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Affinity for the Dopamine D_2 Receptor Predicts Neuroleptic Potency in Blocking the Reinforcing Effect of MFB Stimulation

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GALLISTEL, C. R. AND A. J. DAVIS. *Affinity for the dopamine D_2 receptor predicts neuroleptic potency in blocking the reinforcing effect of MFB stimulation.* PHARMACOL BIOCHEM BEHAV 19(5) 867–872, 1983.—For each of nine neuroleptics, the dose required to block sustained responding for intracranial stimulation of the medial forebrain bundle was determined in the rat. To check whether the blocking of responding was due to effects on reinforcement as opposed to effects on performance factors, the rats were always tested for task-specific extinction of responding by transferring them to another testing box once they refused to respond in the first testing box. With all the neuroleptics, task-specific extinction was seen in at least some of the animals. Task-specific extinction was not seen in control tests with a general anaesthetic (Chloropent) nor with picrotoxin, a drug that can produce pseudo-extinction. Affinity for the dopamine D_2 receptor (from in vitro studies) predicted neuroleptic potency in blocking reinforcement, whereas affinity for other aminergic receptors (D_1, D_3, the α-adrenergic receptor, S_1, and S_2) did not.

Self-stimulation Dopamine Aminergic receptors Reinforcement Extinction D_2 Receptor Affinities

THE attentuation of intracranial self-stimulation (ICSS) following the administration of neuroleptics has long been considered evidence that catecholamine-releasing neurons either carry the reward signal or, at least, can alter the reinforcing effect of that signal [3, 12, 19]. Recent discussion has come to focus on the dopaminergic neurons [6,23]. However, the matter has been complicated by the identification of at least three distinct dopamine receptor sites [1,16]. In addition, neuroleptics interact with other neural receptor sites such as alpha adrenergic and serotoninergic sites [15, 17, 18]. The study we now report gives a pharmacological profile of the neuroleptic action on the reinforcing effect of brain stimulation. For each of the nine neuroleptics used in this study, the dosage required to block sustained self-stimulation behavior was correlated with its affinity for various receptor sites. A high correlation is evidence that that particular site mediates the neuroleptic effect upon ICSS.

The decrease in response rates during ICSS suggests that neuroleptics reduce the perceived rewarding value of brain stimulation. While it is widely argued that these drugs act directly on the reinforcing effect of the stimulation [7, 8, 11], others maintain that the decrease in response rates following neuroleptic treatment is due to some type of performance deficit brought about by these drugs [5, 19]. This is an argument concerning neuroleptic functional specificity (as opposed to pharmacological specificity). If the pharmacology of ICSS behavior is to be effectively studied, it must be established if neuroleptic attenuation of ICSS behavior is caused by a specific effect on reinforcing and/or motivating functions or by a general non-specific effect on one of the many other neurobehavioral functions that play some role in ICSS performance. The present study differs from an earlier study [22] in employing a behavioral test, task-specific extinction, that distinguishes effects on performance from effects on reinforcement.

Rats treated with pimozide exhibit task-specific extinction [11]: They extinguish in a Skinner box (or runway); then resume performance when shifted to a runway (or vice versa); then extinguish in the second task as well (see, also [9]). In the present study, a modification of this method was used to screen nine neuroleptics for their reinforcement specific effect upon attenuation of ICSS behavior. The drugged rats were tested in one Skinner box until they refused to respond even immediately after renewed priming, then they were lifted to a second box.

METHOD

Subjects

The subjects were 15 mature white rats of the Sprague Dawley strain from the Charles River breeding laboratory, weighing between 300 and 400 grams at time of surgery. A monopolar stimulating electrode was implanted, under Clorpent anaesthesia, in the medial forebrain bundle at the level

of the posterior hypothalamus (flat skull coordinates: 4.0 mm behind Bregma, 1.5 mm lateral to sagital suture and 8.5–9.0 mm below skull surface). There was an equal number of implantations to the right and left of the sagital suture. The electrode assembly was Plastic Products model MS303/1, consisting of one uninsulated stainless steel wire, the indifferent, which was laid on the skull at the time of implantation, and one 0.25 mm stainless steel wire insulated with Formvar (except at the bare cross section of its tip) which served as the stimulating electrode. The assembly was fixed to the skull using screws and dental cement.

