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Catalepsy as a rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability

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Abstract The predictive validity of catalepsy as a rodent model for detecting the extrapyramidal side effects (EPS) of antipsychotic drugs was recently questioned when the novel antipsychotic savoxepine produced little catalepsy in rodents while producing significant EPS in schizophrenic patients. Because catalepsy is viewed as an important model for predicting EPS, we decided to re-evaluate the effects of savoxepine. Savoxepine, clozapine, haloperidol, olanzapine, ORG 5222, raclopride, and risperidone were examined in two tests for catalepsy (grid and bar tests) in male Sprague-Dawley rats. The ability to antagonize amphetamine-induced hypermotility was also examined, since this measure is believed to predict clinical efficacy. With the exception of clozapine, all drugs produced dose-dependent catalepsy in both tests. For each drug, the minimum effective dose for producing catalepsy was greater than or equal to the ED_{50} for antagonizing amphetamine-induced hyperactivity (defined as the dose producing a 50% reduction in hyperactivity). Clozapine resulted in the widest separation of effective doses in the catalepsy and activity models. Raclopride produced the next largest separation while the remaining drugs resulted in only a one- or two-fold dose separation between the two behavioral tests. The results with haloperidol and clozapine are consistent with the clinical effects of these drugs (severe versus mild EPS). The ratios of effective doses in catalepsy and activity for the remaining novel drugs are also consistent with preliminary clinical findings indicating some EPS with each of these compounds. Thus, catalepsy remains a suitable rodent model for detecting compounds with EPS liability in humans.

Key words Catalepsy · Rodent model · Antipsychotic drugs · Extrapyramidal side effects

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Introduction

Classical antipsychotic drugs produce adverse neurological side effects involving akathesia, parkinsonism and acute dystonia (Baldessarini 1990). With prolonged exposure, the often irreversible disorder of tardive dyskinesia may develop (Baldessarini 1990). Clozapine is the only antipsychotic that produces a very low incidence of extrapyramidal side effects (EPS) and virtually no tardive dyskinesia (Casey 1989). Unfortunately, the potentially fatal agranulocytosis associated with clozapine prevents its widespread use (Krupp and Barnes 1992).

There is an enormous effort to develop novel antipsychotic drugs that do not produce EPS. A number of behavioral paradigms in both rodents and primates have been developed to predict EPS liability in humans. In rodents, the most common behavioral model is catalepsy, which is defined as an inability to correct an unusual posture (Sanberg et al. 1988). Most drugs that are effective in treating schizophrenia produce EPS in humans and produce marked catalepsy in rodents (Costall and Naylor 1973; Arnt 1982). In contrast, the atypical antipsychotic clozapine produces minimal EPS in humans and fails to produce catalepsy in rodents (Costall and Naylor 1973; Arnt 1982). Largely because of this relationship, catalepsy is viewed as a critical screening model for predicting EPS liability in humans.

The tetracyclic savoxepine (citatepine) is a novel antipsychotic agent (Moller et al. 1989) with high affinity for D_1, D_2, 5-HT_2, and α_1-adrenergic receptors (Waldmeier et al. 1986; Bischoff 1992). The drug also shows preferential binding to D_2 dopamine receptors of the hippocampus relative to the striatum (Bischoff 1992). Savoxepine produced some catalepsy in rodents but the doses were much greater than those necessary to block amphetamine-induced stereotypy or activity (Bischoff 1992). On this basis, the drug was hypothesized to have an "atypical neuroleptic response pattern

with a significantly reduced extrapyramidal side-effect liability" (Wetzel et al. 1991, p. 280). However, when the drug was tested in an open clinical trial of 12 schizophrenic individuals, the majority of patients demonstrated extrapyramidal symptoms of acute dystonic reaction, parkinsonism and akathesia (Wetzel et al. 1991). The authors concluded that "the predictive validity of the animal models in question used to separate antipsychotic effects from extrapyramidal reactions may be ill-founded" (p. 280).

