MECHANISM OF ACTION OF ATYPICAL ANTIPSYCHOTIC DRUGS

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ATYPICAL ANTIPSYCHOTIC DRUGS: WHAT IS TO BE EXPLAINED

The designation of chlorpromazine, and subsequently haloperidol, thioridazine, loxapine, thiothixene, molindone, pimozide, and related compounds as antipsychotic drugs (1) reflects their predominant action in humans, namely the suppression of auditory hallucinations and delusions, in some, but not all, individuals with diagnoses of schizophrenia as well as other psychoses. These drugs are also called neuroleptics because they caused catalepsy in rodents and extrapyramidal side effects (EPSs) in humans (2). Their ability to diminish psychotic symptoms was convincingly shown to be initiated by blockade of dopamine (DA) D2 receptors in mesolimbic nuclei, especially the nucleus accumbens, stria terminalis, and the extended amygdala (2-5). Blockade of D2 receptors in terminal regions, e.g., the striatum, nucleus accumbens, and prefrontal cortex, by these agents initially causes compensatory increases in the activity of dopaminergic neurons in the substantia nigra and ventral tegmentum, respectively, followed by a gradual decrease in the activity of DA neurons, and, ultimately, complete inactivation of DA neuron firing in both regions (6). This so-called depolarization block was suggested to be the reason for the slow onset of antipsychotic action, which is observed in some, but not all, psychotic patients. The development of depolarization block following subchronic haloperidol treatment has been challenged by Melis et al. (7) on the basis of microdialysis studies of DA release in the nigrostriatal system, but those findings have been suggested by Moore et al. (8) to be an artifact.

These first-generation antipsychotic drugs are often referred to as *typical* antipsychotic drugs because they typically produce EPSs, e.g., acute dystonic reactions, subacute par-

kinsonism, and akathisia, and, after chronic use, tardive dyskinesia or dystonia (see Chapter 56) as a direct or indirect result of blockade of D2 receptors in the dorsal striatum, in vulnerable individuals. The immediate cause of acute and subacute EPSs is considered to be blockade of the dopaminergic inhibition of striatal cholinergic neurons, leading to increased cholinergic activity in the basal ganglia (2). Subsequently, clozapine was found to achieve an antipsychotic effect without causing EPSs, whereas loxapine, a clozapine congener, was equipotent in producing its antipsychotic action and EPS in humans and laboratory animals (10). This led Hippius and Angst to describe clozapine as an atypical antipsychotic drug (11). Preclinical scientists almost invariably refer to clozapine and other drugs that have antipsychotic properties and low EPSs as atypical antipsychotics but, as will be discussed, clinical investigators do not universally accept this designation.

The atypical profile of clozapine was initially attributed to its anticholinergic properties, which, along with other unknown features, caused selective depolarization of the A9 DA neurons in the substantia nigra, which project to the dorsal striatum, sparing those of the A10 ventral tegmentum, which project to the cortex and mesolimbic systems (12). The subsequent evidence that clozapine, compared to neuroleptic drugs such as haloperidol, had at least six advantages in addition to producing significantly less EPS and tardive dyskinesia, has attracted enormous interest to clozapine and other subsequently developed atypical antipsychotic drugs. These six effects of clozapine, not all of which are fully shared with other atypical antipsychotic drugs, are (a) absence of tardive dyskinesia; (b) lack of serum prolactin elevations in humans; (c) ability to eliminate positive symptoms without exacerbating motor symptoms in patients with Parkinson's disease who become psychotic due to exogenous dopaminergic agents such as levodopa (L-DOPA); (d) ability to decrease or totally eliminate psychotic symptoms in approximately 60% of the patients with schizophrenia who fail to respond to typical neuroleptic drug; (e) ability to improve primary and secondary negative symptoms; and (f) ability to improve some domains of cognition in patients with schizophrenia, especially secondary memory and semantic memory (verbal fluency) (9,11,13). Some of the atypical antipsychotic drugs have also been shown to be more effective than the typical neuroleptic drugs in improving depression, stabilize mood, and decrease suicidality (9,10). These collective advantages of clozapine led to the search for the mechanism(s) involved in these effects and to find drugs that did not have the panoply of side effects of clozapine, especially agranulocytosis (9).

The other widely available antipsychotic drugs that are classified as atypical, by consensus, are, in order of their introduction, risperidone, olanzapine, sertindole, quetiapine, and ziprasidone. Melperone, a butyrophenone, introduced at about the same time as clozapine, has also been suggested to be an atypical antipsychotic drug because of its many clinical similarities with clozapine (14). Other agents with the essential clinical characteristics of an atypical antipsychotic drug that are currently at an advanced stage of clinical testing are iloperidone, ORG-5222, and aripiprazole (9,10). Zotepine and amisulpride, both of which are widely used antipsychotic drugs in Europe, are also sometimes grouped with the atypical antipsychotic drugs (9,10). With the exception of aripiprazole, a partial DA agonist (15), and amisulpride, a selective D2/D3 antagonist (16), all of the drugs listed above cause potent serotonin (5-hydroxytryptamine, 5-HT) receptor subtype 5-HT_{2A} relative to DA D2 receptor blockade (17-19).

There are a very large number of drugs in development as antipsychotics that have the property of being active in various animal models that predict antipsychotic action, e.g., blockade of amphetamine-induced locomotor activity or of the conditioned avoidance response, at doses 5- to 20fold lower than that which produce catalepsy, a predictor of EPSs. All of these drugs are routinely referred to as putative atypical antipsychotic drugs, at least by preclinical scientists, because of their ability to produce an antipsychotic action at doses that do not cause significant EPSs in humans and a comparable dissociation in animal models of psychosis and EPSs, e.g., blockade of conditioned avoidance response and blockade of DA-induced locomotor activity, and the induction of catalepsy, respectively. These drugs differ greatly in chemical structure and, to some extent, pharmacologic profile, and thus cannot be referred to as a group by either chemical class or pharmacologic profile. However, some clinical investigators find the term atypical antipsychotic drug misleading because there are important clinical differences among the compounds with regard to the six clinical features of clozapine noted above, and they prefer the term *novel* or *new generation* over *atypical* to describe these agents. However, this temporal-based nomenclature is not routed in any meaningful or enduring characteristic of these agents. Others prefer to call them multireceptor antipsychotics, which is clearly preferable to 5-HT/DA antagonists, another commonly used term. It is our view that these other designations have no specific advantages and some disadvantages compared to the classic term *atypical*. Thus, this chapter continues to use the term *atypical* to designate antipsychotic drugs that have a major advantage with regard to EPSs in patients with schizophrenia or Parkinson's disease, or both, to contrast with the typical antipsychotic drugs, and to update some of the key hypotheses for explaining some of the other highly valued advantages of these agents, as well as their unique side effects.

As can be expected, there has been an intensive effort to determine the basis for the differences between the typical and atypical antipsychotic drugs. This chapter reviews the major hypotheses, which are based on the pharmacologic profiles of the numerous classes of agents with atypical properties as well as current theories of the action of drugs effective in animal models of psychosis, but not yet adequately tested in humans, e.g., AMPA antagonists and metabotropic glutamate receptor antagonists (20,21).

The affinities of clozapine and some of its congeners for monoamine receptors are given elsewhere in this volume (see Chapter 56) (22). The affinities reported therein are for the D1, D2, D3, D4, 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₆, 5-HT₇, α_1 , α_2 , H₁, and muscarinic M1 receptors. Of these, the greatest interest is in the role of D2, D4, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α_1 , and α_2 receptors. Clozapine does have effects on glutamate and GABA neurons and interneurons, respectively, but space considerations preclude their discussion here.

ROLE OF D2 RECEPTORS

Most effective antipsychotics, typical as well as atypical, have affinities for the DA D2 receptor high enough to suggest that they produce effective blockade of these receptors in vivo (23,24). The model for atypical antipsychotic drug action proposed by Meltzer et al. (17) postulated that atypical antipsychotic drugs had to have some D2 receptor blockade in vivo, although weaker than 5-HT_{2A} receptor blockade, to achieve a low EPS profile and, possibly, some of the other advantages of clozapine. An exception to this may be amperozide, with is a potent 5-HT_{2A} antagonist and DA reuptake inhibitor with very low affinity for the D2 receptor (25). Recently, NRA0045, which has potent 5-HT_{2A}, D4, and α_1 but no D2 or D3 receptor blockade has been found to have atypical antipsychotic properties (26). Partial DA agonists, which may act as agonists at presynaptic DA receptors, and antagonists at postsynaptic DA receptors are a new class of antipsychotic drugs that has promise (15,27,28). However, clinical testing of these agents is just beginning, and current data support only the view that they are atypical in the classic sense, i.e., they are antipsychotic in preclinical or clinical testing at doses that produce weak or absent EPSs. Other evidence of the importance of α_1 antagonism for atypical antipsychotic drug activity will be discussed subsequently. The *in vitro* affinity of a drug at the DA D2 receptor is a useful predictor of the dose that produces EPSs and control of positive symptoms for typical neuroleptic drugs (2,29), although it does not do so for some atypical antipsychotic drugs, e.g., ziprasidone. Furthermore, there is no agreement on how to determine the doses used in such correlations because of the differences in dosage requirements as a function of stage of illness, body mass index, and age. There is little agreement even on the best dose for haloperidol, the most widely used antipsychotic drug. A wide range of 2 to 15 mg/day has been suggested, far removed from the 20 to 40 mg/day thought to be most effective in 1966 (9,10). To date, no clinically proven antipsychotic with the possible exception of amperozide lacks significant D2 receptor antagonist properties. As will be discussed, the combination of D2 and 5-HT_{2A} receptor blockade, in the right ratio, produces some of the effects of clozapine and other atypical antipsychotic drugs in rodents, e.g., increases DA efflux in the cortex and striatum of rats (30) and blockade of the conditioned avoidance response, an indication of antipsychotic activity (31). There have been only limited tests of this hypothesis in humans, mainly using ritanserin, which is a mixed 5-HT_{2A/2B/2C} antagonist (32). Nevertheless, various comprehensive reviews of the action of the atypical antipsychotic drugs have concluded that the combination of 5-HT_{2A}, D2, and α_1 receptor blockade is the probable basis of their antipsychotic action (10,18,19, 22,33–37). The evidence for this hypothesis will be discussed subsequently.

Counter to the hypothesis of the importance of 5- HT_{2A} receptor antagonism to the action of clozapine and other atypical antipsychotic drugs is the proposal of Seeman and Tallerico (24) and Kapur and Seeman (38) that the basis of atypical antipsychotics may lie in their rapid dissociation from the DA D2 receptor and their relatively easily displacement by surges of endogenous DA. It has also been proposed that rapid and extensive displacement of clozapine and quetiapine from binding sites accounts for the reported low occupancy of striatal D2 receptors by these drugs (24). The authors also suggested that this might account for more rapid relapse following clozapine and quetiapine withdrawal (24). Although the evidence cited for clozapine-induced relatively rapid relapse is robust (39), the evidence with regard to quetiapine and rapid relapse has never been published and does not accord with general clinical experience. Seeman and Tallerico found that the affinity for and rate of dissociation of antipsychotics from the D2 receptor are highly correlated. Drugs with low affinity for the D2 receptor, e.g., clozapine and quetiapine, were found to have a higher dissociation rate constant than drugs with higher affinity, e.g., haloperidol. Rapid dissociation from the D2 receptor was reported to also permit easier displacement of clozapine and quetiapine by endogenous DA, thereby avoiding side effects related to DA receptor blockade such as EPSs and hyperprolactinemia (38). It was also reported that olanzapine, risperidone, and sertindole, all of which are well established as atypical antipsychotic drugs, are com-

