

A DECADE OF SEROTONIN RESEARCH: ROLE OF SEROTONIN IN TREATMENT OF PSYCHOSIS

Serotonergic Basis of Antipsychotic Drug Effects in Schizophrenia

Jeffrey A. Lieberman, Richard B. Mailman, Gary Duncan, Lin Sikich,
Miranda Chakos, David E. Nichols, and John E. Kraus

Recent attention has been focused on the involvement of serotonin (5-HT) in the pathophysiology of schizophrenia and its role in mediating antipsychotic drug effects. There are two reasons for the new emphasis: the tremendous success of the so-called "atypical" antipsychotic drugs (a common feature of which is their high affinity for specific 5-HT receptor subtypes); and the elucidation of a complex family of 5-HT receptors whose function and pharmacology is only beginning to be understood. This paper will review the evidence that pertains to the role of 5-HT in mediating antipsychotic drug effects. The interaction of dopamine and 5-HT systems will be reviewed, and the mechanisms of action of atypical antipsychotic drugs will be evaluated in this context. The impact of serotonin on neurodevelopment, and the involvement of serotonin in the psychotomimetic and psychotogenic properties of hallucinogens, will be discussed. Together, these facts will be placed into the context of changes in serotonergic function in schizophrenia. Biol Psychiatry 1998;44:1099-1117 © 1998 Society of Biological Psychiatry

Key Words: Serotonin, dopamine, antipsychotic drugs, schizophrenia, atypical, neuroleptic, receptors, striatum, raphe, clozapine

Introduction

Since the advent of chlorpromazine and elucidation of its mechanisms of action, there has been a focus on dopamine (DA) neurotransmission both in formulating pathophysiological theories of schizophrenia and in developing new therapeutic agents (Randrup and Munkvad 1965; Carlsson 1974; Snyder et al 1974; Creese et al 1976; Seeman et al 1976; Davis et al 1991). Recently, consider-

able attention has been focused on the potential involvement of serotonin (5-HT) in both the pathophysiology of schizophrenia and its role in mediating antipsychotic drug effects. One reason for this has been the tremendous success of the so-called "atypical" antipsychotic drugs that have as a common feature high affinity for one or more 5-HT receptor subtypes (e.g., 5-HT_{2A}). In fact, it is now known that there is a large family of 5-HT receptors whose function and pharmacology are only beginning to be understood. The molecular biology of serotonin receptors, and the therapeutic implications of drugs acting at these receptors is reviewed in the article by Kroeze and Roth (this issue).

This paper will review evidence linking 5-HT systems to the mediation of antipsychotic drug effects, and also to the possible etiology of the disorder. We shall address the role of serotonin in neurodevelopment, and the functional interactions of DA and 5-HT systems. By examining the psychotomimetic and psychotogenic properties of hallucinogens, and changes in serotonergic function in schizophrenia, we hope to provide insight into how 5-HT systems may play a role in the clinical action of atypical antipsychotic drugs, and to highlight many of the remaining unanswered questions.

Functional Interactions of DA and 5-HT Systems

A major line of evidence supporting a potential role of serotonin in mediating antipsychotic drug effects involves the anatomical and functional interactions of DA and 5-HT. DA and 5-HT neurotransmission interact at different anatomical levels, are mediated by different 5-HT receptor subtypes, and affect different aspects of DA function. Generally speaking, the reduction of 5-HT activity is associated with an enhancement of DA. This interaction has been suggested to account for the beneficial effects of atypical antipsychotic drugs in schizophrenia, specifically the reduction of extrapyramidal symptoms (EPS) and improvement in negative symptoms, attributed to 5-HT_{2A} antagonism.

The neuroanatomical basis for interactions between

From the Department of Psychiatry (JAL, RBM, GD, LS, MC, JEK), Department of Pharmacology (JAL, RBM), Neurosciences Center (RBM, GD), and Mental Health and Neuroscience Clinical Research Center (JAL, RBM, GD, LS, MC), University of North Carolina School of Medicine, Chapel Hill, North Carolina; and Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana (DEN).

Address reprint requests to Jeffrey A. Lieberman, MD, CB #7160, Department of Psychiatry, 7025 Neurosciences Hospital, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7160.

Received February 12, 1998; revised April 2, 1998; accepted April 3, 1998.

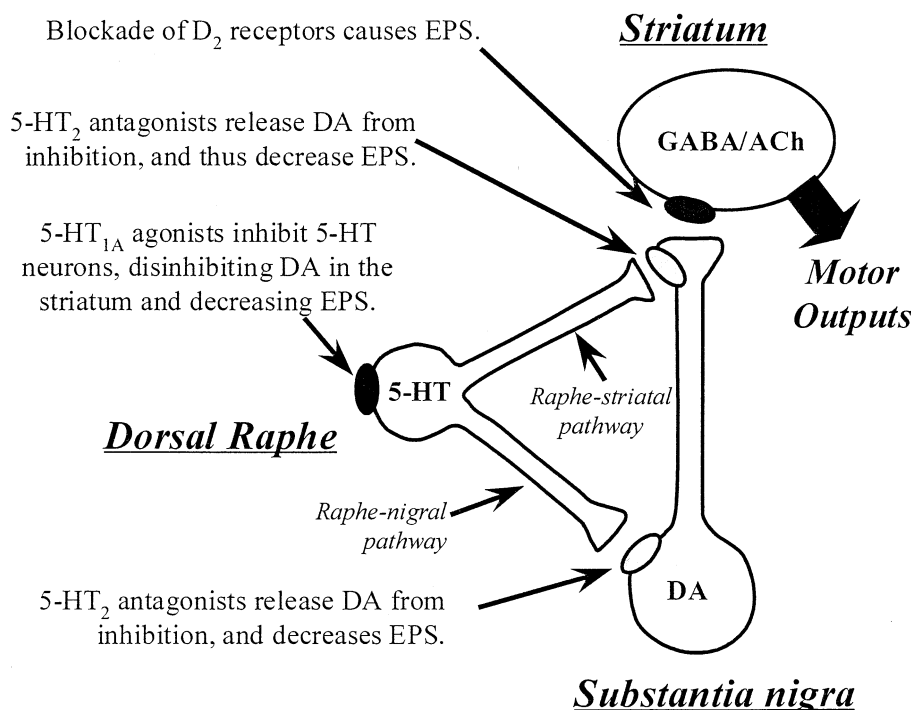


Figure 1. Schematic diagram of functional interactions between dopamine and serotonin systems that affect the occurrence of extrapyramidal side effects induced by antipsychotic drugs (modified from Kapur and Remington 1996). This illustration is a simplification of the varied and complex interactions of DA and 5-HT that are described further in Table 1. ACh, acetylcholine; GABA, gamma-aminobutyric acid.

serotonin and DA systems is well described. Serotonergic neurons in the median and dorsal raphe nuclei innervate DA neurons in the substantia nigra (SN, A9) and the ventral tegmental area (VTA, A10) (Herve et al 1987; van der Kooy and Hattori 1980; Dray et al 1976). Van Bockstaele et al (1994) demonstrated in an electron microscopic immunocytochemical study that serotonergic terminals make synaptic contact with DA neurons in the VTA. In addition to innervation of A9 and A10 neurons, 5-HT neurons project to terminal fields of DA neurons, including the caudate putamen, nucleus accumbens, medial prefrontal cortex, and amygdala (Lvoie and Parent 1990; Steinbusch et al 1981; van der Kooy and Hattori 1980; Imai et al 1986). Thus, neuroanatomical studies provide a basis for interactions between DA and 5-HT at the level of DA cell bodies and in terminal fields of these neurons. Figure 1 depicts a simplified (for illustrative purposes) diagram of 5-HT and DA interactions in the midbrain and striatum.

Behavioral Evidence for 5-HT–DA Interactions

Behavioral studies examining the effects of 5-HT lesions and depletion suggest, in general, that 5-HT produces antagonistic actions on DA-mediated behaviors (Mabry and Campbell 1973; Breese et al 1974; Morrow and Roth 1996). Consistent with this idea, selective 5-HT reuptake inhibitors (SSRIs) such as fluoxetine decrease the self-administration of cocaine (Carroll et al 1990; Richardson and Roberts 1991) and amphetamine (Leccese and Lyness

1984) in rats. While these data indicate that 5-HT normally inhibits dopaminergic function, direct microinjection of 5-HT into the VTA apparently had the opposite effect (Guan and McBride 1989; Mylecharane et al 1996; Gillies et al 1996). Moreover, the selective 5-HT_{2A} receptor antagonists MDL 100,907 and MDL 100,151 potently inhibit amphetamine-induced locomotor activity at doses of the antagonists that do not affect spontaneous activity (Arnt 1995; Sorensen et al 1993). These findings indicate that 5-HT can have a stimulatory effect on mesolimbic DA systems and seem difficult to reconcile with the results of studies showing that 5-HT lesions and depletion potentiate indirectly acting DA agonists. It may be that the results from depletion or lesion studies reflect compensatory changes in brain as much as endogenous function.

Electrophysiological Interactions between 5-HT and DA

A number of studies have demonstrated effects of acute 5-HT receptor activation on the electrophysiological activity of midbrain DA neurons. Most in vivo electrophysiological studies find that 5-HT has slight inhibitory effects on the firing of DA neurons (Fibiger and Miller 1977; Dray et al 1978; Ugedo et al 1989) that are blocked by 5-HT_{2A} antagonists (Ugedo et al 1989). 5-HT has also been shown to potentiate DA receptor-mediated inhibitory effects on neuronal activity in the VTA (Brodie and Bunney 1996). In addition, the effect of the 5-HT₂ antagonists to reverse amphetamine-induced inhibition of

DA neuron activity was blocked by pretreatment with a dose of levodopa that produced no effect on DA neuronal activity alone (Sorensen et al 1992). From these data, Sorensen et al (1992) suggest that the 5-HT₂ antagonists produced this effect in part by interfering with amphetamine-stimulated DA synthesis.

Although most acute in vivo electrophysiological studies involving extracellular unit recording indicate that 5-HT has an inhibitory influence on midbrain DA neurons, the action of 5-HT on the functional activity of DA cells can be complex. (Cameron et al 1997; Kelland et al 1990; Mylecharane 1996; Gillies et al 1996; Guan and McBride 1989). The data from behavioral, microdialysis (Benloucif and Galloway 1991), and in vitro electrophysiological studies appear contradictory to the in vivo electrophysiological observation indicating an inhibitory influence of 5-HT on DA neurons. Thus, further work is required to clarify the physiological role of 5-HT/DA interactions at the level of DA cell bodies.

Chronic administration of the atypical antipsychotic drug clozapine (a drug with 5-HT_{2A} antagonistic properties) results in a reduction in the number of spontaneously active neurons in the VTA, but not the substantia nigra (Chiodo and Bunney 1983). By contrast, chronic administration of the typical antipsychotic haloperidol reduces the number of spontaneously active neurons in both the VTA and substantia nigra (Chiodo and Bunney 1983). The ability of clozapine to inhibit selectively DA neuronal activity in the VTA has been hypothesized to account for its efficacy in the treatment of schizophrenia and lack of EPS. Clozapine interacts with a variety of receptors from different neurotransmitter systems including D₁, D₂, D₄, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, 5-HT₇, α_1 - and α_2 -adrenergic, histamine H₁, and muscarinic M₁ and M₄ receptors. There is no simple explanation relating this mixed neuroreceptor profile to the anatomically selective pharmacologic effects of clozapine on VTA neuronal activity. It is of interest that chronic administration of the selective 5-HT₂ receptor antagonists MDL 100,907 (Sorensen et al 1993) also selectively reduces the number of spontaneously active DA neurons in the VTA. These preclinical data, together with data showing that 5-HT receptor antagonists, particularly of 5-HT_{2A} receptors, block DA-mediated behaviors, suggest that selective 5-HT₂ antagonists may possess atypical antipsychotic activity.

Postsynaptic Interactions between DA and 5-HT in the Medial Prefrontal Cortex

Altered structure and functional activity of DA in the medial prefrontal cortex has been suggested to be responsible for the negative symptoms and cognitive deficits in

schizophrenia (Andreasen et al 1992; Gur et al 1995; Norman et al 1997; Siegel et al 1993; Weinberger et al 1988; 1995). Dopamine characteristically inhibits activity of neurons in the medial prefrontal cortex. Activation of 5-HT₃-like receptors in the medial prefrontal cortex has also been shown to suppress neuronal activity in this region (Ashby et al 1991). Ashby et al (1991) refer to these receptors as 5-HT₃-like because they differ in specific functional characteristics associated with cloned ionotropic 5-HT₃ receptors, but demonstrate pharmacologic selectivity characteristic of these receptors. After lesioning of 5-HT neurons with 5-7-dihydroxytryptamine, 5-HT₃ receptors become functionally supersensitive (Ashby et al 1994). By contrast, in these lesioned rats, there is DA receptor subsensitivity in the medial prefrontal cortex, suggesting that 5-HT exerts a permissive role in the electrophysiological effects of DA in this region (Ashby et al 1994). Support for this hypothesis comes from data showing that 5-HT and 5-HT₃ agonists markedly potentiate the effects of DA on the firing rate of medial prefrontal cortical neurons (Wang et al 1996). This action of 5-HT to potentiate the electrophysiological actions of DA in the medial prefrontal cortex is similar to the electrophysiological interactions of the monoamines in the VTA; however, different 5-HT receptor subtypes appear to be involved in mediating these effects in the two regions (i.e., 5-HT₃ receptors in the cortex and 5-HT_{2A} receptors in the VTA).

Effects of 5-HT on DA Release

There are abundant and consistent data demonstrating that 5-HT can stimulate DA release from nerve terminals by an action on presynaptic receptors. Early in vitro studies in striatal synaptosomes showed that 5-HT could stimulate DA release in this cell-free preparation (De Belleroche and Bradford 1980). In vivo microdialysis studies have also shown that local application of 5-HT and selective agonists can induce the release of DA in both striatum and limbic brain regions. When added to the perfusate, 5-HT induced the release of DA in the dorsal striatum (Benloucif et al 1993) and nucleus accumbens (Parsons and Justice 1993). Benloucif et al (1993) demonstrated that stimulation of DA release by locally applied 5-HT in the striatum could be reduced by 5-HT₁ and 5-HT₃ antagonists. Consistent with those findings, 5-HT₃ receptor stimulation in the striatum increases endogenous DA release (Blandina et al 1989; Chen et al 1991). Locally applied 5-HT also increases DA release in the medial prefrontal cortex, and the magnitude of the potentiation was substantially greater than that observed in the striatum (Iyer and Bradberry 1996). The 5-HT receptor subtype involved in mediating this response in the medial prefrontal cortex may be different from that mediating the

Table 1. Summary of 5-HT–DA Interactions as Assessed by Different Experimental Approaches

5-HT manipulation	Usual effect on DA function	Implication for 5-HT and DA interactions
5-HT lesion or depletion	Potentiate behavioral effects of DA drugs	5-HT antagonizes DA function
5-HT uptake inhibition	Decrease self-administration of DA drugs	5-HT antagonizes DA function
Injection of 5-HT agonists into VTA	Increase locomotor activity	5-HT potentiates DA function
5-HT ₂ blockade	Decrease DA-mediated locomotion	5-HT potentiates DA function
5-HT agonist in vivo	Slight decrease or no effect on DA neuron activity	5-HT antagonizes DA function
5-HT agonist electrophysiological stimulation in vitro	Depolarization of DA neurons	5-HT potentiates DA function
5-HT ₃ agonist	Enhancement of DA-induced depression of medial prefrontal cortex neuron activity	5-HT potentiates DA function
Presynaptic action of 5-HT agonists	Stimulation of DA release	5-HT potentiates DA function
5-HT antagonists	Stimulation of DA release	5-HT antagonizes DA function
5-HT ₂ antagonist	Reduction in ¹¹ C-raclopride binding in vivo	5-HT antagonizes DA function

homologous action in the striatum and accumbens. This is suggested by the fact that 5-HT₃ antagonism was without effect, but a selective 5-HT_{1B}/5-HT_{1D} antagonist completely blocked 5-HT-stimulated DA release (Iyer and Bradberry 1996). Thus, differential presynaptic regulation of DA release by 5-HT in the striatum, nucleus, and medial prefrontal cortex may provide a means to regulate dopamine release in a neuroanatomically sensitive fashion.

Although stimulation of DA release by 5-HT_{1B}/5-HT_{1D} and 5-HT₃ agonists is well documented, systemic administration of 5-HT₂ antagonists also stimulates DA release. For example, Hertel et al (1996) found that systemic administration of clozapine and amperozide (which are both potent 5-HT_{2A} antagonists) increased DA release selectively in the medial prefrontal cortex. By contrast the D₂ antagonist raclopride selectively increased DA release in the nucleus accumbens and striatum (Hertel et al 1996). Local infusion of the 5-HT_{2A} antagonist ritanserin into the medial prefrontal cortex also results in increased DA release (Pehek 1996). Such data suggest that 5-HT is exerting a tonic inhibitory effect on DA release in the medial prefrontal cortex. These findings, together with data indicating a stimulatory role of presynaptic 5-HT_{1B}/5-HT_{1D} and 5-HT₃ receptors in the regulation of DA release, demonstrate a complex but important role of 5-HT in the regulation of DA release via actions on or near DA terminals.

Positron-emission tomography (PET) studies in baboons have demonstrated that the 5-HT_{2A} antagonists altanserin and SR 46349B reduce substantially ¹¹C-raclopride binding, indicating that the drugs increase DA release (Dewey et al 1995). Direct measurement of DA via microdialysis confirmed that conclusion. In a similar study in human subjects, administration of the 5-HT-releasing agent fenfluramine resulted in a significant reduction in the binding of ¹¹C-raclopride, suggesting that the drug increased DA release (Smith et al 1997). This was corroborated by changes of other indices of increased DA release

in plasma (i.e., homovanillic acid, prolactin, and cortisol). In rats, fenfluramine induces a robust induction of Fos in the striatum that is blocked by a D₁ DA antagonist and 6-hydroxydopamine treatment, but not by a variety of 5-HT receptor antagonists (Rouillard et al 1996). These data indicate the induction of Fos by the 5-HT-releasing agent is mediated through DA and are consistent with the findings of the PET studies in humans.

As is clearly apparent from this review of studies, the nature of these 5-HT and DA-mediated interactions are varied and complex. Table 1 describes the different types of regional interactions.

Conclusions

Functional interactions between 5-HT and DA systems have been clearly demonstrated behaviorally, neurochemically, and electrophysiologically. The effects of 5-HT appear to be differentially mediated by distinct 5-HT receptors and are neuroanatomically specific. They provide a potential basis for the beneficial effects of atypical antipsychotic drugs in terms of their improved EPS liability and therapeutic effects against negative symptoms and less clearly cognitive and psychotic symptoms.

Antipsychotic Drug Pharmacology

5-HT_{2A} Receptor Antagonist Properties of Atypical Antipsychotics

Meltzer et al (1989) formalized and popularized a concept that had been previously suggested in a report by Ceulemans et al (1985), to wit, that the ratio of 5-HT_{2A} to D₂ affinities was the key pharmacologic property of atypical antipsychotic drugs. Meltzer et al (1989) suggested that typical and atypical antipsychotics can be distinguished on the basis of lower D₂ and higher 5-HT_{2A} pK_i values (a logarithmic measure of the affinity of a drug for its receptor), parameters derived from in vitro receptor stud-

ies. He proposed that the atypical antipsychotics had 5-HT_{2A}/D₂ pK_i ratios of at least 1.1 (corresponding to a 25-fold selectivity for 5-HT₂ as compared with D₂ receptors). This criterion is met in the new atypical compounds (such as clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone) that have a relative 5-HT₂ to D₂ selectivity.

These atypical antipsychotics have no effect on DA cell firing following acute administration, and most of them selectively decrease the activity of mesolimbic A10 neurons after chronic administration (Chiodo and Bunney 1983, 1985; White and Wang 1983a, 1983b). The preferential blockade of 5-HT_{2A} receptors by atypical antipsychotic drugs may contribute to their superior clinical profile by decreasing the inhibitory effects of DA activity produced by chronic neuroleptics (i.e., postsynaptic D₂ antagonism, depolarization block), functionally increasing DA activity in the striatum and, possibly, certain other brain regions as well. Svensson et al (1995) have proposed a model that attributes the beneficial effect of atypical antipsychotics on negative symptoms to blockade of 5-HT_{2A} receptors, which leads to increased burst firing of DA neurons in the medial prefrontal cortex (mPFC) compared to single spike firing, thereby increasing the signal – noise ratio. In addition, increases in mPFC DA activity produced by 5-HT_{2A} receptor antagonism may contribute to the antipsychotic efficacy of these atypical antipsychotic drugs by decreasing excessive subcortical DA activity (Schmidt et al 1995).

It seems unlikely, however, that the ratio of affinities for 5-HT_{2A} and D₂ receptors is the entire explanation of the novel mechanism and unique clinical features of the atypical antipsychotics. Anticholinergic, α -adrenergic, and/or β -adrenergic blockade, ability to enhance glutamatergic transmission and stimulate neurotensin release, and ability to increase gamma-aminobutyric acid turnover in the striatum and decrease it in the substantia nigra may also contribute, along with other effects, to the spectrum of action of atypical antipsychotics. It may also be that the 5-HT₂/D₂ ratio is relevant only to EPS and tardive dyskinesia liability and not to increased therapeutic efficacy. Some of the newer drugs that have become available are therefore of heuristic value.

Selective 5-HT_{2A} Antagonists

MDL 100,907 is a selective 5-HT_{2A} antagonist that has no D₂ antagonist properties *in vivo*, and which is suggested to have antipsychotic properties by preclinical studies. Like the atypical antipsychotics, it decreases the firing rate of A10, but not A9, neurons after chronic administration (Sorensen et al 1993). It also blocks amphetamine-induced locomotor activity at doses that do not cause catalepsy

(Schmidt et al 1992). Microdialysis studies confirm that 5-HT_{2A} receptor blockade caused by MDL 100,907 produces marked increases in DA efflux in the rat medial prefrontal cortex (Schmidt and Fadaye 1995), suggesting that MDL 100,907 may have therapeutic effects for negative symptoms. Phase II clinical trials of MDL 100,907 to assess the safety and antipsychotic efficacy of this 5-HT_{2A} antagonist in the treatment of schizophrenia have just recently been completed. These preliminary data (Offord, personal communication) suggest that the drug is safe and efficacious, although further studies are needed to determine if selective 5-HT_{2A} antagonism provides marked improvements in the treatment of schizophrenia.

Combined 5-HT_{2A} and 5-HT_{2C} Receptor Antagonists

Clozapine, an effective atypical antipsychotic, has higher affinity for the 5-HT_{2C} receptor (in addition to the 5-HT_{2A} receptor) than the D₂ receptor. Some evidence suggests that combined 5-HT_{2A} and 5-HT_{2C} antagonists, such as ritanserin and mianserin, may have antipsychotic activity in schizophrenic patients, even though they have little activity at D₂ receptors. Three placebo-controlled double-blind studies have demonstrated an effect of ritanserin augmentation of antipsychotics predominantly on negative symptoms in schizophrenic patients who have been poorly controlled on ongoing therapy with a classical antipsychotic agent (Gelders 1989; Reynetjens et al 1986; Duinkerke et al 1993). A recent open-label treatment trial of acutely psychotic patients with 20 mg of ritanserin treatment alone for 4 weeks resulted in an improvement of both negative and positive symptoms (Wiesel et al 1994). The fact that these effects were mediated via 5-HT_{2A} receptors rather than D₂ receptors was confirmed in this study by assessing D₂ receptor occupancy with PET. Ritanserin treatment has also been shown to reduce the EPS associated with antipsychotic therapy (Reynetjens et al 1986; Miller et al 1990). Mianserin augmentation of antipsychotic treatment has been reported to decrease negative and global symptoms in hospitalized patients with chronic schizophrenia (Rogue and Rogue 1992).

5-HT₃ Receptor Antagonists

5-HT₃ receptor antagonists have been examined as potential antipsychotics. This is due to both the 5-HT₃ antagonism properties of effective atypical antipsychotics such as clozapine and the primarily preclinical studies that suggest antipsychotic efficacy of the highly selective 5-HT₃ antagonist, ondansetron. In animal models, ondansetron reduced limbic DA hyperactivity caused by the infusion of DA or amphetamine into the rat nucleus accumbens, and this has traditionally been utilized as a preclinical test of

antipsychotic efficacy. Ondansetron was distinguished from DA receptor antagonists by its ability to return the hyperactivity response to control values, without excessive suppression of locomotion. Furthermore, the use of a selective 5-HT₃ receptor agonist 2-methyl-5-HT increased the hyperactivity response induced by amphetamine, an effect that was antagonized by ondansetron. 2-methyl-5-HT had no direct effect on spontaneous locomotor activity when given alone (Costall et al 1987). These data are consistent with the view that 5-HT, via the 5-HT₃ receptor, has a modulatory function that is only apparent when the mesolimbic DA system is disturbed.

Clinical evidence of the antipsychotic efficacy of ondansetron is less encouraging. Two separate open-label uncontrolled multicenter trials of ondansetron in patients with schizophrenia reported a significant reduction in Brief Psychiatric Rating Scale scores in patients who were treated with 16 mg/day for 4 weeks (DeVaugh-Geiss et al 1992). Gaster and King (1997) note, however, that a double-blind study in 114 patients failed to confirm the initial findings.

PET Studies

PET studies have utilized selective radioligands such as [¹¹C]raclopride and [¹¹C]N-methylspiperone to measure D₂ and 5-HT₂ receptor occupancy, respectively, after treatment with typical and atypical antipsychotics. These studies have demonstrated high D₂ receptor occupancy (70–90%) in patients who have received therapeutic doses of conventional antipsychotic drugs. In contrast, studies of patients treated with the atypical antipsychotic clozapine show a relatively low D₂ receptor occupancy (20–67%; Farde et al 1992, 1994, 1995). This suggested that the lack of EPS with clozapine could be explained on the basis of lower striatal D₂ receptor occupancy, but that the superior antipsychotic efficacy of clozapine in treatment-resistant patients may be mediated by a mechanism that is not totally based on D₂ receptor occupancy. In contrast to D₂ receptor occupancy, 5-HT_{2A} receptor occupancy in the neocortex was very high (range, 84–94%), even at low clozapine doses. This high 5-HT_{2A} receptor occupancy does not prove, but is consistent with the view that 5-HT_{2A} antagonism may be related to the superior antipsychotic efficacy of clozapine in treatment-resistant schizophrenia (Farde et al 1995). PET studies of newer atypical antipsychotics reveal that risperidone at low doses (1–4 mg) produces D₂ and 5-HT_{2A} occupancies that are in the range produced by clozapine (D₂ <70%, 5-HT_{2A} >80%), but at higher doses (>6 mg) produces D₂ receptor occupancies of 70–80% and 5-HT_{2A} receptor occupancies of 80–95% (Farde et al., 1995; Kapur et al personal communication). Olanzapine (10 mg) results in a D₂ and 5-HT₂ receptor

occupancy similar to clozapine [D₂ receptor occupancy of 59–63% and 5-HT₂ receptor occupancy of 74–92% (Nyberg et al 1997)], while doses greater than 10 mg produce D₂ occupancy of greater than 70% (Kapur et al personal communication). Quetiapine at doses of 150–750 mg produces D₂ occupancies <70% and 5-HT_{2A} occupancies >80% (Kapur et al personal communication). Interestingly, EPS do not always occur with risperidone and usually do not occur with olanzapine at doses associated with D₂ occupancies >80%. This suggests that the concurrent 5-HT_{2A} antagonism of these compounds may be mitigating their D₂ antagonism in the striatum.

There is evidence from PET studies that serotonin modulates DA in normal subjects. Studies of normal subjects that have utilized a pharmacologic challenge of the serotonin system with (±)-fenfluramine have demonstrated a decrease in binding of [¹¹C] raclopride, the radioactive ligand that is a competitive antagonist for the striatal D₂ receptor. The observed decrease in [¹¹C] raclopride binding to the striatum after the (±)-fenfluramine challenge is consistent with an increase in presynaptic DA concentrations and with the ability of a serotonin agonist to stimulate DA activity (Smith et al 1997). This implied serotonergic modulation of DA function in normal subjects has implications for both the etiology and treatment of schizophrenia. If there is an abnormality in serotonergic modulation of DA in schizophrenia, we would expect that a (±)-fenfluramine challenge in schizophrenic patients might decrease [¹¹C]raclopride binding to a greater degree than in normal subjects (due to an increase in presynaptic DA release in response to the challenge). 5-HT_{2A}/D₂ receptor antagonists would compensate for this imbalance in the serotonin and dopamine systems; however, these results are not consistent with subhuman primate studies in which the 5-HT uptake inhibitor, citalopram, increased [¹¹C]raclopride binding (Dewey et al 1995). This might be due to the different 5-HT agonists used and the fact that fenfluramine may release DA as well as serotonin from presynaptic storage sites.

Genetic Studies

The role of serotonin receptor genes in the pathophysiology of schizophrenia and in the prediction of response to clozapine in treatment-refractory schizophrenics is an area that has generated much interest. An extensive array of genetically polymorphic sites is now available for molecular genetic dissection of the serotonin system. The 5-HT_{2A} receptor gene (HTR2A) has been localized to chromosome 13 (Hsieh et al 1990), and several restriction fragment length polymorphisms (RFLPs) have been identified. One is silent (Warren et al 1993), another occurs in

the putative promoter region of this gene (Deckert et al 1997), and the third leads to His/Tyr amino acid substitution in the 5-HT_{2A} receptor protein (Erdmann et al 1996). The 5-HT_{2C} gene has been localized to the X-chromosome, and has a coding sequence RFLP (Lappalainen et al 1995). Other candidate genes from the serotonin system include: the 5-HT_{1A} (Khan et al 1990), 5-HT_{1D} alpha (Kasapi et al 1994; Ozaki et al 1995), 5-HT_{1D} beta (Sidenberg et al 1993; Lappalainen et al 1995; Nothen et al 1994), 5-HT_{1E} (Shimron-Abarbanell et al 1996), 5-HT_{1F} (Shimron-Abarbanell et al 1996), 5-HT₆ (Kohen et al 1996), and 5-HT₇ receptors (Gelernter et al 1995).

Williams et al (1996) reported an association between the T102C polymorphism in the gene for the 5-HT_{2A} receptor located on the long arm of chromosome 13 and schizophrenia. This finding has, however, not been replicated by other investigators (Arranz et al 1996). Because clozapine has a high affinity for the 5-HT_{2A} receptor, it was hypothesized that functional variation at the gene for this receptor may affect treatment response. There is some evidence that allelic variation of genes that encode serotonin receptors can influence clinical response to clozapine. Arranz et al (1995a) showed that, for the T102C polymorphism of the 5-HT_{2A} receptor gene, the genotypes T102/C102 and T102/T102 were more common in clozapine responders. Homozygosity for the C102 allele was more frequent among patients who were clozapine nonresponders, findings that have been replicated by Masellis et al (1995). Arranz et al (1995b) have also studied a H452Y polymorphism in the 5-HT_{2A} receptor, and found an association between the allele Y452 and poor response to clozapine. Sodhi et al (1995) reported that a polymorphism of the 5-HT_{2C} receptor (a serine substitution of cysteine at amino acid 23 in the 5-HT_{2C} receptor) was associated with a good response to clozapine. Prediction of antipsychotic response by genotyping has generated interest, because this may permit early identification of treatment responders that could spare them the delay resulting from failure to respond to other medications. The association between clinical response and 5-HT receptor polymorphisms provides a potentially important line of evidence linking serotonin to antipsychotic drug actions.

Psychotomimetic and Psychogenic Properties of Hallucinogens

Another line of evidence linking serotonin to schizophrenia and, by extension, antipsychotic drug activity is the research on hallucinogenic drugs. Several terms are often used for such drugs, including hallucinogen and psychotomimetic. It should be recognized that both terms are misnomers, because not all such drugs reliably produce hallucinations, nor do they usually produce a state that

mimics psychosis. As such, despite the differences between the effects of “hallucinogens” and the symptoms seen in various psychoses, such mechanisms are likely to be heuristic. Administration of hallucinogens to patients with schizophrenia produces an intoxication that includes many of the same manifestations that occur in healthy persons, but is described as qualitatively different than the mental state in schizophrenia. The one exception to this is PCP, a psychotomimetic agent that is believed to model the positive, negative, and cognitive symptoms of schizophrenia (Javitt and Zukin 1991), but does not directly affect the 5-HT system.

Historical Relationship between 5-HT and Hallucinogen Action

Following the isolation and identification of 5-HT, interest in its role as a neurotransmitter and its possible relevance to behavior was greatly stimulated by, and was intertwined with, the virtually contemporaneous discovery of LSD and recognition that this potent psychoactive substance had the ability to interact with 5-HT systems (Twarog and Page 1953; Gaddum 1953; Gaddum and Hameed 1954; Woolley and Shaw 1954). The idea that the effects of LSD could be attributed simply to blockade of brain 5-HT receptors was short lived. A variety of studies provided convincing evidence that blockade of 5-HT receptors was not the primary mechanism of LSD (e.g., Cerletti and Rothlin 1955). Nevertheless, it was evident that even if LSD was not a central antagonist of 5-HT, it did have effects on 5-HT function in the central nervous system (Freedman 1961; Rosecrans et al 1967; Andén et al 1968, 1971, 1974; Fuxe et al 1972; Freedman et al 1970; Leonard 1973; Randic and Padjen 1971). Such data suggested that 5-HT systems may play a role in the etiology and/or therapy of aspects of psychosis.

5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} Receptor Actions of Hallucinogens

At the present time, there seems to be a fairly clear consensus that the key site for hallucinogen action is the 5-HT_{2A} receptor subtype (Branchek et al 1990; McKenna and Saavedra 1987; Pierce and Peroutka 1989; Sadzot et al 1989; Teitler et al 1988, 1990). It should be noted, however, that this conclusion has been developed largely by correlation of the rat behavioral activity of hallucinogenic phenethylamines with their affinities and activities at the 5-HT₂ receptor (Glennon et al 1983, 1984a, 1984b, 1986; Sanders-Bush et al 1988).

Because all of the hallucinogens have nearly equal potency in binding to the 5-HT_{2A} and 5-HT_{2C} receptor subtypes, there has been some uncertainty as to which of these receptors was more important to the mechanism of

action. Nevertheless, Ismaiel et al (1993) developed a spiperone analogue with about 2000-fold selectivity for the rat 5-HT_{2A} over the 5-HT_{2C} receptor that was able to block the discriminative cue of the hallucinogen ($\pm$)-1-(2,5-dimethoxy-4-methyl-phenyl)-2-aminopropane (DOM) in the two-lever drug discrimination paradigm in rats. Schreiber et al (1994) were able to abolish the discriminative cue of the hallucinogen ($\pm$)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI) in rats with the highly selective 5-HT_{2A} receptor antagonist MDL 100,907 (Schmidt et al 1992), a drug with 200-fold selectivity for 5-HT_{2A} versus 5-HT_{2C} receptors. Conversely, the selective 5-HT_{2C} receptor antagonist SB 200,646 (Kennett et al 1994) did not block the stimulus effect of DOI at relatively high doses that were effective in antagonizing behavioral effects caused by 5-HT_{2C} receptor activation.

Although the preponderance of evidence suggests that hallucinogens are agonists, the issue is clouded by studies that show LSD to be a partial agonist (McClue et al 1989; Sanders-Bush et al 1988), or even an antagonist (Norman et al 1989; Pierce and Peroutka 1990) at the 5-HT_{2A} receptor. Glennon (1990) has reviewed this controversy and has concluded that hallucinogens either are agonists or in some cases may be partial agonists. Even though the interoceptive cue produced by hallucinogens in rats may be mediated by 5-HT_{2A} receptor stimulation, the hypothesis that this effect also mediates hallucinogen intoxication in humans is confounded by the fact that the rat and human 5-HT_{2A} receptor subtypes have slightly different structure–activity relationships, apparently based on a single amino acid substitution in transmembrane region V (Kao et al 1992; Gallaher et al 1993). Hence, effects of various hallucinogens on rat behavior may not be strictly analogous to those in humans.

While compelling evidence links stimulation of the 5-HT_{2A} receptor to hallucinogenesis in man, activation of the 5-HT_{2C} receptor also may play a role in the overall intoxication process. Lisuride, a known 5-HT_{2A} agonist, known to suppress the firing of dorsal raphe cells like LSD (Rogawski and Aghajanian 1979), is considered nonhallucinogenic despite possessing the pharmacologic components believed necessary for hallucinogenic effects in man. In contrast to LSD and other hallucinogens, lisuride is an antagonist, not an agonist at 5-HT_{2C} receptors (Sanders-Bush 1994). Indeed, other known hallucinogens are potent 5-HT_{2C} agonists (Sanders-Bush and Breeding 1991; Burris et al 1991), whereas nonhallucinogenic analogues such as 2-bromo-LSD (BOL) and lisuride lack agonist properties. These issues will not be settled until agonists and antagonists selective for the 5-HT_{2A} vs. 5-HT_{2C} receptors are available.

It should be noted that a role for the 5-HT_{1A} receptor should not be completely dismissed. Immunohistochemi-

cal studies have shown that the 5-HT_{1A} receptors located in the midbrain raphe nuclei are almost exclusively localized on the cell membranes of 5-HT neurons (Sotelo et al 1990), and agonist drugs at the 5-HT_{1A} autoreceptor strongly inhibit central 5-HT neuron activity (Williams et al 1988). Even though hallucinogens of the phenethylamine class do not suppress raphe firing, and lack significant affinity for the 5-HT_{1A} receptor subtype (Teitler et al 1988), LSD has high affinity for these receptors, as do potent tryptamine hallucinogens such as 5-methoxydimethyltryptamine (DMT) and psilocin (McKenna et al 1990). LSD and 5-methoxy-DMT are also full agonists at 5-HT_{1A} receptors (DeVivo and Maayani 1986; Dumuis et al 1988).

Potentiating Effects of Interactions at Other Receptor Subtypes

Fiorella et al (1995) reported that only 56% of the variability in the potency of a given antagonist to block the interoceptive cue produced by LSD could be accounted for by 5-HT_{2A} affinity alone. This is consistent with the hypothesis that the primary cue of LSD may be modulated by interactions at other receptor types (Meert et al 1990). Although the LSD cue in rats appears to be expressed through 5-HT_{2A} receptor activation, it may be modulated by effects of LSD at other monoamine receptors. These ancillary monoamine interactions could be important. Because the in vivo potency of LSD is about one order of magnitude greater than for hallucinogenic phenethylamines, some other pharmacologic property may be potentiating its effects. It is difficult to know what this action might be, however, because LSD binds with high affinity to a variety of 5-HT receptors, including 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, DA D₁ and D₂ receptors, and α_1 and α_2 adrenergic receptors (Burt et al 1976; Creese et al 1976; Hoyer 1988; Leysen 1985; Marona-Lewicka and Nichols 1995; Meibach et al 1980; U'Prichard et al 1977; Watts et al 1995). Although there is no evidence to suggest that interactions with other 5-HT₁ subtypes are responsible for potentiation of 5-HT_{2A} effects, these cannot presently be ruled out as possibilities. Almost nothing is known about the functional significance of 5-HT₆ or 5-HT₇ receptors, where LSD also has high affinity.

Hallucinogens: Relevance to Antipsychotic Drugs

At the present time there is compelling evidence that the most salient feature of the pharmacology of hallucinogens, at least in rats, is an agonist interaction with 5-HT_{2A} receptors. There is also some evidence that this is a necessary, but perhaps not sufficient mechanism, and that

the concurrent stimulation of 5-HT_{2C} receptors may also be required. There is no other distinguishing feature, at least of the phenethylamine hallucinogens, to suggest that additional pharmacologic components are required. Tryptamine hallucinogens, including LSD, also potently activate 5-HT_{1A} receptors, and this could distinguish qualitative features of the actions of tryptamines from those of the phenethylamines. It is interesting that LSD has modest affinity for α -adrenergic receptors, and relatively high affinity for DA receptors, especially the D₂ (Watts et al 1995). The affinity of LSD for D₂ receptors ($K_{0.5}$ = 6.4 nM) is certainly in a range where receptor activation might occur at behaviorally relevant doses. The exceptional potency of LSD compared with other types of hallucinogens cannot be explained simply by its affinity for, or interactions with 5-HT_{2A}, 5-HT_{2C}, or 5-HT_{1A} receptors. It is proposed that the high affinity of LSD for D₂ receptors may be a potentiating interaction to explain this high potency. It is also possible that the high potency of LSD may be a consequence of synergistic interactions resulting from the interplay of LSD with many of the receptors for which it has high affinity. In this regard, it may be that the unique actions of clozapine are due to this drug having the “right” proportion of relative affinity to several monoamine receptors of the serotonergic, dopaminergic, and/or adrenergic families.

Lessons from Studies of 3,4-Methylenedioxymethamphetamine (MDMA)

MDMA is a recreational drug that achieved popularity in the United States about a decade ago, but which continues to be highly popular in Europe, particularly at all night dance parties (“raves”). It has unique psychopharmacology, but its salient pharmacologic features, at least in animal models, involve the indirect release both of neuronal dopamine and neuronal serotonin. Furthermore, MDMA induces selective destruction of serotonin axons and terminals. DA has been shown to play a clear role in MDMA-induced neurotoxicity. A linear correlation has been demonstrated between acute DA release and extent of long-term 5-HT terminal deficits (Nash and Nichols 1991). MDMA itself induces DA release (Schmidt et al 1987; Steele et al 1987), but the acute increase in postsynaptic 5-HT that occurs concomitantly markedly amplifies the concentration of extracellular DA (Gudelsky and Nash 1996). Activation of the 5-HT_{2A} receptor has been shown to enhance DA synthesis and release (Nash 1990; Schmidt et al 1990), and the 5-HT released by MDMA may be largely responsible for this activation (Huang and Nichols 1993). Consistent with this notion, increased levodopa utilization and extracellular levels of DA seen after MDMA administration are attenuated by 5-HT_{2A} antago-

nists (Nash 1990; Schmidt et al 1990), as is MDMA-induced neurotoxicity (Nash 1990; Schmidt et al 1990).

Recently, Marona-Lewicka and Nichols (in press) have used a drug discrimination study in rats to demonstrate the potentiation of a dopaminergic cue by pretreatment with 5-HT_{2A} agonists. Rats were first trained to discriminate 1.0 mg/kg of (+)-amphetamine sulfate from saline. Dose-response curves demonstrated that a dose of 0.25 mg/kg produced approximately 50% selection of the drug lever. The 5-HT_{2A} agonists DOI and LSD did not produce amphetaminelike responding at any dose tested or time of administration. Simultaneous administration of DOI or LSD with amphetamine was not significantly different from the response produced by amphetamine alone. Preadministration of DOI (3 hours) or of LSD (2 hours) before amphetamine, however, evoked significant enhancement of the amphetamine cue. The results suggested that the enhanced behavioral response to amphetamine may be due either to an increased sensitivity of dopaminergic neurons in the mesolimbic area, or to an enhanced release of dopamine by amphetamine.

These studies all show that activation of the 5-HT_{2A} receptor can enhance the response to a drug that produces indirect release of dopamine from neuron terminals. Whether or not these findings would extrapolate to schizophrenia is at present an unknown, but highly relevant issue. If basal dopaminergic tone is enhanced through some pathological process, will the activation of serotonin systems further amplify dopaminergic function? Enhanced efficacy of antipsychotic agents possessing 5-HT_{2A} antagonist activity certainly suggests a parallel to the studies cited above.

