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Relationship of the Behavioral Effects of Aprophen, Atropine and Scopolamine to Antagonism of the Behavioral Effects of Physostigmine[1]

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GENOVESE, R. F., T. F. ELSMORE AND J. M. WITKIN. *Relationship of the behavioral effects of aprophen, atropine and scopolamine to antagonism of the behavioral effects of physostigmine.* PHARMACOL BIOCHEM BEHAV **37**(1) 117–122, 1990.—Behavioral effects of aprophen, atropine and scopolamine, in rats, were examined under a multiple schedule of food presentation and at different injection-test times. The effects of the varied treatments were compared to the ability of the drugs, under identical conditions, to prevent the behavioral effects of the anticholinesterase, physostigmine. Potencies of the antagonists to decrease response rates varied across three log units. All three antagonists produced dose-related attenuation of the response suppressant effects of physostigmine. In general, aprophen was a better antagonist than scopolamine or atropine. It blocked behavioral effects of physostigmine across a wider range of doses than the other compounds, and did so with less behavioral disruption. Although substantial differences between the three antagonists were observed, the behavioral effects of all three antagonists (when administered alone) were positively correlated with their efficacy as antagonists of the response suppressant effects of physostigmine.

Aprophen Atropine Physostigmine Scopolamine Rats Cholinergic Operant behavior

MUSCARINIC antagonists differ widely in the spectrum of their pharmacological activities (2,8). For example, the diphenylpropionate antimuscarinic aprophen has been shown to be a competitive inhibitor at muscarinic and not nicotinic receptor sites (7), but has been found to be a noncompetitive inhibitor at nicotinic receptor sites (1). Furthermore, diphenyl antimuscarinics produce qualitatively different effects on behavior from those of tropate compounds like atropine. In both rats and squirrel monkeys, atropine and scopolamine decrease responding under conditions in which aprophen, benactyzine or adiphenine increase responding (15,16).

The distinct pharmacological profiles and behavioral effects of antimuscarinic drugs may bear a significant relationship to the ability of these drugs to block the behavioral effects of direct or indirect muscarinic agonists. The primary treatment for anticholinesterase poisoning (e.g., carbamate and organophosphorous exposure) is the administration of anticholinergics, particularly atropine, along with cholinesterase reactivators (9,12). Thus, further understanding of the behavioral effects of anticholinergics may lead to improved therapeutic methods.

Correlations of behavioral effects of muscarinic antagonists with in vitro assessments of antimuscarinic activity have not been uniformly positive. For example, inhibition of [^{3}H]N-methylscopolamine binding from neuroblastoma cells does not correlate with the response rate depressant effects of a host of antimuscarinics studied in rats (16). Correlations between behavioral effects and in vivo assessments of anticholinergic effects have also reported some inconsistencies with a precise positive relationship [cf. (11)]. For example, atropine produces decreases in responding of squirrel monkeys maintained under fixed-interval schedules of food presentation, electric shock presentation or shock postponement. When physostigmine or oxotremorine are administered in conjunction with atropine, however, rates of responding are often increased above control levels (14,18). In these studies the effects of the drugs alone, time-course determinations, and drug interaction experiments suggest that atropine has nonmuscarinic behavioral

[1]In conducting the research described in this report, the investigators adhere to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The views of the authors do not purport to reflect the position of the Department of the Army or the Department of Defense (para 4-3, AR 360-5).

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excitatory effects that were unmasked in the presence of muscarinic agonists [see (13,15) for overview and discussion].

The present study was conducted to evaluate the relationship between the behavioral effects of muscarinic antagonists and their ability to antagonize the behavioral effects of physostigmine. The behavioral effects of antimuscarinics were systematically varied and compared to their efficacy as physostigmine antagonists under each condition. Thus, correlations between behavioral effects of the antagonists administered alone and in combination with physostigmine were not appreciably influenced by differences in species, pharmacokinetics, or other variables that are known to influence pharmacological activity. Several antagonists with different potencies and spectra of effects were studied. Aprophen, atropine and scopolamine were chosen for this purpose. Dose and time of administration were varied in order to produce a range of behavioral effects of each compound. Finally, behavioral effects of the antimuscarinics were also varied by evaluation under two different schedules of response-produced food presentation.

METHOD

Subjects

Twenty-four adult male Sprague-Dawley rats (Zivic-Miller, Allison Park, PA) were used. Rats were individually housed in a temperature-controlled environment. Water was available in the home cages throughout the experiment. Initially, rats were allowed unlimited access to food (Purina Rat Chow) until their body weights reached approximately 320 g. Thereafter, body weights were maintained at approximately 320 g by supplemental feedings occurring several hours after experimental sessions were conducted. A 12-hr:12-hr light:dark cycle (lights on at 0600, off at 1800 hours) was maintained throughout the experiment. Rats had no prior experimental or pharmacological experience.

Apparatus

Experimental sessions were conducted in twelve standard rodent operant conditioning chambers (model No. E-10-10; Coulbourn Instruments, Lehigh Valley, PA) housed in ventilated, light- and sound-attenuating cubicles. One wall of the chambers contained two response levers and a food trough that could be illuminated and was attached to a food dispenser capable of delivering 45 mg food pellets (Bioserve, Frenchtown, NJ). Two stimulus lights were mounted above each response lever. Pressing a lever with a downward force of at least 0.3 N was considered a response. Experimental events were controlled and monitored by a PDP-11/73 computer using the SKED operating system (State Systems, Kalamazoo, MI).

Behavioral Procedure

Initially, rats were trained to lever-press for food pellets under a FR 1 schedule of reinforcement. When lever-pressing was maintained by food presentation, rats were trained to lever-press under a multiple VI 18 sec, VI 56 sec schedule of food reinforcement. Reinforcement during each component was produced by responses on only one lever and the inactive lever for one component was the active lever during the other component. Responses on the inactive lever were recorded but had no programmed consequences. The stimulus lights above the active lever were illuminated and the order of lever assignments was counterbalanced across subjects. The VI 18 and VI 56 components alternated every 90 sec and were separated by a 5-sec period during which the chamber was dark and responding had no programmed consequences. Interval values for the VI 18 and VI 56 schedules were chosen randomly (without replacement) from distributions generated according to the procedure developed by Fleshler and Hoffman (3) and the ranges of values were 0.77–62.73 sec and 2.44–198.23 sec, respectively. Experimental sessions lasted for 60 min and were conducted at approximately the same time each day, Monday–Friday.

After approximately 70 sessions under the multiple VI 18, VI 56 schedule of reinforcement, performance appeared stable and rats were assigned to 3 groups of 8 subjects each. Groups were matched on the basis of rate of responding with the restriction that each group was balanced with respect to response lever-VI schedule component assignments.

Drugs

Aprophen hydrochloride, atropine sulfate, physostigmine salicylate, and scopolamine hydrobromide (United States Army Medical Research Institute of Chemical Defense, Aberdeen, MD) were dissolved in 0.9% saline. All injections were administered SC in a volume of 1.0 ml/kg body weight. Drug solutions were prepared on the day of injection and all doses are expressed as the salt.

Pharmacological Procedure

Injections were administered on Tuesdays and Fridays and data from Thursday's sessions were treated as noninjection controls. Each antagonist was studied in a single group. The order of drug injections for each group was antagonist, antagonist plus 0.4 mg/kg physostigmine, and 0.4 mg/kg physostigmine. Thus, this series was repeated for each dose of the antagonist administered to a particular group. Doses of the antagonists were in a mixed order. The dose of physostigmine was chosen on the basis of previous research in our laboratories demonstrating that 0.4 mg/kg physostigmine produces a substantial degree of response suppression on schedule-controlled behavior in rats (4–6). Physostigmine was always administered 10 min before the start of the sessions. Initially, atropine, aprophen, and scopolamine were examined when administered 40 min before the start of sessions. Following these regimens dose-effect functions were again determined for these compounds when administered 190 min before the start of sessions.

Data Analysis

When a response or an experimental event occurred, the elapsed time during the session was recorded. From these data the rate of responding during each component of the multiple VI 18, VI 56 schedule was calculated for each subject. Cumulative response records were also generated for each session.

In order to assess the general efficacy and potency of atropine, aprophen, and scopolamine, least-squares estimation procedures were used to calculate a linear or curvilinear function relating drug dose to response rate. Specific values were then interpolated or extrapolated from the function equations. For the antagonists administered alone, dose-effect functions were used to calculate values representing the doses producing response rates at 70% (ED_{70}) of the response rates observed during control sessions. For the antagonists administered in combination with physostigmine, the dose-effect functions were used to calculate values representing the doses producing the greatest degree of responding, that is, the maximum effective dose (MED) for attenuating physostigmine's effects, and the minimum doses producing response rates of 70% (ED_{70}) of control response rates. A range of effective antagonism, defined as the difference (in log units) between the ED_{70} and MED doses, was also calculated.

TABLE 1

AVERAGE CONTROL RATES OF RESPONDING (RESPONSES PER MINUTE) UNDER THE MULTIPLE SCHEDULE OF REINFORCEMENT

Group	VI 18 Sec	VI 56 Sec
(40 min presession)		
Aprophen	97.9 ± 3.2	71.2 ± 5.0
Atropine	102.0 ± 3.6	60.3 ± 3.1
Scopolamine	97.7 ± 5.2	63.7 ± 3.9
(190 min pression)		
Aprophen	102.7 ± 5.1	72.4 ± 4.4
Atropine	112.6 ± 2.9	55.9 ± 2.8
Scopolamine	97.5 ± 5.5	55.0 ± 3.5

Each entry represents the mean ± SEM from 8 rats. Data are from 20 noninjection control sessions during the course of dose-effect determinations.

RESULTS

Baseline Performance

Responding under the multiple VI 18, VI 56 schedule of reinforcement was characterized by a relatively constant response rate during each of the two schedule components. Discrimination between the two schedule components was very accurate and typically 95–99% of responses occurred on the active lever. Table 1 presents the rates of responding observed during noninjection control sessions during the course of pharmacological manipulations. Although differences between rats were observed, response rates under the VI 18 component were generally faster than those under the VI 56 component.

Effects of Physostigmine

Physostigmine (0.4 mg/kg) produced substantial decreases in response rate, under both schedule components, in all rats (unconnected points above 0, Figs. 1–4, bottom panels). In general, physostigmine's response rate decreasing effects were reliably observed throughout the course of experimentation. With repeated administration, however, some diminution in effect was observed.

Effects of the Antagonists After 40-Min Pretreatment

All three antagonists produced dose-dependent decreases in rates of responding under both the VI 18 (Fig. 1, top panel) and the VI 56 component of the multiple schedule (Fig. 2, top panel). Whereas scopolamine was more potent than either atropine or aprophen under both schedule requirements, dose-effect functions for atropine and aprophen were more similar to one another under the VI 56 schedule than under the VI 18 schedule (compare Figs. 1 and 2).

The antimuscarinics produced dose-dependent attenuation of physostigmine's response suppressant effects (Figs. 1 and 2, bottom panels). Larger doses produced less attenuation so that the dose-effect functions for the antimuscarinics in the presence of physostigmine were inverted U-shaped functions of dose. Atropine did not fully prevent the behavioral effects of physostigmine under the VI 18 schedule. Aprophen conferred nearly complete protection against the rate-suppressant effects of physostigmine across a wider range of doses than the other two antagonists and, under the VI 18 schedule, did not further suppress responding at the larger doses.

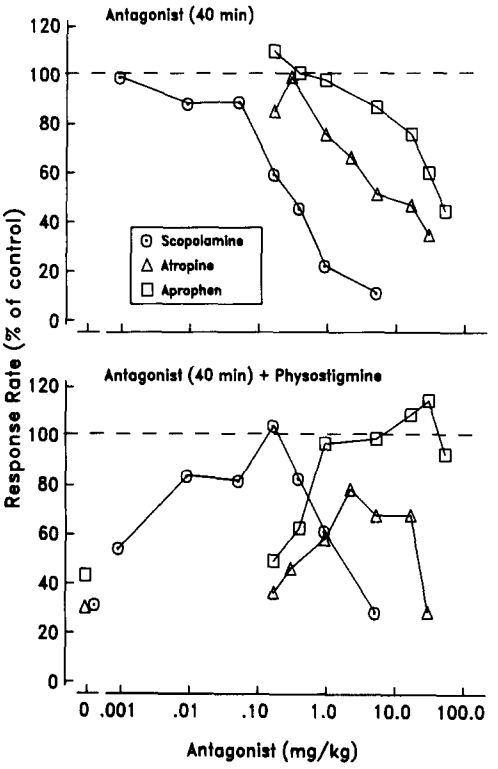

FIG. 1. Comparison of the behavioral effects of antimuscarinics alone (top panel) and as antagonists of 0.4 mg/kg physostigmine (bottom panel) under the VI 18 component of the multiple schedule of food presentation. The antimuscarinics were given 40 min prior to experimental sessions (30 min prior to physostigmine). Points above 0 represent the effects of 0.4 mg/kg physostigmine administered alone. Each point represents the mean effect in 8 rats.

Effects of the Antagonists After 190-Min Pretreatment

Atropine and scopolamine were equipotent in decreasing responding when given alone 190 min prior to testing (Figs. 3 and 4, top panels). Aprophen also decreased rates of responding at larger doses although these effects were minimal under the VI 18 schedule (Fig. 3).

All three compounds prevented the behavioral effects of physostigmine in a dose-dependent manner. The largest doses of scopolamine and atropine generally conferred less protection against physostigmine; however, this was not the case with aprophen where doses spanning about one log unit maximally antagonized physostigmine-induced behavioral suppression.

Comparison of Physostigmine Antagonists

The range of effective physostigmine antagonism is shown in Table 2. Whereas scopolamine and aprophen produced a slightly greater range of antagonism under the VI 18 schedule than that under the VI 56 schedule, this relationship was not observed with atropine. Scopolamine and aprophen also displayed a wider range of effective antagonism than atropine, showing a 0.5 to 1 log-unit advantage. The longer pretreatment time of 190 minutes increased the range of effective antagonism for scopolamine and atropine but did not alter this measure for aprophen.

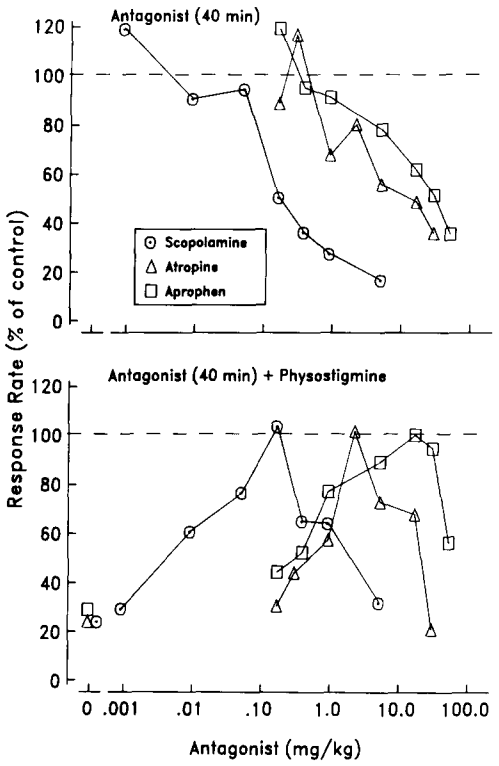

FIG. 2. Comparison of the behavioral effects of antimuscarinics alone (top panel) and as antagonists of 0.4 mg/kg physostigmine (bottom panel) under the VI 56 component of the multiple schedule of food presentation. The antimuscarinics were given 40 min prior to experimental sessions (30 min prior to physostigmine). Points above 0 represent the effects of 0.4 mg/kg physostigmine administered alone. Each point represents the mean effect in 8 rats.

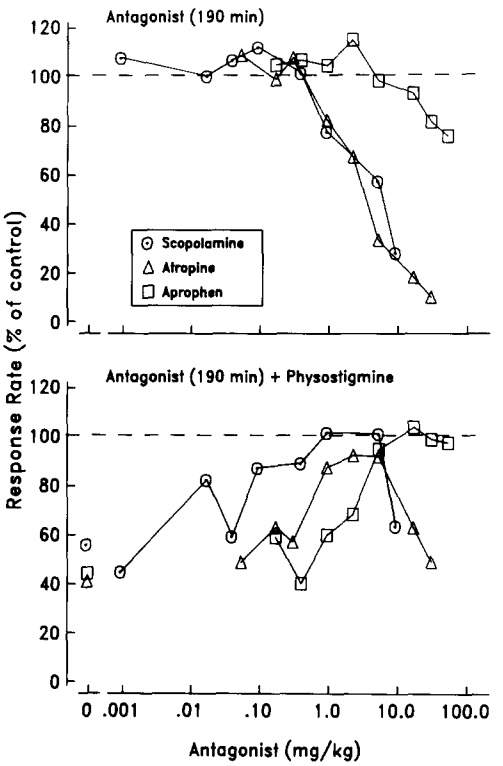

FIG. 3. Comparison of the behavioral effects of antimuscarinics alone (top panel) and as antagonists of 0.4 mg/kg physostigmine (bottom panel) under the VI 18 component of the multiple schedule of food presentation. The antimuscarinics were given 190 min prior to experimental sessions (180 min prior to physostigmine). Points above 0 represent the effects of 0.4 mg/kg physostigmine administered alone. Each point represents the mean effect in 8 rats.

Relationship Between Behavioral Effects and Physostigmine Antagonism

The relationship between the behavioral effects of the antimuscarinics and doses required to block the behavioral effects of physostigmine was positive (Fig. 5). A significant correlation was observed for rate decreasing effects vs. ED_{70} for physostigmine antagonism ($r = .824$, $p<0.01$) and for rate decreases vs. maximal effective dose (MED) for physostigmine antagonism ($r = .99$, $p<0.01$). However, substantial deviation from a 1:1 relationship was only observed for the ED_{70} measure of physostigmine antagonism vs. rate decreasing effects of the antimuscarinics alone (Fig. 5, left panel). Figure 5 also clearly illustrates the potency differences among these antagonists when given alone and as physostigmine antagonists. The alterations in the effects of the antagonists by schedule of reinforcement and pretreatment time are also evident.

Quantitative comparisons of these relationships are further presented in Table 2. The ratio of the potencies of the compounds to decrease responding when given alone to their potencies as antagonists of physostigmine are shown. These data document the greater separation in the doses that decrease responding to the doses that antagonize physostigmine for scopolamine and aprophen than that observed for atropine. Whereas atropine displayed a 4.5-fold separation in the ratio, aprophen and scopolamine showed a maximum separation of 21- and 77-fold, respectively. Table 2 also shows that the magnitude of these relationships was dependent both on the VI schedule under which they were obtained and on the pretreatment time for the antagonists. Larger ratios were seen under the VI 18 schedule for scopolamine and aprophen but not for atropine. The longer pretreatment time increased the ratio for scopolamine and atropine but not for aprophen.

DISCUSSION

In the present study, aprophen, atropine and scopolamine produced dose-dependent decreases in responding under a multiple schedule of food presentation. Although rate increases have been observed with antimuscarinics, especially with diphenyl compounds like aprophen [cf. (15,16)], the particular behavioral baselines under which these compounds were studied were apparently responsible for this discrepancy in reported qualitative effects. The behavioral effects of the antagonists were influenced by the schedule of food delivery and the time of their administration. With respect to potency, time of administration was a critical factor in determining the relative potency of the three compounds.