Because catalepsy is viewed as an important rodent model for predicting EPS liability in humans, we decided to re-evaluate the effects of savoxepine in catalepsy. We also tested the effects of savoxepine on amphetamine-induced locomotor activity, since this measure is believed to reflect the potential efficacy of the drug in treating psychotic symptoms. The effective doses in each of these models were compared with the effective doses of a number of other antipsychotic agents, including the atypical antipsychotic clozapine, the D_2 selective antagonist raclopride and the novel 5-HT_2/D_2 antipsychotics olanzapine, ORG 5222 and risperidone.

Materials and methods

Subjects

Male Sprague-Dawley rats (SASCO, St Louis, Mo.) weighing 200–350 g served as subjects. The animals were housed in groups of two in a temperature-controlled (21 ± 1°C) animal facility on a 12-h light-dark cycle (lights on at 0700 hours) and had free access to food and water. Each rat was experimentally naive and tested once. Testing occurred during the light phase of the day-night cycle.

Apparatus

Catalepsy was estimated using two tests. In the bar test, the forepaws of the rat were placed on a bar covered with rubber tubing (1 cm diameter) located 10 cm above the table surface. In the grid test, the entire rat was placed on a wood-framed (46 cm × 34 cm) wire grid (1.2-cm squares) at an angle of 50 degrees with the table surface.

Locomotor activity was measured in eight computerized Digiscan-16 Animal Activity Monitors (Model 1300JC/CCDigi, Version 2.3, Omnitech Electronics, Columbus, Ohio) equipped with 48 infrared photocell emittors and detectors (2.5 cm between sensors). Each box (41.25 × 41.25 × 30 cm) was constructed of Plexiglas sides and floor. Horizontal activity was detected by 16 horizontal sensors on the front to back walls and 16 sensors on the side to side walls located 5 cm above the cage floor. Vertical activity was detected by 16 sensors on the side to side walls located 13.5 cm above the cage floor.

Procedure

Clozapine, haloperidol, ORG 5222, olanzapine, raclopride, risperidone and savoxepine were administered 15 or 30 min (see Drugs) prior to catalepsy testing. Catalepsy was measured using two methods. The bar test involved placing the forepaws of the rat on a 10-cm high bar. Catalepsy was determined by the amount of time the rat's forepaws remained on the bar. The trial was terminated when one forepaw was removed from the bar and touched the ground or when 60 s had passed. The grid test involved placing the rat on a wire grid. The forelimbs were spread and catalepsy was determined by the length of time the animal maintained this position. Testing was terminated when any limb moved or when 60 s had passed.

Catalepsy tests were repeated at 30-min intervals over a 2-h period (i.e., 0, 30, 60, 90, 120 min). At each time interval, the rat was tested in both models sequentially with the order of testing alternating between rats within a particular group. If the rat did not assume the position on the bar or grid after three attempts, it received a score of 0 s.

The effects of various doses of the putative antipsychotics on amphetamine-induced locomotor activity were tested in separate groups of rats. The rats were pretreated with clozapine, haloperidol, ORG 5222, olanzapine, raclopride, risperidone or savoxepine. Following the appropriate pretreatment time (see Drugs), rats were administered 2.0 mg/kg *d*-amphetamine (IP) and placed immediately into the activity boxes. Horizontal and vertical (rearing) activity were measured for 1 h.

Drugs

Clozapine (Sandoz, USA), haloperidol (Sigma, St Louis, Mo.), olanzapine (Eli Lilly and Company, USA) ORG 5222 (N.V. Organon, The Netherlands), risperidone (Janssen Pharmaceutica, Belgium) and savoxepine (Ciba Geigy Pharmaceuticals, Switzerland) were dissolved in 0.98 ml 1% lactic acid, buffered with 0.02 ml 0.1 N NaOH and 1 ml distilled water (final pH: 2.5–3.0). Raclopride was dissolved in distilled water. *d*-Amphetamine sulfate (Sigma, St Louis, Mo.) was dissolved in physiological saline (0.9%). Amphetamine was administered intraperitoneal (IP); the remaining drugs were administered subcutaneously in a volume of 1 mg/ml. Raclopride was injected 15 min prior to amphetamine in the activity test or 15 min prior to the first catalepsy test. The remaining drugs were administered 30 min prior to amphetamine and catalepsy testing.