At least one week after implantation, the rats were trained to press a lever for brain stimulation (1 train/press, 1 sec train duration, 0.1 msec pulse duration, 50 pulses/sec, variable current). Every rat was taught to press in both Skinner boxes (see Apparatus). Only those rats that readily learned to press at rates in excess of 20 presses/min were used. Rats were permanently housed in individual wire cages with continuous food and water on a reversed cycle illumination schedule, so that all testing was done during the animals' active period.

At the conclusion of the experiment, 8 of the 15 rats were anaesthetized and perfused through the heart with normal saline solution followed by 10% formalin. Their brains were removed, frozen and sectioned to confirm the location of the electrode tip. The tips were found to reside in or near the MFB in the posterior hypothalamus and anterior ventral tegmemtum. The remaining rats either died prematurely of illness or lost their headset before they could be perfused.

Apparatus

Two structurally and visually different Skinner boxes were used for testing. Both boxes measured 50×25×25 cm. The boxes differed in that one was all Plexiglas (Box 1) while the other (Box 2) had 1 side of Plexiglas, and 3 sides of wood. Box 1 had metal rods for flooring and a long rectangular, easily pressed (18 g) lever in the center of one wall; while Box 2 had a hardware cloth floor, and a harder to press (30 g) mushroom shaped lever in a corner.

The electronic hardware consisted of BRS 200 series Digibits, from which the stimulating pulses were also derived [4]. The voltages across the rat and across a 100 ohm resistor in series with the rat were monitored on a Tektronix 5110 oscilloscope. Throughout all procedures, responses at the lever in either box delivered 1 train/press, 1 sec train duration and 0.1 msec rectangular cathodal pulses. Number of pulses per sec and current magnitude varied (see below).

Procedures

Establishing a behavioral baseline. Because the rats in this study were repeatedly drugged at different doses and with different drugs, it was important to establish a baseline that would permit us to judge whether the rat had recovered from the effects of previous drug treatment and whether there were any unwanted cumulative effects of the drug testing on the animal. Because we wished also to combine data from different animals, we needed to equate across animals, as best we could, the strength of the reinforcing effect of the stimulation. To these ends, we adopted the following prodedures.

The current used with each animal was established by testing the animal with a train that delivered 50 pulses and varying the current up and down in 0.1 log unit steps to determine a rate-intensity function. This procedure was repeated over several days until the current required to produce a half-maximal rate varied by less than 0.1 log unit from day to day. The mean current required to produce half-maximal responding became the standard current of that rat, the current used throughout the rest of the experiment. Standard currents ranged from 50 μA (in DS-9) to 240 μA (in DS-13). (The currents for all but DS-9) are given in Table 1.)

Using the standard current for each rat, we then tested them while varying pulse frequency in 0.1 log unit steps to obtain rate-frequency curves. These rate-frequency curves

