Serotonin-Dopamine Interaction and Its Relevance to Schizophrenia

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Objective: The therapeutic success of clozapine and risperidone has focused attention on the interaction between the serotonin and dopamine systems as an avenue for superior therapeutics in schizophrenia. The authors review the neurobiological basis for this interaction and its clinical relevance. *Method:* The authors synthesized information from more than 100 published articles obtained through electronic and bibliography-directed searches. *Findings:* The serotonin system inhibits dopaminergic function at the level of the origin of the dopamine system in the midbrain as well as at the terminal dopaminergic fields in the forebrain. Serotonergic antagonists release the dopamine system from this inhibition. This disinhibition of the dopamine system in the striatum may alleviate neuroleptic-induced extrapyramidal symptoms, and a similar disinhibition in the prefrontal cortex may ameliorate negative symptoms. However, the benefits of combined serotonergic-dopaminergic blockade may be observed in only a narrow dose range and may be lost with doses that produce suprathreshold dopaminergic blockade. *Conclusions:* Serotonergic modulation of dopaminergic function provides a viable mechanism for enhancing therapeutics in schizophrenia, but much remains unclear. Future research will have to establish the existence of this interaction in humans in vivo, specify the conditions under which it leads to optimal therapeutic benefits, and explore the possibility of using specific serotonergic treatments as flexible adjuncts to typical neuroleptics, rather than the present trend toward using single drugs with combined actions.

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T he therapeutic success of clozapine and, more recently, risperidone has focused attention on the serotonin system and its interaction with the dopaminergic system as an avenue for superior treatment of psychotic illnesses. Understanding the interaction between serotonin and dopamine and its therapeutic implications is particularly timely because a number of new antipsychotic medications (e.g., olanzapine, seroquel, sertindole, ziprasidone) with serotonin-dopamine interaction profiles are being tested in clinical trials (1). In the light of this burgeoning scientific and clinical interest, we reviewed the neural basis and clinical relevance of the serotonin-dopamine interaction. Evidence for a primary role of serotonin in the etiology of schizophrenia has been covered recently by others (2, 3) and will not be a focus of this article.

This review is divided into three sections. The first reviews the anatomy and physiology of the dopamine and serotonin systems and the neural bases for their interaction. The second section examines the functional relevance of serotonin-dopamine interaction, as demonstrated in animal models and experimental human studies. The third section evaluates the role of the serotonin-dopamine interaction in the efficacy of the "atypical" neuroleptics like clozapine and risperidone. We conclude by highlighting the unanswered questions regarding the relevance of the serotonin-dopamine interaction and, in doing so, indicate directions for future research.

NEUROBIOLOGICAL BASIS OF THE SEROTONIN-DOPAMINE INTERACTION

The Dopamine and Serotonin Systems

The dopaminergic system arises from groups of cells in the midbrain. Neurons from the substantia nigra ascend to the striatum, via the nigrostriatal pathway, and are primarily involved in the modulation of motor behavior, whereas neurons from the ventral tegmental area project to the limbic (mesolimbic projections) and cortical (mesocortical projections) regions and are involved in cognition and modulation of motivation and reward (4). The
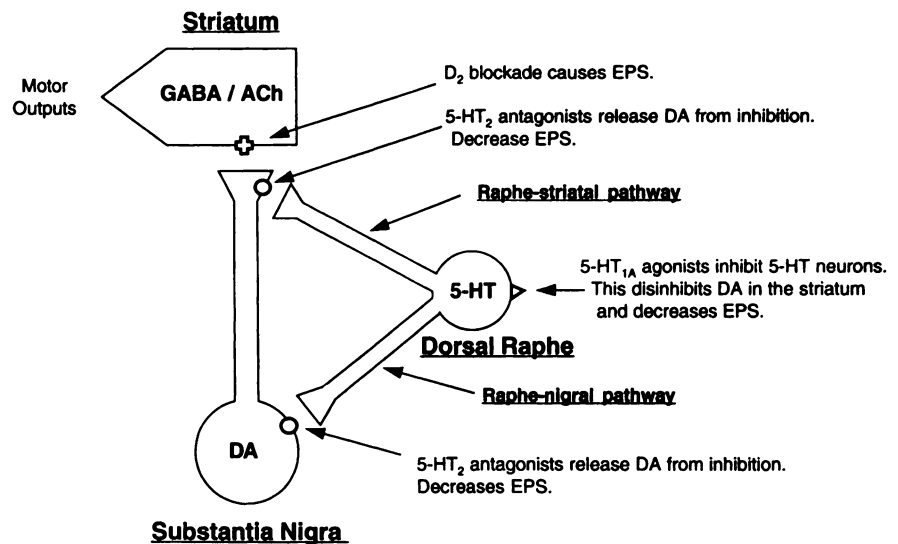
effects of dopamine released by these projections are mediated through a series of dopamine receptors (D_1–D_5) grouped into two families, the D_1 family (D_1 and D_5) and the D_2 family (D_2, D_3, D_4), on the basis of their genetic homology and common second messenger systems. The D_1 receptors are prominent in the cortical regions, D_2 receptors are prominent in the striatum, and D_3 and D_4 receptors have a higher distribution in the limbic regions. Presynaptic dopamine receptors may be localized on the cell bodies in the midbrain (somatodendritic autoreceptors), where they modulate the firing of dopamine neurons, or on the axonal terminals of dopamine neurons (terminal autoreceptors), where they modulate the release of dopamine (5, 6). Postsynaptic dopamine receptors mediate the effect of dopamine on the nondopaminergic postsynaptic neurons.

