 12 patients, and changing again after 8 more days to 2 mg/day intrathecal methysergide in 6 patients. No antipsychotic effect was found, and five patients (three of whom received the drug intravenously and two of whom received the drug intrathecally) showed temporary aggravation of psychosis.

Setoperone and ritanserin. Setoperone is a potent $5HT_2$ receptor antagonist as well as a DA receptor antagonist (Ceulemans et al. 1985*a*), while ritanserin is a very selective $5HT_2$ antagonist (Leysen et al 1985). Ceulemans et al (1985*a*) administered oral setoperone (15 mg/day) to 34 chronic schizophrenic patients (diagnosed by *DSM-III*; American Psychiatric Association 1980), drug free for 1 week, with predominant negative symptomatology, and compared its effect to previous neuroleptic treatment. After 1 month of treatment with setoperone, psychotic symptoms, as measured by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), improved by approximately 50 percent Setoperone was specifically effective in diminishing negative symptoms, with a significant decrease in emotional withdrawal and improvement of blunted affect, and was also found to cause a marked euthymic effect, as shown by corresponding changes in BPRS ratings. Setoperone was also found to cause fewer extrapyramidal symptoms than neuroleptics combined with antiparkinsonian medication

Studies with ritanserin (Ceulemans et al. 1985*b*; Gelders et al. 1985*a*, 1985*b*) have demonstrated results similar to those obtained with setoperone Ritanserin (20 mg/day) was administered to chronic, primarily Type II schizophrenic patients in three studies: (1) a comparison of ritanserin with placebo, both added to existing neuroleptic treatment, for 6 weeks in 35 patients (Gelders et al 1985*a*); (2) a double-blind comparison of ritanserin to haloperidol, 10 mg/day, in 37 patients for a period of 60 days (Ceulemans et al 1985*b*); and (3) a placebo/controlled design in which ritanserin, 20 mg/day, was compared with haloperidol, 10 mg/day, for 6 weeks in 57 patients (Gelders et al 1985*b*) Overall results showed the efficacy of ritanserin in alleviating psychotic symptoms, as expressed by a significant decrease in total BPRS ratings and by ongoing clinical assessment In the first study, when ritanserin was added to a neuroleptic, the total BPRS score decreased approximately 50 percent, while the BPRS negative symptom cluster decreased more than 60 percent. Placebo decreased BPRS (total and negative symptoms) by only about 10 percent

In the second and third studies, where ritanserin was compared to haloperidol, both medications improved the total BPRS, while ritanserin alone improved the negative symptom cluster, and haloperidol was superior in improving

thought disorder. Moreover, ritanserin-treated patients showed significant improvement in extrapyramidal symptoms. The efficacy of ritanserin in improving scores on the negative symptom cluster of BPRS in comparison to a placebo suggests that the neuroleptic withdrawal effect was not significantly reflected in these results, since otherwise it would be expected to be demonstrated clearly in the placebo studies.

In conclusion, it appears that: (1) Treatment studies with 5HT precursors give variable and inconsistent results, possibly because tryptophan and 5HTP have pronounced effects on the DA and NA systems as well as on the 5HT system. (2) Agents that deplete 5HT (pCPA and fenfluramine) do not appear to produce an overall clinical improvement in schizophrenic patients, although some results may show some improvement in the cluster of negative symptoms. (3) Treatment studies with $5HT_2$ antagonists suggest that these drugs may have antipsychotic activity, significantly improve negative symptomatology, and be helpful to those patients who experience extrapyramidal side effects from neuroleptics.

Discussion

At first glance, 5HT studies in schizophrenia seem to show inconsistent, even contradictory findings. Increased whole blood or platelet 5HT levels have been demonstrated in eight studies investigating approximately 200 chronic schizophrenic patients. However, data on 5HT uptake and ^{3}H-imipramine binding in schizophrenia are inconsistent at this time. Direct evaluations of 5HT, 5HIAA, and tryptophan concentrations, as well as 5HT receptor density in post-mortem studies of brain specimens from schizophrenic patients, show contradictory and uninterpretable findings, possibly due to a number of technical problems and inconsistencies in experimental technique. Also, there appear to be no overall consistent differences in CSF 5HIAA levels in schizophrenic patients as compared to control subjects, although decreased CSF 5HIAA levels may well correlate significantly with specific characteristics within the schizophrenic population such as structural brain changes. Treatment studies with 5HT precursors have not demonstrated therapeutic effects. However, agents that are thought to decrease 5HT function have shown antipsychotic effects, particularly when potent $5HT_2$ antagonists have been used. Such inconsistencies in clinical and biological research results of 5HT studies in schizophrenia might reflect heterogeneity of this disorder, as proposed by several authors (Bellak and Strauss 1979; Buchsbaum and Rieder 1979).