parable to haloperidol in their rate of dissociation from the D2 receptor and are not displaced by raclopride or iodobenzamide, as are clozapine and quetiapine (24). Thus, this hypothesis could not explain the basis for their low EPSs. Moreover, for these agents to achieve their antipsychotic action, they would have to be less easily displaced from limbic and possibly cortical D2 receptors. There are no data to support this selectivity with regard to displacement as yet. Although there is evidence for higher occupancy of extrastriatal D2 receptors by clozapine and quetiapine in patients with schizophrenia (40,41), and for atypical antipsychotic drugs that show more potent 5-HT_{2A} receptor blockade in rodents (42), the same appears to be true for olanzapine, which does not show the higher off-rates of clozapine and quetiapine (R. Kessler and H. Meltzer, in preparation). Because clozapine produces a greater increase in DA release in the cortex than in the accumbens or striatum, at least in rodents and monkeys (43), clozapine might be expected to produce greater occupancy of D2 receptors in these regions than the cortex, but, as noted above, this is not the case. It is also not clear how this model could explain any of the advantages of clozapine with regard to efficacy in neuroleptic-resistant patients or for cognition.

Studies on the regulation of prefrontal cortical or limbic DA release also provide no evidence that blockade of D2 receptors alone, regardless of degree of occupancy, can mimic the effects of the multireceptor antagonists such as clozapine (31,44,45). Pharmacologic analysis of this important model for the action of atypical antipsychotic drugs on cognition and negative symptoms strongly supports the importance of combined blockade of 5-HT_{2A}, D2, and possibly α_1 receptors (36,37,44,45).

D3 AND D4 RECEPTOR MECHANISMS

Ever since the cloning and characterization of the distribution of the D3 and D4 receptors, which revealed a limbic and cortical distribution, there has been considerable speculation about the role of these receptors in schizophrenia and the mechanism of action of antipsychotic drugs (19,46–48). As specific antagonists have become available, it has been possible to test their efficacy in animal models of psychosis, cognition, and motor function, as well as to carry out some clinical trials in schizophrenia. Recently, Reavill et al. (49) reported that SB-277011-A, which has high affinity and selectivity for the D3 receptor and good brain bioavailability, has an atypical antipsychotic drug profile. This compound was active in preventing isolation-induced deficits in prepulse inhibition but was not effective in blocking either amphetamine- or phencyclidine (PCP)-induced locomotor activity or, by using microdialysis, to increase prefrontal cortical DA release in rats (49). However, subchronic administration of SB-277011-A selectively decreased the firing rate of A10, but not A9, DA neurons in the rat, indicating a clozapine-like profile (50). These are the most promising data yet that a selective antagonist of D3 receptors might be useful in the treatment of psychosis.

On the basis of the finding that the affinity of clozapine for the cloned DA D4 receptor was two to three times greater than that for the D2 receptor, Van Tol et al. (51) suggested that blockade of the D4 receptor was the basis for the superiority of clozapine over the typical neuroleptic drugs in the treatment of schizophrenia. Other investigators have found less of a difference between the affinity of clozapine for D2 and D4 receptors (48). Several typical antipsychotic drugs, including haloperidol, have nearly equivalent affinity for D2 and D4 receptors, suggesting that D4 affinity per se does not convey any special advantages for an antipsychotic drug (48). The preclinical behavioral and electrophysiologic profile of highly selective D4 antagonists provides mixed evidence with regard to antipsychotic action associated with this receptor (52–54). A D4/ α_1 antagonist, NRA0025, appears to have promise as an antipsychotic agent based on its preclinical profile (26). A clinical trial of a selective D4 antagonist showed no sign of activity (55). A compound with potent 5-HT_{2A} and D4 antagonist properties, finanserin, was also ineffective (56). Further clinical trials of compounds that have D4 or D3 antagonism, or both, together with high affinities for 5-HT_{1A} or α_1 receptors, and without D2 affinity seems indicated.

ROLE OF SEROTONIN IN ANTIPSYCHOTIC DRUG ACTION

Determining the biological basis for the advantages of clozapine and other atypical antipsychotic drugs cited above and described in detail by Miyamoto et al. in Chapter 56 has led to considerable interest in the role of 5-HT in antipsychotic drugs action. We now consider some of this evidence. Other reviews of this topic should also be consulted (18,19,22,34–37,57).

Serotonin Receptors Involved in Antipsychotic Drug Action

The hypothesis that a relatively high affinity for the 5-HT_{2A} receptor compared to an affinity for the D2 receptor was the basis for the difference between atypical and typical antipsychotic agents contributed to the development of the newer antipsychotic agents listed above, all of which support the previously mentioned hypothesis of high affinity for 5-HT_{2A} and low affinity for D2 receptors (17,58,59). However, other 5-HT receptors may be important to the action of clozapine and other recently introduced antipsychotic agents, or of potential value for developing more effective or better tolerated antipsychotic agents. These include the 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃, 5-HT₆, and 5-HT₇ receptors (19,22,33). Although some of the atypical antipsychotic drugs developed on the basis of the 5-HT_{2A}/D2 hy-

pothesis also have affinities for 5-HT_{2C}, 5-HT₃, 5-HT₆, or 5-HT₇ receptors that are in the same range as that for the 5-HT_{2A} receptor, this is not characteristic of all of these agents, and thus it is not likely that affinities for these receptors are primary factors contributing to the low EPS profile of the entire class of agents (19,22,60,61). However, this does not rule out that actions at various 5-HT receptors contribute to low EPSs of specific drugs, or other actions, e.g., cognitive improvement or improvement in negative symptoms. For example, 5-HT_{1A} receptor agonism has also been suggested to be able to contribute to an atypical antipsychotic drug profile (62), and some of the atypical antipsychotics are 5-HT_{1A} partial agonists as well as 5-HT_{2A}/ 5-HT_{2C} antagonists, e.g., clozapine, quetiapine, ziprasidone, and S16924 (63,64). The role of the 5-HT₄ receptor in cognition will be discussed subsequently. Furthermore, there is some evidence of interactions among the 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors (19,35). Because of space limitations, this chapter focuses on these three 5-HT receptors and briefly considers the others.

ATYPICAL ANTIPSYCHOTICS AND THE 5-HT_{2A} RECEPTOR

5-HT_{2A} receptors have been implicated in the genesis of, as well as the treatment of, psychosis, negative symptoms, mood disturbance, and EPSs (17,19,33-36,45). The hallucinogenic effect of indole hallucinogens has been related to stimulation of 5-HT_{2A} rather than 5-HT_{2C} receptors (65). Numerous studies have examined the density of 5-HT_{2A} receptors in various cortical regions of patients with schizophrenia with decreased (66,67), increased (68), or normal levels reported. It is well established that some typical and atypical antipsychotic drugs can decrease the density of 5-HT_{2A} receptors (69,70), so the postmortem results noted above may be related to drug treatment. Positron emission tomography (PET) studies have not found decreased 5-HT_{2A} receptors in the cortex of never-medicated or unmedicated patients with schizophrenia (71). As mentioned above, the antipsychotic effect of clozapine has been attributed, in part, to its ability to block excessive 5-HT_{2A} receptor stimulation without excessive blockade of D2 receptors (17). This conclusion is consistent with the high occupancy of 5-HT_{2A} receptors produced by clozapine at clinically effective doses and its low occupancy of D2 receptors (in the 30% to 50% range as measured with [3H]raclopride), the latter being significantly below the 80% to 100% occupancy usually produced by typical neuroleptic drugs (35,72-75). The occupancy of 5-HT_{2A} and D2 receptors has been studied with other novel antipsychotic drugs such as risperidone, olanzapine, sertindole, and quetiapine with results similar to those of clozapine; all are more potent 5-HT_{2A} and D2 antagonists at appropriate doses, but less so than clozapine

(72–75). Some of these agents (e.g., risperidone and olanzapine) produce high D2 occupancy at high doses (76,77).

The bell-shaped dose-response curve of risperidone, with higher doses being less effective than lower doses (78), is consistent with the hypothesis that excessive D2 receptor antagonism may diminish some of the beneficial effects of 5-HT_{2A} receptor blockade (17,19,33,35,36). The highly selective 5-HT_{2A}agonist M100907, formerly MDL 100907, has been found in a controlled study to have some efficacy for treating positive and negative symptoms in hospitalized schizophrenic patients (79). However, because it was less effective than haloperidol, no further testing in schizophrenia has been scheduled at present. Nevertheless, the concept that 5-HT_{2A} antagonism may be useful to treat some forms of psychosis, especially when combined with weak D2 receptor blockade, warrants further study. Other 5-HT_{2A} selective agents such as SR 46349B (80) are currently being tested. Additional clinical evidence supporting the role of 5-HT_{2A} receptor blockade in the action of clozapine and possibly other drugs with potent 5-HT_{2A} affinities is available from the several reports that the His452Tyr allele of the 5-HT_{2A} receptor, which is present in 10% to 12% of the population, is associated with a higher frequency of poor response to clozapine (81,82). Taken together, the evidence from clinical trial data suggests that 5-HT_{2A} receptor blockade may contribute to antipsychotic drug action.

There is additional basic research that is also consistent with the relevance of 5-HT_{2A} receptor blockade for antipsychotic drug action. Thus, M100907 or other selective 5-HT_{2A} receptor antagonists, either alone or in combination with selective antagonists of other receptors, have been found to be effective in various animal models of psychosis. These include (a) blockade of amphetamine-induced locomotor activity and the slowing of ventral tegmental area (VTA) (A10) dopaminergic neurons (34); (b) blockade of PCP- and dizocilpin (MK-801)-induced locomotor activity (83,84); (c) blockade of MK-801-induced prepulse inhibition (85); and (d) antipsychotic-like activity in the paw test (86) among others. Of particular interest is the report of Wadenberg et al. (31) that the combination of a median effective dose (ED₅₀) of raclopride, a D2 receptor antagonist, and M100907, but not M100907 alone, was effective in blocking the conditioned avoidance response. The authors concluded that 5-HT_{2A} antagonism alone could not achieve an antipsychotic action, but that minimal blockade of D2 receptors was required to achieve such an effect. This corresponds much more closely to the apparent clinical situation than do the models where M100907 alone was effective, e.g., blockade of PCP- or MK-801-induced locomotor activity (34,83,84,87-89). As mentioned previously, administration of even a single dose of atypical antipsychotic drugs, which are relatively more potent 5-HT_{2A} than D2 blockers, has been shown to down-regulate 5-HT_{2A} receptors in rat brain (69,70). This has now been shown to be due to internalization of the receptors (70). Recovery from this process requires the synthesis of new receptors.