The serotonergic neurons also arise from discrete midbrain nuclei; the dorsal raphe nucleus and the median raphe nucleus provide the most prominent projections. The dorsal raphe nucleus projects to the cortex and the striatal regions, and the median raphe nucleus projects to the limbic regions (7). The serotonin receptors are grouped on the basis of shared genetic sequences and second messenger systems into three classifications: 1) the 5-HT_1 family (5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}), which uses G-protein-mediated signal transduction; 2) the 5-HT_2 family (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_4), which uses phosphoinositol-mediated signal transduction; and 3) the 5-HT_3 receptor, which uses ion-gated channels for signal transduction (8). The somatodendritic serotonergic autoreceptors, mainly 5-HT_{1A} type, are found on the serotonergic neurons in the raphe nuclei and modulate the firing of the serotonergic neurons. The terminal autoreceptors, probably 5-HT_{1D} subtype, modulate the release of serotonin from the serotonergic neurons. On the other hand, postsynaptic serotonin receptors mediate the action of serotonin on the nonserotonergic neurons, with the 5-HT_{1A} receptors being prominent in the limbic regions and 5-HT_2 receptors prominent in the motor regions (7–10).

Serotonergic Inhibition of Dopaminergic Function in the Midbrain

Serotonergic projections from the dorsal raphe (11, 12) project directly to the substantia nigra and inhibit

FIGURE 1. Functional Interactions Between the Serotonin-Dopamine Systems and Their Role in Reducing Extrapyramidal Symptoms[a]

Striatum

Motor Outputs

GABA / ACh

D_2 blockade causes EPS.

5-HT_2 antagonists release DA from inhibition. Decrease EPS.

Raphe-striatal pathway

5-HT

5-HT_{1A} agonists inhibit 5-HT neurons. This disinhibits DA in the striatum and decreases EPS.

Dorsal Raphe

Raphe-nigral pathway

DA

5-HT_2 antagonists release DA from inhibition. Decreases EPS.

Substantia Nigra

[a]DA=dopamine neurons, 5-HT=serotonin neurons, GABA=γ-aminobutyric acid neurons, ACh=cholinergic interneurons, EPS=extrapyramidal symptoms. The D_2 dopamine receptors are represented by an open cross, the 5-HT_2 receptors by a circle, and the 5-HT_{1A} receptors by a triangle. This figure is a schematic representation of the mechanism and consequences of the interaction between serotonin and dopamine at the level of the substantia nigra and the striatum. 5-HT_2 antagonists and the 5-HT_{1A} autoreceptor agonists inhibit the serotonin system and thus release the dopamine system from this inhibition (disinhibition of the dopamine system). The release of the dopamine system from serotonergic inhibition ameliorates extrapyramidal symptoms.

the firing of the dopaminergic neurons (7, 13). Most of these raphe-nigral neurons arise as collaterals of the raphe-striatal neurons, thus providing a neural basis for coordinated modulation of midbrain and terminal dopaminergic function (14). The stimulation of dorsal raphe serotonergic fibers releases serotonin in the substantia nigra (13). This is associated with a decrease in the firing rate of the dopamine neurons and antagonizes dopamine-mediated behaviors, suggesting an inhibitory modulation of the dopamine neurons in the substantia nigra by serotonin (11, 12, 15–19). This inhibitory action seems to be modulated by 5-HT_2 receptors located on the somatodendritic surface of the dopamine neurons (9, 12, 17, 20). As expected, anatomical or chemical lesions that disrupt the raphe-nigral projection (17, 18), 5-HT_{1A} agonists that functionally inhibit the raphe-nigral neurons (16, 21, 22), or 5-HT_2 antagonists that antagonize the effect of the raphe-nigral system (20) all lead to a biochemical and functional disinhibition of the dopamine system. Figure 1 illustrates the major elements of this interaction.

Serotonergic Inhibition of Dopaminergic Function in the Forebrain

Tract tracing (23, 24) and immunohistochemical studies (25–27) have shown that serotonergic neurons that arise in the dorsal raphe nucleus project uninterruptedly via the medial forebrain bundle to the striatum

and cortex (7). Stimulation of these raphe-striatal neurons, or the striatal administration of serotonergic agonists, causes an inhibition of striatal neuronal firing, presumably by means of a decrease in synaptic dopamine (24, 28–31). This effect seems to be mediated by the 5-HT$_2$ receptors (30, 32–36) and may result from a decreased release (32, 33, 37, 38) or a decreased synthesis of dopamine in the terminals (18, 35, 39, 40), although the decreased synthesis has not been consistently observed (41, 42). Nonetheless, the concept of serotonergic modulation of dopamine function receives clear impetus from in vivo positron emission tomography (PET) studies in baboons showing that altanserin, a 5-HT$_2$ antagonist, increases the release of endogenous dopamine, while citalopram, a selective serotonin reuptake inhibitor (SSRI), decreases the release of endogenous dopamine (43).