Integration of Data: 5HT Hypothesis. The two-syndrome paradigm proposed by Crow (1980*a*, 1980*b*) at the beginning of this decade seemed to offer the hope of substantial progress in the delineation of more homogeneous subtypes of schizophrenia. When Crow's paradigm is used to reexamine clinical and biological 5HT studies involving both CSF and blood measurements and treatment response to 5HT-influencing agents, a body of fairly consistent findings emerges within a subpopulation of schizophrenia; chronic patients with predominant Type II syndrome seem to show 5HT abnormalities or response to 5HT-influencing agents, thus pointing to a possible role of 5HT dysfunction in Type II schizophrenia.

A recent study by Lewine and Meltzer (1984) reporting elevated platelet MAO activity in male schizophrenic patients with predominantly negative symptomatology may relate to multiple findings of increased whole blood or platelet 5HT levels in chronic schizophrenic patients (Todrick et al. 1960; Torre et al. 1970; Garelis et al. 1975; DeLisi et al. 1981; Freedman et al. 1981; Jackman et al. 1983; Stahl et al. 1983; King et al. 1985). The elevated platelet MAO activity in these patients might reflect a compensatory process for the elevation of the 5HT concentration in the platelet.

The positive correlation between elevated blood 5HT levels and degenerative brain changes (cortical atrophy or ventricular enlargement) found by DeLisi et al. (1981) also suggests a possible link between elevated blood 5HT and Type II schizophrenia. It should be noted, however, that neither the clinical significance of elevated blood 5HT nor its relationship to brain 5HT are clear at this stage.

Several studies have also demonstrated that cortical atrophy, ventricular enlargement or increased VBR are significantly associated with decreased CSF 5HIAA levels in schizophrenic patients (Nybäck et al. 1983; Potkin et al. 1983; Losonczy et al. 1986*a*, 1986*b*). These findings appear to indicate a relationship between Type II schizophrenia and decreased central 5HT metabolism as reflected in lowered CSF 5HIAA.

The apparent contradiction between increased blood 5HT and decreased CSF 5HIAA levels in the same subpopulation of schizophrenic patients (those with degenerative brain changes) might be explained,

in the light of the hypothesis of Freedman et al. (1981), as a consequence of increased uptake and utilization of tryptophan in the periphery, part of which may enter the 5HT pathway. A possible net result would be decreased plasma tryptophan, diminished availability of tryptophan in the brain, and hence decreased central 5HT and CSF 5HIAA.

Another possible link between decreased central 5HT metabolism and brain CT scan abnormalities in schizophrenia is suicidality Several studies (van Praag 1983; Banki et al. 1984; Ninan et al. 1984) found a correlation between decreased CSF 5HIAA and suicide attempts among schizophrenic patients Furthermore, Levy et al. (1984) demonstrated that history of suicide attempts is also correlated with increased VBR among schizophrenic patients, suggesting a trivariate relationship among 5HT function, suicidality, and Type II schizophrenia that should be further studied.

Treatment studies using agents presumed to decrease 5HT function further suggest the possible role of 5HT dysfunction in Type II schizophrenia. Agents that deplete 5HT such as pCPA (Casacchia et al. 1975; DeLisi et al. 1982) and fenfluramine (Stahl et al. 1985) appear to alleviate negative symptomatology in schizophrenic patients. Interestingly, fenfluramine has also been shown to improve certain symptoms of childhood autism (withdrawn behavior, inappropriate affect, and poor eye contact), which share some similarities with the negative symptoms of schizophrenia (Geller et al. 1982) Moreover, childhood autism has been reported to be associated with other features which may also occur in Type II syndrome such as elevated blood 5HT (Hanley et al. 1977) and ventricular enlargement (Hauser et al. 1975)

Finally and most importantly, potent and/or selective $5HT_2$ antagonists, notably setoperone (Ceulemans et al. 1985*a*) and ritanserin (Ceulemans et al. 1985*b*; Gelders et al 1985*a*, 1985*b*) have recently been reported to have a pronounced antipsychotic effect and to be especially effective in alleviating negative symptomatology and dysphoria in chronic schizophrenic patients with predominant Type II syndrome. These findings await corroboration.

The aforementioned data suggest a relationship between 5HT dysfunction and Type II schizophrenia. The reported effect of selective $5HT_2$ antagonists on the negative syndrome, as well as the decreased CSF 5HIAA shown in Type II schizophrenia, might suggest that the nature of this dysfunction involves $5HT_2$ postsynaptic receptor hypersensitivity. Serotonergic postsynaptic receptor hypersensitivity would be expected to lead to a compensatory decrease of central 5HT metabolism (lowered CSF 5HIAA), as has indeed been shown in Type II schizophrenia

One mechanism suggested for the mediation of receptor hypersensitivity may be a reduced level of available neurotransmitter (Charney et al. 1981). According to the hypothesis of Freedman et al (1981), a subgroup of schizophrenic patients with elevated whole blood 5HT levels might have as a result a lowered level of 5HT in the brain, through mechanisms discussed above. This decreased brain 5HT concentration might in turn mediate 5HT receptor hypersensitivity

The hypersensitivity hypothesis can be tested using the neuroendocrine challenge paradigm with selective 5HT agonists such as m-chlorophenylpiperazine (MCPP), which is a direct activator of the 5HT (primarily $5HT_1$) receptor (Murphy et al 1986), and antagonists such as ritanserin, a selective $5HT_2$ receptor blocker (Leysen et al 1985), that have become available recently. The outcome of these tests should be correlated with (1) other central (CSF 5HIAA) and peripheral (blood) 5HT measures; (2) measures of (negative) symptomatology; and (3) CT scan results.

