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The Mechanism of Action of Novel Antipsychotic Drugs

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Abstract

It is no longer tenable to attribute all the antipsychotic action of antipsychotic drugs to dopamine (DA) D_2 receptor blockade and subsequent development of depolarization inactivation of the mesolimbic or mesocortical DA neurons. The chief evidence for this position is that clozapine (CLOZ) does not differ from typical antipsychotic drugs in these regards but is more effective than typical neuroleptic drugs. The mechanism of action of atypical antipsychotic drugs related to CLOZ may involve reduction of dopaminergic activity in the mesolimbic system by a variety of mechanisms, including D_1 and D_2 receptor blockade. Relatively higher affinity for the serotonin $(5HT)_2$ receptor than for the D_2 receptor may also be important to the action of CLOZ-like compounds. Enhanced DA release in the mesocortical system may be relevant to the effectiveness of these agents in treating negative symptoms. Several other classes of new agents alter the dopaminergic system by means of alternative mechanisms. Partial DA agonists may modulate DA neurotransmission more adequately than pure antagonists by producing a mix of direct agonist and antagonistic effects. DA autoreceptor agonists and $5HT_3$ antagonists appear to act by diminishing the release of DA from some, but not all, DA neurons. Substituted benzamides are "pure" D_2 antagonists with some in vivo selectivity for limbic D_2 over striatal D_2 receptors. Highly selective D_1 antagonists have been proposed to produce equivalent antipsychotic activity and fewer extrapyramidal symptoms than D_2 antagonists. Antagonists of the recently identified D_3 receptors are being sought. Excessive stimulation of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, leading to neurotoxicity or diminished activation of this receptor, is the target of novel approaches to treating schizophrenia. Phencyclidine (PCP) antagonists that would activate the NMDA receptor and sigma receptor antagonists are of interest as antipsychotic agents. Therapeutic strategies for treating schizophrenia, schizophrenia-related disorders, and other psychoses will likely be genuinely diverse in the next decade.

The concept that all effective antipsychotic drugs act by blocking dopamine (DA) D_2 receptors in the mesolimbic system has been a basic tenet of neuropsychopharmacology for more than three decades (Matthysse 1974; Meltzer and Stahl 1976). This view was sustained by repeated failure to identify effective antipsychotic agents that were not neuroleptic drugs and the near perfect correlation between the affinity for striatal D_2 receptors and average clinical dose (Seeman and Lee 1975). D_2 receptors are those receptors that are negatively coupled, that is, inhibitory or not coupled to adenylate cyclase (e.g., coupled to ion channels). They are distinguished from D_1 receptors, which are positively coupled to adenylate cyclase (Kebabian and Calne 1979), and the recently cloned D_3 receptor, which is not coupled to adenylate cyclase (Sokoloff et al. 1990). There may well be many other classes of DA receptors (Andersen et al. 1990). A D_4 receptor with high affinity for clozapine (CLOZ) has recently been identified

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(Van Tol and Seeman, personal communication, March 20, 1991). However, varying degrees of evidence now suggest that drugs that act only in part by D_2 receptor blockade—for example, CLOZ amperozide, and melperone—are as effective antipsychotic agents as typical neuroleptic drugs, or even more effective (Kane et al. 1988; Mertens et al. 1989; Meltzer et al. 1989*a*). Other putative novel antipsychotic agents are just beginning to be tested for efficacy and side effects; in some instances, their mechanism of action has not been clearly delineated. Nevertheless, reviewing some of the hypotheses currently being considered concerning their mechanism of action is valuable. We have reviewed elsewhere some of the evidence for the efficacy of some of these novel agents (Meltzer 1986). Gerlach (1991), in this issue, describes more recent evidence for their clinical efficacy. In particular, in this article I consider the mechanism of action of CLOZ and related compounds, specific D_1 and D_2 antagonists, the newly discovered D_3 receptor, DA autoreceptor agonists, DA partial agonists, serotonin $(5HT)_3$ antagonists, sigma and phencyclidine (PCP) antagonists, and glutamatergic agents. Although this list does not exhaust the new approaches currently under investigation for alleviating schizophrenia (e.g., corticotrophin-releasing factor antagonists), it does cover the concepts of greatest current interest.

CLOZ-like Antipsychotic Drugs

CLOZ is the first antipsychotic drug that has been shown to be more effective than typical neuroleptic drugs (Kane et al. 1988). Moreover, it appears to produce little or no tardive dyskinesia (TD), few extrapyramidal side effects (EPS), and no plasma prolactin (PRL) increases in humans, although it does increase plasma PRL concentrations in vivo in rodents (Meltzer et al. 1975, 1979*a*; Meltzer 1989). I have suggested that these four important advantages may derive, in part, from common pharmacological effects (Meltzer 1990). Current theories concerning the mechanism of action of CLOZ are considered in this section.

Mesolimbic Selectivity. Various lines of evidence suggest that the antipsychotic effect of typical neuroleptic drugs is mediated by their ability to decrease dopaminergic activity in the mesolimbic system (e.g., nucleus accumbens, olfactory tubercle, amygdala, and stria terminalis), whereas effects of these drugs on the extrapyramidal system (i.e., EPS and TD) are due to decreases in dopaminergic activity in the caudate-putamen (see Meltzer and Stahl 1976 for review). These effects are believed to be mediated through DA receptor blockade (Carlsson and Lindqvist 1963; Seeman and Lee 1975) and subsequent development of so-called depolarization inactivation of DA neurons due to overexcitation of DA cells activated by a feedback loop from mesostriatal and mesolimbic neurons (Bunney and Grace 1978).

It was originally suggested that the limited ability of CLOZ to produce EPS could be attributed to a relatively selective ability to decrease dopaminergic activity in the limbic system, leaving dopaminergic activity in the striatum region relatively intact (Bartholini et al. 1972). The biochemical evidence that supports this view is mixed. Although many studies have found a greater effect of CLOZ on DA turnover in the limbic system (Andén and Stock 1973; Weisel and Sedvall 1975; Wilk et al. 1975; Zivkovic et al. 1975), most have not (Bartholini et al. 1975; Stewarz et al. 1975; Westerink and Korf 1975; Waldmeier and Maitre 1976; Maidment and Marsden 1987). Postmortem tissue concentration studies of this type have now been complemented by in vivo microdialysis studies, which are reviewed in this article.

Some behavioral studies of DA agonist effects mediated by the striatum (stereotypy, catalepsy) or nucleus accumbens (locomotor activity) indicate a limbic selectivity for CLOZ (Burki et al. 1975; Iversen and Koob 1977; Honma and Fukushima 1978; Ljunberg and Ungerstedt 1978). However, CLOZ can block the effect of electrical stimulation of the substantia nigra on turning behavior in rats, an effect mediated in the striatum (Roffman et al. 1978). Chronic CLOZ has been reported to selectively increase the rate of intracranial self-stimulation in the ventral tegmentum (A10) but not the nigrostriatal (A9) DA neurons (Gardner and Seegar 1983).

The ability of CLOZ to decrease selectively dopaminergic activity of the mesolimbic and mesocortical (A10) versus nigrostriatal DA neurons (A9) is supported by electrophysiological studies. Consistent with the concept of mesolimbic selectivity, acute administration of CLOZ has been reported to increase the firing rate of A10 but not A9 DA neurons, whereas acute haloperidol (HPL) administration increased the activity of both A9 and A10 neurons (Hand et al. 1987). However, Souto et al. (1979), Rebec et al. (1980), and Chiodo and Bunney (1983, 1985) reported an increase in the firing rate

of both A9 and A10 neurons after acute HPL and CLOZ administration. The reasons for this discrepancy are unclear.

It can be concluded that there is some evidence for mesolimbic specificity for CLOZ. This specificity may contribute to its lack of EPS and TD but cannot account for its greater efficacy in decreasing positive symptoms.

Depolarization Inactivation. After chronic administration, CLOZ was reported to reduce the firing rate of only the A10 neurons, leaving the activity of the A9 neurons at basal levels (Chiodo and Bunney 1983, 1985; White and Wang 1983*a*, 1983*b*). Inactivation of the A9 or A10 DA neurons following chronic antipsychotic drug administration has been postulated to be due to depolarization block, because these neurons discharge normally after the microiontophoretic application of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Bunney and Grace 1978, Chiodo and Bunney 1983) or doses of apomorphine, which would be expected to inhibit firing (Bunney and Grace 1978; White and Wang 1983*a*). The delayed onset of depolarization inactivation in the A10 neurons was considered to be related to the slow onset of action of all antipsychotic drugs, including CLOZ (White and Wang 1983*a*; Chiodo and Bunney 1983, 1985), whereas the lack of EPS with CLOZ has been related to preservation of the firing rate of the A9 neurons (Chiodo and Bunney 1983).

