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Discriminable Effects of Antimuscarinics: Dose Response and Substitution Test Studies

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OVERTON, D. A. *Discriminable effects of antimuscarinics: dose response and substitution test studies.* PHARMAC. BIOCHEM. BEHAV. 6(6) 659–666, 1977. – In a shock escape T-maze task, rats were trained to turn right following one drug treatment and left following a second drug treatment. The specific drug and dose conditions were the only discriminative cues available to the animals. The number of training sessions before criterion performance indicated the discriminability of the two training conditions. Drug vs no drug training showed that discriminability was proportional to dosage for low doses, but was constant over a range of higher doses. Such an asymptote of discriminability was observed with scopolamine, atropine, benactyzine and Ditran (JB 329), and was shown not to result from tolerance. High dose vs low dose discriminations involving scopolamine were learned very slowly if both doses were within the asymptotic range; this indicates that similar discriminable effects were produced by high and low doses. To compare various drugs, substitution tests were administered to trained rats. The four antimuscarinic drugs generally substituted for one another but did not mimic and were not mimicked by drugs in other pharmacological classes. Some exceptions to this pattern were noted. The discriminable effects of scopolamine were partially antagonized by physostigmine. The results indicate that the antimuscarinic drugs share discriminable actions probably produced by their anticholinergic actions. The asymptote of action at high doses appears genuine, possibly reflecting receptor saturation.

Drug-discriminations State-dependent learning Scopolamine Atropine Antimuscarinics Benactyzine Ditran Trihexyphenidyl Benzotropine

DRUG discrimination procedures increasingly appear to provide a useful tool for the study of drug actions on the CNS. In this context, it has become important to test the generality of the discrimination technique by determining which types of drugs have discriminable effects, how strong these effects are, and how unique they are to each individual drug or class of drugs.

Both drug discriminations and state-dependent learning produced by antimuscarinic drugs have been reported. Unexpectedly, investigators have reported essentially similar findings even though some used doses of 1–10 mg/kg while others used 100–300 mg/kg [6, 7, 8, 11, 17]. This insensitivity to dosage is unusual as the discriminable effects of most drugs are proportional to dosage [14,15]. White [19] reported that a variety of other behavioral effects of antimuscarinics increased with dosage only up to a point, beyond which an asymptote was observed with further increase in dose producing no further increase in effect. Also, atropine maximally reduced brain acetylcholine at 25 mg/kg with no further decrease produced by 50 mg/kg [5]. Similarly, increasing doses of hyoscine progressively raised the intensity of reticular formation stimulation required to activate the EEG up to 1 mg/kg but further dose increases produced no further increase in threshold [1]. Thus, the discriminable effects of antimuscarinics might also be expected to asymptote, although this has not been systematically investigated in previous studies. (A preliminary report of the present findings, based on a smaller number of animals, was made previously [13].)

The present study had three purposes: First, to investigate the relationship between dosage and the discriminable effects of antimuscarinic drugs. Second, to determine whether the several antimuscarinic drugs share common discriminable effects. Third, to compare the discriminable effects of antimuscarinics with those of other types of drugs so as to determine whether the discriminated effects of antimuscarinics are unique to that class of drugs.

A T-maze drug discrimination procedure was adopted for the present studies. Rats were required to turn right in the T-maze under one drug condition and left under a second condition. After such discriminations were learned to criterion, substitution tests involving novel drugs were administered to test the relationship between the discriminable effects of various drugs.

METHOD

Animals

Male hooded rats of the Long Evans strain were purchased from Blue Spruce Farms and were housed 3 per cage with food and water continuously available. All rats were experimentally naive and weighed 200–300 g at the beginning of training. Prior to training, they were allowed to explore the T-maze for about 20 min.

Drugs

A drug state (D) was defined as the condition existing at a specified period of time after intraperitoneal injection of a specified drug and dosage. The no-drug condition (N) usually indicates no injection, although saline was sometimes injected to demonstrate that behavior was not influenced by the injection procedure per se [16]. Drugs were dissolved in isotonic saline in concentrations such that the injected volume was 1 cc/kg. The most frequently used drugs were atropine sulfate (A), scopolamine HBr (S), benactyzine HCl (B) and Ditran (D). Abbreviations will be used to specify injections; e.g., S5 indicates scopolamine 5 mg/kg. The interval between injection and testing was 15 or 20 min unless otherwise specified [2]. Stated dosages include the weight of the inactive salts.

Apparatus

The T-maze was constructed with a steel-rod floor and plywood walls 60 cm high painted flat gray. The usual T-shape was modified by placing a 90° angle in each side arm so that the goal boxes were not visible from the choice point [11]. The choice point was defined as the area 15 cm square where the 3 alleys converged. A barrier door could be placed in front of either goal box to prevent entry. A Grason Stadler shock scrambler (E1064GS) provided a 1.6 mA electric shock which was applied to the grid floor everywhere except in the goal boxes. A 150 W spotlight bulb was placed one meter above the choice point to illuminate the maze.

Training Procedure

On each individual trial, a rat was dropped from a height of 15 cm onto the floor of the start box facing the choice point with the shock already turned on. The rats choice was defined as the direction in which it first departed from the choice point. It was allowed to run freely in the maze until it reached, and remained in, an accessible goal box. On training trials only one goal box was accessible, whereas on test trials both goal boxes were open so that the rat could escape irrespective of which choice it made. The rat was removed from the maze about 5 sec after it reached a goal box and retained in a wastebasket between trials.

A training session consisted of 10 individual training trials spaced about 1 min apart, with the same choice (either right or left) required on all 10 trials. For each group, two states were selected to act as discriminative conditions. Some rats were trained to differentiate drug from no-drug (D vs N); others were required to differentiate two different drugs or two doses of the same drug (D vs D). On successive days the imposed drug condition alternated, as did the required choice. Hence, a right turn was always required in one drug condition and a left in the other.

Each test session consisted of one or two test trials in which both goal boxes were accessible. After a rat learned to discriminate the training conditions, it was given test sessions under novel drug states which differed from the training conditions. During such test sessions, the rat's choices apparently indicated which of the two training conditions was more closely approximated by the test condition. Test sessions were interspersed with continuing training sessions which served to demonstrate and maintain differential responding under the training conditions. Rats received no more than one training or test session per day, averaging 4 sessions per week.

Analysis of Data

Accuracy on the first trials of successive training sessions was analyzed to provide measurements of drug discriminability. Criterion performance was 8 correct first-trial choices during 10 consecutive training sessions. For each rat the number of sessions to the beginning of criterion performance (STC) was computed. STCs had a skewed distribution which was normalized by logarithmic transformation before computations. An STC of 60 was assigned to rats that failed to show criterion performance within 60 sessions. Note that STC is inversely related to discriminability; high STC values indicate that prolonged training was required to establish differential responding. Learning curves were compared using a two factor mixed analysis of variance (ANOVA) with one factor repeated [4]. Dose response curves were approximated by least squares regression lines and also evaluated by ANOVAs.

RESULTS

Dose Response Curves

To determine the relationship between discriminability and dosage, rats were trained to discriminate various doses of atropine (N = 39), scopolamine (N = 68), benactyzine (N = 31) or Ditran (N = 33) from no drug. Each individual rat was trained with a single drug and dosage using the 10-trial D vs N training procedure with alternating D and N conditions during successive sessions. Figure 1 shows geometric mean STC as a function of dosage for each drug. STC decreased with increasing dose, then asymptoted and finally tended to increase again with very high doses.

The relative potency of the four antimuscarincs cannot be specified in the asymptotic dose range as all drugs had the same activity over a range of doses. Table 1 describes the linear dose response curves obtained with lower doses. Scopolamine and Ditran yielded dose response curves with lesser slopes than did atropine or benactyzine. The atropine slope differed significantly ($p<0.05$) and the benactyzine slope almost significantly ($p\cong 0.07$) from those of both scopolamine and Ditran. The relative potencies of these drugs are indicated in Table 1 which shows the dose required to achieve STC = 10 or STC = 40 with each drug (values inferred from the regression lines).

These data raise several questions: (1) do drug effects on the CNS genuinely fail to increase with dosage in the plateau region, or is the plateau an artifact caused by drug accumulation or tolerance resulting from repeated drug administration? (2) Within the asymptotic region, do all doses produce identical effects, or are different doses discriminable from each other as well as from the no-drug condition? (3) Are the discriminable effects of the four drugs interchangeable? (4) If so, are the discriminable effects of antimuscarinics unique, and not shared by drugs of other classes. The remaining experiments were designed to answer these questions.

Effects of Tolerance

Possibly the asymptote in Fig. 1 results from tolerance. Rats trained with high doses might develop proportionally more tolerance so that net drug effects remain essentially

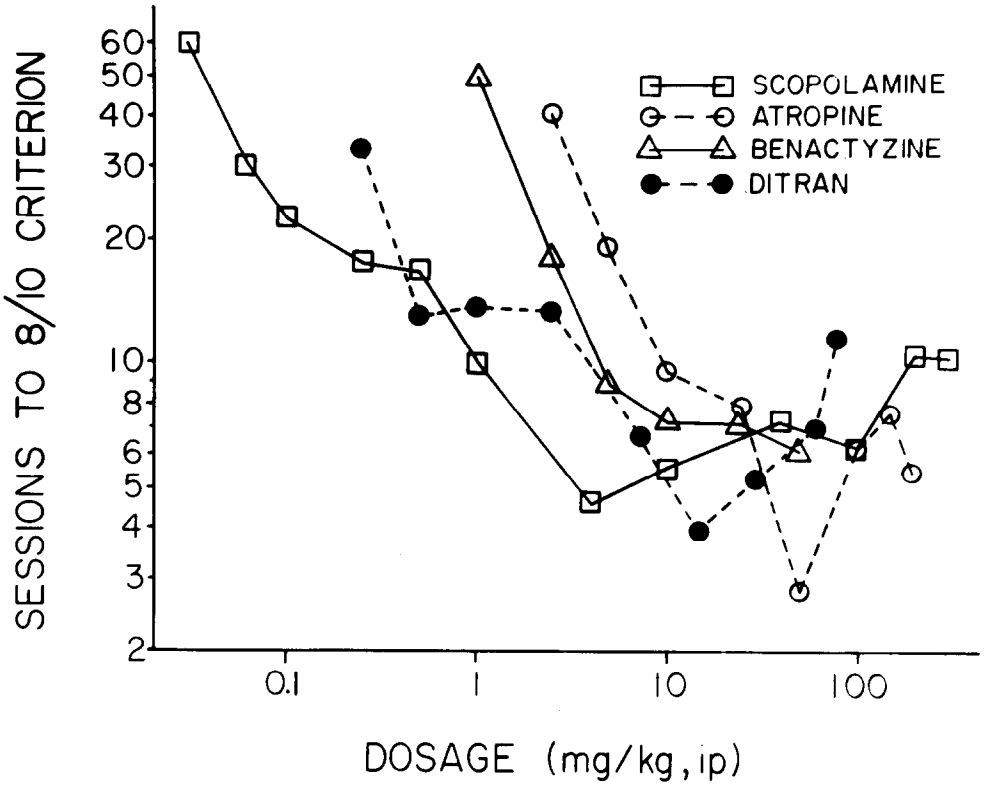

FIG. 1. Dose response curves show number of training sessions before D vs N discriminations were learned with various doses. Abscissa: Dosage in mg/kg. Ordinate: Geometric mean sessions to begin criterion performance. N≥3 per data point. Note that the ordinate and abscissa are on different log scales.

constant. To test this hypothesis the dose response curve for scopolamine was remeasured in rats that were tolerant to S100. It was expected that STCs might increase as the training dose dropped below S100, thus eliminating the plateau. In this experiment 26 rats were divided into 7 groups and required to learn D vs N discriminations based on 7 doses of scopolamine – S40, S10, S4, S1, S.5, S.1 and S.06, respectively. The training dose was administered 20 min before D training and one hour after D training enough extra scopolamine was administered so that the total dosage for the day was 100 mg/kg. This procedure was intended to maintain an equal degree of tolerance in all groups.

Figure 2 compares STCs of tolerant rats to those of the "nontolerant" rats previously described in Fig. 1. Regression lines fitted to the data for doses 0.03 to 4 mg/kg had slopes of −0.46 and −0.39 ($p>0.10$). Discriminability of low doses was somewhat reduced in the tolerant rats, and the dose effect curve was shifted to the right ($p<0.05$). To obtain STC = 20, a dose of 0.22 was adequate in nontolerant rats whereas a dose of 0.77 was required in tolerant rats indicating a 71% reduction in sensitivity to low doses.

TABLE 1

DOSE RESPONSE CURVES FOR D VS N ACQUISITION

Drug	Doses Included (mg/kg)	Number of Rats	Slope‡	Correlation Coefficient	Dose for STC=10	Dose for STC=40
Scopolamine	0.03–4	39	−0.46*	−.79§	0.96†	0.048†
Ditran	0.25–15	24	−0.42*	−.71§	2.6†	0.096†
Benactyzine	1–10	20	−0.82*	−.66§	5.65†	1.04†
Atropine	2.5–50	24	−0.83*	−.75§	12.5†	2.36†

*Slope differed significantly from zero ($p<0.05$, ANOVA).
†Doses in mg/kg are inferred from the regression lines for each drug.
‡Dose and STC were logarithmically transformed before the regression computation.
§Correlation coefficient relates dosage to STCs of individual rats. From r, the significance of the slope is calculated.

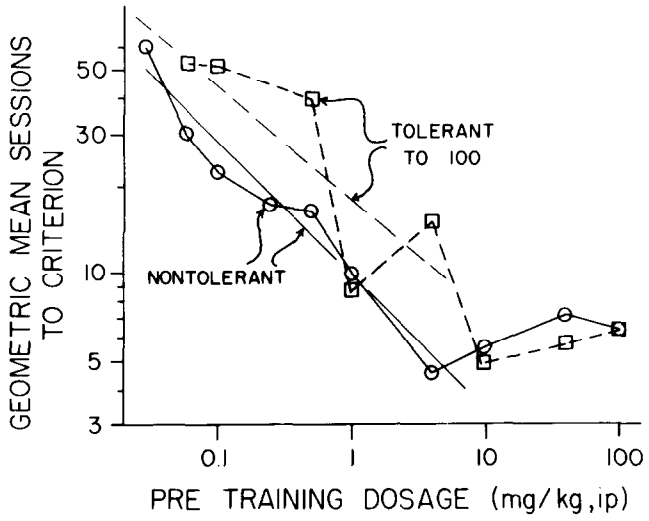

FIG. 2. Dose response curves for D vs N discriminations in tolerant and nontolerant rats. Tolerant rats received additional drug after D training so that the administered dosage totaled 100 mg/kg in all groups. Nontolerant rats received only the indicated training dosage. N≥3 per group.

In the dose range 4 to 100 mg/kg, slopes were 0.1 and −0.1, respectively, and neither the slopes nor levels of the regression lines differed significantly. The basic shape of the dose response curve was not changed, and discriminability asymptoted between 1 and 10 mg/kg in both experiments. Hence, the asymptote appears to be a genuine property of the dose response curve and not an artifact resulting from repeated administration of drug.