On the basis of the hypersensitivity hypothesis, one would expect 5HT antagonists to be particularly effective in Type II schizophrenia. Preliminary treatment studies are promising and should be repeated and expanded, correlating treatment response with the aforementioned parameters

5HT/DA Modulation Effects. Chesire et al. (1982) have found that methysergide diminished akinesia induced by the section of nigrostriatal circuits in rats Ceulemans et al (1985*a*, 1985*b*) and Gelders et al. (1985*a*, 1985*b*) have reported that setoperone and ritanserin, when administered to schizophrenic patients, caused fewer extrapyramidal symptoms than neuroleptics combined with antiparkinsonian medication. The fact that both drugs lack anticholinergic activity might support the hypothesis of a modulating effect of 5HT receptors on the nigrostriatal DA system as a mechanism for the alleviation of extrapyramidal symptoms seen with 5HT selective antagonists.

The possibility of such a modulating effect is supported by the complex anatomical and functional interactions known to exist

between dopaminergic and serotonergic neuronal systems in the forebrain. These interactions occur at axo-axonal synaptic connections between 5HT-containing neurons originating from the medial and dorsal raphe nuclei and nigrostriatal as well as mesolimbic DA circuits (Waldmeier and Delina-Stula 1979; Jenner et al. 1983).

Jenner et al. (1983) have recently reviewed literature on possible 5HT/DA interactions involving 5HT fibers that originate from the dorsal and medial raphe nuclei and that innervate DA-containing areas of the brain such as the substantia nigra, corpus striatum, and nucleus accumbens. The data they review indicate that manipulation of 5HT system activity influences DA function as shown primarily in electrophysiological recording studies and by certain behavioral models that are believed to express DA function (e.g., apomorphine- or amphetamine-induced circling behavior and stereotypy). On the basis of available data, 5HT appears to have an inhibitory modulating effect on cerebral DA mechanisms and function, a modulatory effect that probably depends on the relative state of activity of each system (Jenner et al. 1983). Recently, specific modes of serotonergic modulation of DA function have been identified. In the brains of rats, tyrosine hydroxylase and DA release have been found to be inhibited by 5HT in a concentration-dependent manner in both striatal and nucleus accumbens synaptosomes (Ennis et al. 1981; Hetey et al. 1985; Hetey and Drescher 1986). These inhibitory effects of 5HT are assumed to be mediated via 5HT receptors at the DA terminals (5HT heteroreceptors), because several 5HT antagonists (methiothepine and methysergide) can attenuate these effects.

If one assumes that 5HT indeed modulates dopaminergic function, through the imposition of inhibitory tone, then the excitation or disinhibition of the striatal dopaminergic system presumably produced by potent 5HT antagonists might be effective in diminishing the severity of extrapyramidal symptoms, as suggested by the studies with ritanserin and setoperone cited above. Given the hypothesis proposed by Meltzer and Stahl (1976) and others that negative symptoms of schizophrenia may result from decreased dopaminergic activity, then the same disinhibition effects of 5HT antagonists on the mesolimbic and mesocortical dopaminergic circuits might explain the improvement in negative symptomatology seen when they are administered. This hypothesis is further supported by controlled studies showing a diminution of negative symptoms in schizophrenic patients with the administration of dopaminergic agonists such as L-dopa or D-amphetamine (Buchanan et al. 1975; Gerlach and Luhdorf 1975; Inanaga et al. 1975; Alpert et al. 1978; Cesarec and Nyman 1985).

Conclusion

We propose that while DA pathophysiology may be related to schizophrenia with predominant Type I syndrome, 5HT dysfunction—and more specifically 5HT postsynaptic receptor hypersensitivity—may be associated with Type II schizophrenia. Obviously, the presumed dysfunction of each neurotransmitter system should be considered in relation to the dynamic interactions between the systems, rather than as independent processes. Optimal pharmacotherapy of schizophrenia might include both 5HT antagonist and DA blocking components—the former being more beneficial for negative symptomatology and the latter for overt psychotic symptoms. This perspective might offer promise in treating a disorder that has proved to be discouragingly treatment-resistant.

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The Authors

Avraham Bleich, M.D., is Research Fellow, Department of Psychiatry, Albert Einstein College of Medicine/ Montefiore Medical Center. Serena-Lynn Brown, M.D., Ph.D., is Director, Psychopharmacology Clinic, Department of Psychiatry, Albert Einstein College of Medicine, Bronx Municipal Hospital Center, and Assistant Professor of Psychiatry, Albert Einstein College of Medicine/ Montefiore Medical Center. Rene Kahn, M.D., is Research Fellow, Department of Psychiatry, Albert Einstein College of Medicine/Montefiore Medical Center. Herman M. van Praag, M.D., Ph.D., is Professor and Chairman, Department of Psychiatry, Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY.