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Behavioral Effects of Clozapine and Dopamine Receptor Subtypes

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JOSSELYN, S. A., R. MILLER AND R. J. BENINGER. *Behavioral effects of clozapine and dopamine receptor subtypes.* NEUROSCI BIOBEHAV REV **21**(5) 531–558, 1997.—The atypical neuroleptic clozapine (CLZ) is an extremely effective antipsychotic that produces relatively few motoric side effects. However, CLZ displays limited antagonism at the dopamine (DA) D2 receptor, the receptor commonly thought to mediate the antipsychotic activity of neuroleptics. The mechanism of action behind the efficacy of CLZ remains to be determined. Miller, Wickens and Beninger [*Progr. Neurobiol.*, **34**, 143–184 (1990)] propose a "D1 hypothesis of antipsychotic action" that may explain the antipsychotic effects of CLZ. This hypothesis is built on the interactions between D2, cholinergic and D1 mechanisms in the striatum. These authors assert that although typical neuroleptics block D2 receptors, it is through an indirect action on D1 receptors that their antipsychotic action is manifest. The extra-pyramidal side effects produced by typical neuroleptics are hypothesized to be due to an indirect action on cholinergic receptors. It is argued that the anticholinergic properties of CLZ negate the D2 (motor side effects) action of CLZ, allowing CLZ to diminish psychotic symptoms through a direct action on D1 receptors. Thus, CLZ may function as a D1 receptor antagonist in behavioral paradigms. The current paper reviews and compares the behavioral profile of CLZ to those produced by D2- and D1-selective antagonists with specific reference to unconditioned and conditioned behaviors in order to more fully evaluate the "D1 hypothesis of CLZ action". Although the actions of CLZ remain unique, they do share some striking similarities with D1 receptor antagonists especially in tests of unconditioned behavior, possibly implicating the D1 receptor in the action of this antipsychotic drug. © 1997 Elsevier Science Ltd.

Antipsychotic Schizophrenia Dopamine Behavior Clozapine

1. INTRODUCTION

IT IS well established that neuroleptic drugs owe their antipsychotic efficacy to blockade of the actions of the neurotransmitter dopamine (DA). This immediately raises important questions regarding which DA receptor(s) mediate(s) this effect. Until recently, the pharmacological classification of DA receptors has been fairly straightforward, based on their influence on adenylate cyclase activity (with D1 receptors stimulating and D2 receptors inhibiting or having no effect (157,302)). However, advances in molecular biology have expanded the DA family by identifying new members, including receptors designated D3 (288,289) and D4 (316), neither of which stimulates adenylate cyclase activity. The cloning of a novel DA receptor, the D5 receptor, that, like the D1 receptor stimulates adenylate cyclase activity (304), has further enlarged the DA receptor family (or families). Even D2 receptors have been further divided into short- and long-formed isoforms (284,311). Despite the additions to the DA family of receptors, the subtypes still may be subsumed under the original D1:D2 framework in terms of amino acid homologies and effects on adenylate cyclase activity, with D1-like receptors (D1 and D5) stimulating and D2-like receptors (D2, D3 and D4) not stimulating adenylate cyclase activity (276,286). (It is noteworthy that recent findings have identified a D1-like receptor agonist that inhibits DA-sensitive adenylate cyclase (85).)

The mechanism by which neuroleptics achieve their antipsychotic effectiveness has been attributed widely to an antagonism of the D2-like receptor (69,197,236, 277,279,280). The D2 hypothesis of neuroleptic action is predicated in large part on the observation of a high correlation between the neuroleptic daily dose and the in vitro affinity for D2-like receptors exhibited by many neuroleptic drugs (245,273). Although the so-called 'typical' neuroleptics [for example haloperidol (HAL), chlorpromazine (CPZ)] that are relatively selective for D2-like receptors (54) fall neatly on the line correlating clinical dose

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to D2-like affinity, Seeman (276), in a more recent report of this relationship, noted that clozapine (CLZ) does not fit the main correlation line by one to two orders of magnitude. Thus, the average effective daily dose of CLZ predicts a greater affinity for D2-like receptors than is actually observed.

Apart from considerations of potency, CLZ has a different clinical profile from typical neuroleptics. The 'atypical' neuroleptic CLZ produces limited acute extrapyramidal side-effects (EPS; such as Parkinson or dyskinetic symptoms) or tardive dyskinesia (TD) following chronic use as compared to typical neuroleptics (49,115). These adverse effects are known to contribute to non-compliance with typical neuroleptic medication, which occurs in up to 40% of patients suffering from schizophrenia (180). Furthermore, while the affinity of CLZ for the D2-like receptor is only one-tenth that of CPZ (236,276), CLZ is, none the less, deemed superior to CPZ in the treatment of symptoms in a subset of treatment-resistant schizophrenic patients (55,103,153). CLZ is 'significantly superior' to HAL, a drug with a much higher affinity for D2-like receptors, in the treatment of positive symptoms and 'slightly better' in the treatment of negative symptoms of schizophrenia (37).

The atypicality of CLZ is not limited to the clinical profile but extends to the pharmacological properties as well. CLZ displays a unique neuropharmacological profile, possessing a relatively high affinity for D4, histaminergic (H1), muscarinic, serotonergic (5-HT_2), and alpha-1-adrenergic receptors, moderate affinity for D2, D1, D5, alpha-2-adrenergic and 5-HT_3 receptors while producing a weaker blockade of 5-HT_{1A} receptors (3,69,202,245,275,276,316). Positron emission tomographic (PET) scans reveal that CLZ, at clinically effective doses, occupies D1-like and D2-like receptors in roughly equal proportion. However, CLZ occupies fewer absolute D2-like receptors than do typical neuroleptics (94–96). Specifically, the D2-like receptor occupancy for CLZ is 40% lower for 300 mg/day than with other typical neuroleptics like HAL (86%, 12 mg/day) or CPZ (80%, 200 mg/day). Even with a much higher dosage of CLZ (600 mg/day), the D2-like receptor occupancy is increased to only 65% (96). Of interest, a D1-like-occupancy rate 40% greater than that so far seen with other drugs was observed in one subject receiving CLZ. Overall, since CLZ displays a greater clinical potency than is predicted from its D2-like antagonism and a qualitatively different action from D2-like blocking drugs, the D2 hypothesis of antipsychotic drug action must be questioned.

The mechanism behind the lack of EPS/TD exhibited by CLZ despite antipsychotic potency is the subject of much speculation. It is suggested, for instance, that the antimuscarinic action of CLZ might diminish the EPS normally arising from the DA antagonism produced by CLZ (202,287). An inverse relationship between the affinity displayed by most neuroleptics for the muscarinic receptor and their propensity to elicit EPS supports this view (287). Alternatively, the low incidence of EPS induced by CLZ may be a reflection of a unique and preferential binding to the mesolimbic, rather than the nigrostriatal, DA system (17,30). Results both upholding and opposing this second speculation are reported (3,51,111,281,328).

More recent explanations implicate two newly identified DA receptor subtypes in the distinct action of CLZ. Sokoloff et al. (288) put forward the D3 receptor as a potential target for CLZ. However, Van Tol and colleagues (316) point out that CLZ displays a much greater affinity for the newly cloned D4 receptor than for either D2 or D3 receptors. D4 and/or D3 receptors may contribute to the unique action of CLZ, but thus far, no experimental data have been reported that support this hypothesis. Further investigations centered on these newer DA subtypes are required.

In addition, Meltzer (191) argues that an important mechanism of action of CLZ may involve the interaction between 5-HT_2 and D2-like receptors. Although CLZ exhibits a high affinity for 5-HT_2 receptors, its unique combination of having an effective antipsychotic action without producing extrapyramidal side-effects is not mimicked by ocaperidone, a drug that exhibits a strong affinity for 5-HT_2 and D2-like receptors (227). To clarify the importance of this interaction in antipsychotic action of CLZ, further study is necessary. It is not the purpose of the present paper to contrast the possible roles of DA and 5-HT in the action of CLZ. That would further lengthen this work. Instead, the present focus will be on the possible influence of CLZ on DA receptors.

An explanation for the unique profile of CLZ is offered by Miller, Wickens and Beninger (201), who integrate pharmacology and brain mechanisms to propose a 'D1 hypothesis of antipsychotic action'. The hypothesis is based on the interaction of D2-like, cholinergic and, ultimately, D1-like receptors. A dopaminergic–cholinergic interaction in the striatum has long been recognized. Activation of D2-like receptors inhibits intrinsic cholinergic activity and acetylcholine (ACh) release (78,128,266,296). Activation of D1-like receptors, however, either has no effect (310) or increases ACh release (76). Thus, antagonism of D2-like receptors increases cholinergic tone (128). Miller et al. suggest that increasing cholinergic tone and subsequent motor impairment decreases the firing rate of midbrain DA 'reward' neurons, resulting in a decreased activation of the D1-like receptor. In this scheme, D1-like receptors are suggested to be the ultimate mediators of reward signals, with D2-like receptors (via an action on cholinergic tone) mediating motor performance. The reduction of firing of midbrain DA neurons envisaged to be produced with D2-like antagonists is hypothesized to reduce the rewarding impact of stimuli by an indirect route.

An etiological hypothesis of schizophrenia is also put forward, suggesting that much of the symptomatology of psychotic phases is an exaggeration and distortion of the reward function (21,197,198). Therefore reduction of the rewarding impact of stimuli, whether produced by direct or indirect means, should permit 'extinction' of schizophrenic symptoms. Miller and colleagues hold that the reduction of activation at D1-like receptors is the crucial mode of action in the antipsychotic effect of neuroleptics and it is through D1-like receptors that D2-like receptor blockers indirectly produce their reward-blunting and, hence, antipsychotic consequences.

To summarize, the net outcome of D2-like antagonism is an increase in cholinergic function (leading to parkinsonian rigidity) and an indirect decrease in D1-like receptor stimulation (leading to anti-reward and 'extinction' of psychotic delusions). In contrast, D1-like antagonists should directly decrease activation at D1-like receptors inducing anti-reward effects, but not motor side-effects. It is well known that there is a complex synergistic interaction

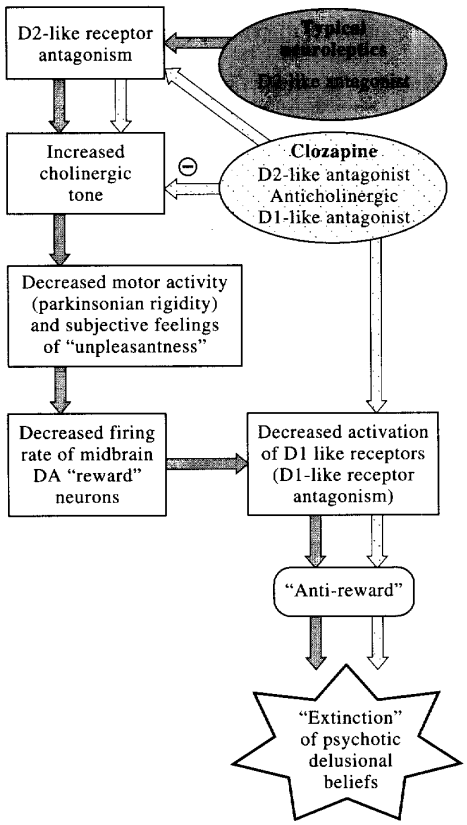

FIG. 1. Schematic diagram of the D1 hypothesis of antipsychotic drug action. Typical neuroleptics, that are basically D2-like antagonists, block D2-like receptors. This increases cholinergic tone in the striatum which leads to decreased motor activity or parkinsonian-type rigidity and a decrease in the firing of midbrain DA neurons. In turn, this decreases activation at D1-like receptors, leading to an 'antireward' state. A reduction of the rewarding impact of stimuli, whether produced by direct or indirect means, should permit the 'extinction' of schizophrenic symptoms. In summary, D2-like antagonists produce extrapyramidal side-effects (EPS) through an indirect action on cholinergic receptors and antipsychotic effects through an indirect action on D1-like receptors. In contrast, the atypical antipsychotic CLZ antagonizes D2-like and cholinergic receptors, in addition to D1-like receptors. Thus, the EPS that may be produced by CLZ are counteracted by decreasing cholinergic tone. Therefore, CLZ may produce antipsychotic effects through a direct action on D1-like receptors.

between D1-like and D2-like receptors shown for a variety of DA-related behaviors (201). Seeman and colleagues (280a), on the basis of experiments on homogenized striatal tissue, have suggested that there may be interaction between these two receptor classes at the level of subcellular biochemistry. However, a recent study, using membrane fractions (186a), fails to confirm this. There is no direct evidence that such intracellular interaction occurs in vivo. The hypothetical interaction between the two receptor types upon which the indirect antireward effects of D2-like agonists is envisaged to occur at the macroscopic level in the free-moving intact animal, mediated by motor performance effects. It provides an alternative explanation for the well known synergy between DA receptor types. CLZ binds to D1-like, D2-like and cholinergic receptors. From the above, it follows that the anticholinergic activity of CLZ may negate its D2-like effects. Thus, CLZ may function as a D1-like receptor blocker, decreasing the reward signal by a direct action on D1-like receptors and consequently decreasing schizophrenic symptoms without producing motor impairments (see Fig. 1).

Although some aspects of the above schema have not yet been demonstrated empirically, recent work by McEvoy et al. (187) lends strong support to the idea that classical neuroleptic drugs act indirectly. These drugs produce effective antipsychotic actions at doses closely related to the dose that produces minimal motoric rigidity (187). According to this hypothesis of the indirect antipsychotic action of D2-like blocking drugs, we would expect that both D1-like and D2-like blockers should produce antipsychotic effects. For drugs that have some affinity for both receptor types, the receptor that determines clinical potency would be the one for which the drug has the greatest absolute affinity. Of the antipsychotic drugs currently used, only CLZ has a higher absolute affinity for the D1-like than the D2-like receptor (and then only slightly higher). This explains why antipsychotic potency does not correlate with D1-like receptor affinity.