TABLE 1

DOSE REQUIRED TO BLOCK SUSTAINED SELF-STIMULATION

Neuroleptic (vehicle) (test latencies)*	Subject†	Log_{10} of Dose Required to Block ICSS
spiroperidol	DS10 (165)	−1.25
(0.2% t.a.‡)	DS12 (160)	−1.25
(3,6)	DS13 (240)	−0.95
	DS14 (190)	−1.55
benperidol	DS6 (65)	−1.37
(0.2% t.a.)	DS11 (215)	−1.37
(0.75,2)	DS12	−1.37
	DS14	−1.07
haloperidol	DS5 (210)	−1.15
(0.2% t.a.)	DS6	−1.15
(0.25,1)	DS7 (100)	−1.45
	DS8 (140)	−0.85
pimozide	DS2 (160)	−0.55
(0.2% t.a.)	DS4 (76)	0.05
(1,4)	DS5	−0.55
	DS6	−0.85
metoclopromide	DS15 (220)	0.85
(H_2O)§	DS6	0.25
(0.25,1)	DS8	0.55
	DS11	−0.05
chlorpromazine	DS1 (130)	0.75
(H_2O)	DS4	0.45
(0.25,1)	DS5	0.45
	DS6	0.45
promazine	DS1	0.75
(H_2O)	DS3 (88)	0.75
(0.25,1)	DS4	0.75
	DS5	1.05
thioridizine	DS5	0.85
(H_2O)	DS8	1.15
(0.5,1.25)	DS10	0.45
	DS11	1.15
	DS13	1.15
clozapine	DS11	1.15
(H_2O/HCl)¶	DS12	1.15
(0.5,1.25)	DS13	1.45
	DS14	0.85

*Test latencies are given in hours from time of drug injection.
†A rat's standard current in (microamps) is given in parentheses the first time the rat appears in the table. ‡t.a.=tartaric acid solution. §The water was distilled. ¶HCl added to adjust pH to 4.1.

served as the baseline against which we measured the recovery of normal performance. In the days following each drug session, the rat's rate-frequency curve was determined one or more times. A new drug session was not initiated until the rate-frequency curve looked normal and the half-maximal frequency (the pulse frequency require to sustain half-maximal responding) was within 0.1 log unit of the original half-maximal frequency determined before drug testing began. In all cases, there were at least 7 days between successive drug sessions, even through the rate-frequency curves generally looked normal within a few days after a drug session.

Neuroleptic testing. Following treatment with a drug, the rats were tested twice for task-specific extinction. The first test was timed to come at what, judging from the literature, would be after the onset of drug action but before the attainment of peak action. The second test was timed to coincide with the drug's peak action. The drugs, the vehicles, and the post-injection testing latencies are given in Table 1. The pulse frequency during drug testing sessions were 100 pps. Because of the manner in which the current intensity was chosen and the steepness of the rate-frequency functions, this pulse frequency was sufficient to sustain nearly maximal performance in each rat when it was not drugged.

Box 1 was used to determine the baseline rate-frequency curves. Following such determinations the rat was allowed to respond for about the same amount of time in Box 2 (at the parameters used in drug testing). This was to insure roughly equal experience in both boxes.

To begin a test for task-specific extinction, the animal was placed in a separate enclosed priming box (25×20×22 cm), constructed of wood with a hardware cloth floor and closable lid, where he received ten free priming stimulations (standard current, 100 pulses/sec.). Neuroleptics do not interfere with the priming effect [14,21].

After priming, the rat was placed in Box 1. It was placed near the center of the floor, 3 to 4 inches from the lever with its head oriented away from the lever at a 45-degree angle. The rat was then given one free stimulation. Following this, the number of bar presses was recorded in 15 sec intervals for the first two minutes and then in one-minute intervals for up to 15 minutes. If a rat refused to press for one minute, he was removed from the Skinner box, given 10 priming stimulations, and returned to the box in the manner previously described. If it refused to press for another minute, we considered it to have extinguished. Otherwise, it was allowed to press until either extinction occurred or 15 minutes total time had elapsed. Each time the rat ceased responding, it was removed, reprimed and replaced. It was consisdered to have extinguished only when it did not give any presses for 1 minute immediately following replacement. Regardless of the outcome, extinction or 15 minutes of responding, the rat was removed from Box 1, primed, and placed into the second Skinner box. The entire procedure was then repeated. When Period 1 testing had ended, the rat was returned to his cage to await the second test period.

