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BRIEF COMMUNICATION

Differential Effects of Neuroleptic Drugs on the Delayed Matching-to-Sample Performance of Pigeons[1]

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PICKER, M. J. AND C. A. MASSIE. *Differential effects of neuroleptic drugs on the delayed matching-to-sample performance of pigeons.* PHARMACOL BIOCHEM BEHAV **31**(4) 953–957, 1988.—The effects of clozapine, thiothixene, sulpiride, chlorpromazine and loxapine were examined in pigeons responding under a delayed matching-to-sample (DMTS) procedure using 0-, 2- and 8-sec delay intervals. Chlorpromazine (3–100 mg/kg), thiothixene (0.03–1.7 mg/kg), clozapine (0.1–5.6 mg/kg) and loxapine (0.1–10 mg/kg) produced dose-related decreases in the percent of correct responses (accuracy). With the exception of chlorpromazine, the relative magnitude of the accuracy-decreasing effects were unrelated to the length of the delay interval and the nondrug levels of accuracy. In contrast to these accuracy-decreasing effects, sulpiride (3–300 mg/kg) failed to decrease accuracy across the range of doses evaluated. Chlorpromazine, loxapine and clozapine increased response rates at low doses and then decreased response rates as the dose was increased. Thiothixene and sulpiride only decreased response rates in a dose-dependent fashion. The order of potency for the rate-suppressing effects of these drugs was thiothixene > clozapine = loxapine > chlorpromazine > sulpiride. The results of the present investigation suggest that, despite similar dopamine antagonist properties, neuroleptics produce qualitatively different effects in pigeons responding under DMTS procedures.

Neuroleptics Delayed matching-to-sample Pigeons Loxapine Chlorpromazine Thiothixene Clozapine Sulpiride Antipsychotics Conditional discrimination

NUMEROUS investigations indicate that there are substantial differences in the effects of neuroleptic agents when evaluated under conditional discrimination tasks. For example, neuroleptics of the phenothiazine (e.g., chlorpromazine), thioxanthene (e.g., chlorprothixene) and dihydroindoline (e.g., molindone) groups decrease the accuracy of pigeons responding under delayed matching-to-sample procedures (DMTS) (10, 18, 20, 23). Similar accuracy-decreasing effects have been reported for the phenothiazines in temporal (1), color (32) and response feedback procedures (12). These accuracy-decreasing effects are in sharp contrast to those obtained with the butyrophenone haloperidol, which has no effect on accuracy levels even at doses that markedly suppress response rates (12, 19, 23). That neuroleptics differ in their accuracy-altering effects under conditional discrimination procedures is not surprising in that these compounds also differ substantially in their pharmacological actions. Even though neuroleptics are antagonists at dopamine D2 receptors, the mechanism believed to mediate their antipsychotic properties (21,27), these compounds possess varying activity at cholinergic, histaminic, alpha-adrenergic and serotinergic receptors (6, 21, 27, 30). Moreover, differences in the pharmacological and behavioral profiles of these compounds are apparent both between and within pharmacological classes. For example, it has been reported that some phenothiazines produce rate-dependent effects when evaluated under various schedules of reinforcement, whereas others do not (13). Thus, identification of procedures sensitive to the different behavioral actions of neuroleptics may provide further insight into the pharmacological actions of these compounds.

The purpose of the present investigation was to evaluate

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TABLE 1

MEAN PERCENT CORRECT RESPONSES DURING CONTROL SESSIONS AT THE 0-, 2- AND 8-SEC DELAY INTERVALS AND RATE OF RESPONDING IN THE PRESENCE OF THE SAMPLE STIMULUS

Subject No.	0-Sec Delay	2-Sec Delay	8-Sec Delay	Responses/ Sec
5428	89(2.3)	78(1.9)	66(2.2)	1.23(0.13)
5339	97(1.4)	94(1.4)	64(2.2)	2.15(0.25)
5459	93(1.6)	93(0.9)	75(2.0)	1.23(0.10)
0985	94(1.6)	85(3.3)	67(2.3)	1.03(0.11)

All data are based on the control performance for individual pigeons and are averaged across all dose-effect determinations. Values in parentheses represent the standard error of these observations.

the effects of the prototypical neuroleptics chlorpromazine (a phenothiazine), loxapine (a tricyclic dibenzoxazepine) and thiothixene (a thioxanthene), and the atypical neuroleptics sulpiride (a benzamide) and clozapine (a dibenzodiazepine) under the DMTS procedure. Unlike the prototypical neuroleptics, sulpiride and clozapine have atypical pharmacological (2, 3, 7, 9, 16, 21) and behavioral (22, 28, 29, 31) profiles and thus may affect responding differently under the DMTS procedure.

METHOD

Subjects

Four experimentally-naive White Carneaux pigeons, maintained at 80% of their free-feeding weights (410–460 g), served as subjects. Each pigeon was individually housed with free access to grit and water in a constantly illuminated room.

Apparatus

Two operant conditioning chambers were used. Each chamber measured 32 cm long, 36 cm high, and 35 cm wide and was equipped with three response keys. Each of the response keys were 2.5 cm in diameter and located 23 cm from the bottom of the front wall, approximately 5.5 cm apart. An aperture horizontally centered on the front wall 7.5 cm above the floor allowed access to a hopper filled with mixed grain when the hopper was raised. The hopper, when raised, was illuminated by a 7-W white light bulb. A white bulb centrally mounted 33 cm above the chamber floor provided ambient illumination. An exhaust fan supplied ventilation and white noise was used to mask extraneous sounds. Scheduling of experimental events and data collection were accomplished through the use of a TRS 80 model IV microcomputer.

Behavioral Methods

Pigeons were exposed to a delayed matching-to-sample schedule in which discrete trials were programmed with an 8-sec intertrial interval (ITI). Each trial began with a 0.25-sec flash of the houselight following which the center key was illuminated red or green (sample stimulus); total responses on the sample stimulus divided by the time this stimulus was illuminated was used to calculate rate of responding. Five responses on the center key darkened the sample stimulus and initiated a fixed duration delay interval of 0, 2, or 8 sec. Delays were selected at random, with each delay programmed to appear equally often. The delay period was followed by the illumination of the two sides keys in green or red. A response to the side key that matched the sample stimulus in color darkened both side keys and on every other correct trial produced 3-sec access to grain; correct trials not followed by food delivery were followed by a 1-sec flash of the hopper light. Trials terminated by a nonmatching response also darkened the keys and were followed by the ITI;

TABLE 2

MEAN PERCENT CORRECT RESPONSES AVERAGED ACROSS THE THREE DELAY INTERVALS (0-, 2- AND 8-SEC) AND RESPONSE RATES IN THE PRESENCE OF THE SAMPLE STIMULUS FOR INDIVIDUAL PIGEONS RESPONDING UNDER A DELAYED MATCHING-TO-SAMPLE PROCEDURE

	Subject No.							
	5428	5339	5459	0985	5428	5339	5459	0985
Dose	Overall Percent Correct				Responses/Sec			
				Chlorpromazine (mg/kg)				
3.0	70	nt	80	83	1.76	nt	1.70	1.60
10.0	70	nt	79	91	1.67	nt	1.32	1.97
30.0	75	nt	67	75	1.24	nt	1.22	0.13
56.0	61	nt	67	—	2.22	nt	1.42	0.00
100.0	—	nt	—	—	0.00	nt	0.00	0.00
				Clozapine (mg/kg)				
0.1	72	78	89	85	1.50	2.85	1.81	1.44
0.3	79	81	79	87	1.76	3.38	1.80	1.34
1.0	72	62	68	72	0.95	3.11	1.74	0.53
3.0	63	70	64	—	1.49	4.41	1.18	0.00
5.6	57	54	70	—	0.40	2.32	0.42	0.00
				Sulpiride (mg/kg)				
3.0	78	nt	78	74	1.00	nt	1.11	0.79
10.0	87	88	86	82	1.06	1.14	0.83	0.60
30.0	82	85	90	81	0.79	1.11	0.86	0.67
100.0	84	77	91	85	1.07	0.79	0.93	0.76
170.0	75	nt	—	—	1.22	nt	0.00	0.00
300.0	82	nt	—	—	1.18	nt	0.00	0.00
				Loxapine (mg/kg)				
0.1	83	79	84	83	2.03	3.47	1.48	1.48
0.3	79	77	87	80	0.96	1.28	1.69	1.02
1.0	78	71	63	79	1.25	1.06	0.48	1.51
3.0	73	58	73	82	1.32	1.12	0.37	0.57
5.6	68	74	59	—	0.68	2.24	0.52	0.00
10.0	75	70	50	—	0.72	2.14	0.11	0.00
				Thiothixene (mg/kg)				
0.03	77	nt	83	84	0.94	nt	0.95	1.15
0.1	82	nt	86	83	1.14	nt	1.63	1.05
0.3	74	nt	—	86	1.22	nt	0.00	1.07
1.0	79	nt	—	77	0.72	nt	0.00	1.15
1.7	72	nt	—	77	0.42	nt	0.00	0.87

nt: indicates not tested.

—: indicates that an individual pigeon failed to complete a minimum of 20 trials during the experimental session.

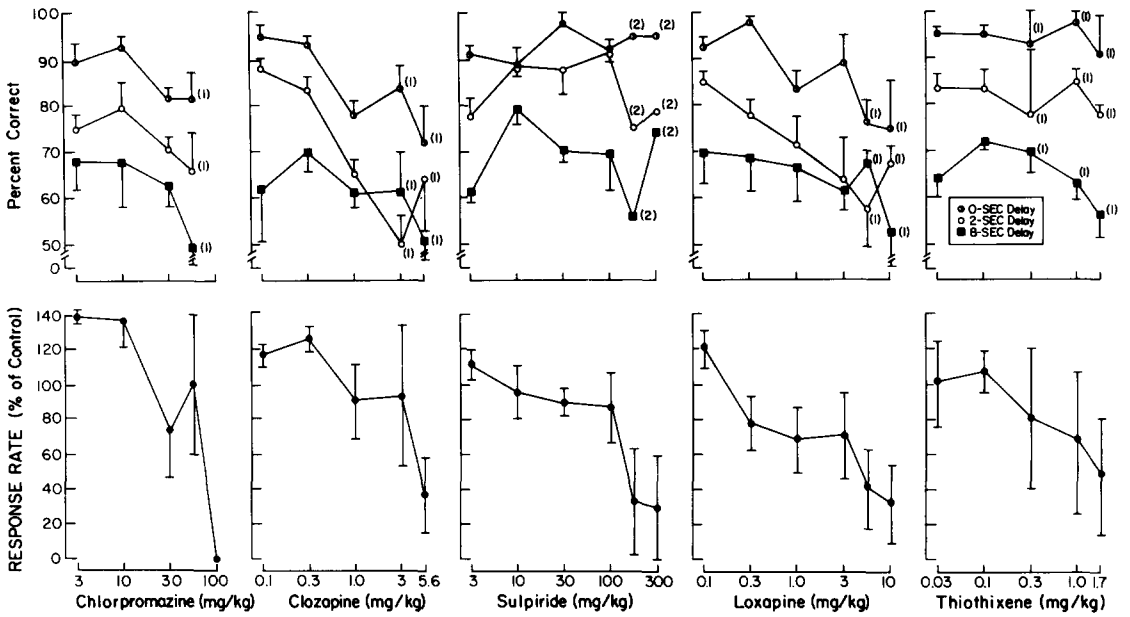

FIG. 1. Effects of chlorpromazine, clozapine, sulpiride, loxapine and thiothixene on percent correct responses at the 0-, 2- and 8-sec delay intervals (top panels) and response rates (bottom panels) in pigeons responding under a DMTS procedure. Chlorpromazine and thiothixene were tested in three pigeons and loxapine and clozapine in four pigeons. Four pigeons were tested at the 10, 30 and 100 mg/kg doses of sulpiride, whereas only three pigeons were tested at the 3, 170, and 300 mg/kg doses. The number next to selected data points in the top panels represent the number of pigeons that failed to complete a minimum of 20 trials during the experimental session. Response rates are expressed as the percent of individual vehicle control performances obtained during each respective dose-effect determination. For all data points, vertical lines represent ±1 S.E.

these trials were repeated until the pigeon responded to the appropriate side key. All trials were terminated if the response requirement on the sample stimulus was not completed within 35 sec after trial initiation, or if the pigeon failed to respond to one of the side keys within 35 sec of their onset. Sessions were terminated after 140 trials or 50 min, whichever came first. Sessions were conducted 5 days per week.