An important effect of 5-HT_{2A} (and 5-HT_{2C}) receptors that may be relevant to their contribution to psychosis is their ability to influence dopaminergic activity in the mesolimbic and mesostriatal systems (19,33,90-94). Increased dopaminergic activity in the nucleus accumbens and other mesolimbic and possibly cortical regions may contribute to positive symptoms, including formal thought disorder (2, 5). Increased dopaminergic activity in the striatum would be expected to diminish EPSs (2,5). The 5-HT_{2A/2C} agonist DOI [1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane], which itself had no effect on basal DA release, potentiated amphetamine-induced DA release and attenuated the ability of apomorphine, a direct acting D1/D2/D3 agonist, to decrease DA release in the striatum (93). Increasing serotoninergic activity, e.g., by administration of selective serotonin reuptake inhibitors (SSRIs) alone or in combination with the 5-HT_{1A} receptor antagonist WAY 100635, has no effect on basal DA output in the striatum. However, the SSRIs can significantly enhance the increase in DA outflow induced by haloperidol. These findings indicate that in the striatum, endogenous 5-HT positively modulates DA outflow when nigrostriatal DA transmission is activated (94). There is now considerable evidence from both behavioral and neurochemical studies involving N-methyl-D-aspartate (NMDA) antagonists such as PCP and MK-801 that 5-HT_{2A} receptors modulate activated but not basal mesolimbic DA function (84,95). Thus, stimulated DA release, e.g., with stress, may be increased in the forebrain terminal regions secondary to enhanced stimulation of 5-HT_{2A} receptors. Agents that block the effect of excessive, but not basal, 5-HT_{2A} receptor stimulation may be the most useful clinically. M100907 has been found to diminish the increase in DA efflux in the nucleus accumbens produced by haloperidol (30) or S-sulpiride (92). Taken together, these data suggest that 5-HT_{2A} antagonism by itself may have antipsychotic action when dopaminergic activity is slightly to moderately increased. More studies are needed to define the ability of 5-HT_{2A} receptor antagonists to potentiate the action of low doses of D2 receptor blockers in animal models as well as in humans.

Jakab and Goldman-Rakic (96) have proposed that the 5-HT_{2A} receptors on cortical pyramidal neurons may play a crucial role in psychosis by virtue of their ability to modulate intracortical and cortical-subcortical glutamatergic neurotransmission. This could contribute to the ability of 5-HT_{2A} antagonists to attenuate some of the behavioral effects of PCP and ketamine. Aghajanian and Marek (97) have proposed a link between the glutamate hypothesis of schizophrenia and the hallucinogen hypothesis. Briefly, stimulation of 5-HT_{2A} receptors on layer V pyramidal cells increases the frequency of postsynaptic potentials (PSPs). These are mostly blocked by the AMPA/kainate glutamatergic receptor antagonist LY293558, indicating that

they are mainly excitatory PSPs (EPSPs), in contrast with the piriform cortex, where 5-HT produces inhibitory PSPs (IPSPs). The selective group II metabotropic agonist LY354740, which inhibits glutamate release by stimulating inhibitory presynaptic autoreceptors on glutamatergic nerve terminals, suppresses the 5-HT-induced increase in the frequency of EPSPs. However, Aghajanian and Marek suggest that the main way in which 5-HT_{2A} receptor agonists increase glutamate release is a retrograde action from stimulation of postsynaptic 5-HT_{2A} receptors. The type of glutamate release induced by 5-HT_{2A} receptor stimulation differs from ordinary depolarization-induced neurotransmitter release, which is called synchronous release. The type of release induced by 5-HT is delayed in onset, slow, and produces small excitatory postsynaptic currents (EPSCs) and is called asynchronous release. Aghajanian and Marek propose that hallucinogens such as LSD enhance asynchronous EPSCs. They suggest that stimulation of other types of 5-HT receptors may oppose this action and that the effect of 5-HT_{2A} receptor antagonists unmasks the effect of these other types of 5-HT receptors (97). A similar proposal has been made by Martin et al. (95). Although Aghajanian and Marek do not mention the 5-HT_{1A} receptor specifically, it would be a good candidate to counter the effect of 5-HT_{2A} receptor stimulation, as will be discussed. They propose that the thalamic filter hypothesis of Carlsson (98) might be related to the effect of 5-HT_{2A} receptor stimulation on thalamocortical afferents to affect cortical function or on corticostriatal or corticothalamic efferents to affect the thalamic filter.

SEROTONIN RECEPTORS AND COGNITIVE FUNCTION

Clozapine, risperidone, ziprasidone, quetiapine, and olanzapine have been shown to improve selected areas of cognitive function in patients with schizophrenia, with the available data suggesting differential effects on specific functions (13). The available data suggest that each of the atypical drugs has a different pattern of effects on cognitive dysfunction in schizophrenia, but more head-to-head studies are needed to confirm this impression. Whether relatively more potent 5-HT_{2A} receptor compared to D2 antagonism has a major or, indeed, any role in the cognitive effects of these agents is not known. However, this is the major characteristic that these drugs share in common. It may be that the effect of these agents on cognition is mainly dependent on their ability to increase the release of DA (99,100) and acetylcholine in prefrontal cortex (101), which may depend, in part, on their serotoninergic actions. The effect of the atypical agents to increase DA efflux in the medial prefrontal cortex (mPFC) of rats appears to be due mainly to actions at the terminal regions rather than cell bodies and not to be related to D2 receptor blockade because local administration of haloperidol is without effect whereas clozapine and olanzapine produce huge increases in DA efflux (102). Studies have suggested that the clozapine, olanzapine, risperidone, and ziprasidone, but not haloperidol, may enhance acetylcholine release in the rat prefrontal cortex (101,103). Interactions between the 5-HT and cholinergic systems have been previously reported (104). 5-HT_{1A}, 5-HT_{2C}, 5-HT₃, and 5-HT₄ receptors have also been reported to have significant effects on acetylcholine release in the rat prefrontal cortex (105–109).

