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Behavioral Effects of Some Diphenyl-Substituted Antimuscarinics: Comparison with Cocaine and Atropine

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WITKIN, J. M., R. F. GENOVESE, K. M. WITKIN AND P. K. CHIANG. *Behavioral effects of some diphenyl-substituted antimuscarinics: Comparison with cocaine and atropine.* PHARMACOL BIOCHEM BEHAV **41**(2) 377–384, 1992.—To more fully characterize the behavioral excitatory effects observed with certain diphenyl-substituted antimuscarinics, various behavioral effects of benactyzine, a prototype excitatory antimuscarinic, was evaluated in rats. These effects were compared to those of cocaine, atropine, and azaprophen, a muscarinic antagonist that contains both the diphenyl substituents of benactyzine and a ring isomeric with the tropane ring of atropine. Under a fixed-interval 5-min schedule of food presentation, cocaine and benactyzine increased response rates. Atropine and azaprophen only decreased responding. The muscarinic agonist oxotremorine attenuated the rate-increasing effects but did not alter the disruptions in the temporal patterning produced by benactyzine or shift the dose–effect function to the right. In rats discriminating 10 mg/kg cocaine from saline, benactyzine partially substituted for cocaine, producing a maximum of 50% cocaine-appropriate responses. Benactyzine fully substituted for scopolamine in rats discriminating 0.056 mg/kg scopolamine from saline. All antimuscarinics increased locomotor activity when activity levels were low in control animals, but the increases were less than those produced by cocaine. Cocaine increased both locomotor activity and fixed-interval responding at comparable doses, whereas 10-fold higher doses of benactyzine were required to increase locomotor activity. These results support the following conclusions: 1) In addition to its classical antimuscarinic behavioral profile, benactyzine has behavioral excitatory actions similar in some respects to those of cocaine; 2) the behavioral excitatory effects of benactyzine do not appear to be due solely to antagonism of muscarinic receptors; and 3) the alkyl-ester may be an important structural feature of diphenyl-substituted antimuscarinics for the induction of behavioral stimulation.

Atropine Benactyzine Azaprophen Cocaine Locomotor activity Fixed-interval schedules
Discriminative stimulus effects Behavioral effects Rats

QUALITATIVE differences observed in the behavioral effects of antimuscarinics suggest that all the activity may not be directly related to antagonism of muscarinic cholinergic receptors. For example, the diphenyl-substituted antimuscarinics with methyl, hydroxy, or hydrogen substituents on the benzylic carbon (aprophen, benactyzine, and adiphenine, respectively; Fig. 1) increased response rates of rats responding under fixed-ratio schedules of food presentation. Under the same conditions, atropine decreased responding (2,23,25). The similarity in the rate-increasing effects of the diphenyl-substituted antimuscarinics and sedative-hypnotic/anxiolytic drugs (22) suggested that anxiolytic-like actions may underlie some of these unique behavioral effects. However, experimental evaluation of this idea yielded negative results (27).

Azaprophen is a novel antimuscarinic (3) that has the diphenyl substituents of aprophen and benactyzine and an azabicyclo[3.2.1]octane ring isomeric with the tropane ring of atropine (Fig. 1). Azaprophen has potent antimuscarinic effects in vitro (3,10,25). However, unlike aprophen and benactyzine, azaprophen appears to be devoid of behavioral stimulatory effects despite its effective in vivo antimuscarinic efficacy (6,25).

The purpose of the present work was two-fold. The first was to determine whether azaprophen was devoid of behav-

This article is dedicated to the memory of Björn Ringdahl.

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ioral stimulatory effects under ideal conditions for observing stimulation. Since azaprophen has been studied previously under conditions that did not optimize behavioral stimulation (6,7,25), the present study provided direct comparisons of benactyzine, azaprophen, and atropine on locomotor activity and under fixed-interval schedules of food presentation, two classical tests of psychomotor stimulation (11). Since benactyzine produced the greatest increases in responding within a series of diphenyl-substituted antimuscarinics (25), this compound was used as the prototype stimulatory antimuscarinic. Behavioral effects of cocaine were also investigated under these conditions to provide a comparison with a psychomotor stimulant. Given the structural similarity of cocaine and atropine (Fig. 1) and the weak antimuscarinic activity of cocaine (21), these studies should provide additional sources of insight regarding antimuscarinic vs. psychomotor stimulant behavioral effects.

The second purpose of this research was to investigate the pharmacological basis of the behavioral stimulation induced by diphenyl-substituted antimuscarinics. It was postulated that if the stimulatory effects of benactyzine are due solely to its antimuscarinic activity, such effects could be reversed by oxotremorine. Similarly, if important nonmuscarinic actions of benactyzine exist, benactyzine may not fully substitute for scopolamine in rats trained to discriminate low doses of scopolamine from saline. Finally, since benactyzine and cocaine share behavioral stimulant effects, benactyzine was evaluated for its ability to mimic the effects of cocaine in rats trained to discriminate cocaine from saline. As a whole, these experiments address the possibility that pharmacological actions other than or in addition to antimuscarinic actions may be responsible for the behavioral excitatory activity of diphenyl-substituted antimuscarinics.

METHOD

Subjects

Adult, male Sprague-Dawley rats (Zivic Miller, Allison Park, PA, and Charles River, Wilmington, MA) were maintained at 320 g (scopolamine discrimination study) or 350 g (cocaine discrimination and fixed-interval schedule) by post-

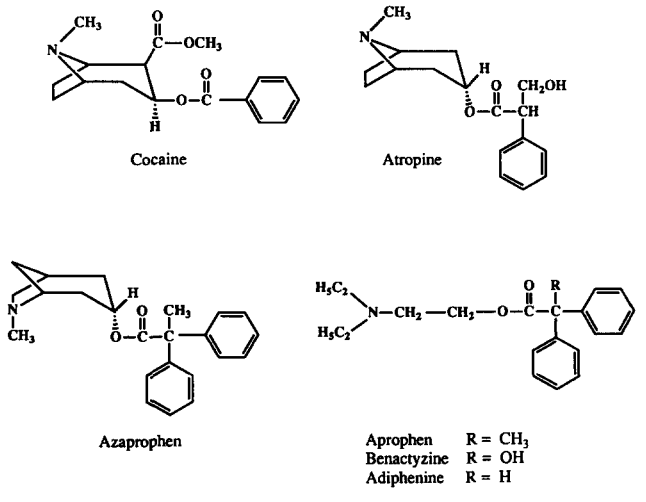

FIG. 1. Structural formulae of diphenyl-substituted antimuscarinics in comparison with atropine and cocaine.

session feeding in separate living cages. Rats used in the locomotor activity experiments were housed in groups of four with unlimited access to Purina rat lab chow and weighed between 340 and 385 g prior to testing. All rats were experimentally naive prior to this study and were housed within a temperature-controlled room with unrestricted access to water. Rats were housed under a 12 L:12 D cycle and tested during the light phase.

Fixed-Interval Schedule

Twelve rats were studied in standard operant conditioning test chambers (BRS/LVE, Laurel, MD) that contained two response levers. Chambers were enclosed within sound- and light-attenuating chambers supplied with white noise to further mask extraneous sounds. Experimental events were scheduled and data were collected with a PDP 11/73 computer operating SKED-11 software (State Systems, Kalamazoo, MI).

After initial training to eat food pellets (45 mg, BioServ, Frenchtown, NJ) delivered to a centrally located receptacle, rats were trained to depress the right lever by requiring these responses for food presentation. When white lamps were illuminated above the right lever, pressing the lever with a minimal downward force of 0.4 N through 1 mm produced food. All responses produced the audible click of a relay. The schedule under which drug effects were assessed was a multiple fixed-interval 5-min, timeout 60-s schedule. In the presence of the lever lights, the first response after 5 min produced food. After food delivery, response lights and overhead houselight were extinguished and a 60-s timeout period followed. During timeout, responses had no scheduled consequences. A 60-s limited-hold specified that if a response did not occur within 60-s after the 5-min interval, timeout occurred without food delivery. Sessions consisted of 7 cycles of the fixed interval and lasted approximately 40 min. Six rats were used to evaluate the effects of the muscarinic antagonists and a separate group of six animals was studied with cocaine.