Statistical analyses

Horizontal and vertical activity represent the total number of photocell beam interruptions during the 1-h test session. The log transformation of each measure was subjected to a one-way ANOVA followed by Fisher's Least Significant Difference post-hoc test. Antagonism of amphetamine-induced hyperactivity was also expressed as the percent decrease in horizontal and vertical activity induced by amphetamine alone. The ED_{50} for antagonism of amphetamine-induced hyperactivity (defined as the dose producing a 50% reduction in hyperactivity) was determined by linear regression analysis of drug-treated groups. The regression analysis was conducted on the average of the horizontal and vertical activity percentage scores.

Catalepsy tests were conducted every 30 min over a 2-h period. The total amount of time spent immobile across the five tests was calculated and a one-way analysis of variance (ANOVA) followed by Fisher's Least Significant Difference post-hoc test was conducted on the log transformation of the catalepsy scores for each drug. The average of the bar and grid catalepsy scores was also analyzed and the minimum effective dose (defined as the lowest dose tested that produced a significant effect relative to the vehicle control group using a Fisher's LSD post-hoc test, $P < 0.05$) was determined.

Results

The effects of each antipsychotic on amphetamine-induced horizontal and vertical activity are presented

in Table 1. Amphetamine produced a large increase in both horizontal and vertical activity; these values were significantly greater than the horizontal and vertical activity scores (10 920 and 1116, respectively, $n = 8$) obtained from rats that were not treated with amphetamine ($P < 0.05$). Each antipsychotic, including clozapine, produced a significant and dose-dependent decline in amphetamine-induced activity (see Table 2). In general, the moderate to high doses of each drug resulted in a significant decrease in horizontal and vertical activity (see Table 1).

Table 1 Mean (± SEM) horizontal and vertical activity scores in rats treated with 2.0 mg/kg *d*-amphetamine

	Horizontal activity	Vertical activity
Clozapine (mg/kg)		
0 ($n = 15$)	25 898 (2177)	2 380 (328)
0.1 ($n = 6$)	22 258 (3042)	2 059 (532)
0.5 ($n = 11$)	23 418 (2177)	1 988 (502)
1.0 ($n = 13$)	17 881 (2423)*	1 044 (290)*
2.0 ($n = 7$)	16 128 (2156)	568 (297)**
5.0 ($n = 12$)	6 508 (2059)**	47 (17)**
10.0 ($n = 5$)	4 258 (1386)**	14 (6)**
Haloperidol (mg/kg)		
0 ($n = 12$)	26 330 (1785)	2 686 (376)
0.005 ($n = 4$)	31 028 (908)	3 269 (536)
0.010 ($n = 10$)	28 807 (2392)	3 031 (497)
0.025 ($n = 8$)	20 683 (2190)	1 729 (280)
0.05 ($n = 7$)	14 465 (1883)**	1 192 (170)*
0.1 ($n = 6$)	5 096 (699)**	442 (113)**
0.5 ($n = 5$)	3 629 (1840)**	215 (155)**
Olanzapine (mg/kg)		
0 ($n = 6$)	27 627 (2520)	2 470 (369)
0.06 ($n = 6$)	27 018 (2373)	2 813 (415)
0.125 ($n = 6$)	25 870 (1800)	3 038 (477)
0.25 ($n = 6$)	22 807 (2157)	2 323 (660)
0.5 ($n = 6$)	22 441 (3389)	1 649 (362)
1.0 ($n = 6$)	18 312 (2057)*	1 518 (201)
2.0 ($n = 6$)	11 037 (2112)**	690 (176)**
4.0 ($n = 6$)	8 072 (707)**	297 (69)**
ORG 5222 (mg/kg)		
0 ($n = 8$)	25 147 (3091)	2 628 (447)
0.01 ($n = 6$)	22 593 (1517)	2 589 (274)
0.05 ($n = 7$)	23 382 (1239)	2 161 (360)
0.1 ($n = 8$)	13 990 (1211)**	950 (171)
0.5 ($n = 7$)	1 686 (319)**	46 (20)**
1.0 ($n = 4$)	533 (134)**	13 (11)**
Raclopride (mg/kg)		
0 ($n = 10$)	30 464 (1874)	2 379 (221)
0.01 ($n = 8$)	29 931 (1593)	2 252 (326)
0.025 ($n = 8$)	26 769 (2812)	1 955 (189)
0.05 ($n = 7$)	17 726 (1432)**	1 415 (139)*
0.10 ($n = 5$)	13 572 (2073)**	1 102 (181)**
0.25 ($n = 4$)	9 182 (1171)**	734 (234)**
0.5 ($n = 5$)	5 583 (998)**	366 (75)**
Risperidone (mg/kg)		
0 ($n = 6$)	20 515 (1167)	1 636 (455)
0.05 ($n = 7$)	22 563 (2331)	1 412 (198)
0.1 ($n = 8$)	19 515 (3478)	1 403 (311)
0.5 ($n = 6$)	11 804 (1942)**	644 (160)*
1.0 ($n = 5$)	6 886 (1693)**	263 (111)**
5.0 ($n = 4$)	765 (80)**	5 (1)**
Savoxepine (mg/kg)		
0 ($n = 6$)	26 921 (1649)	2 707 (442)
0.01 ($n = 6$)	25 746 (2443)	3 058 (402)
0.05 ($n = 6$)	23 057 (1686)	2 572 (366)
0.1 ($n = 6$)	20 239 (1496)	2 035 (165)
0.5 ($n = 6$)	5 809 (1131)**	689 (174)**
1.0 ($n = 6$)	2 783 (373)**	192 (46)**