Recent studies have provided reasons to doubt the importance of depolarization inactivation for antipsychotic drug action. Andén et al. (1990) reported that 3 weeks' treatment with HPL did not increase the concentration of DA in the terminal areas of A9 and A10 neurons, nor did it have any effect on the increase in DA concentration produced by gamma-butyrolactone (GBL), which completely inhibits the firing of the midbrain DA neurons (Roth et al. 1973). Depolarization block with chronic HPL should have itself increased the concentration of DA in these regions and should have blocked the effect of GBL to do so. Andén et al. (1990) suggested that the development of depolarization block during chronic HPL treatment previously reported by others (Bunney and Grace 1978; White and Wang 1983*b*; Chiodo and Bunney 1985; Grace and Bunney 1986) might have been due to the interaction of HPL and chloral hydrate anesthesia or to the use of older rats with better developed feedback loops from the terminal regions to the dopaminergic neurons. Other studies on the effect of anesthesia on DA neuronal activity (Ford and Marsden 1986; Kelland et al. 1989; Ståhle et al. 1990) also support the view that the reports of neuroleptic-induced depolarization inactivation might have been influenced by anesthesia. When awake, freely moving animals were used, apomorphine was unable to reverse the decrease in basal DA release in the striatum produced by chronic HPL administration. Rather, a further decrease was found (Ichikawa and Meltzer 1990*a*), which was attributed to the action of apomorphine on supersensitive DA autoreceptors to inhibit DA synthesis or release. The ability of apomorphine to further decrease DA release in chronic HPL-treated rats was suggested as a possible explanation of why direct-acting DA agonists may potentiate the antipsychotic effect of neuroleptic drugs (Meltzer 1980).

Additional studies using in vivo voltammetry that are consistent with depolarization inactivation (Lane and Blaha 1986, 1987; Blaha and Lane 1987) or not consistent (Maidment and Marsden 1987) are discussed in the next section.

In summary, the importance of depolarization inactivation for the mechanism of action of antipsychotic drugs, in general, is less certain now. Even if it does develop during chronic antipsychotic drug administration, its decisive functional importance is not clear, because release of DA at nerve terminals may be much more independent of cell firing than was previously appreciated (Abercrombie and Zigmond 1990).

Effect of CLOZ on DA Release. The effect of CLOZ on DA release has been studied in vitro and under in vivo conditions by voltammetry and in vivo microdialysis with markedly different results. CLOZ has been shown to produce a dose-dependent blockade of the inhibition of DA release from synaptosomes of rat nucleus accumbens produced by DA, an effect presumably mediated by DA autoreceptor blockade (Hetey and Drescher 1986). This effect would be expected to enhance DA release in vivo. Using a slice superfusion system, Compton and Johnson (1989) reported that neither acute nor chronic CLOZ (20 mg/kg subcutaneously for 21 days) with no washout period had any effect on amphetamine-stimulated DA release in the nucleus accumbens, although chronic CLOZ treatment significantly increased amphetamine's effect in the striatum by 44 percent over vehicle. Acute CLOZ treatment also significantly increased striatal, but not nucleus accumbens, DA release produced by electrical field stimulation; chronic CLOZ had no effect on this process in either region. Thus, tolerance developed to the acute enhance-

ment by CLOZ of DA release in the striatum. The effect of chronic CLOZ on amphetamine-induced DA release differed from that of HPL, which was inactive; it was suggested that this action of CLOZ may allow for a partial compensation or reversal of any blockade of striatal DA receptors by CLOZ (Compton and Johnson 1989). Development of tolerance to the effect of acute CLOZ on striatal DA release was also suggested to be relevant to the low EPS produced by CLOZ, because it suggests loss of effective DA receptor blockade (Compton and Johnson 1989). Thus, one might conclude from these studies that CLOZ produces less DA receptor blockade than HPL, with greater enhancement of DA release. That CLOZ does not block the striatal DA autoreceptors that inhibit DA synthesis has previously been demonstrated (Walters and Roth 1976).

Altar et al. (1988) reported that acute administration of CLOZ and a variety of novel antipsychotic agents (RMI-81582, fluperlapine, flumezapine, rimcazole, and CGS-10764B) produced much less DA release in mouse brain as indicated by 3-methoxytyramine concentrations than did typical neuroleptic drugs such as HPL, chlorpromazine (CPZ), and metoclopramide. However, setoperone and perlapine, which appear to have atypical properties, also produced more DA release. Altar et al. (1988) noted that the acute effects of the atypical drugs were comparable to those of D_1 antagonists such as SCH-23390.

The importance of increased DA turnover and release to the ability of CLOZ and other atypical antipsychotic drugs to produce only a transitory rather than a prolonged increase in rat plasma PRL levels despite blockade of pituitary D_2 receptors has been suggested by Gudelsky and Meltzer (1989). Activation of the tuberoinfundibular DA neurons by the atypical antipsychotic drugs was correlated with the time course in the fall of plasma PRL levels. It is not clear if this same mechanism accounts for the lack of plasma PRL increases following CLOZ in humans (Meltzer et al. 1979*a*).

Using in vivo voltammetry in chloral-hydrate-anesthetized rats, researchers reported that chronic CLOZ administration had no effect on DA release in the striatum, but it did block DA release in the accumbens. This blockade was reversed by low-dose apomorphine. Chronic HPL induced apomorphine-reversible blockade of DA release in both areas, suggesting that the inhibition of DA release was due to depolarization inactivation and that CLOZ was selective for the limbic region (Lane and Blaha 1986, 1987; Blaha and Lane 1987). By contrast, Maidment and Marsden (1987) reported that chronic CLOZ (50 mg/kg subcutaneously for 20 days) failed to produce tolerance to the ability of CLOZ to increase extracellular dihydroxyphenylacetic acid (DOPAC) levels in the striatum or accumbens. Release of DOPAC, a DA metabolite, may reflect intraneuronal DA metabolism or DA reuptake. In any event, the results were inconsistent with depolarization inactivation and again suggested that important processes occur at the nerve terminal that affect DA release and that these processes are independent of depolarization inactivation.

The results of in vivo microdialysis studies of the effect of CLOZ on DA release are mixed. Imperato and Angelucci (1989) reported that low doses of CLOZ produced marked increases in DA release in rat prefrontal cortex. O'Connor et al. (1989) reported that acute CLOZ (40 mg/kg) significantly increased DA release in the dorsolateral striatum of halothane-anesthetized rats, but not in the fundus; DOPAC release increased in both regions. The results suggested a dissociation between the effects of acute CLOZ on DA release and metabolism. Moghaddam and Bunney (1990) reported that acute CLOZ (5 and 10 mg/kg) increased the concentration of extracellular DA in the striatum, nucleus accumbens, and prefrontal cortex in chloral-hydrate-anesthetized rats. The effect of CLOZ was more robust than the effects of sulpiride and HPL in the prefrontal cortex. No studies using in vivo microdialysis have been reported on the effect of chronic CLOZ on DA release in the frontal cortex; however, Mefford et al. (1988) reported that 21 days' treatment with CLOZ increased DA metabolism in the rat frontal cortex. CPZ was almost as effective, whereas thioridazine and HPL were similar but less effective.

The effect of acute versus chronic CLOZ on DA release in the striatum and nucleus accumbens was studied by in vivo microdialysis by Ichikawa and Meltzer (1991) in awake, freely moving rats. CLOZ (20 mg/kg subcutaneously) increased DA and DOPAC release in both the striatum and nucleus accumbens. HPL (2 mg/kg subcutaneously) produced similar effects. The effect of CLOZ on DA release in the striatum was less than that of HPL, but there was no difference in the accumbens. Following chronic treatment with HPL or CLOZ (21 days at 2.0 mg/kg and 20 mg/kg per day in drinking water), basal DA efflux was decreased by HPL by 21 percent and 46 percent in the striatum, whereas CLOZ produced nonsignificant decreases in basal DA efflux in the

striatum and nucleus accumbens. Chronic HPL decreased DOPAC efflux in both regions but CLOZ did not (Ichikawa and Meltzer 1990*b*). Challenge with CLOZ in chronic CLOZ-treated rats no longer increased DA release in the nucleus accumbens but still produced the same modest increase in the striatum (Ichikawa and Meltzer 1991). These results indicate that chronic CLOZ administration does not interfere significantly with DA metabolism in the accumbens or striatum of the rat. Similar results were reported for the striatum by Mefford et al. (1988), who measured DA and its metabolites in post-mortem tissue following chronic treatment.

Caution is in order before these results can be extrapolated to the clinical situation. Even if these same effects did occur in humans, it is not clear that they would persist over years of administration. It is also possible that endogenous abnormalities in DA metabolism in some schizophrenic patients (e.g., increased DA release or supersensitive D_2 receptors) could influence the effect of CLOZ on striatal and accumbens DA metabolism. With these cautions in mind, it is tempting to speculate that the advantages of CLOZ are based on its being able to increase DA release in the frontal cortex and striatum without diminishing DA release in the accumbens. Increased DA release in the striatum following repeated administration and normal basal DA release in the accumbens may explain the lack of effect of CLOZ to produce EPS and contribute to its superior effect on positive symptoms. Deficient DA efflux in the mesolimbic system associated with chronic administration of typical neuroleptic drugs may have an adverse effect on cognitive function. Increased efflux of DA in the prefrontal cortex may be beneficial in treating negative symptoms (Meltzer 1990). We have reported that the onset of the therapeutic action of CLOZ may be delayed for weeks to months (Meltzer et al. 1989*b*). Slowly developing modulation of DA release in relation to DA receptor blockade may be a factor in this process.

DA Receptor Blockade: Effect of CLOZ on D_1 and D_2 Receptors. I have discussed elsewhere (Meltzer 1990) the possible importance of the ability of an antipsychotic drug to increase dopaminergic activity in the cortex while decreasing it subcortically. Although CLOZ does not significantly diminish DA release in the mesolimbic region—as indicated by the studies of Ichikawa and Meltzer (1990*b*, 1991)—it may still produce sufficient decreases in dopaminergic activity in these regions by blockade of post-synaptic D_1 and D_2 receptors. There is evidence that CLOZ in vitro (Andersen and Braestrup 1986; Andersen et al. 1986; Chipkin and Latranyi 1987; Meltzer et al. 1989*c*) or after acute administration (Vasse and Protais 1988; Murray and Waddington 1990) can block D_1 receptors, the subtype of DA receptor that is positively coupled to adenylate cyclase. I have reviewed the earlier literature on the effect of CLOZ on DA receptors elsewhere (Meltzer 1990). Using positron emission tomography (PET) with ^{11}C-SCH-23390 as ligand, Farde et al. (1989) showed that CLOZ occupies D_1 receptors in humans more effectively than typical antipsychotic drugs, but it may be less effective at occupying D_2 receptors in the striatum (Farde et al. 1988*b*, 1989). It should be noted, however, that these PET studies provide a measure of striatal binding and may not represent accurately the occupancy of mesolimbic DA receptors. The methodology of these studies needs to be further validated and extended to a larger number of subjects, and the results need to be related to clinical response.

The importance of D_1 receptor blockade for the action of CLOZ has been emphasized in some recent preclinical studies. CLOZ was found to partially block the locomotor response to the D_1 agonist SKF-38393 in neonatal 6-hydroxydopamine (6-OHDA)-lesioned rats at smaller doses than were needed to block the effects of the D_2 agonist LY-171555. It was also able to block self-mutilation due to L-dopa administration in neonatal 6-OHDA-lesioned rats, an effect that may also be due to D_1 receptor stimulation because it is blocked by the D_1 receptor antagonist SCH-23390 but not by low doses of the D_2 receptor antagonist HPL (Criswell et al. 1989). Murray and Waddington (1990) have presented evidence that low doses of CLOZ blocked the grooming effects of the selective D_1 agonist SKF-77434. CLOZ was less consistently able to block the hyperactivity induced by the D_2 agonist LY-162502 but did induce a syndrome of limb jerking in those animals. This pattern was similar to, but weaker and less consistent than, that of selective D_1 antagonist R-SKF-83566 (Murray and Waddington 1989). CLOZ also blocked the effect of grooming in mice of the D_1 agonist SKF-28293 (Vasse and Protais 1988). CLOZ administration (24–27 mg/kg/d orally), increased striatal D_1 binding with ^{3}H-piflutixol as ligand in rodents after 9 and 12 months but had no effect on adenylate cyclase activity (Rupniak et al. 1985*b*). Ashby et al. (1989) also found no effect of chronic oral CLOZ for 12 months on the ability of the D_1 agonist SKF-

38393 to stimulate striatal adenylate cyclase. CLOZ had no effect on D_2 binding in the striatum (Rupniak et al. 1985). CLOZ treatment was reported to increase D_1 receptor binding in the nucleus accumbens at 28 days but not in the caudate putamen, olfactory tubercle, medial frontal cortex, or substantia nigra. The effect in the accumbens was absent after 8 months (See et al. 1990). However, CLOZ (30 mg/kg i.p. for 21 days) was reported to increase striatal D_1 binding as shown by autoradiography but had no effect on D_2 receptor binding (O'Dell et al. 1990). The reverse was true for HPL: it had no effect on striatal D_1 binding but increased D_2 receptor binding.

These results suggest CLOZ may have significant effects on D_1 receptors in vivo, but it is impossible to assess the functional significance of the results at this time. Furthermore, because of the significant but complex interaction between D_1 and D_2 receptors to regulate a variety of behaviors (Clark and White 1987), this effect of CLOZ may be important to its mechanism of action. There is evidence that D_1 antagonism can synergize with weak D_2 antagonism to block *both* striatal and limbic behaviors (Dall'Olio et al. 1989). However, this possibility raises the issue of why the D_1 antagonist effects of CLOZ would not also lead to EPS. However, some additional studies question the functional importance of D_1 receptor blockade by CLOZ. The sensitivity of rat caudate-putamen neurons to D_1 receptor agonists was also not blocked by 1 year of continuous treatment with CLOZ (Wang et al. 1988). In addition, it is unclear whether the effects on D_1 receptors are characteristic of other atypical antipsychotic drugs (e.g., melperone, amperozide), which lack the affinity of CLOZ for D_1 receptor binding sites (Meltzer et al. 1989*c*). Melperone, for example, does not occupy D_1 sites relative to D_2 sites as effectively as CLOZ in PET studies (Farde et al. 1988*b*, 1989). We have reported that the affinity of atypical drugs for striatal D_1 receptor sites in vitro does not differ from that of typical antipsychotics, whereas that for D_2 sites and for serotonin ($5HT_2$) relative to D_2 sites does discriminate between the two classes (Meltzer et al. 1989*b*).[1] Further study of the importance of D_1 receptor blockade in regard to EPS and antipsychotic action should help to clarify how important this action is for CLOZ and other antipsychotic drugs. A variety of selective D_1 receptor antagonists is now ready for clinical testing in schizophrenia. These agents should clarify whether selective D_1 receptor blockade is sufficient to achieve an antipsychotic effect without EPS or whether the addition of a pure D_1 receptor antagonist to a D_2 antagonist may potentiate the antipsychotic action of the latter while reducing its ability to produce EPS, including TD.

Effect of CLOZ on Sensitivity to DA Agonists. Early studies suggested that chronic CLOZ selectively increased DA receptor supersensitivity (as indicated by behavioral measures) only in the mesolimbic system, whereas HPL induced supersensitivity in both the striatum and nucleus accumbens (Sayers et al. 1975; Seegar et al. 1982). Several recent studies also compared the effect of chronic CLOZ versus HPL on the response to DA agonist administration. Hu and Wang (1989) reported that chronic HPL, but not CLOZ, enhanced the sensitivity of caudate-putamen neurons to the D_2 agonist quinpirole. No alteration in the response to the D_1 agonist SKF-38393 was observed with either treatment. The development of supersensitive striatal D_2 receptors with HPL was linked to HPL's ability to produce EPS. However, Halperin et al. (1989) found that neither chronic HPL nor CLOZ altered the stereotypy scores following intrastriatal DA, whereas both drugs enhanced the locomotor response to intra-accumbens DA. These conflicting results are difficult to interpret and do not appear to be related to the unique features of CLOZ with regard to EPS or its antipsychotic effect.

Schremmer et al. (1990) reported that the potency of CLOZ, the neuroleptics sulpiride and thioridazine, and the 5HT antagonists cyproheptadine and ritanserin to block the supersensitive response to parenteral apomorphine was the same in control and in 6-OHDA-denervated rats following bilateral nucleus accumbens injections 7 days previously. The effect of HPL was diminished in the 6-OHDA-denervated rats. Schremmer et al. attributed this effect of CLOZ, cyproheptadine, and ritanserin to $5HT_2$ receptor blockade and suggested that the model of denervation supersensitivity is capable of differentiating typical and atypical neuroleptic drugs. That sulpiride and thioridazine have atypical antipsychotic properties, however, is cer-

[1] Melperone, in comparison with CLOZ, does not occupy D_1 sites as extensively as D_2 sites in PET studies (Farde et al. 1988*b*, 1989). We have reported that the affinity of atypical antipsychotic drugs for striatal D_1 receptor sites in vitro does not differ from that of typical drugs, whereas that for D_2 sites and for serotonin ($5HT_2$) relative to D_2 sites does discriminate between the two classes (Meltzer et al. 1989*b*).

tainly disputable (Meltzer 1988, 1989, 1990; Meltzer et al. 1989*b*).

D_3 Receptor Antagonism and CLOZ. Recently, a novel DA receptor related to the D_2 receptor, family, called the D_3 receptor, was cloned and sequenced (Sokoloff et al. 1990). DA itself, in the absence of added guanyl nucleotides, has a twentyfold greater affinity at the D_3 receptor than at the D_2 receptor. The affinity of DA for the D_3 receptor, unlike its affinity for the D_2 receptor, is not sensitive to guanyl nucleotides. Although some DA agonists (e.g., apomorphine and bromocriptine) have equal potencies for D_2 and D_3 receptors, other DA agonists with relative selectivity for the DA autoreceptor (e.g., TL-99, quinpirole, and pergolide) are much more potent at the D_3 receptor than at the D_2 receptor. Although all neuroleptics are more potent at the D_2 than at the D_3 receptor, some (e.g., CLOZ, thioridazine, amisulpride, raclopride, and (−)-sulpiride) are only two to three times more potent at the D_2 than at the D_3 receptor. This group of drugs is considered atypical by some (e.g., Sokoloff et al. 1990), but we have discussed why drugs such as thioridazine (Meltzer et al. 1989*c*) and the substituted benzamides should not be classified with CLOZ as atypical (Meltzer 1990). Typical neuroleptics (e.g., HPL and prochlorperazine) are 10 to 20 times more potent at D_2 than at D_3 receptors. On this basis, Sokoloff et al. (1990) suggested that an action at the D_3 receptor might be responsible for the atypical properties of some antipsychotic drugs, including CLOZ. The D_3 receptor does not appear to be linked to formation of cyclic adenosine monophosphate (cAMP). In situ hybridization revealed the following distribution: olfactory tubercle > hypothalamus > striatum > substantia nigra. There was little D_3 hybridization signal in the striatum connected to the substantia nigra, whereas the limbic striatum was rich in D_3 messenger ribonucleic acid (mRNA). Lesioning DA neurons revealed a high concentration of D_3 receptor on the cell bodies of both the A9 and A10 neurons, suggesting that the D_3 receptor may be an autoreceptor. Sokoloff et al. (1990) suggested that D_3 receptor antagonism may be critical for antipsychotic activity—an interesting suggestion, but all the evidence to support it appears to be quite indirect. More specific D_3 antagonists will be developed, no doubt, permitting more definitive evaluation of the functional significance of this receptor.

$5HT_2$ Receptor Antagonism and Atypical Antipsychotic Drugs. The possible importance of the $5HT_2$ antagonist properties of CLOZ to explain its mechanism of action as an atypical antipsychotic drug has emerged from both preclinical and clinical studies (Meltzer 1988, 1989, 1990; Meltzer et al. 1989*c*). CLOZ has been reported to increase 5HT metabolism in rat brain (Ackenheil et al. 1974; Maj et al. 1974; Burki et al. 1975; Ruch et al. 1976). More recently, no increase in the extracellular concentration of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5HT, was found in the nucleus accumbens or striatum of freely moving rats by using in vivo microdialysis (Ichikawa and Meltzer 1991). Ruch et al. (1976) also found no effect of 7 days' CLOZ treatment on 5HT turnover in rat brain. However, CLOZ has been reported to be an effective 5HT antagonist in vivo. Thus, CLOZ has been shown to inhibit the following:

- The hyperthermic effects of fenfluramine and 5-hydroxytryptophan (5-HTP), the precursor of 5HT (Sulpizio et al. 1978; Fjalland 1979).
- The 5-HTP-induced head twitch in rats (Maj et al. 1978).
- Mylohyoid muscle twitch induced in the rodents by the 5HT agonist quipazine (Maj et al. 1978).
- The ability of lysergic acid diethylamide (LSD) to promote apomorphine-induced locomotor activity, an effect that appears to be due to the 5HT agonist properties of LSD (Fink et al. 1984).
- The discriminative stimulus due to the 5HT agonist quipazine (Friedman et al. 1985).
- The hyperthermic response to the $5HT_2/5HT_{1c}$ agonist MK-212 (Nash et al. 1988).
- The ability of the hallucinogen 2,5-dimethoxy-4-methylamphetamine (DOM), which has a strong affinity for $5HT_2$ and $5HT_{1c}$ binding sites to decrease the spontaneous activity and increase the response to peripheral nerve stimulation of locus coeruleus neurons (Rasmussen and Aghajanian 1988).
- The plasma corticosterone and PRL response to MK-212 in rodents (Koenig et al. 1987; Nash et al. 1988).

In humans, CLOZ also blocks the cortisol and PRL responses to MK-212 (Meltzer 1988), and it down-regulates $5HT_2$ receptors in rat frontal cortex (Reynolds et al. 1983; Lee and Tang 1984), even after a single dose (Matsubara and Meltzer 1989). CLOZ also blocks the ability of 5HT or DA to inhibit the release of 5HT from synaptosomes of rat nucleus accumbens (Drescher and Hetey 1988). There is no evidence that CLOZ is an effective antagonist of the $5HT_{1A}$ receptor. All the foregoing effects that are inhibited by

CLOZ are likely due to stimulation of the $5HT_2$ or $5HT_{1c}$ receptor.

The importance of $5HT_2$ receptor blockade in conjunction with D_1 and D_2 antagonism to the action of atypical antipsychotic drugs was studied by Meltzer et al. (1989*c*). The negative log of the affinities (pKi) of 13 typical and 7 atypical antipsychotic drugs for rat striatal D_1 and D_2 and cortical $5HT_2$ receptor binding sites were determined. The atypical antipsychotic drug had a significantly lower affinity for the D_2 sites ($p < 0.0001$) and a trend *in the same direction* for D_1 sites (7.44 ± 0.89 vs. 6.67 ± 0.90, $p = 0.08$, respectively). There was no difference in $5HT_2$ affinities ($p = 0.23$). However, the pKi $5HT_2/D_2$ and $5HT_2/D_1$ ratios were significantly greater for the atypical antipsychotic drugs (1.20 ± 0.05 and 1.30 ± 0.19) than for the typical (0.91 ± 1.08 and 1.10 ± 0.10, respectively). There was no trend for the D_1/D_2 ratio to be greater in the atypical antipsychotic drugs (0.94 ± 0.16) than in the typical (0.84 ± 0.09, $p = 0.08$). The difference in mean pKi values for the D_2 and $5HT_2$ receptor binding sites indicates that, on the average, the affinity of the atypical antipsychotic drugs for the $5HT_2$ receptor is 15.8 times greater than for the D_2 receptor, whereas the affinity of the typical antipsychotic drugs for D_2 receptor is 8.1 times greater than for the $5HT_2$ receptor. Thus, there is a 128.7-fold difference, on average, between these classes of drugs at the D_2 receptor relative to the $5HT_2$ receptor. Because clinical doses are related to D_2 receptor blockade (Seeman and Lee 1975)—a point that relates historically to the capacity of clinical doses to cause EPS—rather than titrated doses, these results suggest that, on average, the atypical antipsychotic drugs could produce two orders of magnitude more $5HT_2$ receptor blockade than the typical antipsychotic drugs produce.

