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Clozapine: New Research on Efficacy and Mechanism of Action

Herbert Y. Meltzer, Bijan Bastani, Luis Ramirez, and Shigehiro Matsubara

Department of Psychiatry, Case Western Reserve University, School of Medicine, 2040 Abington Road, Cleveland, OH 44106, USA

Summary. Clozapine can produce greater clinical improvement in both positive and negative symptoms than typical antipsychotic drugs in neuroleptic-resistant schizophrenic patients. The clinical response may occur rapidly in some patients but is delayed in others. Clozapine has also been reported to produce fewer parkinsonian symptoms, to involve a lower risk of producing tardive dyskinesia, and to produce no serum prolactin elevations in man. It seems likely that these effects are the result of a common biological mechanism or related mechanisms, rather than unrelated effects. Other atypical antipsychotic drugs, such as melperone and fluperlapine, share at least some of these properties. A relatively low affinity for the D-2 dopamine (DA) receptor and high affinity for the 5-HT_2 receptor, producing a high 5-HT_2/D-2 ratio, best distinguishes atypical antipsychotics like clozapine from typical antipsychotic drugs. Through its weak antagonist action on D-2 DA receptors and a potent inhibitory effect on 5-HT_2 receptors, as well as its abiltiy to increase DA and 5-HT release, clozapine may be able to permit more normal dopaminergic function in the anterior pituitary, the mesostriatal, mesolimbic and mesocortical regions. The numerous advantages of clozapine over typical neuroleptics are consistent with the primary importance of DA to the pathophysiology of schizophrenia. The secondary but still significant role of 5-HT in the action of clozapine may either be direct or via the effect of 5-HT on dopaminergic mechanisms. Some aspects of schizophrenia could be due to a dysregulation of the interaction between serotonergic and dopaminergic neurotransmission.

Key words: Clozapine – Schizophrenia – Serotonin – Dopamine – Prolactin

Offprint requests to: H. Y. Meltzer

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Introduction

The somatic treatment of schizophrenia has remained more or less unchanged for 35 years. The many classes of neuroleptic drugs currently available are basically equivalent in their therapeutic potential for schizophrenia (Kane 1987). Some patients do appear to respond better to one such agent than to another, but the likely explanation for such idiosyncratic responses appears to be related more to pharmacokinetics, drug metabolism, or host differences in response to side effects rather than to pharmacodynamic differences which reflect unique mechanisms of action (Donaldson et al. 1985). All neuroleptic drugs have been thought to produce their antipsychotic action via blockade of D-2 dopamine (DA) receptors in the mesolimbic system (nucleus accumbens, olfactory tubercle, stria terminalis) (Snyder 1976), but it has been suggested that blockade of D-2 receptors, i.e., those DA receptors negatively coupled or not coupled to DA-sensitive cyclase, in other brain regions, e.g., the hippocampus (Bischoff 1986), may also be important. It has also been suggested that this ability to increase DA synthesis and release in the frontal cortex is important for the antipsychotic effects of neuroleptic drugs (Imperato and Angelucci 1988; Mefford et al. 1988). Because of these considerations, and the ability of indirect and direct DA agonists to elicit psychotic symptoms under various conditions, the major theory regarding the etiology of schizophrenia has implicated DA abnormalities, either excessive availability of DA or excessive numbers of D-2 receptors (Meltzer and Stahl 1976). Although there is some evidence to support both of these possibilities (e.g., Owen et al. 1978; Lee and Seeman 1980; Memo et al. 1983; Toru et al. 1988), it has proven difficult to provide unequivocal evidence for an abnormality of the dopaminergic system in schizophrenia despite the use of a wide range of methods to assess the DA system in man (see Meltzer 1984, 1987

for reviews). The heterogeneity of schizophrenia as well as methodological limitations have no doubt contributed to this failure.