Substitution Tests Between Antimuscarinics

Are the effects of high and low doses within the plateau interchangeable? Also, do the four antimuscarinics produce similar discriminable effects, or does each drug produce different effects? To answer these questions, well trained rats received substitution tests with novel antimuscarinic drugs [14]. Each rat initially learned a D vs N discrimination with one of the higher or lower doses within the plateau region as shown in Table 2. After criterion performance was achieved, training was continued using the same, or a similar dose of the same drug. Interspersed between these training sessions, each rat received test trials with the other 7 antimuscarinic drug states. A no-drug training session immediately preceded each test trial, presumably biasing the rats to make N choices during testing.

Table 2 shows the number of D choices on test trials for each test condition. During 280 test trials 85% D choices were observed, compared with 93% correct first trial choices on the interspersed D training sessions. In 5 of the 56 test conditions, 50% or fewer D choices were observed; these involved benactyzine tests with scopolamine-trained rats and benactyzine or atropine tests with Ditran-trained rats. The results show that rats trained with any drug and dosage usually made D choices when tested with any other drug and dosage within the plateau region, indicating a high degree of similarity between all the tested drug conditions. However, some individual instances of nonsubstitution suggest that the drug conditions may not have all been completely equivalent. Further testing would be required to determine whether these individual instances of apparent noninterchangeability are replicable.

D vs D Training with Plateau Doses

Drug vs drug training provides a more rigorous test of the similarity of two drug conditions than do substitution tests [16]. This technique was used to further investigate the relationship between various doses of scopolamine. Sixteen groups containing a total of 56 rats learned D vs D dosage discriminations. Eight groups were required to discriminate dosage ratios of approximately 3:1 (e.g., S1 vs S3, S3 vs S10, S10 vs S30, etc.). The other 8 groups were trained with 10:1 dosage ratios (e.g., S1 vs S10, S3 vs S30, etc.). All rats were trained to criterion or for 60 sessions using the 10-trial per session training procedure.

Figure 3 shows geometric mean STCs for the various groups. S vs N data from Fig. 1 is also shown for comparison. In general, the D vs D STC plot resembles the derivative (slope) of the D vs N plot. In regions where D vs

TABLE 2

SUBSTITUTION TEST RESULTS INDICATING THE DEGREE OF INTERCHANGEABILITY OF VARIOUS DRUGS AND DOSAGES WITHIN THE ASYMPTOTIC RANGE OF DOSES

	Training Conditions (D vs N Training)			Percent D Turns in Training States*		Test Conditions and Number of D Choices Observed†			
Drug	Initial Dose(s)	Final Dose	Number of Rats	D Sessions	N Sessions	Atropine 100 25	Scop 100 4	Benac 25 6	Ditran 30 7.5
Atropine	50, 100	100	6	92	1	– 5	5 5	5 6	6 5
Atropine	25	25	6	94	7	5 –	4 5	5 5	5 6
Scop	40, 100	100	6	90	1	4 5	– 5	3 3	6 6
Scop	1, 4	4	6	94	2	6 6	6 –	5 4	6 6
Benac	25	25	3	82	4	2 2	3 3	– 2	3 2
Benac	5	5	3	92	0	3 3	3 3	3 –	3 3
Ditran	15, 30	30	6	100	6	5 3	6 6	6 4	– 6
Ditran	2.5, 7.5	7.5	4	95	4	2 3	4 4	4 0	4 –

*Shows mean performance on first trials of training sessions interspersed between tests.
†Maximum possible number of D choices equals the number of rats tested in each group.

N discriminability changed rapidly with dosage, D vs D dosage discriminations were readily formed. However, D vs D discriminations were slowly learned if they involved doses for which D vs N STC was asymptotic (excluding discriminations involving S300 – see below).

The results indicate that all doses of scopolamine within the plateau region (except S300) produced approximately the same discriminable effects; these doses were all rapidly discriminated from no drug but not from each other. However, D vs D discriminations were formed within the plateau region by some rats after prolonged training suggesting that drug effects did not totally asymptote, but continued to change slowly as dosage was increased.

Nineteen additional groups (N = 3 to 6 each) learned D vs D discriminations involving various other pairs of drugs and doses within the plateau region (e.g., S300 vs A100, S100 vs A25, S10 vs D10, A150 vs B50, etc.). In general the data from these groups was uninformative, but one pattern did emerge. For nine groups in which one state was created by S300 or A150 and the other state by a lower dose of A, S, B or D within the plateau range, the mean STC was 12. In another 9 groups whose training involved only lower plateau doses of A or S or plateau doses of B or D, the mean STC was 39 ($t = 3.9$; $p<0.01$). For a single group trained with S300 vs A150, STC was 41. The results suggest that A150 and S300 differ substantially from other asymptotic doses of A, S, B or D. This apparently explains the relatively low STCs obtained with S300 vs S30 and with S300 vs S100 in Fig. 3. Presumably at these high doses, S300 and A150 act on additional receptors not influenced by lower plateau doses.