It would be expected from this hypothesis that D1-like antagonists produce antipsychotic effects. Admittedly, there is as yet no unequivocal evidence for this supposition. Although Gessa et al. (118) report that SCH 23390 fails to demonstrate 'antipsychotic' efficacy in humans, this work describes the short-term effect of acute injections of SCH 23390 in psychosis, an inadequate test of antipsychotic potency. Preliminary trials with the longer acting D1-like antagonist SCH 39166 similarly were negative but the drug may have had aversive side-effects (79,81,156). A recent preliminary report (114,155) suggests that the selective D1-like antagonist NNC 01-0687 has antipsychotic properties.

The 'D1 hypothesis of antipsychotic drug action' provides a theoretical framework for a re-evaluation of the differences demonstrated by typical and atypical neuroleptics in a variety of behavioral paradigms. From this, it is predicted that the atypical antipsychotic CLZ functions as a specific D1-like receptor antagonist in behavioral tests. Thus, the present paper evaluates this inference by comparing the behavioral profiles elicited by CLZ to D2-like specific antagonists (usually HAL (28)) and D1-like specific antagonists (usually SCH 23390 or other selective D1-like receptor antagonists (28,143,144,229,310)). Although the behavioral tests surveyed in this review are not considered to be valid models of schizophrenia, they do provide valuable experimental data regarding the behavioral effects of CLZ in living animals, and, furthermore, many tasks are used as screening or preclinical tests in the design and evaluation of potential antipsychotic medication.

A variety of D2-like antagonists are referred to below. However, the drug sulpiride (309) is not be used for comparison purposes. Although this drug is a selective D2-like antagonist, the relative lack of motor side-effects exhibited by sulpiride is unusual amongst such drugs for reasons which are not at all clear. This drug may bind to some as yet unknown other receptor, rendering sulpiride different from other D2-like blocking drugs. For instance, sulpiride binds to receptors for gamma-hydroxybutyrate (182), and so may directly reduce DA release.

TABLE 1
EFFECTS OF D2-LIKE ANTAGONISTS, D1-LIKE ANTAGONISTS AND CLOZAPINE ON UNCONDITIONED BEHAVIORS

Behavioral test	D2-like antagonists	D1-like antagonists	Clozapine (CLZ)	Conclusions
(2.1) Inhibition of spontaneous locomotor activity	+ + + +	+ + + +	+ + + +	Unable to discriminate
(2.2) Antagonism of circling behavior				
(a) D1-like agonist induced	+	+ + + +	+ + +	CLZ similar to D1-like antagonists
(b) D2-like agonist induced	+ + + +	+	+ +	CLZ similar to D1-like antagonists
(2.3) Stereotypy antagonism				
(a) Apomorphine	+ + + +	+ + + +	+ +	CLZ unique
(b) Amphetamine	+ + + +	+ + + +	+ +	CLZ unique
(c) Reserpinized stereotypy	+	+ + + +	+ + +	CLZ similar to D1-like antagonists
(d) Release of Waddington's atypical behavior				
(i) D2-like agonist plus antagonist	—	+ + + +	+ + +	CLZ similar to D1-like antagonists
(ii) D1-like agonist plus antagonist	+ + + +	—	—	CLZ similar to D1-like antagonists
(e) Grooming in mice				
(i) Reversal of SKF 38393-induced grooming	+	+ + + +	+ + +	CLZ similar to D1-like antagonists
(ii) Reversal of apomorphine-induced inhibition	+ + + +	—	—	CLZ similar to D1-like antagonists
(2.4) Catalepsy induction	+ + + +	+ + +	—	CLZ unique
(2.4.1) Selective hindlimb effects in the paw test of catalepsy	—	+ + + +	+ + + +	CLZ similar to D1-like antagonists
(2.5) Animal models of dyskinesia				
(2.5.1) Acute dyskinesia				
(a) Single administration to drug-naïve monkey	+ + +	+ +	?	More data needed for CLZ
(b) Single administration to 'primed' monkey	+ + +	+ +	—	CLZ similar to D1-like antagonists
(2.5.2) Tardive dyskinesia				
(a) Subchronic administration to monkey	+ + + +	—	—	CLZ similar to D1-like antagonists
(b) Subchronic administration to rodents	+ + + +	?	+	CLZ unlike D2-like
(2.6) Sensorimotor gating				
(a) Basal	+ +	+ +	+ +	Unable to discriminate
(b) Reversal of apomorphine inhibition	+ + + +	+ + +	+ + + +	Unable to discriminate
(2.7) Inhibition of emesis	+ + + +	—	?	More data needed for CLZ
(2.8.1) Dopamine turnover	+ + + +	+ +	+	CLZ similar to D1-like antagonists
(2.8.2) Dopamine receptor proliferation				
(a) Upregulate D2-like receptors	+ + + +	—	—	CLZ similar to D1-like antagonists
(b) Upregulate D1-like receptors	—	+ + + +	+ + + +	CLZ similar to D1-like antagonists

+ + + +: very strong effect; + + +: strong effect; + +: moderate effect; +: weak effect; —: no effect.
CLZ increased (rather than decreased) amphetamine-induced sterotypy (see text).

2. EFFECTS OF CLOZAPINE ON UNCONDITIONED BEHAVIOR

Table 1 provides a summary of the comparison of the behavioral effects of HAL (or other D2-like antagonists), SCH 23390 (or other D1-like antagonists) and CLZ in tests of unconditioned behavior.

2.1. Inhibition of spontaneous locomotor activity

Dopaminergic activity is intimately linked with ambulation: generally, manipulations of DA neurotransmission by agonists induce motor activation and stereotypy with increasing doses, whereas antagonists produce hypomotility to the point of catalepsy with higher doses (21). It is well established that the D2-like antagonist HAL (146), the D1-like antagonists SCH 23390 (72,119,132,195) or SKF 83566 (195), and CLZ (151,249) all depress spontaneous locomotor activity. Thus, these measures of the locomotor consequences of CLZ administration provide little insight into the hypothesis that CLZ would mimic D1-like receptor antagonism as this paradigm does not permit adequate discrimination between D1-like and D2-like antagonists (Table 1, 2.1).

However, a locomotor experiment could be designed to directly assess the hypothesis in question. The D1-like agonist, SKF 38393, induces diffuse and discontinuous locomotion, sniffing and rearing in animals well-habituated to the test environment similar to the behaviors emitted by naïve animals when first placed in a novel test environment (206,228). The D1-like antagonists, SCH 23390 and SKF

83566 suppress spontaneous locomotion, especially in the first hour of the test (132,195). Taken together, these findings suggest that the initial exploratory locomotion exhibited by a rat in a new environment may depend on endogenous activation of D1-like receptors. Therefore, the increase in behavioral activation provoked by SKF 38393 in a well-habituated rat may be challenged by the reference antagonists (HAL, CLZ and SCH 23390). Antagonism of this specific 'D1-like agonist syndrome' may provide a more sensitive index of DA receptor subtype antagonism. From the D1 hypothesis of antipsychotic drug action, it is predicted that the D1-like antagonist and CLZ would produce a more specific antagonism of D1-like agonist induced behavioral activation, whereas HAL would produce a more generalized blockade of behavior or reduce only some behaviors. To a limited extent, this prediction is supported by experimental evidence. Molloy and Waddington (204,205) report that the behavioral activation produced by SKF 38393 is completely blocked by SCH 23390, whereas the D2-like antagonist metoclopramide only blocks rearing and locomotor components. Unfortunately, to the best of our knowledge, CLZ has not been tested in this regard.

It is not surprising, however, that a D1/D2 distinction fails in the locomotor experiments reviewed above in light of recent electrophysiological (47), neurochemical (257) and behavioral (190,203,241,323) demonstrations of the interdependence of D1-like and D2-like receptors (27,56). Apomorphine, a mixed D1-like and D2-like agonist (28), induces hyperlocomotion in vehicle treated, as well as reserpine treated animals. However, D2-like agonists, including LY 141865, quinpirole and bromocriptine increase locomotion in normal animals but not in animals acutely treated with reserpine to remove synaptic, DA (117,145). When a behaviorally impotent dose of the D1-like agonist SKF 38393 is added to the D2-like agonist in reserpinized animals, increased locomotion results (117,145). Thus, for the D2-like activation to be expressed behaviorally, D1-like receptors must be activated as well (either by endogenous DA as in the case of normal animals or with a D1-like agonist in acutely reserpinized rats).

It follows, therefore, that selective D1-like or D2-like receptor antagonists block the behavioral effects of both D1-like or D2-like agonists in the intact animal (320,323). However, if DA neuronal function has been eliminated by 6-hydroxydopamine (6-OHDA) lesions or chronically interrupted by chronic reserpine treatment, the functional cooperation/synergism between D1-like and D2-like receptors may be severed (7,8,13,163,223,323). Thus, by depriving animals of tonic dopaminergic activity, specific behavioral examination of each receptor subtype may be possible, as exemplified by the study of circling behavior.

2.2. Antagonism of circling behavior

Animals unilaterally treated with 6-OHDA demonstrate contraversive circling to challenges by selective D1-like or D2-like receptor agonists. As a general rule, D1-like agonist-induced circling is selectively blocked by D1-like antagonists and similarly D2-like agonist-induced circling is selectively blocked by D2-like antagonists (10,27,36,54,199).

It is interesting to note that similar asymmetric rotations are observed in unmedicated research subjects with schizophrenia but not in normal control subjects (32). Furthermore, a significant correlation is found between the degree of left-turning behavior and severity of some symptoms in unmedicated schizophrenic subjects (33). Although DA hyperactivity (the presumed basis of the psychosis) is unlikely to cause asymmetry of movement by itself, it could be that the enhanced DA activity combines in some way with other factors perhaps related to the background state of vulnerability from which the psychosis develops in schizophrenia, to produce asymmetric rotations. The findings of asymmetric movements in unmedicated patients, however, provide support for the validity of circling behavior seems as a test of antipsychotic potency.

The contraversive circling induced by the D1-like agonist, SKF 38393 is preferentially blocked by the D1-like, selective antagonists SCH 23390 (11,13,104) and SKF 83566 (13). In contrast, a variety of D2-like antagonists, including HAL, pimozide, spiperidol, metoclopramide or clebopride, fail to modify D1-like agonist circling (11,13,100,104,123) except with very high cataleptic doses (11,12). Thus, D1-like antagonists dose-dependently decrease D1-like agonist-induced circling, whereas D2-like antagonists non-specifically inhibit this circling at cataleptic doses. In this preparation, CLZ inhibits SKF 38393-induced circling (13,123), thus showing a profile similar to the D1-like antagonists (Table 1, 2.2a).

Fenton et al. (100) report that HAL partially antagonizes SKF 38393-induced circling at very high doses (from roughly 80 to 40 contraversive turns in 30 min); this attenuation, however, does not exhibit dose-dependency and is only partial. In contrast, HAL induces a dose-related and more complete inhibition of apomorphine circling (from 80 to less than 20 turns in 30 min in 'low sensitivity' rats). CLZ produces a dose-dependent inhibition of SKF 38393-induced circling that is fairly strong (from 80 to less than 20 circles in 30 min). The doses of CLZ tested also induce motor impairments in non-lesioned animals on the rotorod test.

D2-like antagonist compounds display a high antagonistic potency against the circling produced by D2-like agonists. Thus, comparably lower doses of HAL and pimozide are required to block pergolide-evoked circling than are required to disrupt D1-like agonist induced circling (13,123,131). Generally, SCH 23390 fails to modify D2-like agonist-induced circling (13); however, high doses partially inhibit pergolide (11) or lisuride-induced circling (104). Herrera-Marschitz; and Ungerstedt (131) report that SCH 23390 fails to significantly inhibit pergolide-induced circling but modifies the profile by prolonging the duration of the rotational behavior, while extremely high doses decrease the maximal peak rotation. Therefore, the antagonism of D2-like agonist induced circling emerges as somewhat more complex than its D1-like counterpart as both D1-like and D2-like antagonists modify this circling. In this model, CLZ moderately inhibits D2-like agonist-induced circling (13,123), making CLZ similar to D1-like antagonists (Table 1, 2.2b).

The circling behavior induced by apomorphine has a different time course from that induced by administration of either a D1-like of D2-like agonist alone. Two peaks of maximal intensity, with the first occurring shortly after apomorphine administration and the second occurring towards the end of the drugs period of action, are observed (131). A

trough is noted between these two peaks. This profile may be the result of the mixture of influences from D1-like and D2-like agonists (see (199) for a more comprehensive discussion).

Challenge of apomorphine-induced circling by a D2-like antagonist (e.g. spiroperidol) results in a bell-shaped timer intensity curve with a single high intensity peak occurring between the two circling peaks demonstrated in control experiments (12). On the other hand, Herrera-Marschitz and Ungerstedt (131) report that SCH 23390 dose-dependently decreases the second of the two intensity peaks, while having no effect on the first peak. This finding is confirmed by Arnt and Hytell (12). Thus, in general, D2-like antagonist challenge of apomorphine-induced circling results in a bell-shaped curve with a single peak centered near the middle of the 60-min test session, whereas SCH 23390 preserves a peak at about 10 min, followed by a steady decrease in the number of turns per minute. The lone report of the time course of CLZ challenge to apomorphine-induced circling was performed by Arnt and Hytell (12). Although the actual shape of the time/intensity curve is difficult to discern, it is clear that CLZ fails to produce a bell-shaped time course (indicative of a D2-like antagonist) and may produce a curve more reminiscent of that produced by D1-like antagonists.

Thus, CLZ produces circling effects that are different from D2-like antagonists and, furthermore, may produce effects that are consistent with a D1-like antagonist function.

2.3. Stereotypy antagonism

Stereotyped behavior in rats is characterized by motor excitement, repetitive rearing, sniffing, head movements, compulsive licking and gnawing (14,105) and may be induced by non-selective DA agonists such as apomorphine or amphetamine. Although stereotypy can be a somewhat elusive variable to quantify, several groups of researchers have developed scoring systems. For instance, Costall and Naylor (64) use a five-point scale (0 = no stereotyped behavior, 1 = discontinuous sniffing, 2 = continuous sniffing, 3 = continuous sniffing, discontinuous biting, gnawing or licking and 4 = continuous biting, gnawing or licking). These authors contend that this scale represents a dosing continuum of DA agonists, with the lowest dose to reliably induce a stereotypy rating with an intensity of 4 on the scale being 2.0 mg/kg sc for apomorphine and 10.0 mg/kg ip for amphetamine. Arnt et al. (15) report that a dose of 2.5 mg/kg sc of apomorphine is the supramaximal dose required to induce the full spectrum of 'low component' stereotypy (which includes locomotor and rearing responses) as well as oral stereotypy. Ljungberg and Ungerstedt (173,174) identify two distinct components of the stereotyped behavior produced by a large dose of apomorphine (5.0 mg/kg): compulsive gnawing and increased locomotion accompanied by sniffing and repetitive movements of the head and limbs. Thus, although researchers use different operational definitions of stereotypy, it appears that these definitions seem to map on to two elements: hyperactivity and oral stereotypy.

Although it was originally thought that stereotypy was produced by postsynaptic actions of D2-like agonists (273), more recent evidence suggests that both D1-like and D2-like receptors may play important roles. Arnt et al. (15) find that the D2-like agonists, LY 163 502 and quinpirole, induce low component stereotypy, but not oral stereotypy, when administered on their own. The addition of SKF 38393 'enabled' or 'permitted' the oral stereotypy to be expressed an addition to the low component stereotypy. D1-like receptor tone seems necessary for induction of effects mediated by D2-like receptor stimulation. Murray and Waddington (212) write that the "... tonic activity of D1 receptors serves an important enabling or permissive role in the expression of D2 stimulated behavior and acts synergistically in the generation of typical compulsive stereotyped behavior" (p. 377).

Challenge with D2-like antagonists, including metoclopramide, and HAL or D1-like antagonists, including SCH 23390 and SKF 83566, similarly block the sniffing and locomotor stereotypic elements produced by a moderate dose of apomorphine (31,204,206). Higher doses of apomorphine (2.0 mg/kg) induce the full spectrum of stereotypy and this too is blocked by HAL, pimozide and fluphenazine (64) or D1-like antagonists (54,144,181). While the oral efficacy of SCH 23390 in this paradigm is questionable ((54,144), but see (53)), overall SCH 23390 (when administered ip or sc) and HAL are potent blockers of all the aspects of stereotypy induced by apomorphine.

The literature regarding the action of CLZ in the stereotypy paradigm is, at first glance, confusing. Although early reports found that orally administered CLZ displayed limited efficacy in this task (53,265), more recent research suggests that CLZ may inhibit at least some aspects of apomorphine-induced stereotypy. Thus, Costall and Naylor (64) report that low doses (10 mg/kg) of CLZ have no effect while high doses (20 or 40 mg/kg) decrease the high stereotypy scores produced by apomorphine (2.0 mg/kg). In this experiment, CLZ decreases the continuous gnawing, biting or licking to discontinuous sniffing, biting, gnawing or licking. Using a dose of apomorphine that by itself produces only limited stereotypy characterized by continuous stereotyped activity such as sniffing or rearing along a fixed path but not continuous licking or gnawing (a stereotypy score of 3–3.5 on a six-point scale), Murray and Waddington (215) report that low doses of CLZ (2.5 and 10.0 mg/kg sc) do not affect the apomorphine-induced stereotypy whereas a higher dose (25 mg/kg) reduces stereotypy scores (to a score of 15), primarily by decreasing sniffing and increasing episodes of stillness.

As is the case for locomotion, it is not surprising that other behavioral manifestations produced by a variety of DA agonists may be blocked by either D1-like or D2-like antagonists. The low component stereotypy induced by D2-like agonists is also dependent on D1-like activation produced by endogenous DA, since it is antagonized by either D1-like antagonism or by prior inhibition of DA synthesis by alpha-methyl-*p*-tyrosine (AMPT) (14,15,35,178). In contrast, DA-depleted rats display stereotyped behavior following apomorphine administration (4), presumably because the apomorphine activates D2- and D1-like receptors. Arnt et al. (15) used the irreversible inactivator EEDQ (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) to decrease the density of D2- and D1-like receptors separately, in order to assess the expression of stereotypy induced by D1- and D2-like agonists, and their combination. Decreasing D2-like receptor density decreases the 'low component' stereotypy

produced by quinpirole and reverses the oral stereotypy effects normally produced by the addition of SKF 38393. Both the oral and low component stereotypies produced by apomorphine are antagonized. Somewhat suprisingly, decreasing the density of D1-like receptors by EEDQ does not produce profound changes in stereotypy expression. The reasons for this are unclear, but administration of SCH 23390 in these, and vehicle-treated, animals decreases both oral stereotypy and low component-induced stereotypy, whereas a higher dose (25 mg/kg) reduces stereotypy scores (to a score of 1.5), primarily by decreasing sniffing and increasing episodes of stillness. Therefore concurrent activation of both D1-like and D2-like receptors seems to be necessary for stereotypy. Robertson and MacDonald (250) find that there are two distinct behavioral components produced by apomorphine, depending on the dose. The first component is 'sniffing down', a behavior with an inverted 'U' shaped curve with a peak at 0.3 mg/kg, sc. The second component is licking/gnawing, which first appears at 0.5 mg/kg. Low doses of CLZ block the sniffing down behavior, whereas higher doses (10.0 mg/kg) block both sniffing down and licking/gnawing. Of interest, these researchers find that the hypomotility produced by very low doses of apomorphine, presumably mediated by presynaptic D2-like receptors, is not antagonized by CLZ, but is antagonized by sulpiride.

Assessing the hypermotility induced by apomorphine (0.5 mg/kg), Buus Lassen (41) finds that CLZ (2.3 mg/kg) decreases this hypermotility by 50% in the first half hour of the test. Using independent ratings for oral and locomotor stereotypies produced by a relatively high dose of apomorphine (5.0 mg/kg), Ljungberg and Ungerstedt (174) report that HAL antagonizes the oral stereotypy (at a dose of 0.2 mg/kg) and the locomotor behavior (0.4 mg/kg). CLZ blocks the hyperlocomotion (20 mg/kg) and gnawing (50 mg/kg) behaviors at higher doses. However, CLZ fails to reduce to a score of 2 or less (discontinuous sniffing), the gnawing response induced by apomorphine (1.25 mg/kg iv) (140).

Together, these results indicate that, whereas D2-like antagonists and D1-like antagonists seem to be more potent than CLZ at antagonizing the stereotypic actions of apomorphine, CLZ does demonstrate some antistereotypic actions (Table 1, 2.3a).

Similar to apomorphine-induced stereotypy, all aspects of the stereotypic behavior produced by amphetamine are readily antagonized by HAL, pimozide and SCH 23390 (249). CLZ decreases the sniffing, but not locomotion or head bobbing, produced by amphetamine (1.0 mg/kg) (312). Somewhat surprisingly, Robertson and MacDonald (249) report that, whereas CLZ decreased the locomotor component of the amphetamine (1.0 and 2.5 mg/kg) response, it potentiated the stereotyped components. More recently, this finding was replicated using two different measures of locomotion (208). Amphetamine (3.5 mg/kg) increases locomotor distance traveled by rats in an open field (hyperactivity), especially in paths around the perimeter of the open field (stereotypy). HAL decreases the hyperactivity and changes the spatial distribution of this activity such that the number of perimeter trips is decreased. CLZ, however, antagonizes the distance traveled but does not modify the perserative locomotor patterns of perimeter trips. Thus, HAL, but not CLZ, decreases stereotypy (Table 1, 2.3b).

It may be that the potentiation of amphetamine-stereotypy produced by CLZ and the lack of potency in antagonizing apomorphine-induced stereotypy are attributable to the anticholinergic properties of CLZ. Anticholinergic agents increase amphetamine-induced stereotypy (105,5,222,158). Furthermore, the addition of the muscarinic agonist, oxotremorine, or the cholinesterase inhibitor, physostigmine, to intra-nucleus accumbens injections of CLZ reverses the potentiating effects of CLZ on amphetamine-induced stereotypy (2). In addition, a submaximal dose of CLZ that produces no effect on the stereotypical profile of amphetamine alone, increases these behaviors following administration of the anticholinergic agents scopolamine or atropine (2).

Several investigators failed to precisely mimic the anti-stereotypic actions exhibited by CLZ with a combination of scopolamine or atropine (anti-cholinergic agents) with HAL (a D2-like antagonist) (175,265). According to the D1 theory of antipsychotic action, the behavioral effects of CLZ may be more successfully approximated by a 'cocktail' of D1-like, D2-like and muscarinic, receptor antagonists.

Thus, it is difficult to tease apart the actions of D1-like and D2-like receptors in stereotypy due to the co-operative functional interactions between the receptors and, therefore, it is difficult to come to an unequivocal decision regarding the similarity of CLZ to these compounds.

As in the locomotor experiments, the functional nature of the interaction between D1-like and D2-like receptors may be severed with the use of chronic reserpinization (8). In reserpinized rats, orally administered SCH 23390 and CLZ block the stereotypy induced by a lower dose of apomorphine (0.3 mg/kg) with similarly sloped dose–response curves (53). This pattern of agonist reversal is not observed following HAL administration (53). However, these authors note that, in vehicle pre-treated animals, SCH 23390, but not CLZ, blocks apomorphine-induced stereotypy (Table 1, 2.3c).

In addition to the synergistic interaction, some behaviors depend on an oppositional interaction between D1-like and D2-like receptors For instance, following a challenge by a D1-like agonist plus a D2-like antagonist, 'typical' behaviors (such as grooming) are suppressed, whereas 'atypical' behaviors (such as vacuous chewing) are unmasked or released (73,74,215). Vacuous chewing is neither released by a D1-like agonist given alone nor by a D1-like agonist combined with a D1-like antagonist (212). Therefore, while both D1-like and D2-like antagonists block the typical behaviors produced by a D1-like agonist, only the D2-like antagonist releases this atypical behavior. Vacuous chewing movements may also be produced by administration of SKF 38393 in aged or EEDQ-treated rats, which have relatively fewer D2-like but not D1-like receptors (15,230,252). Thus, mouth movements seem to be mediated by a concomitant increase in D1-like activation and decrease in D2-like activation.

The converse situation, with administration of a D2-like agonist plus a D1-like antagonist, yields a suppression of typical behaviors (e.g. sniffing and locomotor activity) and a liberation of atypical behaviors (e.g. myoclonic limb or body jerks) (74,212). This behavioral profile holds true for a D2-like agonist plus a variety of D1-like antagonists, including SCH 23390, SKF 83566, NNC 756, NO 756,

A-69024 and BW 736/7C (73,74,212). Furthermore, the rank order of effectiveness for releasing jerking movements corresponds to the drugs' selectivity for the D1-like receptor. Atypical behaviors are not unmasked by a D2-like agonist given alone or by a D2-like agonist combined with a D2-like antagonist (213). The jerking responses are reminiscent of behaviors seen after administration of a low dose of apomorphine (that would be D2-like selective) or D2-like agonist administration in reserpine-treated animals (124). Thus, the typical behaviors produced by a D2-like agonist are inhibited by both D1-like and D2-like antagonists but only the D1-like antagonist releases atypical behaviors. Jerking behavior appears to be mediated by a relative increase in D2-like activity and a decrease in D1-like activity. Therefore, a simple test has been developed that demonstrates the separate and opposing contributions of D1-like and D2-like receptors to a behavior and thus provides another means of investigating the behavioral profile of CLZ.

In this test, CLZ blocks the typical grooming response induced by the D1-like agonist but does not release vacuous chewing (214,215); this profile is remarkably similar to that of the D1-like antagonist and suggests that, during CLZ treatment, D2-like receptors are not preferentially attenuated. Atypical body jerking is released by the combination of a 132-like agonist and CLZ (albeit not as strongly nor as consistently as the response produced by SCH 23390 in the same task). Recently, Daly and Waddington (75) extended the profile of CLZ in this test to include the effects of CLZ against the D1-like agonist A68930 and the D2-like agonist RU 24213. As in earlier tests, CLZ completely blocks the typical grooming response induced by the D1-like agonist A68930 but does not influence vacuous chewing. At similar doses, CLZ produces a modest antagonism of RU 24213-induced sniffing and locomotion and weakly releases some episodes of atypical body jerking. The overall pattern of behavior produced by CLZ in this task indicates that CLZ may exert preferential activity at the Dl-like receptor (Table 1, 2.3d).

It is unlikely that CLZ produces this behavioral profile because of an antagonism of 5-HT mechanisms. Murray and Waddington (212) report that the R but not S enantiomer of SKF 83566 releases atypical behavior in response to a D2-like agonist. It should be noted that, although both enantiomers have similar antagonistic affinities for 5-HT receptors (71), only the R form is a D1-like receptor antagonist (212).

Another behavior that taps into the oppositional relationship of D1-like and D2-like receptors in mice is described by Vasse and Protais (318). SKF 38393 increases grooming, a response that is blocked by D2-like agonists (297,318). it may be that grooming occurs when D1-like receptors are relatively stimulated and D2-like receptors are relatively blocked. Thus, the grooming response in mice seems to be due to a shifting balance between D1-like and D2-like receptors. Vasse and Protais (318) find that apomorphine dose-dependently decreases spontaneous grooming in otherwise untreated mice. The decrease in grooming scores induced by apomorphine (0.75 mg/kg) is not modified by increasing doses of SCH 23390 or CLZ but is antagonized by the D2-like antagonists metoclopramide and HAL. In contrast, SKF 38393 induced grooming is abolished by SCH 23390 or CLZ but not by HAL or metoclopramide. The results from this behavioral test clearly show that CLZ acts like a D1-like antagonist and not like a D2-like antagonist (Table 1, 2.3e).

In summary, stereotyped behaviors have been studied in a number of paradigms that show differential sensitivity to D1-like and D2-like antagonists. In most paradigms, CLZ is found to produce effects similar to those produced by D1-like antagonists.

2.4. Catalepsy induction

Cataleptic immobility is demonstrated by an animal allowing its body to be placed in, and maintain, abnormal or usual postures (64,146), and is believed to parallel the Parkinson-like side-effects observed in patients following administration of a typical neuroleptic (65,106).

Commonly, catalepsy is indexed by an animal's latency to descend from a vertical position supported by leaning on a horizontal bar (92). Results from this and similar tests demonstrate that a variety of D2-like antagonists including HAL (64,313), pimozide (64), raclopride (324), fluphenazine (313) and spiroperidol (313) produce catalepsy. These D2-like antagonists all induce an intense rigidity that generally peaks several hours after administration (185,207,313).

Although initial reports suggest that SCH 23390 (orally administered) displays no potency in the catalepsy test (54,144), other researchers have demonstrated that SCH 23390 (when administered sc) induces catalepsy (9,42,54,181,190,194,313). Similarly, catalepsy is also induced by the D1-like antagonist SKF 83566 (194). D1-like antagonist-induced catalepsy has a rapid onset and offset, with peak effects occurring approximately 30 min post-administration (54,138,185,207,313). Thus, there may be differences between the catalepsies induced by D1-like and D2-like antagonists. This difference is probably not due to pharmacokinetic properties of the drugs as the HAL profile is also produced by other D2-like antagonists (spiropeddol, fluphenazine) that have different pharmacokinetic properties.

The finding that D1-like antagonists are cataleptogenic may, at first glance, appear to be at odds with the D1 theory of antipsychotic drug action. According to the hypothesis, D2-like antagonists produce catalepsy by increasing cholinergic tone in the striatum. D1-like antagonists do not directly influence ACh transmission in the striatum, yet these compounds induce catalepsy. The findings that both HAL- and SCH 23390-induced catalepsies may be reversed by anticholinergic agents including atropine and scopolamine ((209,30), but see (54)) suggest that both the D1- and D2-like antagonists are producing catalepsy by increasing cholinergic tone. In addition, AMPT treatment that depletes DA stores potentiates the catalepsy induced by SCH 23390 (209) while D2-like agonists (pergolide, lisuride and bromocriptine) prevent SCH 23390-induced catalepsy (190,209). Together, these findings suggest that SCH 23390 induces catalepsy through D2-like antagonism, thereby increasing cholinergic tone (see (201) for a more complete discussion of this). One possible explanation for this phenomenon is that antagonism at the D1-like receptor induces a state of 'anti-reward' which somehow feeds back on to the midbrain DA 'reward' neurons and decreases firing. A decrease in activation at D2-like receptors, (thereby mimicking D2-like receptor antagonism) increases

cholinergic tone. Thus, D1-like antagonists may induce catalepsy through an indirect action on D2-like receptors.

The finding by Calderon and colleagues (42) lends credence to this line of reasoning. They report that quinolinic acid lesions of the striatum abolish both D1-like and D2-like antagonist induced-catalepsy. These lesions spare DA and other extrinsic striatal axons, but destroy intrinsic neurons, including cholinergic interneurons. Thus, it could be that the quinolinic acid lesions destroy the cholinergic interneurons (as well as other neurons) of the striatum and thus prevent catalepsy normally induced by both D1 and D2-like antagonists. A more specific test of this argument could be performed by testing the cataleptic potency of the various drugs following striatal lesions made with selective cholinergic neurotoxic drugs such as AF64.

Alternatively, D1-like antagonists may produce catalepsy via a more direct mechanism. A model of how this might occur is put forth by Wickens (331) in a simulation of the mutually antagonistic relation in the firing of striatal output neurons. A switch from competition to activation, in this simulation, is considered to correspond to the induction of parkinsonian rigidity or catalepsy. While an increase in cholinergic tone (modeled as a change in potassium conductance) is the main influence mediating this switch, under some circumstances, reduction of the synaptic excitation by glutamate could produce a switch in the same direction. If the D1-like receptor-mediated reward function amounts to a change in efficacy of glutamatergic excitation, a D1-like antagonist might have the same effect, by a direct mechanism. In this way, D1-like antagonists might produce catalepsy.

Unlike both D1-like and D2-like antagonists, CLZ fails to produce catalepsy (18,64,138,265). This may be due to anti-muscarinic actions of CLZ in the striatum as pretreatment with AMPT fails to modify the CLZ non-response (64). The non-cataleptogenic properties of CLZ depend on an intact striatum as electrocoagulatory lesions of the striatum or 6-OHDA lesions of the nucleus accumbens enhance the cataleptic potency of CLZ (139). In contrast, lesions of the frontal cortex do not affect the lack of catalepsy induced by CLZ (148). If CLZ fails to induce catalepsy because of its anti-cholinergic effect in the striatum, it might be expected that the addition of physostigmine, a cholinesterase inhibitor, would increase the cataleptogenic potency of CLZ. Sayers and colleagues (265) tested this prediction. While orally administered CLZ induces no catalepsy on its own (average catalepsy times of zero seconds in the first 180 min of testing), physostigmine produces a slight catalepsy (average catalepsy times of 5 and 7 s in the first 180 min of testing). Co-treatment with CLZ and physostigmine induces a slightly more robust catalepsy (average catalepsy times of 11, 17 and 10 s in the first 180 min of testing, depending on CLZ dose). When CLZ is administered daily for 20 days, and then tested for cataleptic potency along with physostigmine, the latency to resume a normal body posture is 23 s in the first 180 min of testing. Chronic administration of CLZ may be expected to lead to a proliferation of muscarinic receptors (as a compensation for their prolonged blocking) and therefore to increased sensitivity to anticholinesterases. Thus, although the authors report that none of these scores represents a significant difference from the action of CLZ alone (no catalepsy), it appears that the addition of physostigmine to CLZ may induce a weak catalepsy. However, at present, there is little evidence that the anti-catalepsy properties of CLZ can be attributed to anticholinergic mechanisms.

It is unlikely that antagonism of serotonergic 5-HT_2 receptors accounts for the lack of potency of CLZ in tests of catalepsy. While neuroleptic-induced catalepsy is antagonized by lesions of serotonin cells (48), other researchers report that neither raclopride-, fluphenazine- nor SCH 23390-induced catalepsy is reversed or attenuated by the 5-HT_2 receptor antagonist ritanserin (91,324). In addition, Seeman (275) points out that CPZ, while possessing 5-HT_2 receptor blocking properties, nevertheless produces EPS, thereby questioning the serotonergic mechanism. It should be noted, however, that CLZ exhibits far a greater antagonism at 5-HT_2 receptors than CPZ (275).

Therefore, in the catalepsy induction test, CLZ fails to produce behavioral effects similar to either HAL or SCH 23390 (Table 1, 2.4). CLZ even antagonizes the cataleptic immobility induced by HAL (265)! It may be that CLZ produces a unique profile in this paradigm due to its strong anticholinergic properties. The lack of action of CLZ in this test, however, is consistent with its clinical profile of low incidence of EPS (e.g. 115) and argues that antipsychotic medications with a low propensity to induce EPS would also have anticholinergic properties.

It is of interest to note that HAL induces catalepsy and increases the expression of striatal Fos (the product of the immediate–early gene c-Fos) (253a,269a). The similarity of the time courses of the onset of catalepsy and Fos expression following a single injection of HAL (86) argues that the two events may be linked. In contrast, however, CLZ fails to evoke catalepsy and, furthermore, induces little or no increase in striatal Fos (253a,269a). SCH 23390, while producing some catalepsy, does not induce an increase in striatal Fos (86). Thus, HAL induces an increase in striatal Fos expression, whereas both CLZ and SCH 23390 do not.

2.4.1. Paw test

Ellenbroek et al. (90) devised a unique catalepsy-like task that reliably discriminates between typical and atypical neuroleptics (but see (285)) by measuring the forelimb and hindlimb retraction times of animals standing with their limbs in a four-holed box. HAL and the D2-like antagonist, pimozide, influence forelimb and hindlimb retraction latencies equally, whereas CLZ and the D1-like antagonists SCH 23390 and SCH 39166 induce differentially larger effects on hindlimb retraction times (90,240). Thus, typical neuroleptics increase forelimb retraction times at doses comparable to those necessary to increase the retraction time of hindlimbs. In contrast, the atypical neuroleptic, CLZ and the D1-like receptor antagonist, SCH 23390 are much less potent on forelimb retraction times.

Follow-up studies reveal that the D2-like agonist, quinpirole, antagonizes the effects of HAL, but not CLZ, in this test (89). SKF 38393, on the other hand, reduces the hindlimb retraction times induced by CLZ, but not HAL. It is interesting to note that remoxipride, a recently introduced neuroleptic with atypical properties, displays equal potencies on forelimb and hindlimb retraction times (88). This finding is in agreement with the D2-like receptor antagonist properties of remoxipride (276). Together, these results demonstrate that the paw test reliably differentiates between D2-like and D1-like antagonist

compounds. Furthermore, these results show that CLZ produces a behavioral effect similar to SCH 23390 (Table 1, 2.4.1) and thus provide support for the D1-like receptor hypothesis of CLZ action.

The reasons why this paradigm generates different results from the traditional test of catalepsy are not clear, and it remains to be determined whether the paw test is more sensitive or is measuring a different aspect from the traditional tests. It could be that performance on the paw test is not dependent on the functional co-operation between the DA receptor subtypes. Nevertheless, the paw test demonstrates good predictive validity for antipsychotic drug action in that no false positives or false negatives are reported, although at least 20 neuroleptic and non-neuroleptic drugs have been tested (88). Furthermore, this task seems particularly useful for differentiating between D2-like and D1-like receptor antagonists.

2.5. Animal models of neuroleptic-induced dyskinesia

Neuroleptic-induced dyskinesias may be grouped into two types, depending on the onset and potential reversibility (see (68,115) for review). Acute dyskinesias occur in the early stages of typical neuroleptic treatment and are characterized by limb extensions, facial grimacing, chewing and tongue protrusions. These involuntary abnormal movements may be directly related to pharmacological effects of the typical neuroleptics as symptoms disappear upon neuroleptic reduction or withdrawal. At the other end of the continuum, persistent dyskinesia with latent onset or TD is an iatrogenic disease associated with chronic intake of typical neuroleptic drugs (68). This syndrome, characterized predominantly by oral facial-buccal dyskinesias, develops after long-term use of typical neuroleptic agents. Thus, the signs and symptoms of acute dyskinesia and TD are strikingly similar. Furthermore the acute and tardive forms of dyskinesia may be linked; neuroleptics that induce acute dyskinesia have also been correlated with the production of TD in humans (84). However, withdrawal from neuroleptic medication fails to reverse and may even aggravate the symptoms of TD suggesting that the mechanism of action is not simply pharmacological in nature.

2.5.1. Acute dyskinesia

Several animal models that both resemble and predict neuroleptic-induced dyskinesias are described in the literature. These putative models offer good tests for comparing the behavioral effects of CLZ to those produced by prototypic D2-like and D1-like selective antagonists. In one such model, a single orally administered dose of HAL produces mild acute dyskinesia-like symptoms in a high percentage of previously drug-naïve Cebus monkeys (57). Five out of six monkeys tested demonstrate abnormal movements (jaw movements, tongue protrusions, upper and lower limb movements, head pushing and perseverative circling). These researchers also investigated the effects of the D1-like antagonist SCH 23390 (57) and the longer acting D1-like antagonist SCH 39166 (57). All the drug treatments (SCH 23390, SCH 39166 and HAL) produce a similar level of sedation, thus ensuring that all the doses chosen were behaviorally active. However, neither of the D1-like antagonists produces significant effects on the measures of acute dyskinesia.

The finding that D1-like selective antagonists fail to produce acute dyskinesia, although reliably reproduced by two different agents (SCH 23390 and SCH 39166), is not replicated by Casey (50). In this experiment, both SCH 23390 and HAL produce dystonia in previously drug-naïve Cebus monkeys. Although the reason for the discrepancy is not clear, it may be important that the SCH 23390-induced dystonia is less intense and endures for a much shorter length of time than does the HAL-evoked dystonia. In addition, neither drug treatment is observed to induce oral dyskinesias (Table 1, 2.5.1a).

Although the effects of CLZ have not been assessed in this monkey model, Gunne and colleagues (127) report that a single injection of CLZ decreases 'spontaneous or vacuous mouth movements' in rats, whereas a similar administration of HAL causes a decrease followed by a prolonged increase in the presence of these acute dyskinesia-like mouth movements. In addition, the clinical finding that CLZ is associated with an extremely low frequency of acute or TD argues that CLZ may not produce acute dyskinesia-like symptoms in the monkey model. There are parallels between acute neuroleptic-induced dyskinesia in humans and the production of acute dyskinesia-like symptoms in monkeys and chewing movements in rats; nevertheless, it is unclear whether experiments using acute treatments are adequate models of TD.