The dosage used in a given test was determined by the rat's performance in the previous drug trial. If a rat showed task specific extinction, or if it failed to press at all on the previous test, the dosage was reduced by a factor of two. If a rat pressed the full amount of time in at least one box for both time periods in the previous test, the dosage was increased by a factor of two. Tests were conducted in this manner until we found the minimum dose such that the rat would not show sustained responding in either box. The geometric midpoint between this dosage and the next lowest one was taken as the dosage that sufficed to prevent sustained self-stimulation.

Testing for each neuroleptic was conducted on four rats, with the exception of thioridizine, where five rats were used. Each rat experienced a different amount of control and neuroleptic testing. Most rats experienced more than one drug, some up to five. The selection and order of drugs for each rat was random. Injection volume was held constant at 1.0 cc and given IP. The vehicles, by themselves, have no effect on ICSS [24].

Control tests. In addition to the tests with neuroleptics, we ran control tests with Chloropent (5 rats) and picrotoxin (4 rats) and also with saline and no stimulation (4 rats). The tests with Chloropent were to check whether a drug that produced a general debility (ataxia) would produce task-specific extinction under our testing conditions. Chloropent is a general purpose veterinary anaesthetic obtained from Fort Dodge Laboratories. Each cc contains 42.5 mg Chloral hyrate, 21.2 mg magnesium sulfate, 8.86 mg pentobarbital, 14.24% ethyl alcohol, and 33.8% propylene glycol in aqueous solution. In the Chloropent tests we varied the dosage by small amounts within the range of 1–2 cc/kg, the range that produces modest to incapacitating ataxia. We also varied the time of testing to catch the rat at times when the ataxia was coming on or wearing off.

The test with picrotoxin was run because earlier work had shown that this drug can occasionally produce "pseudoextinction" by interacting with the rewarding stimulation to bring on performance-impairing seizure activity [11]. We wanted to see whether a drug that could impair performance by way of an interaction with the stimulation could mimic the effects of neuroleptics. The dosage of picrotoxin was varied in the range from 2–3 mg/kg, a range in which the drug by itself never produces seizures, but in which drugged animals delivering rewarding stimulation to themselves often show subconvulsive or convulsive seizure activity.

The saline-no-reward tests were to give us data on the course of ordinary extinction under our testing conditions. In these tests, the rats were primed as usual and given the usual free train upon placement in the box, but the stimulator was turned off immediately after the free train.

RESULTS

The dose of a neuroleptic required to prevent sustained self-stimulation correlates strongly with its affinity for the dopamine D_2 receptor site, as measured in vitro in two different laboratories [2,16] (see Fig. 1). It does not correlate with in vitro affinity for the D_1 and D_3 dopamine receptors, nor with affinity for the α-adrenergic receptor, nor with affinity for the S_1 and S_2 serotonin receptors (Fig. 2).

The independence assumptions underlying the correlation statistic are not satisfied by our data, because most animals were tested with more than one drug and hence contribute data to more than one average. Similar correlations are obtained, however, when one does post-hoc analyses that allow each rat to contribute data for only one drug, or when one runs within-animal correlations for those rats that got four or more drugs. The data for each animal are given in Table 1.

The comparison of behaviors observed in the two boxes during neuroleptic test and during the three control conditions (saline-no-reward, Chloropent, and picrotoxin) indicates that the effect of all neuroleptics was mediated to some extent by an effect or reinforcement. "Performance" effects