The absence of unequivocal evidence of a dopaminergic abnormality in schizophrenia, together with significant advances in the understanding of the regulation of dopaminergic neurotransmission, has led to a number of major modifications of the DA hypothesis (Carlsson 1988; Meltzer 1988; Friedhoff 1988). Of these, one of the most important is the possibility that DA may be relevant only to the positive symptoms of schizophrenia, while the negative symptoms may represent a separate process related to structural changes in the brain or to neuropeptidergic abnormalities rather than to DA (Crow 1980). However, it has also been suggested that negative symptoms may indeed be related to abnormalities in DA neurotransmission, albeit to decreased rather to than increased dopaminergic activity (MacKay 1980; Meltzer 1985). Other significant modifications of the DA hypothesis include increased emphasis on the potential importance of D-1 DA receptors, the DA receptors positively coupled to adenylate cyclase (Memo et al. 1983; Hess et al. 1987). The role of dysfunction of DA autoreceptors, the DA-sensitive receptors on cell bodies and terminals of DA neurons which regulate DA synthesis and release, as a possible means of causing increased release of DA has also been suggested (Meltzer 1982; Carlsson 1988). Finally, dysfunction of the interaction between DA and various neurotransmitters, especially serotonin (5-HT), norepinephrine (NE), acetylcholine (ACH), gamma-aminobutyric acid (GABA) and excitatory amino acids, rather than an abnormality confined to the DA system itself, has also been proposed as a modification of the simple DA excess or deficiency hypothesis (Meltzer 1987).

The discovery of the antipsychotic properties of the classical neuroleptic drugs was critical to the development of the DA hypothesis in its original form. The development of novel agents with a different spectrum of action could also be of value to further testing, modifying and possibly rejecting the DA hypothesis. This seems to be the case with clozapine, a dibenzazepine compound with many novel clinical actions (Meltzer 1989 a–c). Clozapine is the best-studied example of a group of atypical neuroleptic drugs, including amperozide (Christensen and Gustafsson 1985), fluperlapine (Woggon et al. 1985), melperone (Bjerkenstedt et al. 1979) and RMI-81582 (Young and Meltzer 1980), which have been distinguished from typical neuroleptic drugs because of their decreased potential to cause catalepsy in rodents and extrapyramidal symptoms (EPS) in man (Meltzer et al. 1989b). This article briefly reviews the unique clinical features of clozapine, some basic and clinical research studies on the mechanism of action of clozapine and other atypical antipsychotic drugs, and then considers the importance of these results for the DA hypothesis.

Unique Clinical Features of Clozapine

Clozapine has been repeatedly shown to produce fewer acute and subacute EPS than typical antipsychotic drugs (Angst et al. 1971; Matz et al. 1974; Claghorn et al. 1987; Kane et al. 1988). Other atypical antipsychotic drugs, e.g., melperone (Christensen et al. 1986), fluperlapine (Gerlach et al. 1984; Fischer-Cornellsen 1984) and RMI-81582 (Young and Meltzer 1980) also produce fewer EPS. Clozapine, in low doses, may be given to parkinsonian patients to treat DA agonist-induced psychoses, without worsening the parkinsonian symptoms (Scholz and Dichgans 1985).

Clozapine also has not been reported to produce new cases of tardive dyskinesia despite its use in many thousands of schizophrenic patients over prolonged periods of time (G. Honigfeld, unpublished data); 15%–20% of these patients might be expected to develop tardive dyskinesia (Kane et al. 1986). Clozapine can suppress the symptoms of even severe tardive dyskinesia or tardive dystonia (Simpson et al. 1978; Meltzer and Luchins 1984). While this might raise the possibility that it could cause one of the tardive movement disorders, based on analogy with typical neuroleptic drugs, it more likely indicates another important difference between clozapine and such compounds.