Other researchers report the effects of acute treatment with antipsychotic drugs in monkeys subchronically treated with typical neuroleptics (usually HAL). In these 'primed' monkeys, an acute dose of HAL reliably induces dyskinetic movements similar to those produced by these agents in patients with schizophrenia (113,116,127,166,234,239). Liebman and Neale (166) report that CLZ does not elicit dyskinesias in 'primed' monkeys treated at doses of CLZ that produce an impairment of responding in a Sidman avoidance task in other monkeys. However, the effects of SCH 23390 in this model are not clear. Thus, SCH 23390 is reported to induce dystonic symptoms (234) and an acute dyskinesia-like syndrome (116). In contrast, other findings demonstrate that acute administration of SCH 23390 in monkeys chronically treated with HAL evokes no signs of acute dyskinesia (113). In addition, Coffin et al. (57,58) find that, following 14 weeks of HAL treatment, acute doses of SCH 23390 or CLZ fail to induce abnormal movements, whereas after 37 weeks of HAL administration, SCH 23390 eventually produces abnormal movements (Table 1, 2.5.1b). This time-dependency may account for some of the above noted conflicts in the literature.

2.5.2. Tardive dyskinesia

Supersensitivity of D2-like receptors was originally argued to be necessary and sufficient for the pathogenesis of neuroleptic-induced dyskinesia, especially TD (149,274). However, experimental and clinical evidence challenges the completeness of this hypothesis (see (200) for review). A new mechanism is proposed to account for the development of TD. Miller and Chouinard (200) argue that D2-like receptors are involved in the production of TD through their interaction with striatal cholinergic interneurons. The clinical finding that both acute and tardive dyskinesias can be alleviated or prevented with anticholinergic treatment raises the possibility of the involvement of the cholinergic system in this movement disorder. Previous studies show

that antagonism of D2-like receptors in the striatum increases cholinergic tone that is normally inhibited by DA (301). This prolonged activation may leave these neurons vulnerable to damage and eventual demise. Thus, damage of the striatal cholinergic neurons would be directly responsible for the persistent oral dyskinesia symptoms that typify TD. This model has good predictive validity as it would be expected that typical neuroleptics with high D2-like antagonist affinity would disinhibit cholinergic neurons in the striatum and eventually lead to their destruction, producing TD symptoms. In contrast, CLZ in therapeutic doses, with its possible primary effect at the D1-like receptor (see Introduction), would be less likely to induce the predisposition to TD as D1-like receptors have little if any effect in increasing the tone of the striatal cholinergic system (93).

In one model of TD, non-human primates are subchronically treated with neuroleptic agents and the presence of spontaneously occurring dyskinetic movements assessed (see (200)). A syndrome that is characterized by abnormal mouth movements accompanied by twisting or writhing motions of the trunk or limbs, that closely resembles clinical TD, is produced by repeated HAL administration (57,58).

Subchronic administration of SCH 23390 may not induce the predisposition to spontaneous abnormal TD-like movements. Thus, Coffin et al. (57) find that Cebus monkeys orally administered HAL for 14 weeks show a progressive increase in 'abnormal movements'. However, similar oral treatment with SCH 23390 for over 1 year fails to produce these abnormal movements. These results have been extended to include a D1-like antagonist with a longer duration of action, SCH 39166 (57). This finding occurs despite the fact that SCH 23390 and SCH 39166 are administered at behaviorally active doses. In agreement with this, Hansen and Gerlach (129) report that administration of the D1-like antagonist, NO 01-756 in a gradually increasing dose over 4 months, does not induce dystonia in monkeys. These findings suggest that D2-like, but not D1-like, mechanisms are involved in the production of acute dyskinesia-like as well as TD-like syndromes.

Subchronic treatment with CLZ fails to induce dyskinesias in monkeys (239). This finding is consistent with the clinical observation of the low acute dyskinesia side-effect liability of CLZ (153). In addition, this finding provides evidence that CLZ produces effects consistent with a D1-like selective antagonist (Table 1, 2.5.2a).

Abnormal mouth movements in rodents are increased by subchronic treatment with typical neuroleptics (for review see (321)). Although the validity of this rodent model of acute or TD has been questioned, the vacuous chewing movements that become apparent after withdrawal from subchronic treatment with typical neuroleptics in rats do parallel the withdrawal dyskinesias often seen in schizophrenic patients. Thus, useful information may be garnered from rodent studies of chronic treatment with D2-like selective and D1-like selective antagonists and CLZ. Repeated treatment with HAL induces increased mouth movements and jaw tremor that persists, in some cases, for several months after withdrawal (127,150,270,271,322). Rupniak et al. (255) administered HAL or CLZ to rats for four months. HAL treatment produces the rapid emergence of purposeless chewing, whereas the CLZ treatment produces no effect on mouth movements. Follow up experiments show that, after 1 year of treatment, however, spontaneous chewing movements gradually emerge in the CLZ-treated animals. In contrast, Gunne et al. (127) treated rats for 10 months. Following HAL administration, spontaneous chewing movements gradually emerge in the 5-month withdrawal period and then diminish. Similar administration of CLZ produces no effect. This finding has been replicated (150,270,271).

Although SCH 23390 has not been tested in this model, it would be predicted that treatment with the D1-like receptor antagonist would not induce spontaneous mouth movements as SCH 23390 does not upregulate D2-like receptors following subchronic treatment. CLZ certainly produces behavioral consequences different from HAL in this task suggesting that the effects of CLZ are unlike those of D2-like agonists (Table 1, 2.5.2b).

In summary, the study of animal models of dyskinesias includes behavioral experiments with both acute and chronic treatments with DA receptor antagonists. Generally, where differences are found between the effects of D1-like and D2-like receptor antagonists, CLZ produces effects similar to those produced by D1-like antagonists.

2.6. Sensorimotor gating

An interesting phenomenon involving the eye blink startle reflex in schizophrenic patients is widely reported. The startle reaction is decreased in control subjects if the main startle stimulus is preceded by the presentation of a weaker stimulus, an occurrence known as prepulse inhibition (PPI, see (125)). In schizophrenic patients, PPI is reduced (34). This finding is in agreement with the theory that schizophrenic patients experience difficulties inhibiting, filtering or 'gating' sensory information (188). An animal model using an acoustically evoked startle response similarly finds that presenting a weak prepulse stimulus before a startle-eliciting stimulus decreases the amplitude of the startle reflex (137). Furthermore, a DA mechanism in PPI is implicated. Thus, PPI is reduced, following systemic challenges with apomorphine (184,305), amphetamine (184,308) and or quinpirole (235). In contrast, the D1-like agonist SKF 38393 does not affect PPI (235). This model is argued to have predictive validity as antipsychotic drugs reverse apomorphine-induced disruption of PPI (see below), whereas non-antipsychotic drugs, such as diazepam and imipramine, do not (246). Thus, another behavioral test is available to further characterize the actions of CLZ.

Apomorphine-induced disruptions in PPI are completely reversed upon treatment with D2-like antagonists, including HAL (120,184), spiperone (307), raclopride (307), CPZ (246), risperidone (246) and eticlopride (135).

Notwithstanding the important role of D2-like receptors in PPI, there is also evidence implicating D1-like receptors in this phenomenon. Hoffman and Donovan (135) observe a dose-related reversal of the apomorphine blockade of PPI with SCH 23390 (but see (269,307)), and Schwarzkopf et al. (269) report a synergistic interaction between D1-like and D2-like antagonists in reversing the effects of apomorphine on PPI.

Swerdlow and colleagues (307) find that CLZ produces an inverted 'U'-shaped dose response profile in opposing the inhibitory action of apomorphine on PPI. As CLZ decreases baseline startle scores in this experiment,

TABLE 2
EFFECTS OF D2-LIKE ANTAGONISTS, D1-LIKE ANTAGONISTS AND CLOZAPINE ON CONDITIONED BEHAVIORS

Behavioral test	D2-like antagonists	D1-like antagonists	Clozapine (CLZ)	Conclusions
(3.1) Operant responding for reward				
(3.1.1) Food reward				
(3.1.1.1) Decrease in response rate	+ + + +	+ + + +	+ + + +	Unable to discriminate
(3.1.1.2) Alleyway reacquisition	+ + + +	?	—	CLZ unlike D2-like antagonists and probably unlike D1-like antagonists (see text)
(3.1.1.3) Response decrement pattern				
(a) Within-session decline	+ + + +	+ + +	+	CLZ unique
(b) Across-session decline	+ + + +	+ +	—	CLZ more similar to D1-like antagonists
(3.1.1.4) Anxiolytic-like activity	—	?	+ + +	CLZ action may not be explained by anxiolytic activity
(3.1.2) Brain stimulation reward				
(3.1.2.1) Decrease in response rate	+ + + +	+ + + +	+ + + +	Unable to discriminate
(3.1.2.2) Response decrement pattern				
(a) Within-session decline	+ + + +	+ + +	—	More data needed for CLZ
(b) Across-session decline	+ + + +	?	?	More data needed for CLZ, SCH 23390
(3.1.2.3) Reward summation function	+ + + +	?	?	More data needed for CLZ
(3.1.2.4) Self-regulation of stimulation: duration	+ + +	?	+ + + +	CLZ dissociable from D2-like antagonists
(3.1.2.5) Intensity	+ + +	?	+ + + +	CLZ dissociable from D2-like antagonists
(3.1.3) Psychomotor stimulant reward	+ + + +	+ + + +	+ + +	Unable to discriminate
(3.1.3.1) Progressive ratio	+ + + +	+ + + +	—	CLZ unique
(3.2) Conditioned place preference	+ + + +	+ + + +	+ + + +	Unable to discriminate
(3.3) Drug discrimination				
(a) Amphetamine cue	+ + + +	+ + +	+ + +	Unable to discriminate
(b) Own cue	—	—	+ + + +	CLZ unique
(3.4) Conditioned avoidance responding: impairment	+ + + +	+ + + +	+ + + +	Unable to discriminate
(a) Within-session decline	+ + + +	—	?	More data needed for CLZ
(b) Across-session decline	+ + + +	—	+	CLZ similar to D1-like antagonist

+ + + +: very strong effect; + + +: strong effect; + +: moderate effect; +: weak effect; —: no effect.

however, the shape of the CLZ dose–response curve may be artifactual because PPI was assessed using difference scores. In a later study that employed percentage scores to measure PPI, Swerdlow and Geyer (306) report that CLZ dose-dependently reverses the effects of apomorphine on PPI. Thus, the effects of HAL, SCH 23390 and CLZ on PPI appear to be similar (Tables 1, 2.6b).

Under basal conditions (i.e. in the absence of apomorphine), SCH 23390 (135,269), D2-like antagonists (135) and CLZ (136,306) enhance PPI. Unfortunately, these studies using PPI, like locomotor stimulation studies in intact animals, do not provide adequate discrimination between D1-like and D2-like antagonists to test the D1 hypothesis of CLZ (Table 1, 2.6a). This may be due to the functional synergism exhibited between D1- and D2-like receptors in this behavior.

2.7. Inhibition of apomorphine-induced emesis

Apomorphine-induced vomiting in dogs is presumed to involve the stimulation of D2-like receptors that are in the vicinity of the chemoreceptor trigger zone in the brain stem (54,242). Inhibition of the vomiting response is suggested to be the most sensitive in vivo demonstration of DA (D2-like) receptor blockade (340). All typical neuroleptics are antiemetic agents, blocking apomorphine-induced vomiting (54,147,242). In marked contrast, SCH 23390 (54,144) fails to block emesis, probably due to the lack of D1-like receptors near the chemoreceptor trigger zone (298). To the best of our knowledge, CLZ has not been tested in this paradigm. The results of such a test would be very interesting given that D2-like and D1-like anatagonists produce such diverse behavioral patterns.

2.8. Neurochemical consequences of acute and chronic dopamine receptor antagonist administration

As an addendum to these behavioral results, we include brief sections on the neurochemical consequences of acute and chronic administration of DA receptor blockers.

2.8.1. Dopamine turnover

Released DA may be metabolized at an extraneuronal site through the sequential action of catechol-*O*-methyltransferase (COMT) to produce 3-methoxy-4-hydroxyphenylethylamine (3-MT) and monoamine oxidase (MAO) to finally produce homovanillic acid (HVA) (62). Since COMT is located extraneuronally, the intermediate metabolite 3-MT may be used as an index of DA release and utilization. D2-like antagonists (including HAL, metoclopramide, raclopride and BRL 34778) produce a marked increase in 3-MT concentration in the striatum and nucleus accumbens of rats

(130). All of the D2-like antagonists tested in this experiment produced increases of greater than 100%. In contrast, increases of less than 100% in 3-MT accumulation in these areas are produced by D1-like antagonists (SCH 23390 and A 69024). Consistent with the greater efficacy of the D2-like receptor in mediating 3-MT accumulation are the findings that, although both the D2-like agonist quinpirole and the D1-like agonist SKF 82958 decrease levels of 3-MT, the decrease induced by the D2-like agonist is much greater (130). Thus, different profiles of D1-like and D2-like antagonists emerge with respect to DA turnover in the striatum and nucleus accumbens.

In the same experiment, CLZ is the weakest compound tested, producing very modest increases in 3-MT accumulation of less than 100% (130). Therefore the effects of CLZ on DA turnover are very similar to the effects of D1-like antagonists (Table 1, 2.8.1). In addition, pretreatment with γ-butyrolactone, an inhibitor of DA neuronal firing, completely reverses the effect on 3-MT accumulation provoked by CLZ and the D1-like antagonists, while only partially reversing the D2-like antagonist effects. The authors summarize their findings by writing that "in spite of their affinity for both D1 (like) and D2 (like) receptors in vitro, in vivo (CLZ) acts primarily as a D1 (like) antagonist" (p. 818).

2.8.2. Dopamine receptor proliferation

Repeated administration (followed by a withdrawal) of classical neuroleptics such as HAL, increases the number of striatal D2-like receptors (40,211,231,232,254,272) but not D1-like receptors in rats (231,232,254,256). Upregulation of D1-like receptors, but not D2-like receptors in the striatum is the result of similar treatment with SCH 23390 (70,231). CLZ upregulates D1-like (232,254) but not D2-like receptors ((164,232,254,272), but see (121) who report that CLZ decreases D2-like receptor density). Thus, in tests of the effects of chronic treatment with DA receptor blockers on DA receptor proliferation, CLZ produces effects similar to those produced by D1-like receptor antagonists (Table 1, 2.8.2a, b).