Pharmacological Procedure

After a minimum of 70 sessions of exposure to the DMTS procedure just described, dose-effect curves were determined for the following drugs; loxapine HCl (Lederle, Carolina, Puerto Rico) clozapine (Sandoz, E. Hanover, NJ), sulpiride (Sigma, St. Louis, MO), thiothixene HCl (Pfizer Groton, CT) and chlorpromazine HCl (Smith Kline and French, Philadelphia, PA), in that order. Shortly after the completion of an experimental session preceded by an injection of 56 mg/kg sulpiride, pigeon No. 5339 died of an apparent overdose; other than decreases in response rates no signs of toxicity were evident in the remaining three pigeons even at doses as high as 300 mg/kg. At the completion of selected dose-effect curves, probes were conducted during which a selected dose of each drug, previously determined to decrease response rates by a minimum of 50%, were redetermined. Since these replications indicated that neither tolerance or sensitivity developed to these drugs, these data are not discussed. Dose-effect curves for individual drugs were separated by a minimum of 7 drug-free days. Drugs were administered on Tuesday and Friday, whereas distilled water was injected on Thursday with the data obtained during these sessions serving as the nondrug control data. All drugs and vehicle control were administered IM 30 min prior to the session at an injection volume of 1.0 ml/kg. Clozapine was dissolved in a small amount of 1 N acetic acid, and sulpiride in hydrochloric acid; both were diluted further with distilled water. Solutions of loxapine HCl were obtained by diluting the commercial injectable preparation with a solution consisting of propylene glycol and distilled water. Thiothixene HCl and chlorpromazine HCl were dissolved in distilled water. Doses for all drugs are expressed in terms of the forms described above.

RESULTS

During vehicle control sessions the percent of correct responses (accuracy) decreased with increases in the delay interval; mean accuracy levels were 93%, 88% and 68% at the 0-, 2- and 8-sec delay intervals, respectively (see Table 1). Table 2 shows the effects of chlorpromazine, clozapine, sulpiride, loxapine and thiothixene on the percent of correct responses for individual pigeons averaged across the three delay intervals. Chlorpromazine, clozapine and loxapine produced large dose-dependent decreases in mean accuracy levels, thiothixene small decreases, and sulpiride had no effect on accuracy across the dose range evaluated. Although these effects were obtained in each pigeon tested, the dose required to produce the largest decrease in accuracy varied across pigeons. As illustrated in Fig. 1, the accuracy-decreasing effects of loxapine, clozapine and thiothixene did not differ substantially across the three delay intervals. The relative magnitude of the chlorpromazine-induced decreases in accuracy, in contrast, were directly related to the delay interval. For example, at the 56 mg/kg dose of chlorpromazine, the relative magnitude of these decreases in accuracy increased as the delay interval increased, with accuracy levels decreasing by 10% at the 0-sec

delay, 19% at the 2-sec delay and 37% at the 8-sec delay. At the 8-sec delay interval, chlorpromazine, loxapine and clozapine decreased accuracy to levels approximating chance performance (approximately 50%). At this delay interval, thiothixene produced only small decreases in accuracy. For individual pigeons, clozapine and chlorpromazine decreased accuracy levels at doses that failed to decrease response rates, an effect not obtained with loxapine and thiothixene.

During control sessions, the mean rate of responding in the presence of the sample stimulus was 1.41 responses/sec (Table 1). Relative to control values chlorpromazine, clozapine and loxapine increased response rates at low doses and then decreased response rates as the dose was increased. The largest increases in response rates were 44% at the 3 mg/kg dose of chlorpromazine, 26% at the 0.3 mg/kg dose of clozapine and 22% at the 0.1 mg/kg dose of loxapine. Small increases in response rates were obtained at the low doses of thiothixene, although these increases failed to exceed the range of control values for individual pigeons. Sulpiride decreased response rates in dose-dependent fashion. Considerable individual differences were apparent in the dose that completely suppressed response rates in each of the neuroleptics evaluated (see Table 2).