Clozapine does not increase serum prolactin (PRL) levels in man (Meltzer et al. 1979). Thus, it does not cause galactorrhea. Other atypical antipsychotic drugs, such as melperone (Bjerkenstedt et al. 1979), amperozide (A. Bjork, personal communication, 1988), fluperlapine (Dieterle et al. 1984) and RMI-81582 (Young and Meltzer 1980) also produce smaller or no increases in serum PRL levels in schizophrenic patients.

Most importantly, clozapine appears to have superior efficacy as an antipsychotic agent. This appears to be true for newly admitted schizophrenic patients (Fischer-Cornellsen and Ferner 1976; Claghorn et al. 1987) as well as treatment-resistant schizophrenic patients (Juul-Povlsen et al. 1985; Kane et al. 1988). In the latter study, nearly all of 305 patients who had a history of failure to respond to adequate trials of at least three different neuroleptic drugs of two different classes were shown to be non-responders or intolerant ($N = 22$) to haloperidol in the first phase of the study. Those patients who had had 9.2 ± 7.3 (SD) hospitalizations and had been hospitalized a median of 2.2 years at the time the study began were then randomly assigned to clozapine or chlorpromazine plus benztropine. Only 5 of the 141 (4%) patients treated with

chlorpromazine responded with at least a 20% decrease in total Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962), plus a Clinical Global Improvement score of mild or less, or a post-treatment BPRS score of less than 36. However, 38 of the 126 (30%) clozapine-treated patients were responders by these criteria ($P < 0.001$). The greater improvement in the clozapine group in positive symptoms was noted during week 1 and each succeeding week of the 6-week trial. The mean decrease in total BPRS score was 25% at the end of 6 weeks (from 60 to 45). This compared with a 7.5% decrease in total BPRS score in the chlorpromazine-treated group. BPRS ratings were still steadily improving in the clozapine group at the end of 6 weeks, with no evidence of any decrease in the rate of improvement. Notably, clozapine also produced a significant improvement in the BPRS Anergia subscale, which reflects negative symptoms, but chlorpromazine did not. Independent nurse's rating also revealed a marked improvement in ward behavior in the clozapine-treated patients.

The longer-term effects of clozapine appear equally promising. We have found (Meltzer et al. 1989a) that the clinical benefits of clozapine exceed those reported by us at the end of 6 weeks' treatment (Kane et al. 1988). In an on-going open prospective trial of clozapine in patients with treatment-resistant schizophrenia very similar to those in the U.S. multicenter study of Kane et al. (1988), 31 of 51 patients (60.8%) showed at least a 20% decrease in total BPRS score at the end of 10.8 ± 8.4 months (median 8.9 months) treatment. There were significant decreases in all four BPRS subscales, including Withdrawal-Retardation, which is a good measure of the effect of treatment on negative symptoms. Although in that study the improvement in the BPRS Withdrawal-Retardation subscale was not independent of improvement in the Paranoid Disturbance subscale, we have now found that the improvement in another negative symptom scale during 6 weeks of clozapine treatment in these same patients was independent of the improvement in positive symptoms. Of the 31 improvers noted above (Meltzer et al. 1989a), the 20% on greater decrease in total BPRS was first noted at 6 weeks ($N = 14$), 3 months ($N = 9$), 6 months ($N = 2$), 9 months ($N = 5$), and 12 months ($N = 1$). These results suggest that a clozapine trial should last at least 3 months and preferably much longer before a patient is considered to be a nonresponder. Meltzer et al. (1989a) also noted a significant improvement in social functioning in the Quality of Life Scale (Heinrichs et al. 1984). Improvement was noted in work and school performance, social activities, social initiative and motivation. Lindstrom (1988) also noted a marked improvement in work function in clozapine-treated, neuroleptic-resistant schizophrenic patients. It has been our experience that some, institutionalized patients with pronounced regressive schizophrenic symptoms function effectively after 3–12 months of clozapine treatment for the first time in many years. For these individuals, clozapine appears to have helped to bring many of the symptoms of schizophrenia into full remission. However, even those patients would likely relapse if clozapine were stopped, based on our experience with other patients who have had to discontinue clozapine because of side effects or who have elected to discontinue it for various reasons. No correlation was found between ventricular brain ratio or a measure of cortical atrophy and response to clozapine in these patients (Meltzer et al. 1989a).