Consistent with this inhibitory influence of serotonin on dopamine, lesioning the serotonergic projections disinhibits the dopamine system and causes an increase in striatal dopamine levels (15, 44). Similarly, 5-HT$_2$ antagonists block serotonin's inhibitory action on striatal dopamine and result in increased dopamine levels in the striatum (28, 31, 36, 43, 45). Similar evidence exists for striatal control of limbic and cortical dopamine function (10, 46). It is to be noted, however, that serotonin has a direct influence on the cholinergic and γ-aminobutyric acid (GABA) system, and some of serotonin's effects on the dopamine system may be mediated, indirectly, through its modulation of the GABA and cholinergic system (17, 18, 47–49).

In summary, there is convincing evidence that the serotonergic projections inhibit dopamine function at two levels: at the level of the midbrain they inhibit the firing of the dopamine cells projecting from the substantia nigra, and in the striatum and cortex they inhibit the synaptic release of dopamine and probably the synthesis of dopamine. As a result, serotonergic agonists, serotonin precursors, and SSRIs enhance the inhibition of the dopamine system. Conversely, lesions of the raphe nuclei, 5-HT$_{1A}$ agonists (through their action on autoreceptors), and 5-HT$_2$ antagonists disinhibit the dopamine system.

FUNCTIONAL RELEVANCE OF THE SEROTONIN-DOPAMINE INTERACTION

Relevance of the Serotonin-Dopamine Interaction in Animal Models of Extrapyramidal Symptoms

Neuroleptic-induced extrapyramidal symptoms in humans result from occupancy of D$_2$ receptors in the striatum (50). Neuroleptic-induced catalepsy in animals, which represents a similar mechanism, provides a valuable model to study extrapyramidal symptoms (51). Since serotonin exerts an inhibitory influence on the dopaminergic system, manipulations that inhibit serotonin function (raphe lesions, 5-HT$_{1A}$ autoreceptor agonists, or 5-HT$_2$ antagonists) would be expected to

disinhibit the dopamine system and ameliorate catalepsy. Conversely, enhancing serotonergic function (with serotonin precursors, direct agonists, or SSRIs) would be expected to further inhibit the dopamine system and worsen catalepsy. We now examine evidence in support of these paradigms.

In one of the earliest studies of this phenomenon, Kostowski et al. (37) showed that lesions of the raphe nuclei prevent and ameliorate neuroleptic-induced catalepsy in rodents, a finding subsequently confirmed for anatomical and chemical raphe lesions (52, 53). Furthermore, there is a close relationship between the degree of ablation of the raphe, the loss of serotonin in the striatum, and the degree to which the catalepsy is prevented (54).

5-HT$_{1A}$ agonists, by means of their action on somatodendritic autoreceptors, inhibit the firing of serotonergic neurons. Several studies (55–58) reported a beneficial effect of 5-HT$_{1A}$ agonists in reversing and preventing the development of catalepsy in rodents, and this effect has now been confirmed in primate models of extrapyramidal symptoms (59, 60). It is specific for the 5-HT$_{1A}$ subtype, is not observed with other 5-HT$_1$ receptor subtypes (55), and is distinct from the 5-HT$_2$ effect (56). These findings suggest that the combination of a 5-HT$_{1A}$ agonist and a D$_2$-antagonist may lead to extrapyramidal symptom-free antipsychotic activity (58). However, to our knowledge, no such studies exist in humans.

With respect to 5-HT$_2$ antagonism and its effect on catalepsy in rodents, Maj et al. (61) reported that cyproheptadine, a 5-HT$_2$ antagonist, prevents catalepsy, although this interpretation is confounded by the anticholinergic properties of cyproheptadine. Subsequent reports using specific 5-HT$_2$ antagonists have confirmed a role for 5-HT$_2$ in alleviating catalepsy (53, 55, 56, 62) and have also shown that 5-HT$_2$ antagonists enhance dopamine-mediated motor behavior in models other than catalepsy (63, 64). Other groups, however, failed to find this effect, even though they used drugs with similar 5-HT$_2$ activity and similar animal models (58, 65). The results in primate models of extrapyramidal symptoms also show variance: there have been reports of a beneficial effect of 5-HT$_2$ antagonists in the *Cercopethicus* species (66) but no such effects in several investigations of the *Cebus* species (59, 67, 68).