Rates of responding and the temporal distribution of responding were measured in individual animals. The quarter-life statistic was used to evaluate response distribution across the fixed interval independent of response rate. Response rates from successive 30-s periods of the fixed interval were used to calculate quarter-life values. The quarter-life is defined as the proportion of the interval taken to emit 25% of the total responses and ranges between 0 and 1. A quarter life of 0.25 is indicative of linear responding across the interval; quarter-life values greater than 0.25 represent positively accelerated responding [cf. (9)]. Quarter-life values are not reliable when response rates are low and therefore were not calculated when responding was decreased to less than 10% of control values.

Cocaine or Scopolamine Discriminations

For the cocaine discrimination, 12 rats were studied in the two-lever rat chambers described above. The cocaine-saline discriminations were established and testing with other compounds was conducted as described previously (26). Briefly, rats were trained to discriminate 10.0 mg/kg cocaine, IP, from saline. Following cocaine administration, responses on only one lever produced food; following saline administration, responses on the opposite lever produced food. The lever correlated with cocaine was counterbalanced across animals. After a 5-min timeout period at the beginning of the experimental session (cocaine discrimination only), 20 consecutive responses on the appropriate lever were required for food

presentation. Timeout periods of 20 s followed each food delivery and sessions lasted until 20 food pellets had been presented or 20 min, whichever occurred first. Benactyzine and azaprophen were tested for their ability to produce responding similar to cocaine. During test sessions, a single dose of benactyzine or azaprophen (IP, 30 min prior to testing) was administered and responding on either lever produced food. Similar test sessions were also conducted with cocaine or saline to assess the control of behavior by drug injections. Test sessions were conducted no more than twice weekly.

Eleven rats were studied in similarly equipped test chambers under the scopolamine discrimination (Coulbourn Instruments, Model E10-10, Leigh Valley, PA). For the scopolamine discrimination, rats were trained to discriminate SC injections of 0.056 mg/kg scopolamine from vehicle as described by Genovese et al. (8). These rats had initially been trained to discriminate 0.237 mg/kg scopolamine from saline. Briefly, rats were injected with scopolamine or saline and only responses on one of the two levers produced food according to a variable-interval 18-s schedule of reinforcement. The stimulus lights above both response levers were illuminated during 30-min training sessions. The drug- and vehicle-appropriate levers were randomly assigned with the restriction that an equal number of drug-right lever and drug-left lever assignments were made in each group. Benactyzine (SC, 30 min prior to testing) was studied for its ability to produce discriminative stimulus effects comparable to those produced by 0.056 mg/kg scopolamine. In these benactyzine substitution experiments, responding on neither lever produced food and the sessions were 2 min in duration. Similar test sessions were conducted periodically with scopolamine or saline.

Locomotor Activity

Rats were tested between 0900 and 1300 h under white fluorescent lighting. Six to 8 rats were studied per dose; 13 rats were used for control (saline) injections. The Digiscan activity monitors (Omnitech Electronics, Columbus, OH) were 40 cm^3 clear acrylic chambers equipped with photoelectric detectors 2.5 cm apart. One count was recorded with the crossing of alternate detectors. Prior to injection, rats were individually placed in the activity monitor and allowed to acclimate to the chamber for 20 min prior to testing. Immediately following injection, rats were again placed in the activity monitor and determinations of horizontal ambulatory activity were recorded electronically every 10 min for 60 min. Each animal was only tested once with one drug dose or saline.

Drugs

Azaprophen hydrochloride (Walter Reed Army Inst. Res.), atropine sulfate (Sigma Chemical Co.), benactyzine hydrochloride (Aldrich Chemical Co.), oxotremorine sesquifumarate (Aldrich), scopolamine hydrobromide (U.S. Army Inst. of Chemical Defense, Aberdeen, MD), and cocaine hydrochloride (Mallinckrodt) were dissolved in isotonic saline and administered by IP injected (SC for the scopolamine discrimination) in a volume of 1 ml/kg. Drug doses are expressed as the salts. The muscarinic antagonists were given 30 min prior to the experimental sessions; oxotremorine was given immediately prior. Drugs and drug doses were studied in a mixed order with dose-effect functions for one compound generally being completed prior to investigation of another drug. Each dose or dose combination was generally studied on two separate occasions in each animal except in the locomotor activity experiments and the scopolamine discrimination, where only one dosage was administered per rat.