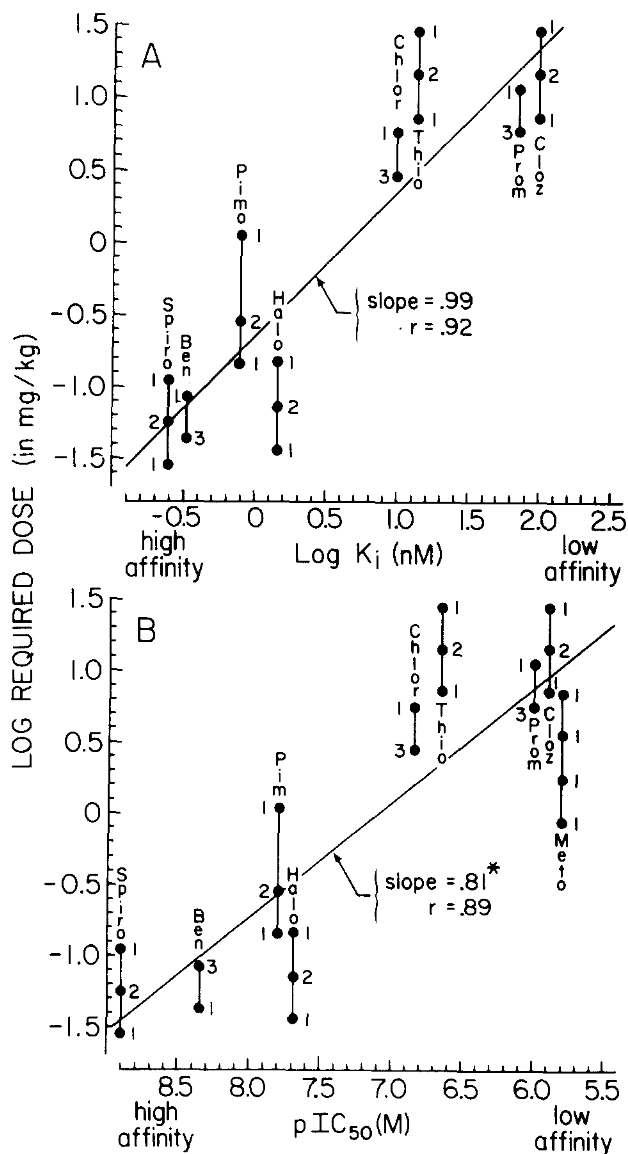

FIG. 1. The logarithm of the neuroleptic dose required to block sustained self-stimulation plotted against the logarithm of affinity for the dopamine D_2 receptor, as measured in two in vitro studies. The number beside a point gives the number of rats for which that was the required dose. The best fitting linear regressions (solid lines) were computed from the logarithmic mean of the required doses of a given drug. Both correlations are significant beyond the .005 level. Abbreviations: Ben=benperidol; Chlor=chlorpromazine; Cloz=clozapine; Halo=haloperidol; Meto=metoclopromide; Pim=pimozide; Prom=promazine; Spiro=spiroperidol; Thio=thioridizine. A. Affinity measured by Creese, Burt, and Snyder [2] using ^{3}H-halopridol as the radioactive ligand and calf striatal tissue. (K_i is proportional to IC_{50}, which is the concentration of a drug required to displace 50% of the stereospecifically bound ligand.) B. Affinity measured by Leysen, Gommeren, and Laduron [15] using ^{3}H-spiroperidol and rat striatal tissue. ($pIC_{50} = -\log IC_{50}$. *In calculating the linear regression, the sign of the numbers on the abscissa was changed where necessary to make them increase in value from left to right.)