This variance in the findings may reflect differences in the relevance of the serotonin-dopamine interaction across different species or differences in the models used to study extrapyramidal symptoms (68). The latter suggestion is buttressed by the demonstration in physiological experiments (38) that 5-HT$_2$ antagonism may ameliorate the functional effects of D$_2$ antagonism when it is partial but may not be able to reverse the effects if D$_2$ blockade is complete. In addition, a recent report (69) showed that ritanserin, a 5-HT$_2$ antagonist, was able to antagonize haloperidol-induced catalepsy when induced with low doses of haloperidol but was ineffective when suprathreshold doses of haloperidol were used to induce catalepsy. Thus, 5-HT$_2$ blockade

may bestow only a limited protection from the effects of D_2 blockade, a concept that will be of particular relevance in the discussion of the antagonism between 5-HT_2 and D_2 in the clinical context.

In keeping with the overall argument, serotonergic agonists would be expected to further inhibit the dopamine system and worsen extrapyramidal symptoms. Indeed, it has been reported that 5-hydroxytryptophan (a precursor of serotonin) and quipazine (a direct acting agonist) worsen haloperidol-induced catalepsy in rats (53, 62). Similarly, SSRIs enhance serotonergic transmission and worsen extrapyramidal symptoms in rodent and primate models, although the effect in primates may be species-dependent (62, 66, 67).

In summary, manipulations that inhibit the serotonin system (e.g., raphe lesions, 5-HT_{1A} agonists, and 5-HT_2 antagonists) disinhibit the dopamine system and offer an indirect avenue to alleviate neuroleptic-induced extrapyramidal symptoms. The different interactions and their functional effects on extrapyramidal symptoms are illustrated in figure 1.

Relevance of the Serotonin-Dopamine Interaction in Alleviating Extrapyramidal Symptoms in Humans

The earliest convincing evidence for serotonin-dopamine interaction in humans came from Ceulemans et al. (70), who treated patients with schizophrenia with setoperone, a 5-HT_2 antagonist, in an open trial and demonstrated a beneficial effect on extrapyramidal symptoms. It was unclear in this study, however, whether the benefit resulted from the discontinuation of the typical neuroleptic or from the initiation of the setoperone. In subsequent studies, Reyntjens et al. (71), Gelders (72), and Bersani et al. (73) used ritanserin, a more specific 5-HT_2 antagonist, in double-blind, placebo-controlled, add-on trials and showed a significant improvement in extrapyramidal symptoms. Beneficial effects of ritanserin have now been reported in neuroleptic-induced akathisia (74, 75) and in tremor and akinesia observed in Parkinson's disease (76–78). Silver et al. (79) have reported a beneficial trend for cyproheptadine in ameliorating extrapyramidal symptoms in patients receiving neuroleptics, although its anticholinergic properties confound the role of its 5-HT_2 blockade. In contrast, Korsgaard and Friis (80), using mianserin in a double-blind crossover trial in patients with neuroleptic-induced parkinsonism, failed to find a beneficial effect of 5-HT_2 antagonism.

SSRIs, the most commonly used serotonergic agonists, are known to induce an akathisia-like syndrome (81–83). More recent reports (77, 84, 85) also implicated SSRIs in a variety of extrapyramidal symptoms, ranging from tremor to dystonic reactions. Although some of the subjects in these studies were receiving neuroleptics or had Parkinson's disease (86), cases of de novo onset of characteristic parkinsonian symptoms have also been reported (85). Epidemiologic studies (87) suggest that SSRI-induced extrapyramidal symptoms are definite, but rare, occurrences reported in one

out of 1,000 individuals treated with these drugs. This suggests that in some individuals who are either receiving drugs inducing D_2 antagonism or have asymptomatic Parkinson's disease the marginal increase in dopamine antagonism caused by the SSRI is enough to push them over the threshold for extrapyramidal symptoms (87). However, for the majority of individuals the degree of D_2 antagonism induced by SSRIs does not by itself cross the extrapyramidal symptom threshold.

The Serotonin-Dopamine Interaction and Negative Symptoms

Negative symptoms of schizophrenia involve a syndrome of flattened affect, alogia, and amotivation accompanied by emotional and social withdrawal. Typical antipsychotics have limited efficacy against negative symptoms, and many patients freed from their delusions and hallucinations are still unable to resume productive lives due to enduring negative symptoms. Despite their critical clinical importance, there are few, if any, convincing animal models of negative symptoms (88). However, the neuropsychological similarity of patients with prominent negative symptoms to patients with frontal lesions and data from neuroimaging studies link negative symptoms to frontal dysfunction (89–91). It has been suggested that this may reflect, at least in part, hypodopaminergic function in the prefrontal cortex (92–95). Such a model would predict that increasing dopaminergic function in the prefrontal cortex may relieve negative symptoms, a view that led to the use of dopamine agonists with some success (96, 97).