Evidence for 5-HT Dysfunction in Schizophrenia

There is sparse evidence for 5-HT involvement in the pathophysiology of schizophrenia. Direct evidence for abnormal 5-HT_{2A}-mediated neurotransmission in schizophrenia comes primarily from cerebral spinal fluid (CSF) studies of 5-HT metabolites and postmortem ligand binding studies of 5-HT, 5-HT metabolites, 5-HT transporters, and 5-HT receptors. Indirect evidence comes from pharmacologic challenges probing the 5-HT system, the observed effects of antipsychotic drugs with clinical efficacy in schizophrenia that have pharmacologic properties involving 5-HT modulation, and pharmacogenetic studies that will be discussed in the next section.

Studies of 5-hydroxyindoleacetic acid (5-HIAA) concentration in the CSF of patients with schizophrenia have generated inconsistent results, reporting both an increase (Gomes et al 1980; Wode-Helgodt et al 1977) and a decrease in CSF 5-HIAA concentration (Ashcroft et al

1966; Bowers et al 1969). Low CSF 5-HIAA concentration in schizophrenia was associated with increased ventricle–brain ratio (Potkin et al 1983; Losonczy et al 1986; Jennings et al 1984), prominent negative symptoms (Pickar et al 1986), and poor prefrontal activation during prefrontal neuropsychological tasks (Weinberger et al 1988).

Postmortem studies have reported an increase in 5-HT and 5-HIAA levels in subcortical areas such as the putamen, nucleus accumbens, and globus pallidus (Crow et al 1979; Farley et al 1980) and a decrease in 5-HIAA levels in cortical regions including the cingulate and frontal cortices (Winblad et al 1979). Serotonin transporters, located on presynaptic 5-HT terminals, are believed to provide an index of 5-HT innervation, and generally are reported to be decreased in the frontal cortex of patients with schizophrenia (Joyce et al 1993; Laruelle et al 1993). Studies of 5-HT₂ receptors in the frontal cortex of patients with schizophrenia have generated conflicting results. Several postmortem studies report a decrease in 5-HT_{2A} receptor number in the prefrontal cortex (Arora and Meltzer 1991; Whitaker et al 1981; Bennett et al 1979). Other studies, however, show no change in receptor density in the frontal cortex of schizophrenics (Owen et al 1981; Joyce et al 1993). The difference in the 5-HT₂ receptor densities in studies of the frontal cortex in schizophrenia may be related to the heterogeneity of the disease or may represent differences in medication effects, because 5-HT_{2A} antagonists down-regulate 5-HT_{2A} receptors.

Indirect evidence of serotonin dysfunction in schizophrenia comes from the observed effects of largely antipsychotic drugs with clinical efficacy in schizophrenia that have pharmacologic properties involving 5-HT modulation; PET studies implicating 5-HT₂ antagonism in the clinical efficacy of atypical antipsychotics; and pharmacogenetic studies.

The drug m-chlorophenylpiperazine (mCPP) is a partial agonist at 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{2C} receptors, and an antagonist of 5-HT₂ and 5-HT₃ receptors (Kahn and Wetzler 1991). Several groups have used mCPP to probe 5-HT receptors in schizophrenia, yet these studies have produced apparently conflicting results. In antipsychotic drug free schizophrenic patients, mCPP has been reported to increase (Iqbal et al 1991; Krystal et al 1993), reduce (Kahn et al 1992), or have no effect (Breier et al 1993; Koreen et al 1997; Owen et al 1993) on psychotic symptoms. These discrepancies have been attributed to differences in the mode of mCPP administration, or the heterogeneity of patients in terms of their vulnerability to the psychotogenic effects of mCPP. Krystal et al (1993) hypothesized that the symptom-exacerbating effects were mediated by 5-HT_{2C} stimulation that was

blocked by clozapine. In a separate study, however, the effects of the indirectly acting DA agonist methylphenidate (known to exacerbate symptoms in schizophrenics) were compared to mCPP in the same patient sample. Methylphenidate was a more potent and consistent psychotogen (Koreen et al 1997), suggesting that mCPP may produce nonspecific anxiogenic effects that could elevate psychotic symptoms in unstable patients.

Finally, the amino acid L-tryptophan is the dietary precursor of 5-HT. Administration of large doses of tryptophan does not exacerbate psychosis and may produce a decrease in aggression and in negative symptoms (Gillin et al 1976; Morand et al 1983). Studies of 5-HT-depleting agents, such as fenfluramine, suggest that these agents are of no benefit in treating schizophrenic patients (Shore et al 1985; Stahl et al 1985) and may even further impair cognitive functioning of patients (Soper et al 1990).

Serotonin and Neurodevelopment: Implications for Atypical Antipsychotics

Serotonin plays a role in the development of multiple tissues and organs, including the fertilized ovum, the heart, the intestines, craniofacial structures, and the central nervous system from the earliest stages of gastrulation through adulthood (Lauder 1990). Within the brain, serotonin influences neuronal and glial morphology, connectivity, and function (Azmitia and Whitaker-Azmitia 1991). Some of these effects are direct, some are mediated by growth factors (the best characterized of which is 5-HT_{1A} stimulation of the release of S100 β from astrocytes), and some appear to be mediated by counteracting the morphogenic influences of other neurotransmitters. It is likely that most or all of these effects are initiated by the binding of 5-HT to one of more than a dozen different serotonin receptors. Activation of particular serotonin receptors accounts for some, but not all, of the specificity observed. In addition, the particular effects observed appear to be temporally and spatially determined. Consequently, activation of a particular serotonin receptor may result in opposing actions during different developmental periods or in different regions. The spatial resolution of effects of 5-HT is extreme; within a single neuron, some neurites respond to serotonin with elongation, whereas others cease their growth (Goldberg et al 1990). Of course, 5-HT is not unique among the neurotransmitters in having such a neurodevelopmental role.

Ontogeny of the Serotonergic System

The serotonergic system is among the first neurotransmitter systems to innervate the brain and to demonstrate functional activity (cf. Lauder 1990, 1995). In the rat,

rostral raphe neurons are generated between embryonic day 12 (E12) and E15, and serotonergic axons from the raphe emanate toward the diencephalon almost immediately. They travel to the ventral thalamic area and then to the septal region via the diagonal band of Broca. Cortical innervation occurs 1) from the septal region to the medial part of the frontal cortex, where it splits into two tracts on either side of the cortical plate; 2) from ventral parts of the ganglionic eminence, ventral to the internal capsule and into the lateral cortex; and 3) from the ventral surface of the cortical poles, then dorsally and rostrocaudally in a radial fashion. In somatosensory cortex there are two distinct forms of serotonergic terminals: 1) fairly sparse large synapses in the molecular layer from median raphe (concentrated in limbic cortex); and 2) numerous pleomorphic fine synapses present in all layers of granular cortex from dorsal raphe (Kosofsky and Molliver 1987). The first serotonergic fibers in the cerebellum are seen postnatally. In early postnatal life, there is a general pattern of escalating serotonergic innervation that peaks, and then falls rapidly. In the somatosensory region and visual cortex this peak seems associated with the “critical periods” for development of representational maps. This critical period generally overlaps with periods of excess synaptogenesis and roughly ends as synapses begin to be eliminated.