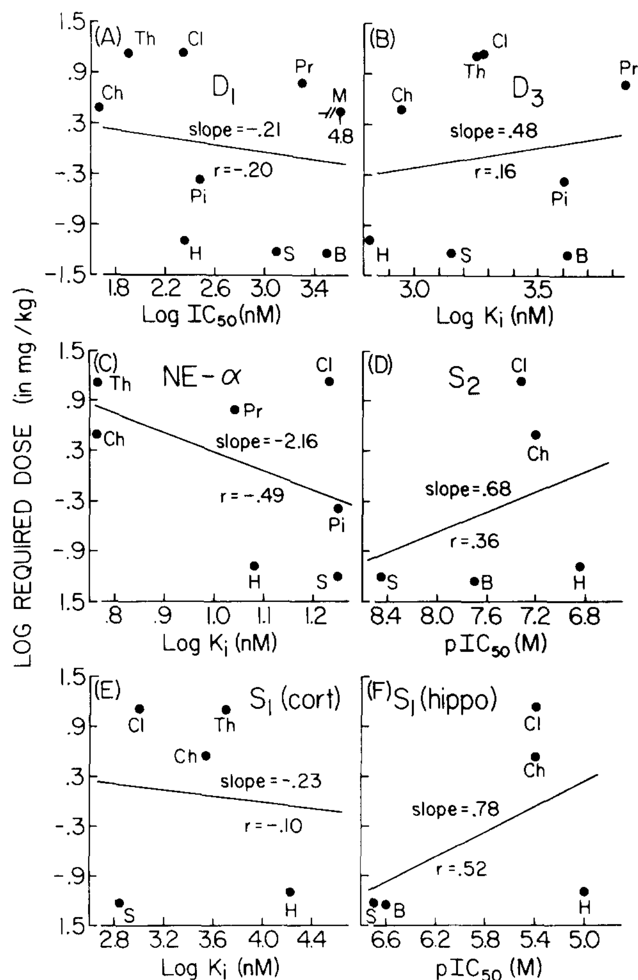

FIG. 2. The mean logarithm of the neuroleptic dose required to block sustained self-stimulation plotted against the logarithm of the drugs' affinities for various aminergic receptors. (In each case the high affinity is placed at the left end of the abscissa. In calculating the linear regression, the sign of the numbers on the abscissa was changed where necessary to make them increase in value from left to right. None of the correlations approaches statistical significance. For definitions of IC_{50}, pIC_{50}, and K_i see caption to FIG. 1. Abbreviations: B=benperidol; Ch=chlorpromazine; Cl=clozapine; H=haloperidol; M=metoclopromide; Pi=pimozide; Pr=promazine; S=spiroperidol; Th=thioridizine.) A. Affinity data for the D_1 dopamine receptor from [12] with the ^{3}H-cis (2)-flupenthixol ligand and rat striatal tissue. B. Affinity data for the D_3 dopamine receptor from [2] with the ^{3}H-dopamine ligand and calf striatal tissue. C. Affinity data on the α-adrenergic receptor from [17] with the ^{3}H-WB-4101 ligand and rat whole brain. D. Affinity data for the S_2 serotonin receptor from [14] with the ^{3}H-spiroperidol ligand and rat frontal cortex. E. Affinity data for the S_1 serotonin receptor in the cortex from [16] with the ^{3}H-serotonin ligand and rat cortical tissue. F. Affinity data for the S_1 serotonin receptor in the hippocampus from [14] with the ^{3}H-serotonin ligand and rat hippocampal tissue.

TABLE 2
EFFECT OF VARYING THE CRITERION FOR TASK-SPECIFIC EXTINCTION

	Fraction of Rats Failing to Meet Criterion			
Drug	Criterion 1 (Weakest)	Criterion 2	Criterion 3	Criterion 4 (Strongest)
Spiroperidol	2/4	3/4	4/4	4/4
Benperidol	0/4	0/4	2/4	3/4
Haloperidol	0/4	0/4	1/4	3/4
Pimozide	1/4	1/4	2/4	3/4
Metoclopramide	0/4	1/4	3/4	3/4
Chlorpromazine	2/4	2/4	4/4	4/4
Promazine	0/4	1/4	4/4	4/4
Thioridizine	2/5	3/5	3/5	4/5
Clozapine	1/4	2/4	2/4	4/4
Saline-No-Reward	0/4	1/4	1/4	2/4

Note: Criterion 1: At least 5 presses in the two boxes combined, with at least 1 in each. Criterion 2: At least 10 presses in two boxes combined, with at least 3 in each. Criterion 3: At least 10 presses overall, with at least 3 in each and with at least one resumption of responding following renewed priming. Criterion 4: At least 25 presses in two boxes combined, with at least 5 in each, and with a total of at least two resumptions following renewed priming.