DISCUSSION

Under the DMTS procedure, the prototypical neuroleptics chlorpromazine, loxapine and thiothixene, and the atypical neuroleptic clozapine produced dose-related decreases in accuracy. With the exception of chlorpromazine, the relative magnitude of these accuracy-decreasing effects did not differ substantially across the 0-, 2- and 8-sec delay intervals. That these neuroleptics decreased accuracy is consistent with those reported for neuroleptics of the phenothiazine, thioxanthene, and dihydroindoline groups in pigeons responding under the DMTS procedure (18, 20, 23, 24, 26). Similar accuracy-decreasing effects have been reported with the phenothiazines and dihydroindolines under other discrimination tasks (12, 19, 20, 32).

These neuroleptic-induced decreases in accuracy, however, are in sharp contrast to those obtained with sulpiride. Across the dose range evaluated, sulpiride had no effect on accuracy. The failure to obtain accuracy-decreasing effects has also been reported with the neuroleptic haloperidol when evaluated under the DMTS and other discrimination procedures (5, 12, 19, 23). Unlike the neuroleptics that decrease accuracy, sulpiride and haloperidol are highly D2 receptor selective with low affinity for cholinergic, histaminic alpha-adrenergic serotinergic or dopaminergic D1 receptors (6, 21, 30, 31). Nevertheless, the benzamides and butyrophenones differ in many respects, including their ability to induce increases in dopamine D1 and D2 receptor numbers following chronic administration and inhibit apomorphine-induced locomotion (17,31).

When evaluated in pigeons responding under the DMTS procedure, the actions of neuroleptics can be differentiated into two groups on the basis of their ability to alter the accuracy of responding. In one group are the phenothiazines, thioxanthenes, dibenzodiazepines, dihydroindolines and tricyclic dibenzoxazepines which decrease accuracy in a dose-related fashion, and in the second group the butyrophenones and benzamides which have no effect on accuracy. Although any one of a number of neurotransmitter systems (or other pharmacological actions of these drugs) may mediate these effects, it is clear that activity at dopamine receptors cannot fully account for these differential actions. However, these differential accuracy-altering effects are generally consistent with the anticholinergic actions of these compounds. For example, while the benzamides and butyrophenones have only limited anticholinergic actions, the phenothiazines, thioxanthenes, dibenzodiazepines, dihydroindolines and tricyclic dibenzoxazepines have moderate to pronounced anticholinergic actions (6, 21, 25, 27, 30, 31). Indeed, it has also been reported that the response rate-suppressing effects of neuroleptics with pronounced anticholinergic actions (i.e., clozapine and thioridazine) can be reversed completely by the concomitant administration of the cholinergic agent oxotremorine (14), thus suggesting that the anticholinergic actions of these compounds play a crucial role in mediating at least one of their effects.

It should also be noted that neuroleptics within the same general class (e.g., phenothiazines) differ markedly in their pharmacological and behavioral profiles. For example, when contrasting the effects of the phenothiazines chlorpromazine, fluphenazine and trifluoperazine, only chlorpromazine produces rate-dependent effects (13). These three phenothiazines also differ in their relative affinity for muscarinic cholinergic receptors (30) as well as other pharmacological actions (25). Differences in the accuracy-decreasing effects have also been obtained when the thioxanthenes (e.g., chlorprothixene, thiothixene) are evaluated under conditional discriminations. For example, chlorprothixene has been reported to produce large decreases in accuracy (23) under DMTS procedures, whereas in the present investigation thioxanthene produced only small decreases. Whether other drugs within a neuroleptic class produce similar effects on accuracy when evaluated under conditional discrimination tasks remains to be determined.

Of the neuroleptics evaluated in the present investigation, only chlorpromazine, loxapine and clozapine consistently increased response rates above the range of individual control values. Sulpiride and thiothixene only decreased response rates. It has similarly been reported that under certain schedules of reinforcement (e.g., fixed-interval, fixed-ratio) chlorpromazine and clozapine, but not thiothixene and sulpiride, increase response rates (4, 13, 15).

In the present investigation, the order of potency for the rate-decreasing effects of these drugs was thiothixene > clozapine = loxapine > chlorpromazine > sulpiride. In contrast, to the accuracy-decreasing effects of these neuroleptics, this potency ranking is generally consistent with the potency ranking for these drugs in terms of their ability to antagonize dopamine D2 receptors (6,21) as well as their antiavoidance activities (8,11). These data suggest that under conditional discrimination procedures like the DMTS procedure used in the present investigation, distinct pharmacological actions mediate the accuracy-decreasing and rate-decreasing effects of neuroleptics.

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