In view of the 1%–2% incidence of agranulocytosis or granulocytopenia produced by clozapine (Andevran and Griffith 1977), compared with the 0.05%–0.1% produced by typical neuroleptic drugs, it is essential that the advantages of clozapine be weighed against the increased risk. With weekly monitoring of the white blood count indefinitely or at least for the first 18-week period when 80% of the marrow depression occurs, it should be possible to restrict morbidity and mortality to very low levels. Under such circumstances, the advantages of clozapine for treatment-resistant schizophrenic patients appear substantial. Further study is needed to determine whether this is also true for non-treatment-resistant schizophrenic patients.

Biological Basis of Clozapine Advantages

The responsiveness of those treatment-resistant patients whose illness markedly improves during clozapine treatment strongly suggests that neuroleptic resistance is not an indicator of structural brain damage that portends irreversible deterioration. No patients with only negative symptoms were included in the study of Kane et al. (1988), so it is not possible to reject the type II schizophrenia model advoacted by Crow (1980) on the basis of this study. However, the results obtained in our study (Meltzer et al. 1989a) in some neuroleptic-intolerant schizophrenics do support other evidence that negative symptoms can respond to antipsychotic drug treatment (Meltzer et al. 1985). If treatment resistance is not based upon structural brain damage, the question arises as to what is the nature of the functional lesion that underlies the failure to respond to conventional neuroleptics. Why is it that decreasing D-2-mediated dopaminergic activity by typical neuroleptics is insufficient to bring about a remission whereas clozapine frequently is successful?

The multiple clinical advantages of clozapine over typical antipsychotic drugs could have important im-

plications for further research in schizophrenia. It seems highly unlikely that multiple unrelated processes account for the ability of clozapine to produce fewer parkinsonian symptoms, to involve a lower risk of producing tardive dyskinesia, not to elevate serum prolactin correlations in man, and to have greater efficacy in reducing positive and negative symptoms. Rather, all four effects may be due to a common mechanism. However, it is not entirely clear what this mechanism is.

The average clinical dose of clozapine (300–600 mg/day) in relation to its affinity for the striatal D-2 receptor is consistent with that of typical neuroleptic drugs (Snyder 1976). However, clozapine produces functional blockade of some but not all D-2 receptors in man. This has been discussed in detail elsewhere (Meltzer 1989c). Similarly, the effects of clozapine on D-2 receptors in rodents are mixed. Clozapine blocks rat pituitary D-2 receptors in vitro (Meltzer 1989a). However, clozapine administration for 1–12 months does not block apomorphine-induced stereotypy or upregulate striatal D-2 receptors (Rupniak et al. 1985). It is not apparent that the differences in D-2 receptor blockade produced by clozapine, and typical neuroleptic drugs are sufficient to account for clozapines unique properties.