Physostigmine Antagonism to Scopolamine

Bemegride antagonizes discriminable effects of pentobarbital [11]. mecamylamine blocks nicotine [9,12], naltrexone antagonizes morphine and physostigmine antagonizes Ditran [7]. The present study tested for antagonism between scopolamine and physostigmine. Nineteen rats were trained to discriminate S1 vs N and were then tested with various doses of scopolamine (20 min) and with scopolamine (20 min) plus physostigmine 1 mg/kg (7.5 min) as shown in Fig. 4. Data from test trials bracketed by incorrect first-trial performance in the training states was discarded.

Figure 4 shows that animals receiving physostigmine plus S made fewer D choices than those receiving S alone; the two curves differ significantly ($p<0.01$, t-test). The dose response curve was shifted to the right far enough so that a 50% increase in scopolamine dosage was required to obtain any specified percentage of D choices. However there was no dosage of S that produced 100% D choices and could be totally antagonized by physostigmine.

Artane and Cogentin

These antimuscarinic antiparkinson drugs were tested after the other sections of this study were complete. Rats achieved D vs N criterion with trihexyphenidyl Hcl (artane) 10, 25, 50 and 100 mg/kg after a mean of 5.6, 3.9, 7.7 and 14.7 sessions, respectively. Hence the dose-effect data indicate asymptotic drug action over the dose range 10–50 as observed with other antimuscarinic drugs. Rats trained with trihexyphenidyl 50 made 11/12 D choices under S5 but only 2/8 D choices with A25–50. Rats trained with S5 vs N made only 8/16 D choices with trihexyphenidyl 10–50. The substitution test data suggest that the effects of trihexyphenidyl may not closely resemble those of scopolamine or atropine.

Rats trained with benzotropine mesylate (cogentin) 40

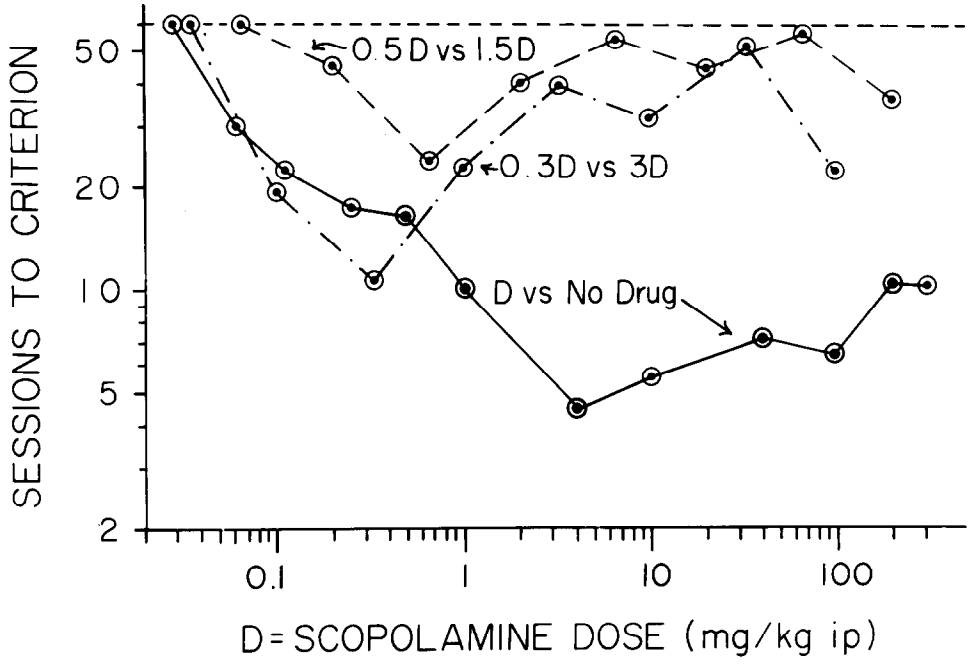

FIG. 3. Geometric mean sessions to criterion for rats trained to discriminate between various pairs of doses of scopolamine. Within the dose range where D vs N discriminability was asymptotic, D vs D discriminations were slowly acquired. X axis is the training dose for D vs N rats, and is a computed intermediate dosage in between the two training doses for D vs D rats.