The $5HT_2$ and D_2 receptor affinities of the seven atypical antipsychotic drugs were highly correlated (*rho* = 0.89, $p = 0.07$). The same was not true for the 13 typical antipsychotic drugs. A discriminant function analysis showed that the two classes of drugs could be distinguished on the basis of their D_2 and $5HT_2$ affinities. The D_1 affinity did not contribute to the discrimination. A linear discriminant function equation was developed and applied to 7 other typical, and 10 other putative atypical, compounds. The equation was essentially validated with this procedure. Only four drugs—loxapine, amoxapine, zotepine, and HP-370—were incorrectly identified by class of antipsychotic drugs. Zotepine probably should have been classified as typical on the basis of available clinical data. HP-370 was subsequently found to be less potent in vivo at $5HT_2$ receptors than would have been predicted by the in vitro data (H.Y. Meltzer, and C.A. Stockmeier, unpublished data). For all 17 atypical antipsychotic drugs, the correlation between $5HT_2$ and D_2 receptor pKi values was highly significant (*rho* = 0.85; $p = 0.0001$). The importance of $5HT_2$ antagonism to the action of CLOZ has also been discussed by Altar et al. (1986).

Additional atypical antipsychotic drugs that have a greater affinity for the $5HT_2$ receptor binding sites than for the D_2 receptor binding sites have been identified: ORG-5222 (Tonnaer et al. 1990), ICI-204636 (Fabre et al. 1990), SM-9018 (Hirose et al. 1990), and risperidone (Leysen et al. 1988; Castelao et al. 1989). Early clinical data on these compounds are consistent with the view that they have some CLOZ-like features, especially low EPS at clinically effective doses. However, some of them (e.g., risperidone) do increase serum PRL levels in humans; CLOZ does not do so in humans (Meltzer et al. 1979*a*), but it does in rats (Meltzer et al. 1975). There is evidence that some atypical antipsychotic drugs with high potency at $5HT_2$ receptors are effective in neuroleptic-resistant schizophrenia—for example, amperozide (A. Bjork, personal communication, December 16, 1990) and melperone (Meltzer et al. 1989*a*).

It is beyond the scope of this review to discuss why $5HT_2$ receptor blockade might be so significant. I have discussed elsewhere some of the evidence in terms of the ability of $5HT_2$-dependent neurotransmission to modulate dopaminergic activity as well as the role of $5HT_2$ receptor stimulation in hallucinations (Meltzer 1988, 1989, 1990). It is noteworthy that the $5HT_2$ receptor antagonist ritanserin, which does not occupy striatal or limbic D_2 receptors in vivo (H.Y. Meltzer and C.A. Stockmeier, unpublished observations), dose-dependently increased the firing rate and burst firing of A9 and A10 DA neurons (Ugedo et al. 1989). This finding could be relevant to the ability of atypical drugs such as CLOZ to maintain DA release; it is based on the connections between the midbrain raphé and DA cells in the A9 and A10 regions (Dray et al. 1976; Fibiger and Miller 1977; Hervé et al. 1979, 1981, 1987; Imai et al. 1986; Nedegaard et al. 1988). The importance of $5HT_2$ receptors for schizophrenia is supported by the evidence that $5HT_2$ receptor density is decreased in frontal cortex of patients with schizophrenia (Mita et al. 1986; Arora and Meltzer, in press) and that the cortisol and PRL responses to MK-212 are blunted in

schizophrenia (Lee et al., unpublished observation). Perhaps increased serotonergic activity in schizophrenia leads to down-regulation of $5HT_2$ receptors although 5HT transmission is still increased. CLOZ and other atypical drugs may further decrease 5HT neurotransmission by virtue of their potent antagonism of $5HT_2$ receptors.

Effect of Atypical Antipsychotic Drugs on $5HT_3$ Receptors. There is recent evidence that stimulation of $5HT_3$ receptors on DA nerve terminals can increase DA release (Blandina et al. 1988). Therefore, $5HT_3$ antagonists would be expected to have an antipsychotic effect by decreasing DA release. A similar strategy underlies the development of DA autoreceptor agonists. CLOZ has been found to have a moderate action as a $5HT_3$ antagonist (Ashby et al. 1989; Watling et al. 1990). The importance of this effect for the action of CLOZ is unknown at present. Clinical trials with specific $5HT_3$ antagonists such as odansetron may clarify the value of $5HT_3$ antagonism for schizophrenia. The effect of indirect DA agonists can be blocked by $5HT_3$ antagonists in vivo (Costall et al. 1987). Chronic administration of the $5HT_3$ antagonist MDL-73147EF decreases the activity of A9 and A10 DA neurons (Sorensen et al. 1989). However, even if "pure" $5HT_3$ receptor antagonists are not effective as antipsychotic drugs, $5HT_3$ receptor antagonism could contribute to the unique effects of CLOZ by acting on those DA neurons with $5HT_3$ heteroreceptors that stimulate DA release.

Adrenergic Mechanisms of CLOZ. CLOZ had moderately potent antagonist effects at $alpha_1$ (Peroutka et al. 1977), $alpha_2$ (Perry et al. 1983), and beta-adrenergic receptors (Gross and Schümann 1982). Lane et al. (1988) reported that the combination of HPL and prazosin, an $alpha_1$-noradrenergic antagonist given for 21 days, mimicked the effect of CLOZ to selectively decrease DA release in the nucleus accumbens as measured by in vivo voltammetry. They suggested that this finding indicated the importance of $alpha_1$-noradrenergic blockade for the selective effect of CLOZ on the mesolimbic DA neurons. These results need to be replicated with in vivo methods that do not use anesthetized animals. Chronic administration of CLOZ leads to a down-regulation of $alpha_1$ (Cohen and Lipinski 1986) and beta (Gross and Schümann 1982) adrenergic reports. These effects, plus an inhibitory effect on norepinephrine (NE) reuptake, lead to an increase in NE turnover (Bartholini et al. 1973; McMillen and Shore 1978). There is no evidence yet that these effects of CLOZ on noradrenergic mechanisms are related to its unique clinical features. For example, its effects on $alpha_1$ receptor binding are shared by fluphenazine (FLU), HPL, CPZ, and thioridazine. However, there is increasing evidence that enhanced noradrenergic activity does contribute to some aspects of schizophrenia, for example, intensification of negative and positive symptoms (van Kammen et al. 1990). Therefore, it is possible that blockade of adrenergic receptors may have some clinical relevance.

Cholinergic Mechanism of CLOZ. CLOZ is a potent antimuscarinic agent: Ki = 5.5×10^{-8} M, versus 1.3×10^{-9} M for benztropine (Miller and Hiley 1974). It has been suggested that this potency may account for the low EPS with CLOZ (Miller and Hiley 1976). The discriminative stimulus provided by CLOZ is related to its anticholinergic properties (Nielsen 1988). CLOZ, like trihexyphenidyl and benztropine, decreased striatal acetylcholine content without increasing the turnover rate of acetylcholine; both CLOZ and trihexyphenidyl reversed the increase in the turnover of striatal acetylcholine elicited by HPL—further evidence that the low EPS produced by CLOZ could be due to its anticholinergic properties (Racagni et al. 1976). However, it is also possible that the latter effects are related to its $5HT_2$ antagonist effects.

Friedman et al. (1983) reported that 12 weeks of CLOZ administration increased (1) muscarinic binding of [^{3}H]quinuclidinyl genzilate in mouse striatum, cortex, and hippocampus and (2) striatal choline acetyl transferase activity. These effects contrasted with those of FLU. Chronic CLOZ did not alter FLU- or pilocarpine-induced catalepsy. This pattern of effects was attributed to its antimuscarinic effects and suggested to be related to its inability to induce TD. The inability of CLOZ to upregulate D_2 receptors in striatum (Rupniak et al. 1985*b*) was found not to be due to its anticholinergic properties, because the combination of fluphenazine decanoate (FD) and atropine or trihexyphenidyl did not block the upregulation of striatal D_2 receptor binding observed after administration of FD alone (Boyson et al. 1988). Coadministering CLOZ with HPL failed to block both the development of behavioral hypersensitivity and the increase in striatal DA turnover and D_2 receptor binding sites induced by HPL alone (Carvey et al. 1990*b*). CLOZ is thereby distinguished from thioridazine, benztropine, and other anticholinergic drugs which blocked HPL-induced DA receptor supersensitivity

without increasing D_2 receptor binding (Carvey et al. 1986, 1988, 1990*a*).