Based on estimates of the range of effective antagonism, scopolamine and aprophen were better antagonists of physostigmine-induced behavioral suppression than atropine. Effective antagonism for clinical purposes, however, must also be weighed against the potential adverse effects of the antagonists alone. Based on these experiments, aprophen would be predicted to be the better choice of antimuscarinics for treatment and prevention

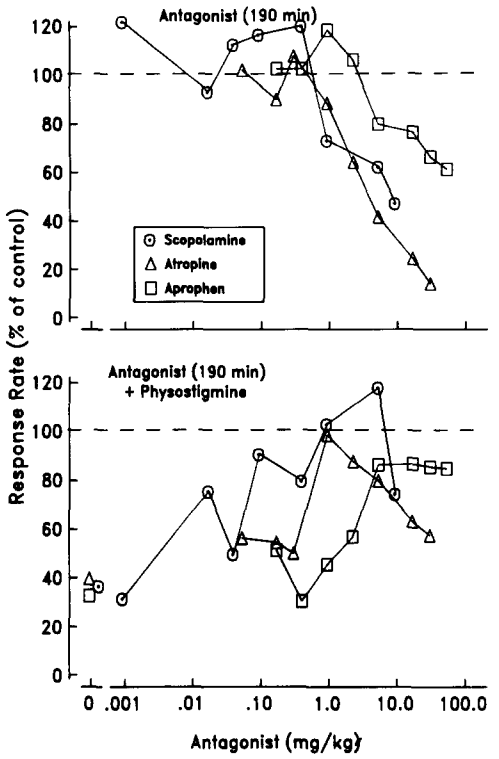

FIG. 4. Comparison of the behavioral effects of antimuscarinics alone (top panel) and as antagonists of 0.4 mg/kg physostigmine (bottom panel) under the VI 56 component of the multiple schedule of food presentation. The antimuscarinics were given 190 min prior to experimental sessions (180 min prior to physostigmine). Points above 0 represent the effects of 0.4 mg/kg physostigmine administered alone. Each point represents the mean effect in 8 rats.

of physostigmine behavioral toxicity. Aprophen exhibited complete blockade of the behavioral effects of physostigmine over a wider range of doses than the other compounds and generally did so at less behavioral debilitating doses. Atropine and scopolamine displayed sharper inversions in their dose effect functions against physostigmine than observed with aprohen at larger doses.

The decreases in rates of food-maintained responding observed with the muscarinic antagonists were generally positively related to their efficacy as antagonists of physostigmine. Detailed examination of this correlation, however, reveals that physostigmine antagonism can occur at doses that do not produce behavioral effects. Doses required to decrease responding to 70% of control values were uniformly greater than those required to attenuate the effects of physostigmine to 70% of control values (Fig. 5, left panel). Thus, physostigmine antagonism was observed with the drugs prior to observation of any behavioral activity of their own. Vaillant (10,11) also noted that physostigmine antagonism occurred over a longer time period than the behavioral effects of scopolamine alone.

In the present study, larger doses of the muscarinic antagonists did not always appear to block the effects of physostigmine but produced marked behavioral effects when given alone. Similar observations were made in studies with antagonists against oxotremorine and oxotremorine-M (16,17). The strong positive correlation observed between behavioral effects of the antagonists administered alone (i.e., ED_{70}'s) and maximal physostigmine antagonism suggests that efficacy against physostigmine's effects was masked by the behavioral effects of the larger doses of the antagonists. In come cases, especially with aprophen, pronounced response rate decreases were observed with the antagonists alone, without any diminution of their efficacy against physostigmine.

The relationship between the behavioral effects of aprophen, atropine, and scopolamine and muscarinic antagonism (as quantified by attenuation of physostigmine's effects) is generally very positive. Substantial differences in potency and duration of action were observed among all three compounds. The schedules of reinforcement used in the present study influenced the effects of the antagonists, although to a much lesser degree than in