*$P < 0.05$, **$P < 0.01$, significantly different from the Vehicle (0 mg/kg) group

Table 2 Degrees of freedom (*df*) and *F*-values resulting from one-way ANOVAs conducted on the horizontal and vertical activity scores

	df	*F*-values Horizontal	Vertical
Clozapine	(6, 62)	15.04*	28.51*
Haloperidol	(6, 45)	47.48*	22.32*
Olanzapine	(7, 40)	14.89*	12.49*
ORG 5222	(5, 34)	148.92*	40.59*
Raclopride	(6, 40)	39.13*	19.66*
Risperidone	(5, 30)	55.78*	47.39*
Savoxepine	(5, 30)	72.13*	36.21*

*$P < 0.001$

The total bar and grid catalepsy scores (in seconds) for each drug are presented in Table 3. Clozapine failed to produce catalepsy while the remaining classical and novel antipsychotics produced dose-dependent catalepsy. These observations were supported statistically. Each drug, with the exception of clozapine, produced a significant main effect of dose within each catalepsy test (see Table 4). In general, the moderate to high doses of each drug resulted in significantly greater immobility time compared to the appropriate vehicle group (see Table 3); the grid test tended to be somewhat more sensitive than the bar test in detecting cataleptic effects.

A comparison of the effects of clozapine, haloperidol and savoxepine on amphetamine-induced locomotor activity and catalepsy are illustrated in Fig. 1. Unlike clozapine, savoxepine produced dose-related catalepsy. The magnitude of the cataleptic response was similar to that observed in haloperidol-treated rats. Savoxepine was also like haloperidol in that the effective dose range for producing catalepsy overlapped with the effective dose range for antagonizing amphetamine-induced locomotor activity.

The similarity between haloperidol and savoxepine is also illustrated when the minimum effective dose (MED) for catalepsy and the ED_{50} for antagonizing amphetamine-induced locomotor activity are compared (see Table 5). In general, for each drug the MED for producing catalepsy was either greater than or equal to the ED_{50} for antagonizing amphetamine-induced activity. Clozapine resulted in the widest separation of effective doses in the catalepsy and activity models. Raclopride produced the next largest separation while the remaining drugs, including savoxepine, resulted in only a one- or two-fold dose separation between the two tests.