Given the inhibitory effect of serotonin on dopaminergic transmission, it has been hypothesized that drugs inhibiting serotonergic function may disinhibit dopaminergic transmission in the prefrontal cortex and, as a result, may improve negative symptoms (97). This hypothesis is supported by reports that clozapine, which is thought to improve negative symptoms, induces an increased turnover of dopamine in the prefrontal cortex of rodents, an effect not seen with typical antipsychotics (98, 99). More recent studies (100–102) suggest that this property of clozapine can be explained by its 5-HT_2 antagonism. Thus, if current speculations regarding the role of the prefrontal cortex in negative symptoms are correct, 5-HT_2 antagonists could ameliorate negative symptoms by means of their effects on the dopaminergic system. It is worth noting that serotonergic projections also have a direct inhibitory effect on the prefrontal neurons, separate from their effect on the dopaminergic projections. Accordingly, some of the effects of 5-HT_2 blockers on negative symptoms in animal models and humans may reflect a direct effect rather than a dopamine-mediated effect on prefrontal neurons (46, 103).

Ceulemans et al. (70) provided the first supporting clinical evidence by demonstrating that setoperone, a 5-HT_2 antagonist, resulted in a significant improvement in emotional withdrawal, autistic behavior, and dysphoria in patients with schizophrenia. Reyntjens et

al. (71) and Gelders (72), in an add-on, double-blind, placebo-controlled study of ritanserin, found a significant improvement in negative and affective symptoms in the ritanserin-treated patients only. This finding has now been replicated in another study (104), where maximum improvement was noted in affective flattening and social relationships. Similar results have also been reported in a study employing cyproheptadine in patients with predominantly negative symptoms (79), although the 5-HT$_2$ activity of cyproheptadine is confounded with its histaminergic and cholinergic effects.

A little surprising, then, are the results of Silver and Nassar (105), Spina et al. (106), and Goff et al. (107), who found equally significant improvement in negative symptoms with SSRI treatment. This presents an interesting puzzle—5-HT$_2$ antagonists and SSRIs have opposing effects on the serotonergic system and, through the serotonin-dopamine interaction, on the dopaminergic system, so how do both of these drugs improve negative symptoms? The answer lies, perhaps, in the possibility that what are currently recognized as negative symptoms may in fact reflect separate pathophysiological entities (90, 108, 109). Therefore, it is conceivable that both SSRIs and 5-HT$_2$ antagonists may improve manifest negative symptoms: the SSRIs may exert an effect on the depressive component of negative symptoms, and the 5-HT$_2$ antagonists may exert an effect on the extrapyramidal symptom component of negative symptoms.

ROLE OF THE SEROTONIN-DOPAMINE INTERACTION IN THE EFFECTS OF CLOZAPINE AND RISPERIDONE

Extrapyramidal Symptoms

Numerous reports have established clozapine's virtual freedom from extrapyramidal symptoms in usual doses (110–113). Is this related to clozapine's serotonin-dopamine interaction profile? It had been postulated that clozapine's high ratio of 5-HT$_2$ to D$_2$ affinity may account for its diminished extrapyramidal symptoms (114, 115). However, recent PET studies suggest otherwise. It has been shown that patients receiving conventional neuroleptics experience extrapyramidal symptoms only when D$_2$ occupancy exceeds a threshold, somewhere in the range of 75%–80% D$_2$ occupancy (50). Extrapyramidal symptoms are not observed below these levels of D$_2$ occupancy, even with the classical neuroleptics. Clozapine's D$_2$ occupancy varies from 20% to 67% (116, 117) and has never been shown to exceed the putative threshold for extrapyramidal symptoms. Thus, clozapine's low extrapyramidal symptom profile is explained more parsimoniously on the basis of its low D$_2$ occupancy, and there appears to be no need to invoke the role of the serotonin-dopamine interaction to explain its superiority in alleviating extrapyramidal symptoms (118).

As for risperidone, a series of trials have confirmed that, in doses ranging from 4 to 8 mg/day, risperidone produces significantly fewer extrapyramidal symptoms than haloperidol (119–121), although the superiority of risperidone in producing fewer extrapyramidal symptoms is not as striking as that of clozapine. First, the difference between risperidone and haloperidol in terms of extrapyramidal symptoms became statistically indistinguishable at doses beyond 6–8 mg (119, 120). Second, no significant difference in producing extrapyramidal symptoms was found when risperidone was compared with perphenazine, a medium-potency agent with a tendency to produce fewer extrapyramidal symptoms than haloperidol (122). Furthermore, recent PET data suggest that risperidone and haloperidol are almost equipotent at the dopamine D$_2$ receptor (123, 124); therefore, the comparative dose of haloperidol in these clinical trials (10–20 mg/day of haloperidol) may have been too high (1, 125). Studies have shown that mean doses of 3.7 mg/day (126), 4 mg/day (127), or 3.3 mg/day (128) are as effective as 10–50 mg/day of haloperidol and produce significantly fewer extrapyramidal symptoms. This raises the question of whether 4–8 mg day of risperidone would have shown the same superiority in terms of extrapyramidal symptoms had it been compared with a lower dose of haloperidol. Although clozapine causes virtually no extrapyramidal symptoms, risperidone's superiority is only relative to high-potency neuroleptics and disappears with increasing dosage. This suggests that the mechanism for risperidone's superiority in terms of extrapyramidal symptoms may be different from that of clozapine.