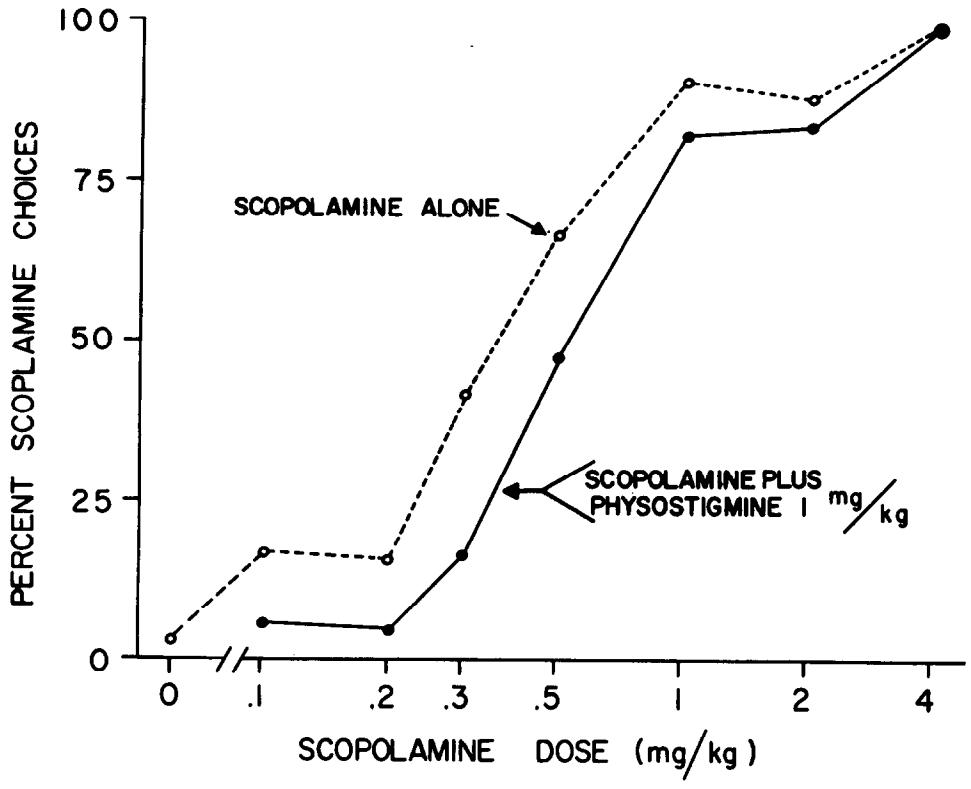

FIG. 4. Test for antagonism between scopolamine and physostigmine. After rats had discriminated scopolamine 1 mg/kg vs no drug, tests were conducted with various doses of scopolamine alone and with scopolamine plus physostigmine. Abscissa: Dosage of scopolamine administered 20 min before tests. Ordinate: Percent drug choices. Physostigmine significantly antagonized the effects of scopolamine.

or 20 mg/kg yielded mean STCs of 6.2 and 13.5, respectively. Even though we separated sessions by several days to allow drug elimination, rats tended to die from toxic effects of this drug. Substitution test data were not collected.

Substitution Tests with Other Drugs

After D vs N training with an antimuscarinic drug, substitution tests were sometimes performed with pharmacological agents of other classes. The results of such tests were accepted as data only if the rats maintained 75%

TABLE 3

RESULTS OF SUBSTITUTION TESTS IN WHICH ANTIMUSCARINIC DRUGS WERE ADMINISTERED TO RATS THAT HAD LEARNED TO DIFFERENTIATE DRUGS OF OTHER CLASSES FROM NO DRUG

Training Drug*	Test Drug*	No. D Choices/No. Tests
d-Amphetamine 6	Atropine 100-200	14/22
d-Amphetamine 6	Benactyzine 50	3/8
d-Amphetamine 6	Scopolamine 300	4/6
Dextromethorphan 40-50	Scopolamine 5	0/14
Mescaline 50	Atropine 50-150	4/10
Mescaline 50	Scopolamine 10-300	6/8
Pentylenetetrazol 20-30	Scopolamine 5	2/6
Morphine 15	Scopolamine 5	4/24
Pentobarbital 10-20	Atropine 50-150	45/161
Pentobarbital 10-20	Benactyzine 5-50	57/148
Pentobarbital 10-20	Ditran 15-30	6/30
Pentobarbital 10-20	Scopolamine 5-50	2/54

*Doses in mg/kg IP.