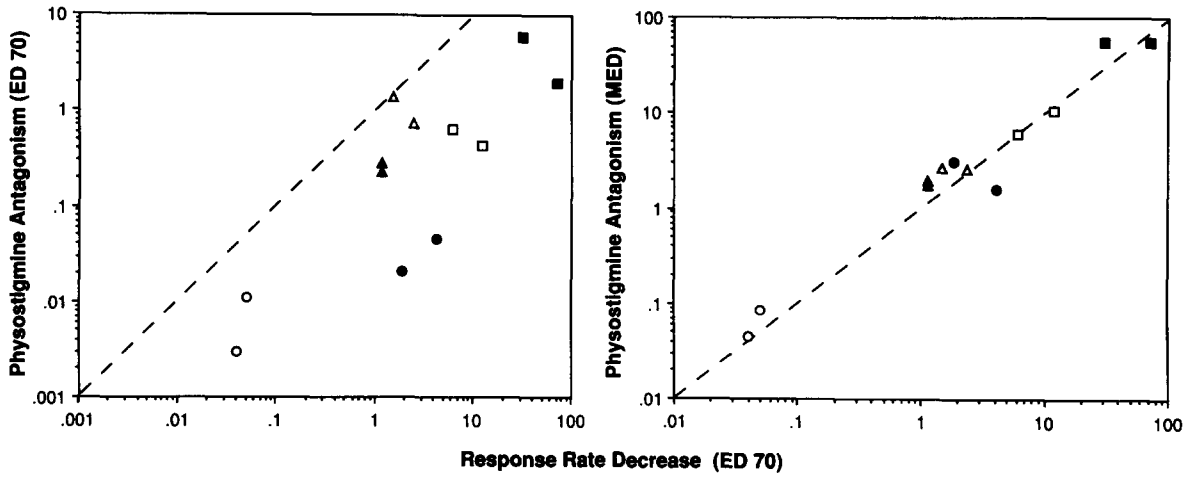

FIG. 5. Relationship of the rate-decreasing effects of antimuscarinics to their ability to prevent the behavioral effects of physostigmine. The dose of the antimuscarinics that decreased responding to 70% of control values is plotted on the abscissae. The dose of the antimuscarinics that returned physostigmine-suppressed responding to 70% (left panel) or that maximally prevented physostigmine-induced behavioral suppression (right panel) is plotted on the ordinates. Circles: scopolamine; triangles: atropine; squares: aprophen. Open symbols: 40 min antimuscarinic pretreatment; filled symbols: 190 min antimuscarinic pretreatment. Duplicate symbols represent effects under the VI 18 and VI 56 schedule components. Left panel: $y = 0.84 \times - 0.95$ ($r = .82$, $p<0.01$); right panel: $y = 0.94 \times + 0.12$ ($r = .99$, $p<0.01$). The dashed diagonal represents a theoretical 1:1 relationship between variables. Each point represents the mean effect in 8 rats.

TABLE 2

COMPARISON OF THE BEHAVIORAL EFFECTS AND THE PHYSOSTIGMINE-ANTAGONIST ACTIONS OF APROPHEN, ATROPINE AND SCOPOLAMINE

	Aprophen			Atropine			Scopolamine		
	VI 18	VI 56	Mean	VI 18	VI 56	Mean	VI 18	VI 56	Mean
Range*									
40 min	1.4	1.0	1.2	0.3	0.6	0.5	1.2	0.9	1.0
190 min	1.5	1.0	1.2	0.9	0.9	0.9	2.2	1.7	1.9
Decrease/ED_{70}†									
40 min	28.4	9.9	19.2	1.1	3.2	2.2	13.3	4.5	8.9
190 min	36.2	5.2	20.8	5.0	4.1	4.5	88.1	65.2	76.6

*Range of effective antagonism in log units. See the Method section for a description of this measure. †Ratio of the response rate-decreasing effects (ED_{70}) and the dose of antagonist that blocks effects of physostigmine to 70% of noninjection control levels (ED_{70}).

previous studies (14,16). In some respects, the diphenylpropionate antimuscarinic, aprophen, showed qualitatively different effects than atropine and, to a lesser degree, scopolamine. Further research is needed to more fully define the conditions under which differences in the behavioral effects of muscarinic antagonists are observed and to characterize the pharmacological nature of these effects.