The clue to risperidone's having few extrapyramidal symptoms at lower doses, as well as the diminution of this benefit at high doses, may lie in the operation of the mechanism of the serotonin-dopamine interaction. At a dose of 6 mg/day, risperidone demonstrates higher 5-HT$_2$ than D$_2$ occupancy (its 5-HT$_2$ occupancy ranges from 80% to near saturation [129], and its D$_2$ occupancy lies in the 74%–83% range, bordering on the extrapyramidal symptom threshold [123, 129]). At this dose, the presence of potent 5-HT$_2$ antagonism may reduce risperidone's risk of extrapyramidal symptoms in comparison with a conventional neuroleptic. However, as discussed earlier, the ability of 5-HT$_2$ antagonism to counter the effects of D$_2$ antagonism is limited. As the dose of risperidone is increased beyond 6 mg/day, suprathreshold D$_2$ blockade may result, and the serotonin-dopamine interaction mechanism may no longer be able to alleviate extrapyramidal symptoms (123).

It has been proposed that antipsychotics require a particular ratio of 5-HT$_2$ to D$_2$ affinities (greater affinity for 5-HT$_2$ than D$_2$) to obtain the beneficial effects of serotonin-dopamine interaction with respect to extrapyramidal symptoms (114, 115). However, the 5-HT$_2$ to D$_2$ affinity ratio of a drug is a fixed number, while the relative level of 5-HT$_2$ and D$_2$ blockade produced by a drug is a function of the dose. This is illustrated in figure 2. At low doses, a drug with combined 5-HT$_2$ and D$_2$ antagonist activity shows marked preference for the 5-HT$_2$ receptors, whereas at the higher dose, both the D$_2$ and the 5-HT$_2$

receptors are almost completely blocked. Figure 2 demonstrates how the difference between the 5-HT₂ blockade and D₂ blockade is notable when the level of D₂ occupancy is just beyond the extrapyramidal symptom threshold, and this may prevent the clinical expression of extrapyramidal symptoms. However, at doses that result in suprathreshold D₂ occupancy, the preponderance of 5-HT₂ blockade as well as the benefits related to the serotonin-dopamine interaction may be lost. This view is borne out by recent studies in animals (69), as well as reports using PET imaging with risperidone in humans (123). Therefore, the therapeutic window observed in clinical trials with risperidone (119, 120) may not be peculiar to risperidone but may simply reflect limits of serotonergic protection in the face of high D₂ dopamine blockade.

Negative Symptoms

Prospective, controlled studies have demonstrated clozapine's superiority to conventional neuroleptics in the treatment of negative symptoms (110, 130, 131). In the case of risperidone, the evidence is less clear. Of the published prospective, double-blind trials, two (119, 120) reported risperidone to be superior to haloperidol, but another two studies (132, 133) failed to find such a difference. In addition, these effects may be lost over time (121) and may be evident only when low doses of risperidone are compared with relatively higher doses of haloperidol (119, 120, 132). Moreover, few of these studies have appropriately controlled for changes in factors such as depression, extrapyramidal symptoms, and psychotic withdrawal, which could confound the improvement in negative symptoms. When these confounding factors are controlled statistically, some studies (134, 135) found an effect of clozapine and risperidone on primary negative symptoms, but others (136) failed to distinguish these effects from changes in extrapyramidal symptoms and psychosis.

If we assume that these drugs have a primary effect on negative symptoms, how do we explain this effect? The preferential 5-HT₂ antagonism and resulting serotonin-dopamine interaction are promising candidates for an explanation. This is supported by independent clinical trials that have shown the superiority of selective 5-HT₂ antagonists in ameliorating negative symptoms and by the fact that the shared feature distinguishing clozapine and risperidone from conventional neuroleptics is their relatively higher 5-HT₂ than D₂ antagonism. However, these drugs are multifaceted, and clozapine demonstrates high affinities for the dopamine D₄, serotonin 5-HT₁C, adrenergic α₁, muscarinic, and histamine H₁ receptors, while risperidone also exhibits high affinity for dopamine D₄, histamine H₁, and ad-