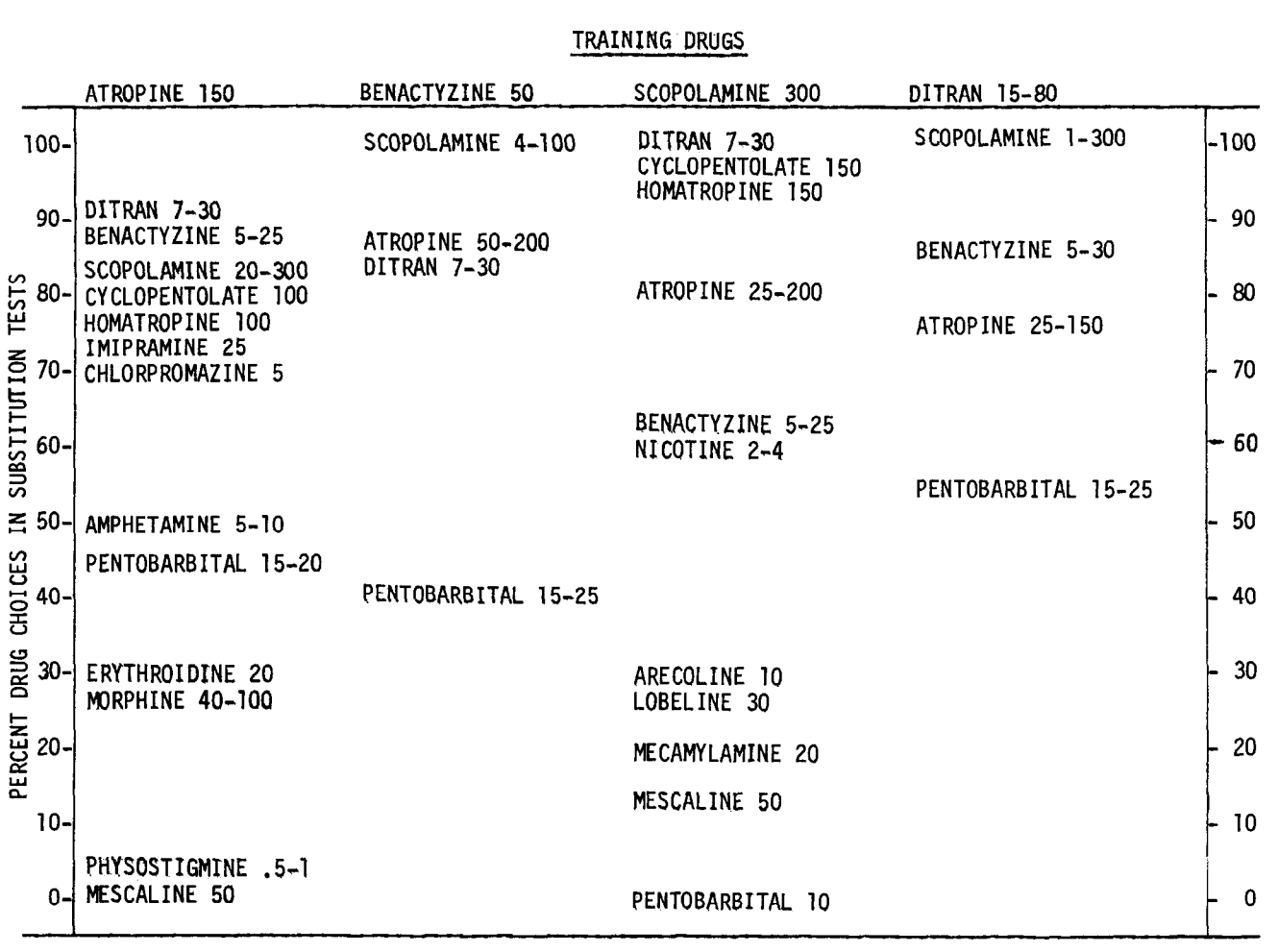

FIG. 5. Results of substitution tests with various drugs. All rats had learned to discriminate one of the four antimuscarinic drugs vs no drug before testing. The vertical position of the name of a test drug in the figure indicates the percentage of D choices observed with that test drug and dosage.

accuracy on first trials of both D and N training sessions interspersed between the test sessions. Figure 5 shows the results in all cases where 8 or more acceptable test trials were available as data (median = 20 test trials per test drug). In general, antimuscarinic test drugs caused 70% or more D choices whereas drugs in other classes yielded 60% or less D choices. However, some overlap occurred.

Table 3 shows results obtained when rats learned D vs N discriminations with drugs of other pharmacological classes, and were then tested with antimuscarinic compounds. To some degree, antimuscarinic drugs appeared to mimic mescaline and amphetamine; these instances of partial substitution may reflect anticholinergic actions of the training drugs. In other cases, substitution was not observed.

DISCUSSION

The results show that antimuscarinic drugs provide a basis for rapidly learned differential responding in the T-maze. At low doses, discriminability was proportional to dose. At higher doses, discriminability asymptoted so that further increases in dose did not increase discriminability. The asymptote of discriminability was apparently a genuine effect, possibly caused by receptor saturation, and not an artifact produced by tolerance or residual drug. It encompassed doses ranging from scopolamine 4 to 100, atropine 10 to 100, benactyzine 5 to 50, Ditran 7 to 60 and trihexyphenidyl 10 to 50. Within the range of doses where effects were asymptotic, the antimuscarinics were sufficiently similar to substitute for one another in most instances, but sufficiently dissimilar so that D vs D discriminations could generally be formed after prolonged training. This pattern of substitution test and D vs D training results resembles that found in some other classes of drugs [16]. The discriminable effects of drugs from other classes were usually not interchangeable with those of antimuscarinics, and vice versa. The properly stated conclusion is that the discriminable effects of asymptotic doses of antimuscarinic drugs are considerably more similar to one another than they are to discriminable effects of drugs in other classes.

The antagonism of scopolamine by physostigmine was not strong in our task, and we were more impressed by the weakness of this interaction than by its occurrence. In a similar drug discrimination task, Jarbe *et al.* [7] recently reported that physostigmine and tetrahydroaminoacridine (THA) could antagonize the discriminable effects of Ditran.

Their data appear similar to ours as they found this antagonism only when parameters were carefully selected. In other behavioral tasks as well, the antagonism of scopolamine by physostigmine is not always strong, depending on the timing of injections and other factors [3, 7, 18]. In contrast, other agonist/antagonist interactions have been very robust in drug discrimination tasks; e.g., pentobarbital vs bemegride [11] and nicotine vs mecamylamine [9,12]. At a practical level we might note that scopolamine does not protect rats against the lethal effects of physostigmine. Therefore 1 mg/kg of physostigmine is about the highest dose that can be used. Perhaps higher doses would produce a more robust antagonism to the effects of scopolamine, if they were not lethal.