Rubinstein et al. (1989) found no effect of 12 months' treatment with CLOZ or HPL on the carbachol-induced increase in phosphoinositide hydrolysis. They concluded that effects on cholinergic mechanisms do not explain the difference between these drugs with regard to TD or EPS.

These results provide little support for the view that the unique features of CLOZ with regard to EPS, TD, and antipsychotic efficacy are due to its anticholinergic properties. Administering large doses of cogentin with HPL or CPZ did not achieve the same effects as CLOZ on EPS, positive symptoms, or negative symptoms (Kane et al. 1988).

CLOZ and GABAergic Mechanisms. Drew et al. (1990) recently reported that when in vivo microdialysis was used, acute CLOZ increased GABA release in the fundus striati (a region of the ventral striatum) but not in the globus pallidus in halothane-anesthetized rats. The effects of chronic HPL treatment on GABA release were the opposite in these two regions. Both drugs increased GABA release in the dorsolateral striatum (caudate putamen). Both drugs increased DA more than GABA in both regions of the striatum. Drew et al. (1990) suggested that the differential effects on GABA release could account for the superior antipsychotic effect of CLOZ and the high EPS of HPL. They attributed the ability of CLOZ to increase GABA release in the striatum to its D_1 antagonism. However, no evidence was offered to relate the antipsychotic effect of CLOZ to the release of GABA in the ventral striatum. GABAergic drugs have rarely been found effective in schizophrenia, either alone or in addition to neuroleptic drugs (Meltzer 1986).

CLOZ and Glutamatergic Mechanisms. The possible role of glutamatergic effects in the action of antipsychotic drugs will be discussed subsequently. It has recently been reported that CLOZ and another putative atypical antipsychotic drug, Umespirone, selectively block the stereotyped behavior produced by the NMDA antagonist DL-2-amino-5-phosphonovaleric acid AP-5 (Schmidt et al. 1991). Typical neuroleptic drugs are also effective but they also block DA agonist-induced stereotyped behaviors. This suggests the possible importance of a selective enhancement of glutamatergic activity by atypical antipsychotic drugs.

CLOZ and Neuropeptides. A few studies of the effect of CLOZ on neuropeptides have been done. CLOZ had no effect on striatal met-enkephalin levels (Hong et al. 1978), but it did alter substance P in the substantia nigra and striatum, and dynorphin A and B in the substantia nigra (Nylander and Terenius 1986). The effects of HPL were quite different (Hong et al. 1978; Nylander and Terenius 1986). It was suggested that these differences are related to the differences in EPS produced by the two drugs, but no specific evidence linking these effects on peptides to EPS was presented.

Both chronic CLOZ and HPL were reported to increase neurotensin-like immunoreactivity in the nucleus accumbens and to decrease it in the medial prefrontal and cingulate cortex and in the interstitial (bed) nucleus of the stria terminals. However, only HPL increased this material in the caudate. It was suggested that this latter difference may have developed from the different pattern these drugs have on DA release in the caudate and that it may be relevant to their difference in EPS, but again, no convincing evidence for this linkage was presented.

Chronic administration of HPL significantly decreased preprosomatostatin mRNA in neurons of the nucleus accumbens, frontal cortex, and medial—but not lateral—striatum. On the other hand, chronic CLOZ increased mRNA for preprosomatostatin in the nucleus accumbens but not in the striatum or the frontal cortex (Salin et al. 1990). It was suggested that somatostatin may be related to motor function. Merely presenting differences between CLOZ and a typical antipsychotic drug is not a sufficient basis for relating it to differences in the behavioral effects of CLOZ and typical antipsychotic drugs.

Conclusions. The biological basis for the special advantages of CLOZ has been greatly illuminated by recent studies; it is no longer possible to accept selective depolarization inactivation of the A_{10} neurons as the sole basis for the antipsychotic action of CLOZ, which exceeds that of typical neuroleptic drugs that produce the same effect. Evidence points toward increased DA release in the prefrontal cortex and maintenance of dopaminergic activity in the mesolimbic and mesocortical DA neurons as being of key importance. The strong effect of CLOZ to block $5HT_2$ receptors may contribute to those effects.

Substituted Benzamides

Substituted benzamides, of which sulpiride is the most widely known, are clinically effective antipsychotic

agents with possible advantages with regard to EPS. The clinical profile of substituted benzamides is reviewed elsewhere in this issue (Gerlach 1991). Their mechanism of action appears to be D_2 receptor blockade, because most of them, but not all, lack significant affinities for other types of monoamine receptors (Jenner and Marsden 1986). The advantages of these compounds, if any, are believed to lie in their relative specificity for limbic versus striatal D_2 receptors, including the possibility that they may act only on a subgroup of striatal D_2 receptors (Köhler et al. 1984). It has also been suggested that some of their uniqueness may be related to an action of D_3 receptors (Sokoloff et al. 1990).

There is evidence that sulpiride has a greater ability to increase DA turnover in the mesolimbic system, and that it preferentially blocks apomorphine-induced hyperactivity rather than stereotypy (Fuxe et al. 1977; Costall et al. 1987). It has been reported to preferentially block D_2 receptor binding in vivo in the olfactory tubercle and septum rather than in the striatum (Köhler et al. 1979, 1984). A similar profile has been reported for remoxipride (Ögren et al. 1983). These compounds produce weak effects on catalepsy (Jenner and Marsden 1979; Ögren et al. 1983).

There is some evidence that the substituted benzamides may have a greater potency to block specific types of D_2 receptors. Thus, Meltzer et al. (1979*b*) reported that sulpiride was markedly more potent in its ability to stimulate rat PRL secretion than would be predicted on the basis of its ability to bind to D_2 receptors in the pituitary or striatum. A specific [^{3}H]-sulpiride binding site distinct from the [^{3}H]-spiperone binding site was described in rat striatum by Theodorou et al. (1983). [^{3}H]-sulpiride has also been reported to bind to two striatal sites that classical neuroleptics do not compete for (Memo et al. 1980; Spano et al. 1980). This conclusion was challenged by Zahniser and Dubocovich (1983), who found that [^{3}H]-spiperone and [^{3}H]-sulpiride identified the same number of sites in striatal membranes in vitro. However, the possibility of in vivo differences is not thereby ruled out in the binding of benzamides versus typical neuroleptics of the butyrophenone and phenothiazine series. The greater potency to block limbic versus striatal behaviors in vivo (Ljunberg and Ungerstedt 1978) favors the latter possibility.

Remoxipride and amisulpride are the two benzamide drugs most likely to be available in the United States within the next 5 years. Remoxipride may be distinguished by its potency for the sigma binding site, which is higher than that for the D_2 site—0.06 μM for the [^{3}H]-3PPP site versus 0.97 μM for the [^{3}H]-spiperone site (Köhler et al. 1990). Whether the binding to this site is important to the antipsychotic action of remoxipride is unknown. It may be an agonist or an antagonist. Remoxipride has been shown to bind to subgroups of D_2 receptors in the rat striatum and to be particularly potent at blocking septal D_2 receptors in vivo (Köhler et al. 1990). This selectivity may contribute to its possible clinical advantages.

D_1 Receptor Antagonists

The pharmacology of the D_1 receptor has been extensively reviewed by Clark and White (1987). Only selective aspects are considered here. The interest in the D_1 receptor with regard to schizophrenia has been whether selective D_1 receptor antagonists might have advantages as antipsychotic agents and whether D_1 receptor antagonism contributes to the atypical aspects of the action of CLOZ. The latter issue has been considered previously and is not further discussed here.