Because cognitive enhancement is critical for functional improvement in schizophrenia, establishing the mechanism for the ability of the atypical antipsychotic drugs to increase DA efflux is of the greatest importance. The evidence concerning 5-HT receptors and cognition has been reviewed in detail elsewhere (110,111). 5-HT $_{2A/2C}$ antagonists have little adverse effect and no apparent beneficial effects on learning and memory (112). There is some evidence that 5-HT₄ agonists, e.g., RS 67333, can improve learning and memory in rodents (113). Impairment of working memory in humans following administration of the 5-HT_{1A}agonist flesinoxan has been reported (114). However, Sumiyoshi et al. (115) have found that tandospirone, a 5-HT_{1A} partial agonist, can improve other domains of cognition in patients with schizophrenia treated with typical neuroleptic drugs. Neurochemical differences in the patient populations, including possible abnormalities in the density of 5-HT_{1A} receptors in schizophrenia, concomitant administration of a neuroleptic to the patients with schizophrenia, and differences in the type of cognitive domain studied, may account for this discrepancy. Further study in patients with schizophrenia is clearly indicated.

5-HT_{2A} RECEPTOR BLOCKADE AND EXTRAPYRAMIDAL FUNCTION

There have been numerous suggestions to explain the low EPSs of clozapine, namely its anticholinergic properties, lack of ability to increase acetylcholine in the striatum, D1 or D4 receptor blockade, and its effects as an α_1 - or α_2 adrenoceptor antagonist (2,18,33,116). In addition, several lines of evidence suggest that potent 5-HT_{2A} receptor blockade is relevant to the low EPS profile of clozapine, but that 5-HT_{2A} receptor blockade by itself cannot explain the low EPS liability of these agents (17,58,59). Meltzer et al. (17) studied a group of compounds that had antipsychotic activity in humans or in animal models that are thought to be predictive of antipsychotic activity, e.g., conditioned avoidance response or blockade of amphetamine-induced locomotor activity, and which produced weak EPSs in humans or weak catalepsy in animals relative to their antipsychotic efficacy. These compounds shared in common relatively weaker D2 compared to 5-HT_{2A} receptor affinities, whereas D1 receptor affinities did not contribute to this effect.

Among the drugs studied were melperone, a butyrophenone long used in Europe and Scandinavia as an antipsychotic and reported to produce low EPSs (14). Indeed, it has been found to be tolerable to patients with Parkinson's disease (117), even more so than risperidone and olanzapine. The ∩-shaped dose−response curve of risperidone as well as the increasing incidence of EPSs as the dose increases for olanzapine and ziprasidone, together with PET studies of DA receptor occupancy previously discussed, strongly suggests that lower D2 receptor occupancy, possibly in relation to high 5-HT_{2A} receptor is necessary to avoid EPSs with these compounds.

As previously discussed, numerous compounds of diverse chemical structure that share this pharmacologic profile have been identified or deliberately synthesized and tested for antipsychotic action and EPS liability. These include risperidone, olanzapine, sertindole, quetiapine, ziprasidone, and iloperidone. All of these compounds can produce fewer EPSs than haloperidol at comparable doses. Clozapine and quetiapine have been shown to produce the least EPSs in studies of patients with Parkinson's disease. Consistent with this concept, the 5-HT_{2A} antagonist mianserin has been reported to be effective in neuroleptic-induced akathisia (118). There are also a variety of preclinical data to support the importance of relatively high 5-HT_{2A} compared to D2 receptor affinity to preserve striatal function. For example, Ishikane et al. (119) reported that M100907 is able to block haloperidol-induced catalepsy only at low doses of haloperidol. Consistent with this, Spampinato et al. (120) reported that specific 5-HT_{2A} and 5-HT_{2C} antagonists were able to modulate the ability of haloperidol at 0.01 mg/kg but not at a higher dose (1.0 mg/kg) to increase striatal DA release in freely moving rats.

THE ROLE OF THE 5-HT_{2C} RECEPTOR IN ANTIPSYCHOTIC DRUG ACTION: 5-HT_{2A} AND 5-HT_{2C} INTERACTIONS

There has been some consideration given to the role of 5-HT_{2C} receptors in the action of atypical antipsychotic drugs. The 5-HT_{2C} receptor is found throughout the central nervous system (CNS), including the ventral tegmentum and the nucleus accumbens (121). With the availability of specific 5-HT_{2C} agonists and antagonists, evidence for a tonic inhibitory action of 5-HT_{2C} receptors on the burst firing of mesolimbic and mesocortical dopaminergic neurons has been obtained. Thus, the firing rate of VTA DA neurons is inhibited or increased by 5-HT_{2C} agonists or antagonists, respectively. This is consistent with microdialysis studies that show that 5-HT_{2C} antagonists increase extracellular concentrations of DA in the nucleus accumbens, striatum, and medial prefrontal cortex (91,122). Early studies found no significant differences between groups of novel antipsychotic drugs and typical neuroleptics with re-

gard to the affinity for 5-HT_{2C} receptor or the difference between 5-HT_{2C} and D2 affinities (22,60). Of the approved novel antipsychotic drugs, some have equivalent affinities for the 5-HT_{2A} and 5-HT_{2C} receptors (clozapine, olanzapine, sertindole), whereas others are more selective for the 5-HT_{2A} receptor (risperidone, quetiapine, ziprasidone). This difference roughly corresponds with the potential to produce weight gain, in that clozapine and olanzapine cause the greatest weight gain and risperidone and ziprasidone the least (see Chapter 56). There is little available data for sertindole and quetiapine, but they appear to be intermediate. There is no apparent relationship between 5-HT_{2C} affinity relative to 5-HT_{2A} affinity with regard to EPSs because quetiapine and ziprasidone are comparable to olanzapine and sertindole in this regard. Similarly, there is no apparent relationship to efficacy in treatment-resistant schizophrenia. There could be a relationship to differences among the atypical antipsychotic drugs with regard to improvement in specific types of cognitive function in schizophrenia (13).