Table 3 Total (± SEM) amount of time (s) spent immobile in each catalepsy test

	Bar test	Grid test
Clozapine (mg/kg)		
0 (n = 8)	10 (2)	11 (7)
1.0 (n = 6)	5 (2)	10 (5)
5.0 (n = 7)	8 (2)	5 (2)
10.0 (n = 6)	14 (2)	3 (1)
20.0 (n = 4)	15 (8)	4 (2)
40.0 (n = 4)	10 (5)	10 (7)
Haloperidol (mg/kg)		
0 (n = 8)	10 (2)	11 (7)
0.05 (n = 6)	16 (5)	23 (11)
0.1 (n = 6)	21 (6)	69 (11)**
0.5 (n = 6)	144 (31)**	181 (31)**
1.0 (n = 6)	176 (33)**	265 (16)**
Olanzapine (mg/kg)		
0 (n = 10)	5 (2)	9 (4)
1.0 (n = 6)	14 (6)	21 (6)**
2.0 (n = 7)	13 (9)	40 (8)**
4.0 (n = 8)	45 (14)**	58 (18)**
8.0 (n = 8)	117 (26)**	151 (24)**
16.0 (n = 8)	221 (18)**	221 (15)**
ORG 5222 (mg/kg)		
0 (n = 6)	3 (1)	1 (1)
0.1 (n = 8)	14 (4)*	25 (8)**
0.5 (n = 7)	103 (23)**	164 (27)**
1.0 (n = 7)	173 (34)**	215 (33)**
Raclopride (mg/kg)		
0 (n = 8)	3 (1)	2 (1)
0.1 (n = 5)	8 (4)	24 (22)
0.25 (n = 5)	13 (7)	7 (4)
0.5 (n = 8)	21 (9)*	15 (7)
1.0 (n=11)	89 (25)**	107 (27)**
2.0 (n = 8)	88 (20)*	108 (19)**
5.0 (n = 8)	119 (27)**	131 (29)**
10.0 (n = 10)	158 (29)**	157 (25)**
20.0 (n = 8)	142 (29)**	153 (34)**
40.0 (n = 4)	203 (30)**	189 (21)**
Risperidone (mg/kg)		
0 (n = 9)	11 (2)	15 (7)
0.5 (n = 6)	13 (6)	48 (17)**
1.0 (n = 8)	31 (14)	55 (20)**
2.0 (n = 7)	174 (32)**	200 (25)**
5.0 (n = 9)	137 (34)**	212 (21)**
10.0 (n=6)	173 (43)**	269 (20)**
Savoxepine (mg/kg)		
0 (n = 6)	11 (3)	9 (4)
0.1 (n = 8)	10 (3)	17 (5)
0.5 (n = 8)	55 (24)	73 (22)**
1.0 (n = 8)	78 (20)**	115 (28)**
5.0 (n = 8)	159 (22)**	197 (8)**

*P < 0.05, **P < 0.01, significantly different from the Vehicle (0 mg/kg) group

Table 4 Degrees of freedom (df) and F-values resulting from one-way ANOVAs conducted on the bar and grid catalepsy scores and the average of these scores

	df	F-values Bar	Grid	Average
Clozapine	(5, 29)	1.7, $P > 0.1$	0.19, $P > 0.1$	0.22, $P > 0.1$
Haloperidol	(4, 27)	26.46*	23.01*	31.33*
Olanzapine	(5, 41)	16.96*	23.36*	27.09*
ORG 5222	(3, 24)	30.42*	47.14*	53.43*
Raclopride	(9, 65)	12.79*	12.56*	14.58*
Risperidone	(5, 39)	11.03*	19.70*	21.91*
Savoxepine	(4, 33)	10.50*	16.47*	18.12*