were clearly a factor however. Because the rats in this study experienced extinction repeatedly, both during the establishment of the baseline rate-frequency curves and during neuroleptic testing, they showed extinction that was extremely rapid. In the saline-no-reward condition, the rats gave from 2 to 37 presses in the first box, resuming pressing on between 0 and 6 occasions when removed, reprimed, and replaced in the box, and then they gave from 0 to 49 presses when placed in the second box following complete refusal to respond in the first. When treated with neuroleptics at doses that prevented sustained responding, the rats always showed some responding before they quit, that is, the drug-induced suppression of responding was never complete at the beginning of testing. Extinction was always seen in at least one box. However, the rats generally quit after fewer responses than in the saline-no-reward condition, they were less likely to resume responding after being removed, reprimed and replaced in the same box, and they sometimes failed to resume responding when placed in the second box. Nonetheless, for all neuroleptics, at least some of the rats met our criterion for task specific extinction, which was that the rat give at least 10 presses across the two boxes and that there be at least 3 presses in each box. (Note that one rat failed to satisfy this criterion in the saline-no-reward condition; in the course of two separate 2-box tests spaced 45 minutes apart it gave only one press in the second box on the first test and none in this box on the second test.)

To what extent a given neuroleptic impairs self-stimulation purely because of its reinforcement blocking effect as opposed to its other non-specific effects may be estimated by applying increasingly stringent behavioral criteria to the data. The more stringent the criterion the more nearly one requires the behavior of the drugged animal to resemble the extinction seen in undrugged animals under no-reward conditions. The effect of strengthening or weakening the criterion for task-specific extinction is shown in Table 2.

In rats treated with Chloropent or picrotoxin, we never saw task-specific extinction, no matter what criterion we applied. With Chloropent, the rat was either capable of performing or it was not. If it succeeded in pressing the lever at all, then it kept on pressing, usually with increasing vigor, since the stimulation seemed to antagonize the effects of the drug. With higher doses of picrotoxin, the rats often gave no presses even in the first box, apparently because of seizure activity induced by the priming. Those that did press, pressed fairly steadily unless and until their pressing was interrupted by the onset of seizure activity, in which case removal, repriming, and replacement in the same box never led to the immediate resumption of pressing, nor did transferal to the other box.

DISCUSSION

Our results speak primarily to the question of the neurochemical mechanism through which neuroleptics affect self-stimulation rather than to the question of the behavioral function that they interfere with (whether reinforcement or some performance function). There is ample evidence that at least pimozide attenuates reinforcing efficacy in addition to having a variety of effects on performance variables (see [10,23] for critical discussions of the literature on this question). We used task-specific extinction to check whether one or more of the drugs' effects were entirely on performance factors, in which case one would want to exclude them from the pharmacological profile. At a dose that abolished sustained responding, we saw extinction-like declines in all animals tested and task-specific extinction in at least some no matter what neuroleptic we used. The extinction-producing effects of the neuroleptics were not counterfeited by drugs that produced performance deficits, even performance defects brought on by the self-stimulation itself (picrotoxin). We conclude, therefore, that the dose that blocks

sustained responding is approximately the dose that blocks reinforcement. The effects of neuroleptics on performance factors are seldom or never sufficient to conceal entirely their effect on reinforcement.

Among the receptors for biogenic amines for which we could find neuroleptic affinity data, only the affinity for the dopamine D_2 receptor predicted the dose required to block reinforcement. While affinity for this receptor predicts rather well the dose required to block reinforcement (correlations of .89–.92), there are some discrepancies worth noting. Pimozide, for example , has a twofold greater affinity for the D_2 receptor than does haloperidol, but haloperidol is 5–10 times more potent for blocking reinforcement. Metoclopromide is about 4 times more potent at blocking reinforcement than would be expected from its D_2 affinity. These differences may reflect differences in the ease with which the various neuroleptics penetrate to the sites of action. In any event, the pharmacological profile suggests that the effects of neuroleptics on the reinforcing effect of brain stimulation reward is mediated by their binding to the dopamine D_2 receptor.

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