Much of our understanding of the functional significance of D_1 receptor blockade is based on studies with SCH-23390, a compound that has strong D_1 affinities and weak D_2 affinities but that also has moderate potency for the $5HT_2$ receptor (Meltzer et al. 1989*c*). This property could influence its behavioral effects, particularly on the motor system, because $5HT_2$ antagonism is known to diminish catalepsy. Low doses of SCH-23390 reduce locomotor activity; inhibit conditioned avoidance responding in rats and squirrel monkeys without impairing the escape response; diminish intracranial self-stimulation; and can block the hyperlocomotion, stereotypies, or grooming behavior produced by selective D_2 or D_1 agonists (see Clark and White 1987 for review). However, they also produce catalepsy. This profile suggests that selective D_1 antagonists should be effective antipsychotic agents but that they could also produce EPS. The combination of subthreshold doses of a D_2 antagonist, (−)-sulpiride, and D_1 antagonist, SCH-23390 effectively blocked apomorphine-induced stereotypy, hyperactivity produced by the D_2 agonist LY-171553, and basal exploratory activity (Dall'Olio et al. 1989). These results suggest that D_1 and D_2 antagonism can potentiate each other, at least at threshold doses.

Several recent studies indicate the complex interaction between D_1 and D_2 receptors. Parashos et al. (1989) reported a synergistic effect between SCH-23390 and the D_2 antagonist raclopride on catalepsy in rats. The

authors speculated that this synergy might also apply to the antipsychotic effect of the two drugs, but there is, in fact, no evidence that the D_1 receptor affinities of the available neuroleptic drugs modify their potency to produce EPS or an antipsychotic effect. Parashos et al. (1990) reported complex effects of D_1-mediated effects on grooming behavior following chronic administration of SCH-23390, HPL, or the combination. Murray and Waddington (1989) reported that the D_2 agonist LY-163502, in the presence of the D_1 antagonist R-SKF-83566, induced episodes of limb- or body-jerking behavior or both, at the same time the stimulatory effects of LY-163502 on sniffing and locomotion were blocked. The former effect was considered evidence for an inhibitory effect of D_1 receptor stimulation on D_2-mediated behaviors, whereas the latter was considered evidence for a cooperative effect. Only clinical trials will tell if there is value to diminishing dopaminergic activity selectively without blockade of D_2 receptors. This point is particularly true if there is any validity to the evidence that at least some schizophrenic patients have increased numbers of D_2 receptor in the striatal or limbic system, or both.

DA Autoreceptor Agonists

The strategy behind developing drugs that are selective agonists at DA autoreceptors has been reviewed elsewhere (Meltzer 1980; Carlsson 1988*b*). Briefly, DA autoreceptors are present on the cell bodies and nerve terminals of some, but not all, dopaminergic neurons. DA autoreceptors have at least three distinct regulatory functions: inhibition of DA synthesis, release, and neuronal firing. Thus, DA nerve terminals in the prefrontal and cingulate cortex have been reported to possess autoreceptors that regulate DA release (Plantue et al. 1981; Galloway et al. 1986; Talmaciu et al. 1986), unlike mesolimbic and mesocortical dopaminergic neurons, which have few or no autoreceptors that modulate DA synthesis (Wolf et al. 1986). Some of the mesolimbic DA neurons may also lack autoreceptors (Kilts et al. 1987). Mesoprefrontal DA neurons have synthesis-regulating autoreceptors (Fadda et al. 1984). Mesocortical DA neurons possess impulse-modulating somatodendritic autoreceptors (Wolf et al. 1987). The differences in autoreceptor type among the mesoprefrontal, mesocingulate, and other DA neurons (nigrostriatal, mesolimbic, and mesopyreform) may be the basis for differences in basal DA activity among these neuronal groups and their response to DA agonists and antagonists (Wolf et al. 1987).

DA autoreceptor agonists that are highly selective relative to their ability to stimulate postsynaptic DA receptors have been found to produce fewer EPS in laboratory animals than neuroleptic drugs (Carlsson 1988*b*). Nor do they appear to have the same liability to produce the primate model of TD.

Various drugs are being tested as DA autoreceptor agonists with the main aim of achieving selective decreases in dopaminergic activity in the mesolimbic region: 3-(-3-hydroxyphenyl)-N-n-propylpiperidine (Hjorth et al. 1981), U-66444B and U-68553B (Piercy et al. 1990); SND-919; BHT-920; and PD-128483.

Partial DA Agonists

Partial agonists are, by definition, agents that do not produce a full agonist effect at a receptor. Their ability to stimulate the receptor is characterized by their intrinsic activity, which is always less than that of the full agonist. Because they cannot elicit as great a response as the full agonist, they may act as partial antagonists under situations in which the full agonist effect might otherwise be expressed. Thus, the partial DA agonist SDZ-208911 produces only weak catalepsy but can block apomorphine-induced gnawing behavior 100 percent, even at low doses (Coward et al. 1990). On the other hand, they can produce at least a partial agonist effect under conditions in which little or no other agonist is present, such as low concentrations of a neurotransmitter. SDZ-208911, like apomorphine, produces contralateral circling in rats with 6-OHDA lesions of the substantia nigra. It also decreases rat serum PRL levels (Coward et al. 1990).

Thus, a partial DA agonist may produce excitation or inhibition of neurons postsynaptic to dopaminergic neurons, depending on the concentration of DA at the synapse and the intrinsic activity of the partial agonist. This type of compound appears to be of particular interest for schizophrenia in that it might be expected to diminish activity in the mesolimbic system, which is believed to have excessive dopaminergic activity in schizophrenia (Meltzer and Stahl 1976) and, conversely, might stimulate dopaminergic activity in the mesocortical dopaminergic system, which had been suggested to be hypodopaminergic (Mackay 1980). A number of partial DA agonists are currently being tested in patients with schizophrenia—for example, SDZ-911 and SDZ-912 (Coward et al. 1990). Preliminary results of open trials with SDZ-912 have been prom-

ising—for example, they have shown effective antipsychotic action with fewer EPS (see Gerlach 1991, this issue), but controlled trials are needed to support these observations.

Mesohippocampal DA System

The possibility that the hippocampus may be abnormal in schizophrenia has been intensively explored in recent years. Increasing interest has focused on the hippocampus as a possible disease locus in schizophrenia. Postmortem (Stevens 1973; Bogerts et al. 1985) as well as magnetic resonance imaging (MRI) studies could have identified hippocampal abnormalities in schizophrenia. These abnormalities could be particularly relevant to memory disturbance dysfunction in schizophrenia. Bischoff (1986) has suggested that selective blockade of DA receptors in the hippocampus, sparing DA receptors in the striatum, might produce an atypical antipsychotic drug. Savoxepine was developed to selectively block D_2 receptors in the hippocampus, based on a slower dissociation from hippocampal binding sites than from striatal binding sites (Bischoff et al. 1986). Clinical data are still insufficient to evaluate this strategy.

Sigma and PCP Receptor Antagonists

Martin et al. (1976) suggested that the psychotomimetic effects of certain opiate compounds—for example, pentazocine and N-allylnormetazocine (SKF-10047) (Telford et al. 1961; Haertzen 1970)—were due to an action at a unique opiate receptor. The action of these agents in rodents was not blocked by naloxone and its stereospecificity was different from that of the classical opioid analgesics, that is, the analgesic effect was more potent for the (−)- than the (+)-isomer. Subsequently, it was suggested that the psychotomimetic effect was due to the (+)-isomer (Largent et al. 1984; Deutsch et al. 1988; Steinfels et al. 1988). This view has now been challenged.

The psychotomimetic effects of PCP are well known; originally, they were partially attributed to PCP's indirect DA agonist properties (Meltzer et al. 1981). Subsequently, PCP was shown to bind with high affinity and saturability to a unique binding site, and the behavioral effects of a series of related drugs were found to correlate with its affinity for this site (Vincent et al. 1979; Zukin and Zukin 1979). The hypothesis of Zukin and Zukin (1981) that there was a single sigma/PCP recognition site for both types of agents was supported by various types of evidence (Quirion et al. 1981; Itzhak et al. 1985). Subsequently, a unique site for the sigma opiate compounds, not related to the PCP site, was suggested by Su (1981) on the basis of the binding of the ligand [^{3}H]SKF-10047. This view was supported by subsequent studies with (+)-[^{3}H]SKF-10047, which identified the sigma site as having high affinity for this ligand, and the PCP site as having low affinity for it. The PCP site has been shown to be located within the Ca^{++} channel gated by the NMDA subtype of the glutamate receptor complex and to close the channel (Westbrook and Jahr 1989). PCP-type drugs have been shown to act as noncompetitive NMDA antagonists in electrophysiological studies (Lodge et al. 1988), neurochemical studies (Johnson 1987), and behavioral studies (Koek et al. 1990).