*P < 0.001

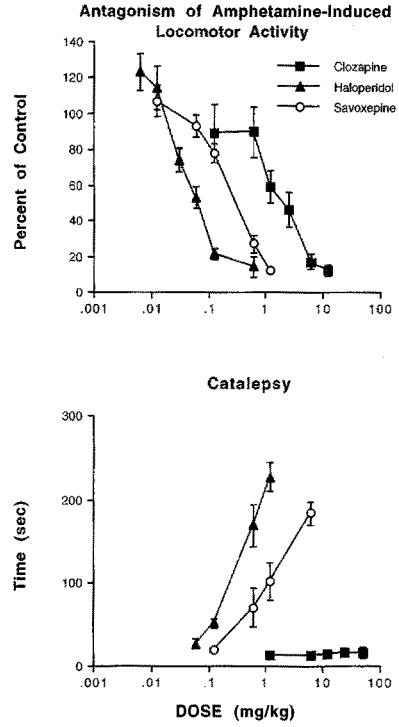

Fig. 1 Effects of clozapine, haloperidol, and savoxepine on amphetamine-induced locomotor activity (*top panel*) and catalepsy (*bottom panel*). Antagonism of amphetamine-induced locomotor activity is expressed as the percent decrease in activity induced by amphetamine alone (Vehicle control group). The values represent the average of the percent decrease on horizontal and vertical activity. The catalepsy scores represent the average of the bar and grid catalepsy scores; these scores were calculated as the total amount of time spent immobile across the five tests

Discussion

In the present study, each antipsychotic produced dose-related decreases in amphetamine-induced horizontal and vertical activity. These data support the idea that antagonism of amphetamine-induced locomotor activity in rodents is predictive of therapeutic efficacy in schizophrenic patients. This is not surprising given that the antagonism of amphetamine-induced activity correlates significantly with D_2 receptor affinity (McInerney et al. 1994), and there exists a significant correlation between D_2 receptor affinity and the average clinical dose for treating schizophrenia (Seeman 1992). Furthermore, in vivo PET studies in schizophrenic patients demonstrate a significant amount of D_2 receptor occupancy (in the range of 70–89%) following conventional dosages of antipsychotic medication (Farde et al. 1992).

Table 5 Minimum effective dose (mg/kg) in the catalepsy tests (average of bar and grid tests) and the ED_{50} (mg/kg) for antagonism of amphetamine-induced activity (average of horizontal and vertical activity)

	Catalepsy	Activity	Ratio[a]
Clozapine	>40	1.58 (0.97–4.54)[b]	>25
Haloperidol	0.1	0.06 (0.05–0.11)	2
Olanzapine	1.0	1.27 (1.01–1.78)	1
ORG 5222	0.1	0.1 (0.089–0.17)	1
Raclopride	0.5	0.087 (0.084–0.092)	6
Risperidone	0.5	0.46 (0.36–0.69)	1
Savoxepine	0.5	0.22 (0.20–0.24)	2

[a] Ratio=$MED_{catalepsy}/ED_{50\,activity}$
[b] 95% confidence interval

It was also demonstrated in the present study that, with the exception of clozapine, each antipsychotic produced dose-related catalepsy in the bar and grid tests. The cataleptic properties of haloperidol are well known (Costall and Naylor 1973; Arnt and Christensen 1981), but catalepsy has also been observed with the novel antipsychotics olanzapine (Moore et al. 1992), ORG 5222 (Broekkamp et al. 1990), raclopride (Ogren et al. 1986), risperidone (Janssen et al. 1988), and savoxepine (Bischoff 1992). In each of these studies, the dose required to produce catalepsy was greater than the dose required to antagonize dopamine agonist-induced motor activity or conditioned avoidance responding. This separation between doses was regarded as a clozapine-like behavioral profile in rodents that may be predictive of fewer EPS in humans. In the present study, the MED for producing catalepsy was greater than or equal to the ED_{50} for antagonizing amphetamine-induced activity. Clozapine demonstrated the widest separation of effective doses while haloperidol, olanzapine, ORG 5222, risperidone and savoxepine showed the narrowest separations. Raclopride was the only novel compound which produced a greater than 1- or 2-fold dose separation.