A summary of the effects of HAL and related drugs, SCH 23390 and related drugs, and CLZ in tests of unconditioned behavior appears in (Table 1). In many paradigms, SCH 23390 and CLZ have similar profiles.

3. EFFECTS OF CLOZAPINE ON CONDITIONED BEHAVIOR

DA is implicated in reward-related incentive learning (21,24) and a dysfunction of this learning process may underlie the neuropsychological etiology of schizophrenia (21,22,196–198). Together, these findings led Miller (197) to suggest that clinical potency of antipsychotic drugs may be more reliably predicted by tests assessing rewarded, rather than motor, behavioral elements. Such tests also may provide an opportunity to examine the D1 hypothesis of CLZ's therapeutic action. Table 2 provides a summary of the behavioral effects of HAL and related drugs, SCH 23390 and related drugs, and CLZ in tests of conditioned behavior. As will be concluded in this section, D1- and D2-like antagonists generally fail to produce different behavioral effects in tests of conditioned behavior, thus, tests of conditioned behavior do not provide a means for clearly dissociating the action of CLZ at D1- vs. D2-like receptors.

3.1. Operant responding for reward

Numerous reviews discuss the ways that DA is necessary, sufficient, or at least involved in operant responding for conventional rewards (food or water), brain stimulation reward (BSR) and psychomotor stimulants such as amphetamine or cocaine (e.g. (102,108)). However, this literature remains fraught with interpretative difficulties as drug-evoked disruptions may be due to a combination of reward and/or performance deficits (23,26). Results from operant paradigms, therefore, should be interpreted with this reward/performance distinction in mind.

3.1.1. Responding for food

3.1.1.1. Decreases in response rate. It is widely established that typical neuroleptics (such as HAL or pimozide) (1,97,98,259), SCH 23390 (216,217,260) and CLZ (1,45,97,98,259,293,327) decrease the rate of operant responding for food presented on continuous reinforcement (CRF) or fixed ratio (FR) schedules. Thus, it is not possible to determine whether the effects of CLZ are related to its action at D1- or D2-like receptors. As previously noted, the mechanism underlying observed decreases in responding is unclear, and it is difficult to exclude drug-induced performance deficits. Diminished response rates may be attributed to deficits in reward (attenuation of rewarding impact of stimuli) or performance (reduced ability to meet the response demands of the task). However, as described below and elsewhere (21,24,26,201), some paradigms do allow for a dissociation of reward from performance effects.

3.1.1.2. Alleyway reacquisition paradigm. One approach to dissociating reward and performance effects is reported by Horvitz and Ettenberg (141) who amended the operant task and tested animals free from drugs. In the alleyway reacquisition test, animals run along the straight arm of a T-maze to obtain food. Following partial extinction, some animals are given a single food-rewarded priming trial. In the subsequent test, animals that previously received the priming trial had shorter runway latencies than animals that did not receive the priming trial, thus demonstrating the reacquistion effect. If HAL is administrated before the food-primed trial, animals do not show the reacquisition effect (141,335). One interpretation of these data is that HAL diminishes the rewarding value of the priming food, thus producing a trial that is the functional equivalent to the non-primed situation.

In the same preparation, CLZ fails to block the reacquisition effect (333). Again, the results from this paradigm are difficult to interpret, but it would be of interest to examine the actions of SCH 23390. From our observations of the reward-blocking effects of DA antagonists (see below), we would predict that a D1-like receptor antagonist, like HAL, would block the reacquisition effect. If this is so, the effects of CLZ would not be like those of HAL or SCH 23390.

3.1.1.3. Response decrement pattern. In another attempt to address the problems inherent in the study of simple rate measures, Wise and collaborators examined the temporal pattern of neuroleptic disruption of operant behavior (338). Specifically, these researchers demonstrate that rats repeatedly administered pimozide exhibit a gradual day-to-day abatement in bar-pressing for food. The across-session decrease in responding is reported to be strikingly similar to the pattern seen in animals no longer receiving reward. Explanations attributing the behavioral decline to drug accumulation or pharmacological sensitization are ruled out with home-cage controls that receive similar quantities of drug but do not demonstrate decreased response levels (25,258,338). The inter-session declines in responding induced by specific antagonists for D2-like receptors have been replicated (112,172,186,338) and extended to include within-session declines (107,186,259). Animals treated with neuroleptics respond at roughly drug-free rates in the initial portion of the test session, thus showing the capacity of drugged animals to perform the task. Typical neuroleptics may interfere with operant behaviors by attenuating the rewarding impact (hedonic value) of the food reward, much like extinction. Between- and within-session declines are argued to represent behavioral manifestations of 'anhedonia' produced by typical neuroleptics.

The D1-like antagonist SCH 23390 induces a within-session decline (216) or flattening (25,260) (whereas vehicle-treated rats typically display a within-session increase in responding (e.g. 25,260)) but fails to consistently induce the gradual across-session decline displayed by D2-like antagonists. Ljungberg (172) notes that SCH 23390 most potently attenuates lever-pressing for water reward following the first of four daily injections. This attenuation, however, is not maintained over the course of the test period. Supporting this observation, Beninger and colleagues (25) report a step-wise decline in responding, especially in the first two days of the test, rather than a decline across all test sessions. Thus, while D2-like and D1-like receptor-specific antagonists disrupt intra-session responding roughly equally, D2-like antagonists seem to be more potent at producing inter-session declines.

Further experiments clearly demonstrate additional differences between the actions of D1-like and D2-like antagonists on operant responding. Both HAL (169) and SCH 23390 (171) decrease overall bar-pressing rates for water reward. Pretreatment with scopolamine counteracts the deficit produced by HAL (170) but not SCH 23390 (171). This finding provides compelling support for a corollary of the D1-hypothesis of antipsychotic drug action that explains that D2-like antagonists produce performance deficits by functionally increasing ACh tone in the striatum (201). The failure of the anticholinergic to alleviate the SCH 23390-produced decline, on the other hand, argues that the deficits evoked by D1-like receptor antagonists are primarily reward-based. Perhaps the across-sessions decline in responding, seen with HAL, is a cumulative consequence of repeated minor performance impairments, reflected in an indirect anti-reward effect. Although CLZ has not been tested in this paradigm, we believe that the atypical neuroleptic may induce a response pattern similar to SCH 23390 as the anticholinergic properties of CLZ would counteract the motor deficit and directly decrease reward.

In support of this inference that D2-like, but not D1-like, antagonists principally produce deficits through performance mechanisms are the results of experiments using different reward schedules (216). Thus, the same dose of SCH 23390 produces a greater deficit when animals are responding on variable interval (VI) rather than CRF operant schedules. If the mechanism of these disruptions is simply motoric in nature, similar doses of SCH 23390 would produce similar disruptions. This is the case for raclopride, a D2-like antagonist (217). In a similar experiment, raclopride fails to induce differential response decrements on CRF vs. VI schedules; raclopride produces the same dose-related decrement independent of reward density. Together, these findings provide compelling evidence for the argument that the DA antagonists disrupt operant performance by two different avenues; D2-like antagonists via motor mechanisms and D1-like antagonists via reward mechanisms (see (201)). By distinguishing the response decrement patterns induced by D2-like and D1-like antagonists, possible comparison groups for the effects of CLZ emerge.

An early report suggests that low doses of CLZ induce a within-session decline (259). Recent experiments, however, clearly show that CLZ decreases responding for food, but does not produce the within session decline (264). As it has been suggested that an important mechanism of action of CLZ may be at D2-like and 5-HT_2 receptors, these researchers investigated whether a combination of HAL and ritanserin (a 5-HT_2 antagonist) would produce a response decrement pattern similar to CLZ. However, ritanserin and HAL produce a significant within-session decline. These authors conclude, therefore, that the unique action of CLZ in this test could not be attributed to a combination of D2-like and 5-HT_2 antagonism. As both D2-like and D1-like receptor specific antagonists induce similar intra-session patterns, the profile produced by CLZ appears to resemble neither (Table 2, 3.1.1.3a).

In a modification of a classic experiment of Wise and colleagues (338), Faustman and Fowler (98) examine whether CLZ produces the 'anhedonic' inter-session declines in lever-pressing. On the first day of test, CLZ induces a reduction of bar-pressing but this decrease is not progressive over subsequent test days. With the highest dose, behavioral tolerance seems to develop, with non-drug rates being observed on the final CLZ test day. This inter-session pattern of disruption is reminiscent of the effects produced by SCH 23390. Both drugs generate the most pronounced decline on the first (or second) test day, not a gradual across-session decline. Thus, the lack of across-session 'anhedonic' qualities produced by CLZ tends to support the argument that the important action of this atypical neuroleptic, at least in this paradigm, may be at the D1-like receptor (Table 2, 3.1.1.3b).

It may be that the demonstration of an across-session decline is not a valid predictor of antipsychotic activity. This pattern may reflect motor, rather than reward, dysfunction. Sanger and Blackman (262) argue that CLZ's proven antipsychotic effectiveness yet lack of across-session disruption questions whether this test is a good pre-clinical predictor of antipsychotic efficacy.

3.1.1.4. Anxiolytic-like activity. It is suggested in the literature that the pattern of responding induced by CLZ

in operant paradigms may reflect anxiolytic properties (261). The rate-reducing effects of typical neuroleptics such as HAL and CPZ are largely independent of schedule conditions that maintain responding. Thus, HAL and CPZ dose-dependently decrease response rates in the differential reinforcement of low rates (DRL) schedule (46,44). Anxiolytic agents such as diazepam and chlordiazepoxide (CDP) increase operant responding at low doses and decrease rates with higher doses (perhaps due to muscle relaxation or sedation) (45,221,261,263). CLZ also induces a biphasic pattern of responding, with low doses increasing (44) and higher doses decreasing (44–46) the low rates of responding maintained under a DRL schedule. While it is tempting to draw comparisons between CLZ and diazepam or CDP based on these findings, it should be noted that the increases may be attributable to different mechanisms. While diazepam increases burst responding (responses emitted less than 1 s apart) (45), CLZ produces no significant effect on burst responding (44).

The profile produced by typical and atypical neuroleptics on responding suppressed by shock presentation has also been investigated. CPZ and HAL decrease (290,293,294) whereas CLZ and CDP increase responding subdued by shock (291,293). The increase induced by CDP, however, is much greater than the corresponding increase induced by CLZ (293). Furthermore, CLZ (but not HAL or CDP) increases responding maintained by shock presentation on a fixed interval (F1) schedule (294). Thus, HAL and CLZ produce opposite effects in these paradigms, and the unique effects of CLZ may not be attributed solely to anxiolytic properties. These results further testify to the supposition that, although CLZ may possess anxiolytic properties, these are clearly distinguishable from those of 'classic' anxiolytics such as CDP.

Wiley et al. (332) used a Geller-Seifter conflict test wherein rats may press a bar to obtain food (unpunished) in one segment of the test and the bar press results in food and shock presentation (punished responding) in another segment to study the effects of typical and atypical neuroleptics and classical anxiolytic agents. In this way, nonspecific changes in motor behavior may be assessed. The anxiolytic drug, CDP, dose-dependently increases punished responding (reaching 6 or 7 punished responses per min) without affecting unpunished responding. Low doses of CLZ selectively increase punished responding, although not to the same extent as CDP (2 responses per min). CPZ and HAL both fail to increase punished responding. Unlike typical neuroleptics, therefore, CLZ demonstrates some anxiolytic potency in the conflict test, although not as great as CDP (Table 2, 3.1.1.4).

Although the aforementioned results are important to define the behavioral profile of CLZ, they say little about the similarities and differences between the profile of CLZ and D2-like and D1-like antagonists as, in most experiments of this type, D1-like selective antagonists are not tested. Rosenzweig-Lipson and Bergman (253), however, examine the effects of the D2-like antagonist eticlopride, D1-like antagonist SCH 39166 and CLZ on monkeys responding under an FR schedule of stimulus-shock termination. Under this schedule, the D2-like agonist, PHNO, dose-dependently reduces responding. Pre-treatment with eticlopride induces a rightward shift in the PHNO dose–response function, indicating a surmountable antagonism. In contrast, a dose-related downward shift of the PHNO dose–response curve is elicited by pretreatment with SCH 39166. Similarly, CLZ induces a dose-related decrease in the dose–effect curve of PHNO. Thus, both CLZ and SCH 39166 produce strikingly similar behavioral profiles, both of which are different from that produced by the D2-like antagonist. It is important to note that, in this experiment, all antagonist challenges were performed by the same investigators, using the same protocol, thus decreasing the potential confounds that may be caused by differing task demands in different labs.

3.1.1.5. Responding for food: summary. Overall, the results from paradigms involving operant responding for food suggest that the actions of CLZ is, in many cases, unique. CLZ (like HAL, SCH 23390 and large doses of anxiolytics) depresses response rates. However, CLZ (unlike HAL and SCH 23390) fails to induce a within-session decline or flattening. HAL produces a pronounced across-session decline, SCH 23390 produces a weak across-session decline, but CLZ fails to induce such a pattern of decline. As the action of CLZ was more similar to that of SCH 23390 than that of HAL, this latter finding may be seen as providing some support for the D1 hypothesis of antipsychotic drug action. Under more diverse schedules of responding, further differences emerge between CLZ and HAL, with CLZ demonstrating anxiolytic effects. Although the effects of SCH 23390 have not been tested thoroughly in all of the paradigms reviewed above, some evidence demonstrates a similarity between the response profiles produced by CLZ and SCH 39166.

3.1.2. Brain stimulation reward (BSR)

3.1.2.1. Decreases in response rates. D2-like antagonists, such as HAL (109,325,326), pimozide (109) and metoclopramide (109), as well as SCH 23390 (161,219) and CLZ (109,342) decrease response rates maintained by BSR (Table 2, 3.1.2.1). However, as several authors point out, rate measures of self-stimulation represent a poor index of reward magnitude (314) and are vulnerable to nonspecific drug influences on performance (167).