FIGURE 2. Relationship Between Dose of Antipsychotic, 5-HT₂ and D₂ Receptor Occupancy, and Extrapyramidal Symptoms[a]
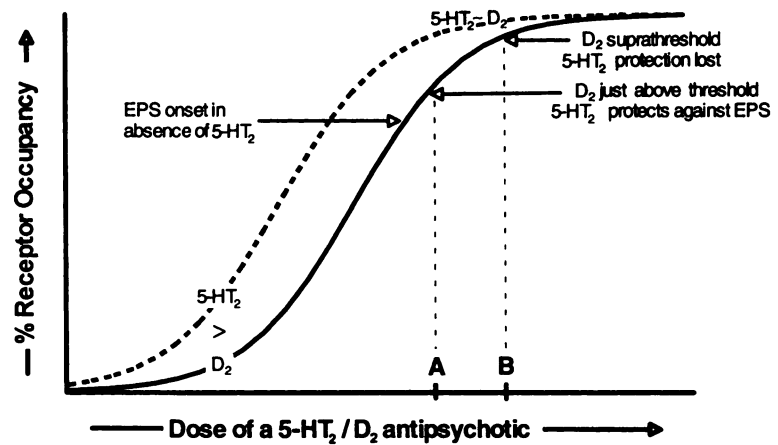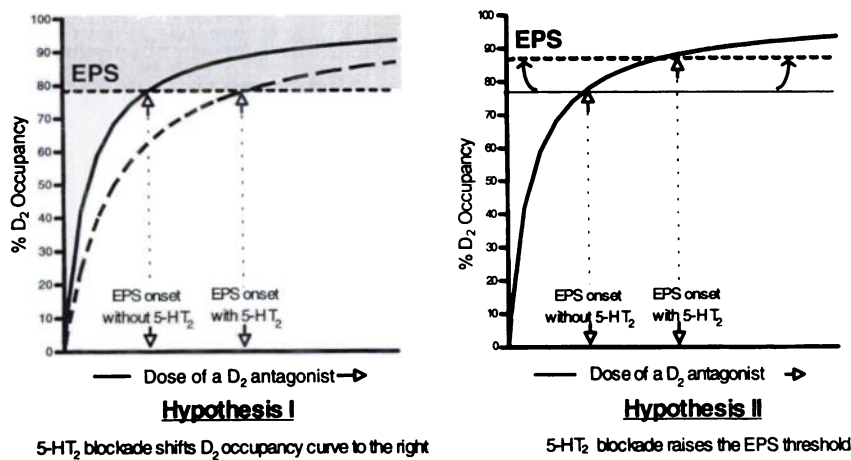

[a]The figure demonstrates that levels of both 5-HT₂ (dashed curve) and D₂ receptor occupancy (solid curve) rise with increasing doses of an antipsychotic with 5-HT₂ and D₂ properties. At low doses, the 5-HT₂ occupancy is much higher than D₂ occupancy (5-HT₂>D₂). However, at high doses the difference is negligible (5-HT₂~D₂). The arrow on the left represents the threshold for extrapyramidal symptoms in the absence of 5-HT₂ blockade. At dose A, the level of D₂ blockade is just above the extrapyramidal symptom threshold, but extrapyramidal symptoms are prevented because the 5-HT₂ blockade is greater than the D₂ blockade. However, at dose B, the D₂ blockade is suprathreshold and the difference between 5-HT₂ and D₂ blockade is minimal, conditions that result in the appearance of extrapyramidal symptoms despite the presence of 5-HT₂ blockade.

renergic α₁ receptors (137, 138). In view of the putative roles of these other neurotransmitters in negative symptoms (79, 96, 139), it may be premature to assign the superiority of clozapine and risperidone in the treatment of negative symptoms solely to their serotonin-dopamine interaction properties.

FUTURE DIRECTIONS

In summary, convincing evidence for the functional relevance of the serotonin-dopamine interaction in alleviating extrapyramidal symptoms in humans is available from clinical trials in which specific 5-HT₂ blockers have been added, and this is further buttressed by the superior extrapyramidal symptom profile of risperidone. The question still remains as to how 5-HT₂ antagonism prevents or alleviates extrapyramidal symptoms in humans. Animal data permit us to postulate two plausible hypotheses, outlined in figure 3. Concomitant 5-HT₂ antagonism could release endogenous dopamine in the striatum, which in turn may displace the neuroleptic from D₂ sites in the striatum. Such a hypothesis would predict that the addition of a 5-HT₂ antagonist would shift the D₂ occupancy curve to the right, thus increasing the dose at which the extrapyramidal symptom threshold is crossed (hypothesis I in figure 3). On the other hand, 5-HT₂ blockade may elevate the threshold for extrapyramidal symptoms through the modulating influences on cholinergic or GABA-ergic mechanisms without a direct effect on D₂

FIGURE 3. Two Hypotheses Regarding the Mechanisms Whereby 5-HT$_2$ Antagonists Diminish Extrapyramidal Symptoms[a]

— Dose of a D$_2$ antagonist—▷

Hypothesis I

5-HT$_2$ blockade shifts D$_2$ occupancy curve to the right

— Dose of a D$_2$ antagonist ▷

Hypothesis II

5-HT$_2$ blockade raises the EPS threshold

[a]EPS=extrapyramidal symptoms. Hypothesis I depicts how the addition of 5-HT$_2$ blockade releases endogenous dopamine and shifts the curve of D$_2$ occupancy to the right (solid curve depicts original D$_2$ occupancy curve, and the curve with dashes depicts the D$_2$ curve under the influence of 5-HT$_2$ antagonists). The extrapyramidal symptom threshold remains the same, but the dose at which extrapyramidal symptoms manifests shifts because of a shift in the curve. In hypothesis II, the addition of the 5-HT$_2$ blockade raises the threshold of extrapyramidal symptoms, without a direct effect on D$_2$ occupancy. This mechanism also increases the dose at which the extrapyramidal symptoms become clinically observable, but there is no change in the curve for D$_2$ occupancy. Both mechanisms plausibly explain the observed finding that the addition of 5-HT$_2$ antagonism delays extrapyramidal symptoms.