An interesting aspect of the 5-HT $_{2C}$ receptor with regard to antipsychotic action is that 5-HT $_{2C}$ antagonism may be functionally opposed to 5-HT $_{2A}$ antagonism. Meltzer et al. (123) reported that atypical antipsychotic drugs were more likely to be weak 5-HT $_{2C}$ and potent 5-HT $_{2A}$ antagonists compared to typical neuroleptic drugs. Subsequently, neurochemical (120) and behavioral (96,124) data have been reported that support the notion of a functional antagonism of these two receptors that may coexist on the same neurons. Thus, Martin et al. (95) found that ritanserin, a mixed 5-HT $_{2A/2C}$ antagonist, blocked the ability of M100907 to antagonize the effect of MK-801 to increase locomotor activity in mice.

THE ROLE OF THE 5-HT_{1A} RECEPTOR IN ANTIPSYCHOTIC DRUG ACTION

The 5-HT_{1A} receptor is located pre- and postsynaptically. The presynaptic 5-HT_{1A} receptor is an autoreceptor located on cell bodies of raphe neurons; stimulation leads to inhibition of firing of 5-HT neurons. Stimulation of postsynaptic 5-HT_{1A} receptors generally leads to hyperpolarization of neurons, which is opposite of the effect of stimulation of 5-HT_{2A} receptors. There is extensive evidence that cannot be reviewed in detail here that indicates that 5-HT_{1A} receptor agonists and 5-HT_{2A} receptor antagonists produce similar neurochemical and behavioral effects on a variety of measures (125,126). For example, DOI injected bilaterally into the rat medial prefrontal cortex elicits a dose-dependent head twitch response. This effect is inhibited by M100907 and ketanserin, relatively selective for 5-HT_{2A} receptors at appropriate doses, but not the selective 5-HT_{2C} antagonist SDZ SER082. Pretreatment with the 5-HT_{1A} agonist 8-OH-DPAT also inhibited the head twitch response to DOI (127). Ahlenius (128) first suggested that stimulation

of 5-HT_{1A} receptors might produce an antipsychotic like action on the basis of behavioral studies in animals using the direct 5-HT_{1A} agonist 8-OH-DPAT. Subsequent studies demonstrated that 8-OH-DPAT enhanced the antipsychotic-like effect of the D2/D3 antagonist raclopride (129) and of haloperidol (130), and antagonized the catalepsy induced by the D1 agonist SCH23390 in rats (131). The ability of clozapine to reverse olanzapine-induced catalepsy is blocked by the selective 5-HT_{1A} antagonist WAY 100635, suggesting the effect of clozapine was mediated by stimulation of 5-HT_{1A} receptors. The beneficial effect of 5-HT_{1A} agonists appears to be mediated by inhibition of median raphe serotoninergic neurons (132).

5-HT_{1A} agonists have different regional effects on DA release in the rat brain. 5-HT_{1A} receptor stimulation appears to inhibit DA release in subcortical regions. Thus, Ichikawa et al. (133) demonstrated that the 5-HT_{1A} agonist 8-OH-DPAT inhibited the ability of amphetamine to increase extracellular DA levels in the nucleus accumbens and the striatum of conscious rats. The effect of 5-HT_{1A} receptor stimulation in the nucleus accumbens would be expected to enhance the antipsychotic effect of these agents by reducing dopaminergic activity. Several atypical antipsychotic drugs, including clozapine, ziprasidone, quetiapine, and tiospirone, are partial agonist at the 5-HT_{1A} receptor. Their affinities for the 5-HT_{1A} receptor are similar to their affinities for the human D2 receptor (22). Rollema et al. (134) demonstrated that the ability of clozapine to increase DA release in the rat prefrontal cortex was due, in part, to its 5-HT_{1A} agonist properties, as it could be blocked by WAY-100635, a 5-HT_{1A} antagonist. Ichikawa et al. (92) have extended these findings in a variety of ways; e.g., the ability of risperidone and the combination of M100907 and sulpiride to increase prefrontal cortical PFC DA efflux were both blocked by WAY100635. These findings suggest that the combination of D2 antagonism and 5-HT_{1A} agonism provides some of the key features of atypical antipsychotic agents. S16924, a 5-HT_{1A} partial agonist D2 antagonist, is an example of a putative atypical antipsychotic drug based on this model. It has atypical antipsychotic properties very similar to those of clozapine in a variety of relevant animal models (64). Whether this or similar compounds will have the same spectrum of efficacy and side effect advantages as the multireceptor antagonists that are relatively more potent 5-HT_{2A} than D2 antagonists remains to be determined. Significant differences should be expected. It is noteworthy that clozapine has both relatively more potent 5-HT_{2A} antagonism than D2 antagonism as well as 5-HT_{1A} partial agonism. This may be part of the mixture that accounts for its particular advantages over other atypical antipsychotic drugs. Wedzony et al. (135) found that WAY100135, a 5-HT_{1A} antagonist, attenuated the effect of MK-801, an NMDA antagonist on locomotor activity, prepulse inhibition, and the detrimental effect of MK-801, a noncompetitive NMDA antagonist on working memory and selective attention in rats. They cite other evidence that 5-HT_{1A} antagonists may improve learning and memory in animal models and suggest this may be due to blocking the inhibitory effects of 5-HT_{1A} receptor stimulation on the firing of hippocampal neurons. This suggests that a partial agonist, acting as an antagonist, may sometimes be of benefit with regard to effects relevant to schizophrenia.