This literature was recently reviewed by Musacchio (1990), who challenged the view that the psychotomimetic effects of SKF-10047 are due to the (+)-isomer and its related high-affinity binding site. According to Musacchio (1990), the current concept is that the sigma site binds nonpsychotomimetic (−)-isomers of opioids with greater affinity than the (+)-isomers and is identical to that of the high-affinity binding site for dextromethorphan and other antitussives. The sigma site has the following ligand affinity rank order: HPL, 1,3-d:(2-tolyl)guanidine (DTG), 3-(3-hydroxyphenyl)-N-(1-propyl) piperadine (3-PPP), (−)-cyclazocine, and SKF-10047 (Quirion et al. 1987). Musacchio (1990) cited evidence that psychotomimetic opioids such as nalorphine, cyclazocine, and MR-2034 are blocked by naloxone (Jasinski et al. 1968; Pfeiffer et al. 1986), suggesting that their action is linked to classical opioid-binding sites. The fact that HPL is a very potent sigma antagonist (IC_{50} 1.9 ± 0.3 nM) (Schmidt et al. 1989)—as are some of its metabolites (Bowen et al. 1990)—but lacks any unique antipsychotic properties also casts some doubt on the importance of the sigma mechanism for psychosis. There is also some evidence that effects at sigma receptors may influence the EPS produced by HPL and other typical neuroleptics with potent affinity for the sigma receptor (Bowen et al. 1990).

Nevertheless, studies are under way to test drugs with moderate to high affinity for the sigma site—for example, BMY-14802 (Taylor and Dekilva 1987), HR-375 (Hock et al. 1985), and remoxipride (Snyder and Largent 1989)—as antipsychotic agents. Remoxipride, however, also has moderate D_2 blocking properties (Ögren et al. 1983). We have ob-

tained similar results with CLOZ. That these drugs are active in animal models suggests antipsychotic activity. Despite intensive effort, no good clinical candidates have emerged from drug discovery programs to identify specific PCP antagonists.

In summary, the efforts to develop effective antipsychotic drugs that are sigma or PCP antagonists have yielded a few promising candidates of the former type, but except for remoxipride (Farde et al. 1988*a*), which may be effective as an antipsychotic because of its D_2 antagonist properties, data are insufficient to determine whether any of the sigma antagonists are clinically effective.

Glutamatergic Mechanisms and Antipsychotic Drug Action

Several different theories have been proposed linking the excitatory amino acid glutamate to schizophrenia (Javitt and Zukin 1990). Kim et al. (1980), on the basis of low levels of glutamate in the cerebrospinal fluid (CSF) of schizophrenic patients, proposed that decreased glutamatergic activity in the corticostriatal and corticomesolimbic glutamatergic systems might lead to increased dopaminergic activity in these areas. That the direction of the influence might be the opposite however (i.e., increased dopaminergic activity leading to decreased glutamatergic activity), could not be excluded (Mitchell and Doggett 1980). A significant negative correlation between CSF concentrations of glutamate and homovanillac acid (HVA), the major metabolite of DA, has been reported in normal volunteers (Alfredsson et al. 1988). Various postmortem findings suggest glutamatergic abnormalities in schizophrenia (Nishikawa et al. 1983; Kerwin et al. 1988; Deakin et al. 1989; Kornhuber et al. 1989). The ability of PCP to antagonize NMDA receptors has already been noted.

It has been suggested that antipsychotic drugs may act, in part, by increasing glutamatergic activity, which would, in turn, inhibit dopaminergic activity (Gattaz et al. 1982; Kim et al. 1983). Carlsson (1988*a*) suggested that diminished activity of the corticostriatal glutamatergic pathway might lead to sensory overload of the frontal cortex by disinhibiting the DA-dependent thalamic filter that gates input to the frontal cortex. This theory suggests that glutamatergic drugs might have therapeutic potential in schizophrenia. The possible role of a selective increase in glutamate activity by CLOZ has been previously discussed.

Current approaches to enhancing glutamatergic activity in schizophrenia involve manipulation of the NMDA subtype of glutamate receptor. The NMDA receptor is exceedingly complex (Mayer et al. 1989). At least 12 amino acids are known to have agonist activity at this receptor. One of those amino acids, glycine, promotes the activity of the NMDA receptor complex in a variety of ways (Johnson et al. 1989). Glycine, or a proglycine agent, milacemide, is being tried as therapy for schizophrenia.

PCP has been shown to be an NMDA antagonist (Johnson et al. 1989); the PCP binding site is part of the NMDA complex, and the effects of PCP may be antagonized by NMDA agonists. Consequently, another rationale is provided for the NMDA agonist strategy.

Finally, excessive levels of glutamatergic activity may be excitotoxic (see Olney 1989 for review). It has been suggested that excessive glutamatergic activity early in development might lead to destruction of neurons that possess glutamate receptors (Olney 1989). This hypothesis suggests that neuroprotective agents may have value in schizophrenia if neurons are being damaged by excessive levels of excitatory amino acids or by altered levels of any of the agents that regulate the excitatory amino acid receptors. Various approaches to the development of such agents are discussed by Wilmot (1989). Partial glutamate agonists may be most valuable to stimulate the NMDA receptor without causing neurotoxic effects.

Conclusions and Future Directions

The unitary hypothesis that the antipsychotic effects and EPS of all antipsychotic drugs were based on DA receptor blockade in the mesolimbic and striatal systems, respectively, survived for more than three decades, despite many types of evidence that the hypothesis did not fit comfortably into this narrow mold. Specifically, the clinical profiles of CLOZ and related drugs, as well as that of the substituted benzamides, could not be easily reconciled with this view. The attempt to prop it up with arguments about regional selectivity and differences in distribution within the brain were sustainable until recently, but they are no longer convincing.

The primacy of DA in psychosis and as a target for drug action has not been superseded. Many of the new approaches reviewed here may be seen as refinements of the DA hypothesis (e.g., specific D_1 antagonists, specific D_2 antagonists, D_3 antagonists, and DA partial or autoreceptor agonists). Many of the other

neurotransmitters or neuromodulars or their receptors of current interest (e.g., $5HT_2$ and $5HT_3$ receptors, GABA, neurotensin, and glutamate) are seen as primarily modulating dopaminergic neurotransmission, although some researchers believe agents acting on these systems may influence psychosis independent of their effects on DA. There are, indeed, approaches that are only weakly or indirectly linked to DA at this time (e.g., sigma antagonists, PCP antagonists, partial glutamate agonists), but perhaps they, too, will be linked to DA in the future.

The most interesting putative antipsychotic compounds today are CLOZ and related atypical antipsychotics. CLOZ, the most intensively studied antipsychotic of this type, has a truly staggering variety of effects on multiple neurotransmitter systems, many of them with some plausible connection to antipsychotic action, low EPS, or unique effects on the neuroendocrine system. Although we have argued that it is reasonable in this situation to focus on those properties that CLOZ shares with other atypical antipsychotic drugs—for example, weak D_2 relative to $5HT_2$ antagonist effects (Meltzer et al. 1989*c*)—it is also possible that the unique pharmacologic features of CLOZ account for at least some of its special clinical profile. There is still so little literature comparing various atypical antipsychotic drugs that speculating which of its properties might not be shared by other atypical antipsychotic drugs is difficult. Indeed, a pressing need is for more clinical studies to determine which drugs share the ability of CLOZ to achieve superior antipsychotic efficacy with fewer EPS and no TD.

The next 5 years should be ample time for clinically testing the concepts reviewed in this article. We can reasonably expect to know if there are any advantages to pure D_1 antagonists, partial DA agonists, $5HT_3$ antagonists, and so on. Some of the novel concepts such as D_3 antagonists and sigma compounds may take longer to test, because the ideal compounds to test these theories have not yet been developed.

For the immediate future, compounds of the CLOZ class such as amperozide, melperone, risperidone, and ICI-204636, and substituted benzamides such as amisulpride and remoxipride (which also has sigma receptor affinity) are likely to prove at least as efficacious as typical neuroleptics, but with fewer EPS. As they are approved, they are likely to be widely accepted into clinical practice and replace the typical neuroleptic drugs.

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