occupancy. In this case, one would expect no change in the curve relating D$_2$ occupancy to dose, but one would expect that the level of D$_2$ occupancy producing extrapyramidal symptoms would be higher, i.e., the extrapyramidal symptom threshold would be raised (hypothesis II in figure 3). It is now possible to measure the effects of 5-HT$_2$ antagonism on endogenous dopamine and D$_2$ blockade in humans, in vivo, and to relate these findings to clinical outcomes. Therefore, these two hypotheses concerning the role of the serotonin-dopamine interaction in alleviating extrapyramidal symptoms are eminently testable, and it is hoped that future research will address them.

The second major therapeutic role for the serotonin-dopamine interaction is in alleviating negative symptoms. The clinical evidence available demonstrates improvement in negative symptoms with 5-HT$_2$ antagonists but does not unequivocally distinguish between primary and secondary improvements in negative symptoms. Nonetheless, how might the serotonin-dopamine interaction help in the amelioration of negative symptoms? It is postulated that negative symptoms result from hypodopaminergic function in the prefrontal cortex. One could hypothesize that 5-HT$_2$ antagonism, by disinhibiting the dopaminergic system, would lead to enhanced dopaminergic transmission in the prefrontal cortex, which in turn could ameliorate negative symptoms. Although current neuroimaging technologies permit the measurement of dopamine receptors in the striatum, methods for evaluating D$_2$ receptors or dopamine levels in the prefrontal cor-

tex are still in their infancy. Therefore, investigating this aspect of serotonin-dopamine interaction in humans may have to await the development of valid in vivo measures of the cortical dopamine system.

An assumption implicit in the above explanations of the serotonin-dopamine interaction is that the effect of the serotonin-dopamine interaction is different in different brain regions. It is conventionally held that antipsychotic action results from inhibiting dopaminergic function in the mesolimbic system and that similar inhibition in the striatum and the prefrontal cortex leads to the production or exacerbation of extrapyramidal symptoms and negative symptoms, respectively. We have argued here that antipsychotics with a serotonin-dopamine interaction profile may ameliorate extrapyramidal symptoms and negative symptoms by disinhibiting the dopamine system in the striatum and the prefrontal cortex. However, a similar functional disinhibition in the mesolimbic regions would counteract the primary antipsychotic action. Therefore, our reasoning can be held together only if we can demonstrate that serotonin's influence on the dopamine system in the mesolimbic regions is either quantitatively or qualitatively different from its effect in the striatum and the prefrontal cortex.

Finally, we raise the issue of using two drugs, one with specific 5-HT$_2$ and another with specific D$_2$ antagonism, to obtain the benefits of the serotonin-dopamine interaction. It is claimed (140) that newer antipsychotic agents like risperidone have an optimal balance of 5-HT$_2$ and D$_2$ affinities, which provides the benefits of the serotonin-dopamine interaction. However, the crucial element is not the balance of 5-HT$_2$ and D$_2$ affinities of a given drug in a test tube, but the relative levels of 5-HT$_2$ and D$_2$ antagonism it produces in a given patient. The limitation inherent in any drug that has both 5-HT$_2$ and D$_2$ antagonism is that any effort to increase 5-HT$_2$ blockade inexorably increases D$_2$ antagonism and vice versa (figure 2). Although recent clinical trials have demonstrated the success of drugs like risperidone, it is quite likely that independent control over the 5-HT$_2$ and D$_2$ system may provide for even more effective treatment. Low-potency neuroleptics that can be regarded as fixed combinations of anti-D$_2$ and anticholinergic activity have been largely replaced by higher potency neuroleptics that provide relatively selective D$_2$ blockade and that are electively and flexibly combined with doses of anticholinergics. Thus, with better understanding of the role and implications of the serotonin-dopamine interaction, clinicians may

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find that using two agents that permit independent control over the D_2 and 5-HT_2 systems permits more individualized and efficacious therapy.

The widespread study of the serotonin-dopamine interaction from a basic and clinical viewpoint promises a certain and substantive change in the pharmacotherapy of schizophrenia. The evidence is not unequivocal. The discovery of new receptor subtypes and a better understanding of their functional relevance will call for a constant reevaluation of existing knowledge. However, the facts are sufficiently coherent to permit the specification of testable hypotheses and to provide a logical framework for understanding the therapeutic benefits of the serotonin-dopamine interaction. The next few years will lead to a clearer understanding and, we hope, a more effective use of the serotonin-dopamine interaction for the benefit of our patients.

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