THE ROLE OF SEROTONIN RELEASE IN ANTIPSYCHOTIC DRUG ACTION

The antagonism of multiple 5-HT receptors by clozapine would be expected to enhance the release of 5-HT by feedback mechanisms. Thus, it is surprising that Ferré and Artigas (136) reported that clozapine decreased 5-HT release in the nucleus accumbens. However, Ichikawa et al. (137) reported that clozapine (20 mg/kg) and risperidone (1 mg/ kg) significantly increased extracellular 5-HT levels in the nucleus accumbens and medial prefrontal cortex, respectively, whereas amperozide (1 and 10 mg/kg) increased extracellular 5-HT levels in both regions. Hertel et al. (138) reported similar results with risperidone and suggested that this might be relevant to its ability to improve negative symptoms. If so, this is not the explanation for the effects of clozapine or olanzapine on negative symptoms because olanzapine, sulpiride, haloperidol, and M100907 had no effect on extracellular 5-HT levels in either region. The latter consideration also indicates that blockade of 5-HT_{2A} receptors is not the basis for the ability of clozapine, risperidone, or amperozide to increase 5-HT levels. The enhancement of 5-HT efflux in the prefrontal cortex may contribute to the ability of these agents to improve mood disorders and cognition.

α_2 - AND α_1 -ADRENERGIC MECHANISMS AND ATYPICAL ANTIPSYCHOTIC DRUGS

Most of the atypical antipsychotic drugs are potent antagonists of the α_1 or α_2 adrenoceptors, or both. Thus, risperidone 9-hydroxyrisperidone, clozapine, olanzapine, zotepine, quetiapine, ORG-5222, sertindole and ziprasidone are potent α_1 antagonists (22). Prazosin, an α_1 adrenoceptor antagonist, has, like clozapine and other atypical antipsychotic drugs, been shown to increase DA efflux in the shell but not the core of the nucleus accumben, signifying a limbic rather than a striatal effect of α_1 antagonism (91). These authors also suggested that α_1 antagonism may explain the atypical properties of sertindole, which has been reported to achieve as high an occupancy of D2 receptors as typical antipsychotic drugs (36). All of the atypical agents mentioned above are also potent α_2 antagonists, with the exception of zotepine and sertindole (22). Kalkman et al. (116) raised the possibility that the α_{2C} subtype may be particularly relevant to the anticataleptic as well as other actions of clozapine and iloperidone. However, McAllister and Rey (139) were unable to reverse the effects of loxapine or haloperidol on catalepsy with α_2 antagonists and showed that the effect of clozapine to reverse loxapine-induced increase in catalepsy was due to its anticholinergic rather than its adrenoceptor blocking properties. Clozapine produces massive increases in plasma norepinephrine, which may indicate that it can cause effective stimulation of α -adrenoceptors receptors in brain (140). The addition of idazozan, an α_2 antagonist, to fluphenazine, a typical neuroleptic, was reported by Littman et al. (141) to have efficacy comparable to clozapine in a small group of neuroleptic-resistant patients with schizophrenia. These results need to be replicated. Idazoxan has also been shown to improve attentional and executive dysfunction in patients with dementia of the frontal type (142), suggesting that some of the cognitive enhancing effects of the atypical antipsychotic drugs might be related to their α_2 blocking properties. Another α_2 antagonist, atipamezole, has been reported to improve cognitive performance in aged rats (143). Polymorphisms of the α_1 and α_2 receptors have been reported not to predict response to clozapine (144).

In this regard, it is of interest that idazoxan has been shown to preferentially increase DA efflux in the rat mPFC by an action at the terminal area (145). This effect appears to be independent of dopaminergic activity (146). Westerink et al. (147) demonstrated that systemic administration of clozapine, risperidone, ziprasidone, and olanzapine, as well as haloperidol, produced a dose-dependent increase in noradrenaline in the mPFC of rats. This effect was closely coupled to the increase in DA efflux. Increased levels of norepinephrine might also be related to the cognitive and antidepressant effects of the atypical antipsychotic drugs (148,149).

CONCLUSION

Typical neuroleptic drugs such as haloperidol have been reliably shown to produce their antipsychotic action by blockade of D2 receptors in the mesolimbic system, suggesting that increased dopaminergic activity in these terminal areas of the ventral tegmental DA neurons are of importance to the etiology of schizophrenia. Striatal D2 receptor antagonism is the critical element in the EPSs produced by these drugs. Atypical antipsychotic drugs are those antipsychotics that achieve an antipsychotic action with quantitatively less EPSs in humans or a clear distinction between doses that affect mesolimbic and striatal dopaminergic function in rodents. Clozapine was the first atypical antipsychotic drug by the definition noted above, but more importantly it showed that antipsychotic drugs might also be effective in some patients with schizophrenia whose positive symptoms do not respond to neuroleptic-type agents and to improve negative symptoms, cognitive impairment, depression, and possibly suicidality of schizophrenia and other psychotic disorders as well (150-152). There is strong evidence of

the role of 5-HT_{2A} receptors and suggestive evidence of the roles of the 5-HT_{1A}, 5-HT_{2C}, and α_1 receptors in various actions of clozapine, risperidone, olanzapine, quetiapine, ziprasidone, iloperidone, sertindole, and related atypical antipsychotic drugs. Atypical antipsychotic drugs that are potent 5-HT_{2A} antagonists relative to their D2 receptor blocking property appear to potentiate 5-HT_{1A}-mediated effects on dopaminergic neurons in the mesocortical, mesolimbic, and mesostriatal regions. The effects in the mesocortical regions appear to be mediated by modulation of glutamate release from pyramidal neurons. These agents have been found to preferentially increase DA efflux in the mPFC compared to limbic and striatal regions. They also increase acetylcholine release in the PFC. Effects on 5-HT_{2C}, 5-HT₃, 5-HT₄, 5-HT₆, and 5-HT₇ receptors may also be relevant to some of their actions, e.g., improvement of cognition, weight gain, etc. Other models of atypicality appear to be effective, including partial DA agonists such as aripiprazole. Selective D2/D3 antagonists such as amisulpride may also have atypical properties. At this time, multireceptor agents appear to be more promising as antipsychotic agents for the majority of psychiatric patients because of important interactions between neural circuits that employ multiple neurotransmitters.

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