There are clear developmental patterns of different serotonergic receptors. For example, 5-HT_{1A} receptors appear at E12 and peak between E14 and E16 in rat cortex. In humans, a similar peak is seen between the 16th and 22nd weeks of gestation. In contrast, 5-HT_{1A} receptors on glial cells appear to increase with advancing age (Whitaker-Azmitia et al 1993). 5-HT_{1B} receptors have been most clearly described on the thalamocortical afferents during the first 2 weeks of rat life and then fall to negligible levels (Bennett-Clark et al 1995). 5-HT_{1D} receptors that appear to be autoreceptors are relatively rare at birth, but increase during the first year and then fall (del Olmo et al 1996). 5-HT_{2A} and 5-HT_{2C} receptors are expressed in midgestation (E14) by developing monoamine neurons. They appear to mediate the cell differentiation effects of serotonin (Lauder and Liu 1994). In addition, 5-HT_{2A} and 5-HT_{2C} receptors are expressed in several target regions prior to the arrival of serotonergic fibers and may play a role in the guidance of serotonergic fibers (Wallace and Lauder 1983).

Effects during the Embryonic Period

During the embryonic period, serotonin appears to have trophic effects upon several different types of neurons and some glia, to influence the formation of synapses, and to influence the shape of the dendritic trees of some neurons.

Increased serotonin delays the maturation of the serotonergic system, leading to a transient decrease in synaptosomal serotonin (Heuther et al 1992). Exogenous serotonin also leads to increases in noradrenergic (TH+) cells, dopaminergic cells, and cholinergic cells [the latter seem to be mediated by 5-HT_{1A} receptors (Riad et al 1994)]. Exogenous serotonin also results in an increase in neurite outgrowth from raphe neurons, but not mesencephalic serotonin neurons, and an increase in neurite length and branching in cholinergic neurons, although results in vitro are very dependent upon the characteristics of the cultured neurons.

Effects during the Postnatal and Adult Periods

Serotonin has also been demonstrated to have numerous actions during the early postnatal period. Depending on experimental factors, serotonin can increase the number of fibers, the extent of myelination, and the number of synapses (Chubakov et al 1986; Gromova et al 1983). It also can increase the number of neurons with spontaneous electrophysiological activity, and increase the percentage of neurons that have patterned bursts of firing rather than random discharges. In dissociated culture systems, it appears that serotonin depletion reduces the number of dendritic spines. Both 5-HT_{1A} and 5-HT₂ receptors appear to be involved in these processes (Rorig and Sutor 1996).

For these reasons, it is not surprising that manipulation of serotonergic systems in intact animals also has effects. For example, among the changes caused by treatment with fenfluramine at postpartum days 1–6 (P1–6) was a decrease in the area of the cytoarchitectonic representation of individual whiskers (known as barrels) with broader spaces between them (Bennett-Clark et al 1995). More prolonged depletion of serotonin (P2–16) led to decreased growth and differentiation of layers II–VI and delayed barrel formation. Depletion after P21 did not change the cytoarchitecture (Osterheld-Haas and Hornung 1996). These studies suggest that serotonin acts to increase the specificity of the thalamocortical circuit during the critical period of somatosensory cortical development such that serotonin depletion results in a larger number of neurons that respond to input from multiple whiskers rather than the highly specific pattern of innervation that is usually observed. Rhoades et al (1994) have postulated that electrical inhibition resulting from 5-HT_{1B} receptor activation is critical during the period of synapse overelaboration to set up the most appropriate connections. Again there appears to be temporal specificity such that microscopic cytoarchitectonic organization is sensitive to the effects of serotonin depletion for a shorter period than the synaptic organization.

Importantly, serotonin depletion during the early post-

natal period also is associated with an array of behavioral effects. Decreasing serotonin by ~30% on P10–20 resulted in deficits in spatial learning, extinguishing learned responses, and learning in a new set (e.g., executive functions) that persisted for at least 40 days (Mazer et al 1997). Animals with these behavioral changes also had transient decreases in synaptophysin but long-standing changes in MAP2 (a dendritic marker). Concurrent treatment with 5-HT_{1A} agonists (or dexamethasone) prevented the negative effects of serotonin deprivation on synaptophysin and MAP2. Behavioral changes have also been reported with reduction of activity at 5-HT₂ and 5-HT₃ sites (De Ceballos et al 1985; Bell et al 1992).

Although relatively few studies have been done, the regulatory effects of serotonin appear to persist in the adult brain, albeit at a more limited level. These effects seem confined to areas that still have relatively high levels of serotonergic innervation or are near areas with high levels of innervation. Sprouting of serotonergic fibers into basal ganglia areas that have been experimentally deafferented has been reported (Zhou et al 1991). Exogenous serotonin, however, decreases the extent of sprouting observed (Baker and Croll 1996). Significant serotonergic effects have also been demonstrated in living adult chickens and rodents. In the chick spinal cord, serotonin depletion results in a decrease of synapses only in the dorsal laminae, where the serotonergic innervation is relatively high (Chen et al 1997). Serotonin depletion led to decreases in synaptophysin and MAP2 in both cortical and hippocampal brain sections of adult rats. These changes could be prevented by concurrent administration of the 5-HT_{1A} agonist ipsapirone (Azmitia et al 1995). Taken together, these results suggest that serotonin may be required in adult brain to regulate the density of dendritic spines and synapses.

Serotonin, Development, and Schizophrenia

The bulk of evidence suggests that the overall role of serotonin during brain development is to promote the development of specific and appropriate connections between neurons. In addition, serotonin appears to have a role in the maintenance and appropriate remodeling of synapses in some brain regions during adult life. The role of serotonin during adolescence, when there is continuing development in the frontal cortex and in some regions of the limbic system, has not yet been defined. In the context of neurodevelopmental models, existing evidence clearly suggests a potential role for serotonin in the pathophysiology of schizophrenia. The evidence is less clear for a link between the trophic effects of serotonin and therapeutic mechanisms of antipsychotic drug effects. One could speculate, however, that atypical antipsychotics might act

during the initial phases of psychotic illness to prevent stabilization of aberrant or inappropriate connections that have led to the emergence of psychotic symptoms. Further one could postulate that during later phases or chronic stages of the illness, there is improvement because the more recently established (presumably aberrant) connections are more sensitive to the destabilizing effects of serotonin.

Conclusions

In summary, a broad array of evidence (both direct and indirect) implicates 5-HT in the pathophysiology of schizophrenia, and as a key substrate mediating atypical antipsychotic drug effects (Kapur and Remington 1996; Kapur 1996). Moreover, in view of the role of serotonin in neurodevelopment and neuronal plasticity, there is a strong rationale for the potential involvement of serotonin in the pathogenesis and neurodevelopmental diathesis of schizophrenia. This evidence, however suggestive of and consistent with a role for serotonin, remains inconclusive and largely circumstantial. The results of studies with the selective 5-HT_{2A} antagonists currently in development could provide critical information on this question.

At the same time, 5-HT could well play an important role in the modulation of pathologic neurochemical systems (e.g., DA, glutamate) and thereby provide a target for therapeutic agents. The pharmacologic evidence at this point in time most strongly suggests that the 5-HT activity of antipsychotic drugs works through the DA system to produce atypical clinical effects that principally reduce the EPS liability of D₂ antagonism, but also possibly improve negative symptoms (either through decreased striatal D₂ antagonism or through increased DA release in the medial prefrontal cortex).

This work was supported, in part, by US Public Health Service research grants MH00537, MH-40537, and MH-42705, and Center grants MH33127 and HD03310.

This work was presented at the Neuroscience Discussion Forum "A Decade of Serotonin Research" held at Amelia Island, Florida in November, 1997. The conference was sponsored by the Society of Biological Psychiatry through an unrestricted educational grant provided by Eli Lilly and Company.

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