We have previously reported that clozapine and other atypical antipsychotic drugs increase the activity of the tuberoinfundibular dopaminergic (TIDA) neurons following the administration of clozapine and other atypical neuroleptics (Gudelsky et al. 1989). This appears to account for the transient nature of the increase in rat serum PRL levels produced by clozapine (Gudelsky et al. 1987), since the increased release of DA from the hypothalamus overcomes the blockade of D-2 receptors at the pituitary. In vivo dialysis studies also have demonstrated that clozapine increases DA release in the dorsal striatum and prefrontal cortex or the striatum and nucleus accumbens of freely moving rats in a dose-dependent manner (Imperato and Angelucci 1988; Ichikawa and Meltzer, unpublished data). However, other evidence does not reveal that clozapine increases DA release in the striatum (see Altar et al. 1988 for references), which indicates that further study is needed. It is possible that the increased release of DA from TIDA neurons following clozapine also occurs in man and prevents any stimulation of PRL release which might result from clozapine-induced D-2 DA receptor blockade at the pituitary. The clinical significance of the absence of hyperprolactinemia with clozapine has yet to be fully studied. Since intracerebral PRL administration has been shown to affect the activity of striatal DA neurons (Kovacs et al. 1984) and the ability of neuroleptics to induce DA-receptor supersensitivity (Hruska 1986), it is at least theoretically possible that the absence of increased PRL secretion during clozapine treatment may partially contribute to the diminished parkinsonism and tardive dyskinesia associated with clozapine administration. The inability of clozapine to produce depolarization blockade of the firing of DA neurons with cell bodies in the substantia nigra, achieved with typical neuroleptic drugs, has been suggested to be the major reason for its lesser extrapyramidal side effects, at least with subchronic administration (Chiodo and Bunney 1983). This effect of clozapine was inferred to be due to its anticholinergic and/or alpha-1-noradrenergic blocking properties (Chiodo and Bunney 1985), but no direct proof that these mechanisms are solely or partially responsible for this effect has yet been offered. Prolactin has also been reported to activate the mesolimbic DA system through local actions on presynaptic terminals of DA neurons in the nucleus accumbens without affecting the substantia nigra or the ventral tegmental areas (Chen and Ramirez 1988). Thus, the absence of hyperprolactinemia with clozapien treatment compared with the large increases in serum prolactin produced by typical neuroleptics could also contribute to a greater normalization of dopaminergic activity in the mesolimbic terminal areas and, thus, to a greater antipsychotic effect.

Clozapine has also been found to have a number of significant effects on serotonergic neurotransmission. These are briefly discussed here because they could be important for the clinical advantages of clozapine, in part through serotonergic influence on dopamine neurotransmission. There is some evidence that clozapine increases brain 5-HT synthesis (Ruch et al. 1984), but this needs to be confirmed by more modern methods. Clozapine has also been shown to affect 5-HT release by several mechanisms (Drescher and Hetey 1988). Clozapine was found to enhance 5-HT release from synaptosomes from the rat nucleus accumbens by blocking the inhibitory effect of 5-HT on a 5-HT autoreceptor and to a lesser extent by blocking a DA presynaptic receptor which gates 5-HT release (Drescher and Hetey 1988). The authors also found that clozapine more potently blocked the inhibitory effect of DA on DA release at the autoreceptor in accumbens synaptosomes than through an action on the 5-HT heteroreceptor which inhibits DA release. Drescher and Hetey (1988) concluded that the antipsychotic effect of clozapine might be mediated, in part, by the action of clozapine to promote DA release by blocking the 5-HT autoreceptor.

There is extensive evidence from animals studies, which we have reviewed elsewhere (Meltzer 1989a, c), that clozapine is a 5-HT antagonist (Sulpizio et al. 1978; Fink et al. 1984; Nash et al. 1988), that it has a relatively high affinity for the 5-HT_2 receptor (Altar et

al. 1986; Meltzer et al. 1989b) and that it can produce, with chronic administration, down-regulation of the rat frontal cortical 5-HT_2 receptor (Reynolds et al. 1983). We have recently found that a single dose of clozapine, 20 mg/kg, can produce a significant decrease in frontal cortex 5-HT_2 receptor binding sites which lasts at least 72 h (Matsubara and Meltzer, to be published).

Clozapine has been shown to inhibit the cortisol response to MK-212, a direct-acting 5-HT agonist (Lowy et al. 1988), after 4–6 weeks treatment with clozapine (Meltzer 1989b). This is most likely due to its 5-HT_2 blocking properties or to down-regulation of 5-HT_2 receptors, since the effect of MK-212 on the hypothalamic-pituitary-adrenal axis is mediated by a 5-HT_2 mechanism (Koenig et al. 1987). The effect of MK-212 on serum cortisol was not inhibited in patients treated with chlorpromazine, molindone, or haloperidol (Meltzer 1989a). This is noteworthy since at least one of these agents, e.g., chlorpromazine, has a very similar affinity for the 5-HT_2 receptor in vitro as does clozapine and, like clozapine, can down-regulate cortical 5-HT_2 receptor in vivo. This suggests that clozapine is a particularly potent 5-HT_2 antagonist in vivo or that MK-212 may be stimulating cortisol secretion via a non-5-HT_2-dependent mechanism.