The comparative effects of these antipsychotics in catalepsy and amphetamine-induced activity are generally consistent with their clinical effects. Haloperidol is a prototypical antipsychotic that produces marked EPS, and clozapine is an atypical antipsychotic that produces very minimal EPS. The remaining drugs are in the clinical phase of development, but preliminary observations in schizophrenic patients suggest that with the exception of olanzapine (in which case preliminary reports have not yet been published), these novel antipsychotic drugs produce EPS. For example, in an open clinical trial, therapeutic doses of savoxepine produced marked EPS in patients suffering from paranoid schizophrenia and schizophreniform disorder (Wetzel et al. 1991). In a double-blind clinical trial comparing ORG 5222 and haloperidol, very few patients treated with ORG 5222 developed EPS, but the main reason for termination in the ORG 5222 group was an inadequate treatment effect (Sitsen and de Vries 1992). Increasing the dose of ORG 5222 to achieve optimal therapeutic efficacy might result in a greater incidence of EPS. Finally, raclopride and risperidone also produced EPS in schizophrenic patients. In a double-blind comparison of raclopride and haloperidol, the raclopride group showed EPS but the incidence was lower than that observed in the haloperidol-treated group (McCreadie 1992). Although this is consistent with the six-fold separation of effective doses in the activity and catalepsy models, the clinical dose of raclopride in humans may have been too low, since the haloperidol group showed a superior therapeutic effect. In two double-blind placebo-controlled studies of risperidone and haloperidol, increasing doses of risperidone (2–16 mg/kg) resulted in a linear increase in parkinsonian side effects; however, patients treated with 6.0 mg/kg risperidone showed a significant improvement in schizophrenic symptoms without showing a significant increase in EPS (Chouinard et al. 1993; Marder and Meibach 1994). Based on this latter finding, one might have predicted a separation of effective doses in the activity and catalepsy tests; the failure to observe this separation may be because the therapeutic dose range of risperidone that is associated with minimal EPS is too narrow.

The most important finding of the present study is the narrow separation of effective doses in catalepsy and activity with savoxepine; this is in line with the clinical effects of savoxepine in schizophrenic patients. The potent cataleptic effects observed in the present study are not consistent with the preclinical findings of Bischoff (1992), who demonstrated little catalepsy with savoxepine at doses that were much higher than those needed to antagonize dopamine agonist-induced behavioral effects. The reason for the discrepancy between studies may be related to the measure of catalepsy; it is known that the magnitude of the cataleptic effect is influenced by apparently minor methodological changes (Morelli and DiChiara 1985; Sanberg et al. 1988). The present study employed the well-known bar and inclined grid tests while Bischoff (1992) employed 3- and 8.5-cm cork tests as well as an ipsilateral fore- and hind-himb crossing test. Savoxepine produced very different effects in the three tests used by Bischoff (1992): while only weak cataleptic effects were observed in the 8.5-cm cork test and the ipsilateral fore- and hind-limb crossing test, over 75% of the rats treated with the lowest dose of savoxepine (1.0 mg/kg) showed catalepsy in the 3-cm cork test. This dose is the same dose that produced a greater than 75% incidence of catalepsy in the haloperidol-treated rats using the same test (Bischoff 1992). Thus, using

the 3-cm cork test, the results from the present study are in fact similar to those of Bischoff (1992). The 3-cm cork test, as well as the bar and grid tests, appears to be more sensitive for detecting catalepsy and may be better suited for predicting EPS liability.

The effects of savoxepine in the present study are also consistent with a recent preclinical study which examined the effects of savoxepine in active avoidance and spontaneous activity. Savoxepine produced potent effects in both of these models and the authors concluded that savoxepine's effects were similar to those produced by classical antipsychotics (Bugarski-Kirola et al. 1994). These data are also consistent with the incidence and severity of EPS in schizophrenic patients treated with savoxepine.

Together, the results from the present study support the predictive validity of catalepsy (using the bar and grid tests) as a rodent model for detecting the EPS liability of potential antipsychotics, especially when the effective cataleptic doses are compared to the effective doses for antagonizing dopamine-mediated behaviors (such as amphetamine-induced activity). Like haloperidol, all of the novel antipsychotics produce dose-related catalepsy in rodents and elicit EPS in schizophrenic patients (olanzapine's effects are still unknown). Clozapine, on the other hand, does not produce catalepsy and produces very minimal EPS in humans. The magnitude of the separation between effective doses in catalepsy and amphetamine-induced activity varies amongst drugs with raclopride producing the largest separation next to clozapine. This suggests that raclopride, although not necessarily free of EPS, may have a superior side-effect profile compared to the other antipsychotics tested. Determination of raclopride's-side effect profile awaits further clinical testing over a wider dose range.

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