Gallistel and Davis (109) were the first to systematically examine the involvement of DA receptor subtypes in BSR. In their task-specific extinction paradigm, rats are transferred to a different apparatus following extinction (defined as no responding for 1 min). Responding is temporarily reinstated in the second apparatus, thus showing that the extinction-like decline demonstrated in the first apparatus could not be sufficiently explained by motoric impairment. The potency of nine neuroleptics in blocking BSR was surveyed. A strong correlation between BSR-attenuating potency and D2-like affinity emerges (with no such correlation with D1-like affinity), leading these authors to conclude that the D2 receptor is critically associated with BSR. This interpretation, however, should be received cautiously as the neuroleptics studied did not include selective D1-like antagonists such as SCH 23390 or SCH 39166 and, indeed, heavily sampled D2-like receptor specific antagonists. Nakajima and colleagues (218) propose that, similar to many unconditioned behaviors, responding for BSR depends on both D2-like and D1-like receptors,

with D1-like receptors serving an enabling or permissive role.

3.1.2.2. Response decrement pattern. The temporal pattern of operant disruption may be analyzed in an attempt to address the entanglement of performance and reward variables afforded by rate measures. Reasoning that if neuroleptics diminish rewarding capacity of a stimulus, then an extinction-like decline would result from their administration, several researchers find that the D2-like receptor antagonists, pimozide (107) and HAL (101), induce intra-session declines in response rates. The inference is that the effects of typical neuroleptics on BSR are analogous to withdrawal of reward, a 'pharmacological extinction'. Further, these researchers maintain that the behavioral deficit is reward-specific (i.e. not motoric) as animals demonstrate their capacity to emit responses in the beginning of the session.

The results of Nakajima and Baker (217) suggest a prominent role for the D1-like receptor in BSR. Within-session declines are produced by SCH 23390 and the D2-like receptor antagonist, raclopride. However, the suppressive effects of SCH 23390 are dependent upon the magnitude of reward such that responses rewarded with more pulses of stimulation are more resistant to the disruptive influence of SCH 23390. This finding argues that the deficit is not purely motoric in origin. In contrast, similar disruptions in operant responding are produced by raclopride, regardless of the number of pulses delivered, a finding that can be attributed more easily to motor impairments. Thus, the disruptive effects of SCH 23390, but not raclopride, are sensitive to the magnitude of reinforcement, a finding that also holds for food-maintained operant responses, as reviewed in the previous section. These results suggest that, whereas both D1-like and D2-like antagonists are critically involved in the production of within-session declines, their modes of action may be quite different. D1-like receptors seem to mediate the reward attenuation, whereas D2-like receptors may mediate performance effects. This finding is consistent with the D1 hypothesis of antipsychotic drug action.

In an extension of this work, Kurumiya and Nakajima (161) performed a well-controlled study by placing electrodes in the ventral tegmental area and microinjecting SCH 23390, HAL, raclopride or sulpiride into either the ipsilateral or contralateral nucleus accumbens. Ipsilateral injection of SCH 23390 produces striking within-session declines in responding, to levels of almost zero. Comparable injections to the contralateral nucleus accumbens are without effect, thus excluding motor impairment as a likely explanation for the effect. HAL injections into the ipsilateral nucleus accumbens also induce a within-session decline, albeit less pronounced than the one evoked by SCH 23390. Both raclopride and sulpiride fail to evoke long-lasting extinction-like declines. Thus, the results from this series of experiments clearly argue that the D1-like receptor is the crucial one for the reward component of brain stimulation originating in the ventral tegmental area.

There is a lone report of the action of CLZ in this paradigm (99). In their abstract, Fenton and colleagues describe CLZ's response decrement pattern as closely resembling those produced by prazosin and methocarbamol. Prazosin and methocarbamol produce declines that are not progressive within the session (101). However, as details of the experiment involving CLZ are not reported, definite conclusions regarding the actions of CLZ are not warranted (see Table 2, 3.1.2.2a,b).

3.1.2.3. Reward summation function. The reward summation function paradigm is a modification of the basic BSR methodology that aims to distinguish motor from performance variables (87). In this procedure, a rat performs an operant (runs a runway or bar presses) for a fixed-duration burst of self-stimulation at a variety of frequencies. Plotting the log pulse frequency on the x-axis of a graph against the operant rate (or running speed) on the y-axis results in a steep sigmoidal-shaped curve reminiscent of pharmacological dose–response curves. Lateral shifts in this curve are produced by changing the stimulating current (with decreased currents resulting in rightward shifts and increased currents resulting in leftward shifts) and are independent of vertical shifts (representing maximal response rate). A change in the locus of rise (half-maximal level of responding) indicates a change in the reward value of the stimulation that is relatively free of performance effects as increasing the number of pulses (increasing the magnitude of the reward) restores the running speed, thus displaying the animals' capacity to respond.

D2-like antagonists, such as pimozide, shift the reward summation curve to the right in a dose-dependent manner such that a higher number of pulses is required to sustain half-maximal performance (108,110,300). Whether pimozide also decreases maximal responding cannot be ascertained from the data (110) and large individual differences may hamper a clear interpretation (108,300). Another D2-like antagonist, raclopride, also shifts the curve to the right while decreasing the asymptote with higher doses (217). SCH 23390, in this paradigm, shifts the curve to the right with little attenuation of asymptotic responding levels (161,218,220,251,292,337).

Taken together, these results indicate that both D1-like and D2-like antagonists produce reward blunting effects and, further, that D2-like antagonists may also affect motor output. These results provide some support for the idea that D1-like receptors mediate the reward signal, and provide a standard to which the effects of CLZ may be compared. Unfortunately, the effects of CLZ have not been tested using this approach (Table 2, 3.1.2.3).

3.1.2.4. Self-regulation of stimulation: duration. Atrens and colleagues (16) employ a rate-independent shuttle-box variation of the self-stimulation paradigm with two levers to concurrently measure the reward (latency to initiate BSR, i.e. ON latency) and performance (latency to terminate BSR, i.e. OFF latency) aspects of the task. Placing a physical barrier in the runway to increase the performance demands of the task similarly increases both ON and OFF latencies (168). However, if a drug selectively elevates the initiation latency (ON), then the drug may be interpreted as having a selective effect on reward mechanisms. Treatment with HAL (0.025, 0.05 and 0. 1 mg/kg, ip) produces parallel increases in both ON and OFF latencies (16). These results are difficult to interpret as a reduction in reward induced by HAL challenge cannot be separated from the motoric

impairment. HAL (0.03 mg/kg, ip) is also reported to selectively increase ON latency with higher doses (0.1 and 0.3 mg/kg) producing non-selective increases in both ON and OFF latencies. CLZ selectively and dose-dependently decreased reward, an effect that is clearly dissociable from motoric impairment (16,168). Thus, in this paradigm, CLZ seems to have exclusively anti-reward effects while HAL may have anti-reward and/or performance effects. This is precisely the result that the D1-like hypothesis of antipsychotic drug action predicts. It would also be predicted that SCH 23390, or similar antagonists selective for the D1-like receptor, would decrease reward without affecting motor performance. Unfortunately, the effects of SCH 23390 have not been studied in this paradigm (Table 2, 3.1.2.4).

3.1.2.5. Self-regulation of stimulation: intensity. Using the premise that animals regulate stimulation intensity, Stein and Ray (299) developed a modification of the BSR paradigm. Depression of one of the two levers, the active lever, results in BSR delivered to the animal. With each operant emission, however, the current intensity decreases. If the animal presses the (second) reset lever, the current intensity on the active lever is reset to a safe maximal level. Threshold is defined as the mean current intensity at which animals perform the reset response. HAL induces a dose-dependent decrease in response rate (a measure of performance) and an increase in reward threshold (a measure of reward) (267). Thus, the reward-reducing effects of HAL occur at doses that produce motoric effects. In contrast, CLZ increases reward thresholds at doses that do not produce motoric deficits (267). With higher doses of CLZ, decreases in response rates become apparent. These authors also point out the similarities between the behavioral disruption produced by low doses of CLZ and that which resulted from equipment failure-induced extinction. Therefore, in yet another operant paradigm, CLZ seems to have an anti-reward effect that is independent of any performance effects, whereas HAL appears to impair both reward and performance. We know of no reports of the effects of a D1-like receptor antagonist in this paradigm (Table 2, 3.1.2.5).

3.1.2.6. Brain stimulation reward: summary. The findings based on BSR implicate both D2-like and D1-like receptors in reward. However, it appears that D2-like antagonists may decrease reward via an action on (or at least in concert with) performance variables, whereas D1-like antagonists may have specific reward-antagonizing properties. The D1 hypothesis of antipsychotic drug action predicts that CLZ would decrease reward without motor interference. The present findings provide some support for this hypothesis.

3.1.3. Psychomotor stimulant reward (amphetamine and cocaine)

Psychomotor stimulants, such as cocaine and amphetamine, are readily self-administered by laboratory rats (237). Animals learn to press a lever to receive intravenous amphetamine or cocaine and compensate for a decrease in concentration of drug per injection (e.g. decrease in reward value) by increasing the number of operant responses emitted (238,336,341). When saline is substituted for the psychomotor stimulant, the animal increases and then decreases responding to extinction (238).

Patterns of self-administration are also sensitive to manipulations of DA function. Thus, low doses of classic neuroleptics (D2-like antagonists), such as pimozide (83,339,341) and HAL (247), increase the rate of self-administration. This effect is interpreted as reflecting a partial blockade of DA receptors that produces a partial blockade of the rewarding effects of cocaine. With higher doses of typical neuroleptics, animals initially exhibit higher, followed by lower, responding, in a profile argued to be functionally analogous to extinction (339,341). Challenges with typical neuroleptics, therefore, induce a dose-dependent biphasic effect on cocaine self-administration.

The effects of D1-like receptor antagonists on the self-administration of cocaine are ambiguous. SCH 23390 has been reported to dose-dependently increase operant responding for cocaine in rats (38,159), or produce no effect or decrease responding in monkeys (although one out of five monkeys show an increase following the lowest dose) (339). The D1-like antagonist, A69045, induces a biphasic pattern of responding (38). Discrepancies in the above findings may be due to differences in species, cocaine and/or antagonist dose, schedule of reinforcement and inclusion of 'time out' periods that minimize the direct effect of a drug on behavior and decrease cumulative effects of drug injection (63). By varying both the doses of cocaine and antagonist, a biphasic pattern of responding emerged following SCH 23390 challenge (63). Thus, at low doses, SCH 23390 increases responding (decreases the rewarding efficacy of cocaine). In contrast, with high doses, SCH 23390 decreases responding irrespective of cocaine dose, thus showing direct response-reducing effects. Recently, Maldonado and colleagues (183) report that injections of SCH 23390 directly into the nucleus accumbens increase self-administration of cocaine on an FR 5 schedule. This increase is not accompanied by a change in the pattern of responding, except for a decrease in interval between injections of cocaine. Therefore, D1-like receptor antagonists may induce increases or decreases in responding, depending on the doses of agonist and antagonist used.

Discrepancies are reported regarding the effects of CLZ in the self-administration paradigm. Roberts and Vickers (247) report that CLZ produces a dose-dependent decrease in rats. However, a recent paper finds that a biphasic pattern of responding emerged following CLZ administration in rats self-administering cocaine. Thus, low doses of CLZ increase responding, in a profile the authors describe as similar to that produced following a decrease of cocaine dose in an otherwise untreated monkey (317). On the other hand, a decrease in responding is produced by a higher dose of CLZ. This pattern of responding is consistent with the interpretation that CLZ blocks the rewarding effect of cocaine (although the authors question the specificity of this effect as several monkeys failed to 'sample' the reward). The reasons for the discrepancy regarding the effects of CLZ in this test are unclear; possible factors are species or methodological differences.

Overall, the results from this paradigm are inconclusive. Self-administration behavior when challenged with a DA antagonist is complex and not easy to predict from theory. "A decrease in the rate of drug intake has been thought to indicate either an increase or a decrease in the drug's

reinforcing efficacy'' (176, p. 559). Furthermore, there is no clear consensus on the effects of the D1-like and D2-like receptor antagonists in this paradigm, making these difficult comparison groups. However, the most recent studies suggest that both D1-like and D2-like receptors are involved in psychomotor stimulant self-administration and that CLZ may produce a pattern of behavior similar to antagonists acting at either receptor subtype (Table 2, 3.1.3).

3.1.3.1. Progressive ratio. In a modification of the traditional schedules used in the self-administration paradigm, the progressive ratio schedule systematically increases the number of responses required to obtain the reward (cocaine injection) until response levels fall below some criterion (176,248). This breakpoint is used as an indicator of the rewarding value of the drug. The breakpoint maintained by cocaine is generally increased as a function of increasing cocaine dose. Very low doses of HAL decrease the breakpoint for cocaine administration (248). Similarly, SCH 23390 produces a dose-dependent decrease in cocaine breakpoint (82,142) across a variety of cocaine doses (82). Loh and colleagues, however, report that CLZ (10 mg/kg) significantly increases the break point for cocaine, whereas higher and lower doses of CLZ (5 and 20 mg/kg) are without effect (176). However, CLZ (20 mg/kg) significantly decreases the break point in some animals. Depoortere et al. (82) speculate that the somewhat surprising effects produced by CLZ in this paradigm may be traced to the single dose of cocaine tested. It is interesting that the increase in breakpoint produced by CLZ fails to display dose-dependency (Table 2, 3.1.3.1).

The increase in breakpoint that may be produced by CLZ may not be explained by an anti-serotonergic action. Although Loh and Roberts (177) report that selective lesion of brain 5HT systems could increase cocaine self-administration by rats responding under a progressive ratio schedule, Lacosta and Roberts (162) found that a mixed 5-HT_1/5-HT_2 antagonist as well as a 5-HT_2 and 5-HT_3 antagonist had no effect on breakpoints maintained by cocaine.