The importance of the D-1 DA receptor has been clarified by recent biochemical, electrophysiological and behavioral studies (Clark and White 1987). The clinical importance of D-1 receptors has been discussed by Beaulieu (1987). Briefly, it has been demonstrated that some DA-dependent neurochemical, electrophysiological and behavioral effects reflect the cooperative or antagonistic action of D-1 and D-2 receptor stimulation. Such interactions may be mediated on the same or different DA neurons, or a combination thereof (Saller and Salama 1986; Stoof and Verheijden 1986; Pugh et al. 1985; Goldstein et al. 1987). Some interactions may be present only after chronic administration (Morelli et al. 1987). It has recently been demonstrated that clozapine and other atypical neuroleptics are relatively more potent inhibitors of the binding of ^{3}H-SCH-23390, the major ligand used to quantify D-1 receptor binding sites (Iorio et al. 1983) to D-1 receptors in vivo (Andersen et al. 1986), compared with typical neuroleptics. Furthermore, clozapine and fluperlapine are more potent in inhibiting DA-stimulated adenylate cyclase than would be predicted on the basis of their potencies to displace ^{3}H-SCH-23390 binding, whereas the reverse is true for typical neuroleptics (Andersen and Braestrup 1986). This may be due to a high affinity of clozapine for D-1 receptor sites actually coupled to adenylate cyclase. These authors suggested that the antipsychotic efficacy of clozapine and fluperlapine is due to a blockade of adenylate cyclase-coupled D-1 receptors. Chronic administration of clozapine (1–12 months) at doses of 24–27 mg/kg per day increased D-1 receptor density in rat striatum whereas chronic haloperidol (1.4–1.6 mg/kg per day) treatment had no effect.

In a small group of typical and atypical antipsychotic drugs ($N = 13$), we found that the D-1 affinities of the atypical antipsychotic drugs were lower than those of the typical drugs (Matsubara and Meltzer 1988); however, as the number of drugs studied was increased to 30, we found no differences between the two groups with regard to D-1 affinities (Meltzer et al. 1989b). We observed a blockade of the effect of clozapine on DOPA accumulation in the median eminence by a D-1 agonist, SKF-38393 (Gudelsky and Meltzer 1989). However, we have found that melperone and setoperone are almost inactive as D-1 dopamine receptor antagonists in vitro (Meltzer et al. 1989b) and the selective D-1 antagonist SCH-23390 was ineffective in increasing the accumulation of DOPA in the median eminence (Gudelsky and Meltzer 1989). Thus, although some of the actions of clozapine appear to involve D-1 receptor mechanisms, the exact nature of this interaction remains unclear. This will be considered subsequently.