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REFERENCES

1. Amitai, G.; Herz, J. M.; Bruckstein, R.; Luz-Chapman, S. The muscarinic antagonists aprophen and benactyzine are noncompetitive inhibitors of the nicotine acetylcholine receptor. Mol. Pharmacol. 32:678–685; 1987.
2. Eglen, R. M.; Whiting, R. L. Muscarinic receptor subtypes: A critique of the current classification and a proposal for a working nomenclature. J. Auton. Pharmacol. 5:323–346; 1986.
3. Fleshler, M.; Hoffman, H. S. A progression for generating variable-interval schedules. J. Exp. Anal. Behav. 5:529–531; 1962.
4. Genovese, R. F. Effects of azaprophen, scopolamine, and trihexyphenidyl on schedule-controlled behavior, before and after chronic physostigmine. Eur. J. Pharmacol. 176:271–279; 1990.
5. Genovese, R. F.; Elsmore, T. F.; King, L. R. Tolerance to oxotremorine's effects on schedule-controlled behavior in physostigmine-tolerant rats. Life Sci. 43:571–576; 1988.
6. Genovese, R. F.; Elsmore, T. F.; Witkin, J. M. Environmental influences on the development of tolerance to the effects of physostigmine on schedule-controlled behavior. Psychopharmacology (Berlin) 96:462–467; 1988.
7. Gordon, R. K.; Padilla, F. N.; Moore, E.; Doctor, B. P.; Chiang, P. K. Antimuscarinic activity of aprophen. Biochem. Pharmacol. 32: 2979–2981; 1983.
8. Hoss, W.; Ellis, J. Muscarinic receptor subtypes in the central nervous sytem. Int. Rev. Neurobiol. 26:151–199; 1985.
9. Taylor, P. Anticholinesterase agents. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. Goodman and Gilman's The Pharmacological basis of therapeutics. New York: Macmillan Publishing Co.; 1985:110–129.
10. Vaillant, G. E. Antagonism between physostigmine and atropine on the behavior of the pigeon. Arch. Exp. Pathol. Pharmacol. 248: 406–416; 1964.
11. Vaillant, G. E. A comparison of antagonists of physostigmine-induced suppression of behavior. J. Pharmacol. Exp. Ther. 157: 636–648; 1967.
12. Weiner, N. Atropine, scopolamine and related antimuscarinic drugs. In: Gilman, A. G.; Goodman, L. S.; Rall, T. W.; Murad, F., eds. Goodman and Gilman's The pharmacological basis of therapeutics. New York: Macmillan Publishing Co.; 1985:130–144.
13. Witkin, J. M. Non-muscarinic behavioral neurotoxicity of oxotremorine. In: Dowdall, M. J.; Hawthorne, J. N.; eds. Cellular and molecular basis of cholinergic function. Chichester: Ellis Horwood Ltd.; 1987:800–813.
14. Witkin, J. M. Central and peripheral muscarinic actions of physostigmine and oxotremorine on avoidance behavior of squirrel monkeys. Psychopharmacology (Berlin) 97:376–382; 1989.
15. Witkin, J.M. Behavioral pharmacology of compounds affecting muscarinic cholinergic receptors. In: Barrett, J. E.; Thompson, T.; Dews, P. B., eds. Advances in behavioral pharmacology, vol. 7. Hillsdale, NJ: Lawrence Erlbaum; 1990:79–118.
16. Witkin, J. M.; Gordon, R. K.; Chiang, P. K. Comparison of in vitro actions with behavioral effects of antimuscarinic agents. J. Pharmacol. Exp. Ther. 242:796–803; 1987.
17. Witkin, J. M.; Alvarado-Garcia, R.; Perez, L.; Witkin, K. M. Central oxotremorine antagonist properties of pirenzepine. Life Sci. 42: 2467–2473; 1988.
18. Witkin, J. M.; Markowitz, R. A.; Barrett, J. E. Physostigmine-insensitive behavioral excitatory effects of atropine in squirrel monkeys. Pharmacol. Biochem. Behav. 32:309–315; 1989.