3.2. Conditioned place preference

The conditioned place preference (CPP) paradigm involves pairing one distinct but neutral environment with a rewarding stimulus and another neutral environment with a non-rewarding stimulus. Animals subsequently given a chance to spend time in both environments exhibit a CPP for environments previously associated with rewarding stimuli, such as amphetamine (e.g. (295)) or cocaine (e.g. (210)). A strength of this paradigm is that animals are tested drug-free, thus circumventing the reward/performance debate.

Administration of D1-like or D2-like antagonists during the environment-reward pairings phase of the experiment antagonizes the subsequent CPP. The development of a CPP to amphetamine is blocked by HAL (e.g. (295)) as well as SCH 23390 (133,165). In addition, CLZ blocks the acquisition of a CPP to amphetamine (134) or cocaine (160).

Thus, in a paradigm argued to directly assess a drug's reward properties, with little interference from possible motor confounds, CLZ, like D1- and D2-like antagonists, blocks the rewarding properties of amphetamine and cocaine. The findings with CLZ are at odds with the Loh et al.'s report (176) that CLZ increases the breakpoint of cocaine self-administration; the reasons for the discrepancy remain unclear. With respect to the comparison of CLZ with HAL and SCH 23390, as both antagonists similarly block CPP, this paradigm does not provide a means of discriminating the possible differential effects of CLZ at D1-like vs. D2-like receptors (Table 2, 3.2).

3.3. Drug discrimination

Psychoactive drugs induce a unique set of physical stimuli that permit animals to discriminate between a drugged and a non-drugged state, and may thus function as the discriminative stimuli or 'internal cues' for response selection in drug discrimination paradigms (see (20)).

Both D1-like and D2-like antagonists (at least partially) block the cue effect generated by amphetamine or cocaine (43,60,225,315). Although Schecter (268) finds that high doses of CLZ fail to antagonize the cueing effect of amphetamine, this dose range may have been too high as Nielsen and Jespen (225) report that a lower dose of CLZ (1–2 mg/kg) partially disrupts amphetamine's cue. Recently, CLZ has been reported to block the discriminative stimulus properties of cocaine (317). Thus, D1-like and D2-like antagonists and CLZ disrupt the cue effect of psychomotor stimulants (Table 2, 3.3a).

Unlike SCH 23390 (152) and typical neuroleptics (59), the cue properties produced by CLZ may serve as a discriminative stimulus (334) (Table 2, 3.3b). In rats trained to discriminate CLZ from saline, a D2-like receptor antagonist (HAL (122,334)), a D1-like receptor antagonist (SCH 23390 (224,319)), serotonergic agents (5-HT_2: ketanserin (224), ritanserin (334); 5-HT_3: MDL 72222 (334); 5-HT_{1A} agonist: buspirone (334)) and prazosin (224) fail to substitute for the CLZ stimulus. In contrast, a complete substitution for the CLZ cue is supported by high doses of atropine or scopolamine (224). A report of the failure of atropine to substitute for the CLZ cue may be attributed to the low dose of atropine used (6 mg/kg, po) (122). Taken together, these results show that CLZ does not rely for it cue effects on either D2-like, D1-like or serotonergic blockade alone. Instead, support is given to the anticholinergic properties of CLZ, at least in the cue effect. These results do not provide support for the D1 hypothesis of antipsychotic drug action as the cue properties of CLZ cannot be attributed to a D1-like or D2-like mechanism alone. However, neither class of DA antagonist has, by itself, any definite cue effect, as judged from experiments with receptor-specific drugs. On the other hand, the results are consistent with the prediction that the anticholinergic mechanism of CLZ may be important to its mechanism of action.

3.4. Conditioned avoidance responding (CAR)

The development of modern methods of neuroleptic research may be traced back to the finding that CPZ disrupts the performance of rats trained to jump on to a pole in order to avoid an impending shock (66). The conditioned avoidance response (CAR) paradigm requires animals to emit an operant (for instance pressing a bar, performing a shuttle or

jumping on to a platform) in response to a warning tone or other conditioned stimulus (CS) in order to avoid the onset of an aversive stimulus (such as a shock). Failure to perform the operant results in the presentation of the aversive stimulus, from which the animal can then escape by performing the operant (77,226). This paradigm is of particular interest to the study of antipsychotic drugs as these compounds produce a unique profile; they disrupt the animals' ability to avoid shocks at doses that do not prevent escape from the shocks (6,77). Anxiolytic and sedative compounds disrupt avoidance and escape responding at roughly equal doses (61,258). Thus, the CAR paradigm may predict potential antipsychotic activity in humans (189).

In previously trained animals, acute administration of D2-like antagonists, including HAL (6,39,258,329), pimozide (6), and metoclopramide (6), disrupt the performance of CAR. Likewise, D1-like antagonists, such as SCH 23390, (113,144,260,330) and SCH 39166 (52), and the atypical antipsychotic, CLZ (6,39,258,329), produce dose-related disruptions of avoidance responding (Table 2, 3.4).

Using a variety of DA antagonists with differing affinities for D1-like and D2-like receptor subtypes, McQuade and colleagues (189) find that both D1-like and D2-like selective antagonists impair CAR performance. For drugs that exhibit affinities for both receptors, the receptor for which the drug shows greatest absolute affinity determines the behavioral response. Thus, correlations between D1-like antagonism and D2-like antagonism and minimal effective dose for CAR disruption are noted.

Several researchers have assessed the response decrement patterns produced by drugs in the CAR paradigm. Both within-session (260) and across-session (29,39,258) declines in avoidance responding are produced by HAL. SCH 23390, on the other hand, fails to produce a within-session or across-session decline in CAR responding (260). CLZ induces a performance decrement that is greatest on the first (258) or second (29) day of administration but responding returns to control levels within 3 days. The effects of CLZ on intra-session patterns of avoidance responding have not been reported. Thus, as in other paradigms reviewed in the present article, HAL induces both a within- and across-session decline. CLZ and SCH 23390 clearly do not induce across-session decrements, possibly attesting to their similarity (Table 2, 3.4a,b).

Britton and colleagues (39), using the mouse shuttle avoidance and rat step-up versions of the CAR paradigm, find that both HAL and CLZ impair the performance of avoidance responding. At higher doses, HAL also increases escape failures, whereas CLZ does not, even at the highest dose tested. Thus, at least part of the HAL induced-disruption of CAR may be due to motor impairments. This is consistent with the D1 hypothesis of antipsychotic action, which predicts that HAL would produce antipsychotic actions through a performance deficit.

4. CONCLUSIONS

The present review suggests the following conclusions. When unconditioned behavioral effects of dopaminergic agents are considered, it is clear that D1-like and D2-like receptor antagonists can be seen to have different effects in a number of paradigms. In a majority of these paradigms, when CLZ is evaluated, CLZ is found to produce behavioral effects similar to those produced by D1-like antagonists (Table 1). These results provide strong support for the hypothesis that CLZ may produce its behavioral effects by its action at the D1-like receptor, as suggested by Miller et al. (201).

The same conclusion is not possible when conditioned behaviors are considered. However, this situation arises, not because CLZ and D1-like receptor antagonists generally have different effects in these paradigms (they do not), but because D1-like and D2-like antagonists generally fail to produce different behavioral effects in tests of conditioned behaviors (Table 2) as concluded previously by Beninger (24). Thus, in the majority of conditioned behaviors that are used in the evaluation of DA antagonist effects, D1-like and D2-like receptor antagonists are found to produce similar effects. In these same paradigms, CLZ usually produces effects that cannot be discriminated from those of DA receptor subtype-specific agents. Generally, tests of conditioned behaviors do not provide an appropriate vehicle for assessing the possible similarly of CLZ to D1-like or D2-like antagonists.

From the present review, we conclude that, in most instances, when a behavioral test is employed that reveals clear differences between the actions of D1-like and D2-like receptor antagonists, CLZ produces effects similar to those produced by the D1-like antagonists. There are, in addition, a number of behavioral paradigms where data are incomplete (indicated by '?' in Tables 1 and 2). Some of these areas may provide additional incisive tests of the similarity of CLZ to D1-like antagonists. Overall, the evidence reviewed supports the hypothesis of Miller et al. (201), suggesting that the important aspect of the pharmacological action of CLZ in its effectiveness as an antipsychotic agent is its ability to block D1-like receptors. This conclusion is consistent with the suggestion that it may be excessive activation of D1-like receptors that leads to schizophrenia (179,198,201).

CLZ has similar in vitro affinities for D1-like and D2-like receptors (96). However, as pointed out by Coward et al. (67), in vitro conditions never completely mimic the in vivo environment and may contribute little to our understanding of the functional consequence of these binding affinities. Using a trans-striatal dialysis technique in the unanesthetized rat, Coward and colleagues concluded that, functionally, CLZ exerts a preferential blockade of D1-like receptors (67).

The mechanism by which CLZ exerts its atypical antipsychotic actions is not yet known definitively. The most popular views for the action of atypical antipsychotic drugs are that they combine D2 with 5-HT_{2A} blockade (191–193) or that they bind with high affinity to D4 receptors (316). The first hypothesis has empirical support, in terms of correlations between clinical effects and receptor affinities. However, this D2/5-HT_{2A} hypothesis has little theoretical support, from either biophysics, electrophysiology or animal behavior, which would explain how 5-HT_2 receptors may be involved in psychosis or antipsychotic actions. Furthermore, ocaperidone, a new drug that has a strong affinity for 5-HT_2 and D2 receptors produces extrapyramidal side-effects, unlike CLZ (227). None the less, the possibility that an interaction between 5-HT_2 and D2-like receptor blockade contributes to the unique action of CLZ

remains intriguing, and further study is clearly indicated to clarify the role of these mechanisms in the antipsychotic action of CLZ.

Data both supporting and refuting the D4 hypothesis have also been reported. For instance, Roth and colleagues (253a) determined the affinities for D2, D4 and 5-HT_{2A} receptors of 25 antipsychotic drugs, classified as typical or atypical depending on their liability to induce EPS. These authors report that neither the D4 affinity nor the D2/D4 ratio nor D4/-$5HT_{2A}$ ratio reliably differentiated between typical and atypical antipsychotic drugs, whereas the D2/5-HT_{2A} ratio had some predictive validity. They conclude that the "D4 receptor cannot be used as a single indicator of typical or atypical nature of an antipsychotic drug" (p. 368).

Support for the D4 hypothesis of the antipsychotic action of CLZ derives from the finding that the striatum of schizophrenic patients has a sixfold higher than normal density of D4 receptors (278,282,283). Raclopride displacement was used to examine the D4 component of D2-like receptors in this study as no D4 receptor-specific ligand is currently available. As no significant changes are observed between schizophrenic patients who were on long-term antipsychotic drug treatment and drug-naïve patients, the author concludes that the increased density was not as a result of drug treatment. The finding of elevated D4 densities in the striatum of schizophrenic patients remains controversial (211a,303). The result is not replicated in a similar study (243,244). Further study focusing on the D4 receptor in the mechanism of action of atypical antipsychotics is needed. This process is currently hampered by the lack of a D4 receptor-specific ligand.

The present paper examines the merits of the D1-like hypothesis of antipsychotic action. There may be a variety of pathways to antipsychotic action that converge on a final common pathway (e.g. reduction of activation of D1-like receptors). We admit that the central piece of empirical evidence for our hypothesis is not yet available, viz., a controlled clinical trial with a D1-like antagonist in psychotic patients. Recently, the results of three open trials with SCH 39166 in schizophrenic patients have been reported (79,81,156). No convincing benefit for positive symptoms is found, although some improvement in negative symptoms is seen in the study by DenBoer et al. ((81), cf. (19)). In a number of patients, SCH 39166 produces aversive side-effects that led to early withdrawal from the study. An interesting observation reported by de Beaurepaire et al. (79) is that five of their six patients had an exacerbation of symptoms upon withdrawal of treatment with SCH 39166. This implies that rebound activation of D1-like receptors may contribute to psychotic symptoms. In the present context, it is noteworthy that a similar observation of psychotic rebound was reported following termination with CLZ (233). One report of preliminary clinical evidence from a phase II study on the selective D1-like antagonist NNC 01-0687 reveals a mild antipsychotic effect without EPS (114,155). As Barnes and Gerlach (19) point out, "...the effects of other D1 antagonists have to be evaluated in schizophrenia as different D1 antagonists may have different effects" (p. 288).

The great merit of our hypothesis, however, is that it attempts to provide a theoretical basis for: (i) the fact that, with classical neuroleptic drugs, the effective dose is closely related to the dose that produces minimal motor side-effects (187); (ii) the fact that CLZ, a known D1 like antagonist, produces antipsychotic effects, while producing relatively few acute dyskinesias, and with levels of D2-like occupancy apparently too low to be effective; (iii) by a rather complex set of arguments, the details of positive symptoms can be explained in terms of excess D1-like activation (198); (iv) this theoretical framework has been extended recently to give an explanation of the basis of those cases of neuroleptic-refractory schizophrenia that respond favorably to CLZ (200).

CLZ was first developed and tested in the 1960s (154). In 1975, granulocytopenia developed in 16 patients treated with CLZ, whereas agranulocytosis developed in 13 patients (80,126). Eight deaths resulted (80,126). Because of these associated risks, the use of CLZ is restricted in many countries (153,154). Thus, it is imperative to understand the unique mechanism of action of CLZ in an effort to reproduce its superior clinical efficacy. From the evidence presented in this paper, we would recommend that D1-like antagonists be developed and tested for antipsychotic effectiveness without motor side-effects. Like CLZ, such drugs may also be elective antipsychotic agents in otherwise drug-refractory psychotic patients, which would be an indication that they are acting at the final target for several classes of antipsychotic drugs, rather than indirectly.

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