In order to clarify further the relative importance of D-1, D-2 and 5-HT_2 affinities for the mechanism of action of atypical antipsychotic drugs, we determined the pKi negative log values of 13 unequivocal typical and 8 putative atypical antipsychotic drugs for rat striatal D-1 and D-2 dopamine receptor binding sites and cortical serotonin (5-HT_2) receptor binding sites (Matsubara and Meltzer 1988; Meltzer et al. 1989b). The atypical antipsychotics had significantly lower pKi values for the D-1 and D-2 but not for 5-HT_2 binding sites. The 5-HT_2 and D-1 pKI values were correlated for the typical compounds, whereas the 5-HT and D-2 pKi values were correlated for the atypical antipsychotic drugs. The 5-HT_2/D-2 and 5-HT_2/D-1 ratios were significantly higher for the atypical drugs than for the typical drugs, but there was no difference in the D-1/D-2 ratio. Altar et al. (1986) also found a higher 5-HT_2/D-2 ratio for atypical drugs. In a stepwise discriminant function analysis to determine the independent contribution of each type of affinity to classification as typical or atypical type the D-2 pKi value was entered first, followed by the 5-HT_2 pKi value. The D-1 pKi value was not entered into the model. A discriminant function analysis correctly classified 20 of 21 of these compounds plus 14 of 17 additional test compounds as typical or atypical antipsychotic drugs for an overall correct classification rate of 89.7%. A cluster analysis based only on the 5-HT_2/D-2 ratio grouped 16 of 18 atypical plus 1 typical in one cluster and 19 of 20 typical plus 2 atypicals in a second

cluster for an overall correct classification rate of 92.1%. These data suggest that determination of D-2 and 5-HT_2 pKi values may be useful for rapid screening of potential atypical antipsychotic drugs with only minimal false positives.

The potent 5-HT_2 antagonism of clozapine and other atypical antipsychotic drugs relative to their D-2 antagonism does not necessarily imply that this is critical to their mechanism of action. However, there is considerable evidence that there are important interactions between the serotonergic and dopaminergic systems in both the nigrostriatal and mesolimbic pathways (Costall et al. 1975; Dray 1981; Meltzer et al. 1979; Meltzer 1989b, c). To give a few examples, Nicolaou et al. (1979) presented evidence of a tonic inhibitory effect of the dorsal and median raphé nuclei on DA metabolism in the striatum. Hervé et al. (1979, 1981) presented evidence that the dorsal raphé regulates DA turnover in the nucleus accumbens and not the frontal cortex, whereas the median raphé has effects on DA metabolism in the accumbens and frontal cortex.

There is both preclinical (Waldmeier and Delini-Stula 1979) and clinical (Bersani et al. 1986) evidence that decreasing serotonergic activity, and 5-HT_2 blockade in particular, may diminish neuroleptic-induced EPS. Setoperone, a fairly potent antagonist of both 5-HT_2 and D-2 receptors, has been reported to be more effective than typical drugs in decreasing negative symptoms (Ceulemans 1985). These results suggest that the 5-HT_2 antagonism of clozapine and other atypical neuroleptics may be of particular importance for their action. Because clozapine only blocks 5-HT_2 receptors, the enhanced 5-HT release might facilitate neurotransmission at 5-HT_{1A}, 5-HT_{1D} or 5-HT_3 receptors.

The evidence reviewed here that a DA-5-HT interaction is important for the action of atypical neuroleptics does not necessarily imply that an abnormality in the interaction of 5-HT and DA is etiologically related to schizophrenia or some aspects thereof. However, this seems a particularly promising variation of the DA hypothesis to pursue. It would be compatible with the failure to find consistent changes in dopaminergic activity through fairly gross measures, such as CSF or plasma concentrations of homovanillac acid, the major metabolite of DA, or measures of D-2 receptor density using positron tomography or in post-mortem studies. Relative imbalances between dopaminergic and serotonergic neurotransmission in specific regions might be of greater importance.

In conclusion, clozapine has been shown to have multiple advantages over typical neuroleptic drugs. Other atypical antipsychotic drugs, such as melperone, share at least some of these advantages, but further study is needed to determine whether they are also more effective as antipsychotic drugs. There are numerous biological differences between typical and atypical drugs and it is not yet possible to ascertain which are critical to their major advantages. However, the ratio of antagonism of 5-HT_2 to D-2 receptors appears a strong possibility. Further, the ability to enhance the release of DA and 5-HT via a direct rather than just the short-loop feedback mechanism may be of importance. Further study is needed to establish whether some aspects of schizophrenia represent an abnormality in the interaction of serotonergic and dopaminergic mechanisms.

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