Presumably, the discriminable actions of antimuscarinic drugs are produced by their characteristic anticholinergic actions within the CNS. Recall that the antinicotinic drug mecamylamine neither mimics nor is mimicked by scopolamine [12]. Hence the cueing effects of antimuscarinics differ substantially from those of antinicotinics. Neither antimuscarinics nor antinicotinics are mimicked by their respective peripherally acting analogs such as methyl atropine, methyl scopolamine and tetraethylammonium cloride; this indicates that CNS actions underlie the discriminable actions of the antimuscarinics [8,13]. Finally, the antagonism of physostigmine to scopolamine suggests an antimuscarinic basis for discriminability.

Although many dose effect curves are supposed to be sigmoidal, it is often impossible in behavioral preparations to explore the high-dose end of the sigmoid due to severe behavioral disruption. However, the margin of safety of the antimuscarinics was substantial. In order to produce severe behavioral disruption in our rats (and death due to curare-like actions), the required dose was 10 to 100 times that adequate to produce a maximal discriminable effect. Unfortunately, we failed to test one practical application of our results. Since actions of scopolamine asymptote, it might be possible to obtain maximal CNS effects within 2–3 min after IP injection by administering an elevated dose of scopolamine (e.g., 50 mg/kg). Although conceptually trivial, this technique could be useful in studies on learning and memory since the drug state could be rapidly induced after the learning experience.

Generally speaking, the antimuscarinics were a well behaved class of drugs in the drug discrimination paradigm. They were readily discriminated, maintained highly accurate asymptotic performance despite interspersed substitution tests, and shared a common discriminated effect which was relatively unique to this class of compounds. Hence drug discrimination procedures can readily be used to study the central actions of antimuscarinics.

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REFERENCES

1. Bradley, P. B. and B. J. Key. A comparative study of the effects of drugs on the arousal system of the brain. *Br. J. Pharmac. Chemother.* **14:** 340–349, 1959.
2. Buresova, O., J. Bures, Z. Bohdanecky and T. Weiss. Effect of atropine on learning, extinction, retention and retrieval in rats. *Psychopharmacologia* **5:** 255–263, 1964.
3. Crowell, E. B. and J. S. Ketchum. The treatment of scopolamine-induced delerium with physostigmine. *Clin. Pharmac. Ther.* **8:** 409–414, 1967.
4. Edwards, A. L. *Statistical Methods.* New York: Holt, Rinehart and Winston, 1967.
5. Giarman, N. J. and G. Pepeu. The influence of centrally-acting cholinolytic drugs on brain acelytcholine levels. *Br. J. Pharmac. Chemother.* **23:** 123–130, 1964.
6. Gruber, R. P., G. C. Stone and D. R. Reed. Scopolamine-induced anterograde amnesia. *Int. J. Neuropharmac.* **6:** 187–190, 1967.
7. Jarbe, T. U. C., J. O. Johansson and B. G. Henriksson. Drug discrimination in rats: The effects of phencyclidine and Ditran. *Psychopharmacologia* **42:** 33–39, 1975.
8. Kubena, R. K. and H. Barry III. Generalization by rats of alcohol and atropine stimulus characteristics to other drugs. *Psychopharmacologia* **15:** 196–206, 1969.
9. Morrison, C. F. and J. A. Stephenson. Nicotine injections as the conditioned stimulus in discrimination learning. *Psychopharmacologia* **15:** 351–360, 1969.
10. Overton, D. A. State-dependent or "dissociated" learning produced with pentobarbital. *J. comp. physiol. Psychol.* **57:** 3–12, 1964.
11. Overton, D. A. State-dependent learning produced by depressant and atropine-like drugs. *Psychopharmacologia* **10:** 6–31, 1966.
12. Overton, D. A. Control of T-maze choice by nicotinic, antinicotinic, and antimuscarinic drugs. *Proc. 77th Annual Convention, American Psychol. Assn.* 869–870, 1969.
13. Overton, D. A. Discriminative control of behavior by drug states. In: *Stimulus Properties of Drugs,* edited by T. Thompson and R. Pickens. New York: Appleton-Century-Crofts, 1971, pp. 87–110.
14. Overton, D. A. Experimental methods for the study of state-dependent learning. *Fedn Proc.* **33:** 1800–1813, 1974.
15. Overton, D. A. Discriminable effects of benzodiazepines. *Psychopharmac. Communs.* **2:** 339–343, 1976.
16. Overton, D. A. Comparison of ethanol, pentobarbital and phenobarbital using drug vs drug discrimination training. *Psychopharmacology* 1977 (in press).
17. Paskal, V. Dissociative effects of atropine on a simple learned task in the rat. *Undergrad. Research Reports in Psychol.* McGill University, 1962, pp. 37–43.
18. Rech, R. H. Effects of cholinergic drugs on poor performance of rats in a shuttle box. *Psychopharmacologia* **12:** 371–383, 1968.
19. White, R. P., C. B. Nash, E. J. Westerbeke and G. J. Possanza. Phylogenetic comparison of central actions produced by different doses of atropine and hyoscine. *Archs int. Pharmacodyn. Ther.* **132:** 349–353, 1961.