Data Analysis

For fixed-interval responding, drug effects on response rates were expressed as a percentage of saline and nondrug control values in individual subjects. Dose-effect functions were established by averaging these values across subjects. In the scopolamine or cocaine discrimination experiments, the percentage of responses on the drug-designated lever was also calculated. In the locomotor activity experiments, separate groups of rats were studied under control (saline) or drug conditions. Analysis of variance (ANOVA) was used to determine the overall significance of dose-response functions. Where significant overall effects were obtained, posthoc comparisons were performed using Dunnett's test, the least significant difference test, or appropriate Student's *t*-tests. A maximal acceptable error rate of 0.05 was set. For the drug discrimination experiments, drug effects greater than 20% drug-correlated responses were considered significantly differ-

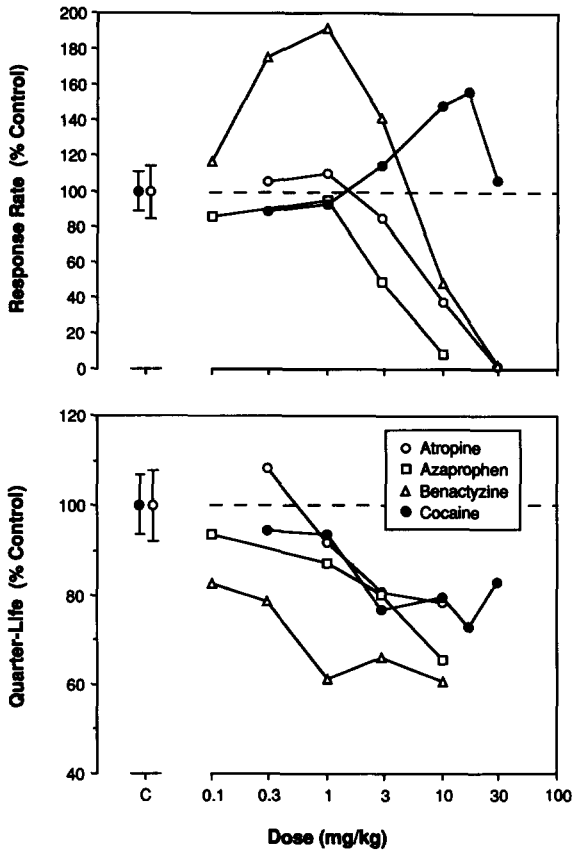

FIG. 2. Effects of diphenyl-substituted antimuscarinics studied in comparison with atropine and cocaine on rates of responding (top) and on the temporal distribution of responses (bottom) under a fixed-interval 5-min schedule of food presentation in rats. Each point represents the mean effect in six rats except for quarter-life values at the highest doses where response rates were suppressed below 10% of control in some rats. Points above C represent control variability ± SEM.

ent than the effects of saline; drug effects greater than 80% drug-appropriate responses were considered comparable to the effects of the training dose of cocaine or scopolamine.

RESULTS

Fixed-Interval Responding

Behavior under the fixed-interval schedule was characterized by little or no responding at the beginning of the interval followed by increasing rates of responding as the 5-min interval elapsed. Overall rates of responding ranged from 0.02–0.25 responses/s across animals. Control quarter-life values ranged from 0.45–0.62 across animals, confirming quantitatively the positively accelerated rates of responding across the fixed interval.

Benactyzine produced behavioral effects characteristic of psychomotor stimulants, increasing response rates and altering the temporal patterning of responding. Benactyzine dose-dependently increased response rates with peak increases of 200% of control values occurring at 1 mg/kg. Significant increases were observed in all subjects. Neither atropine nor azaprophen increased response rates under the fixed-interval schedule (Fig. 2, top). Quarter-life values, an index of temporal response patterning, were decreased in a dose-dependent manner by benactyzine with asymptotic effects occurring at 1 mg/kg, the dose that maximally increased response rates. In contrast, with the exception of the highest dose of azaprophen, atropine and azaprophen only modestly decreased quarter-life values, even at doses that substantially reduced rates of responding (Fig. 2, bottom).

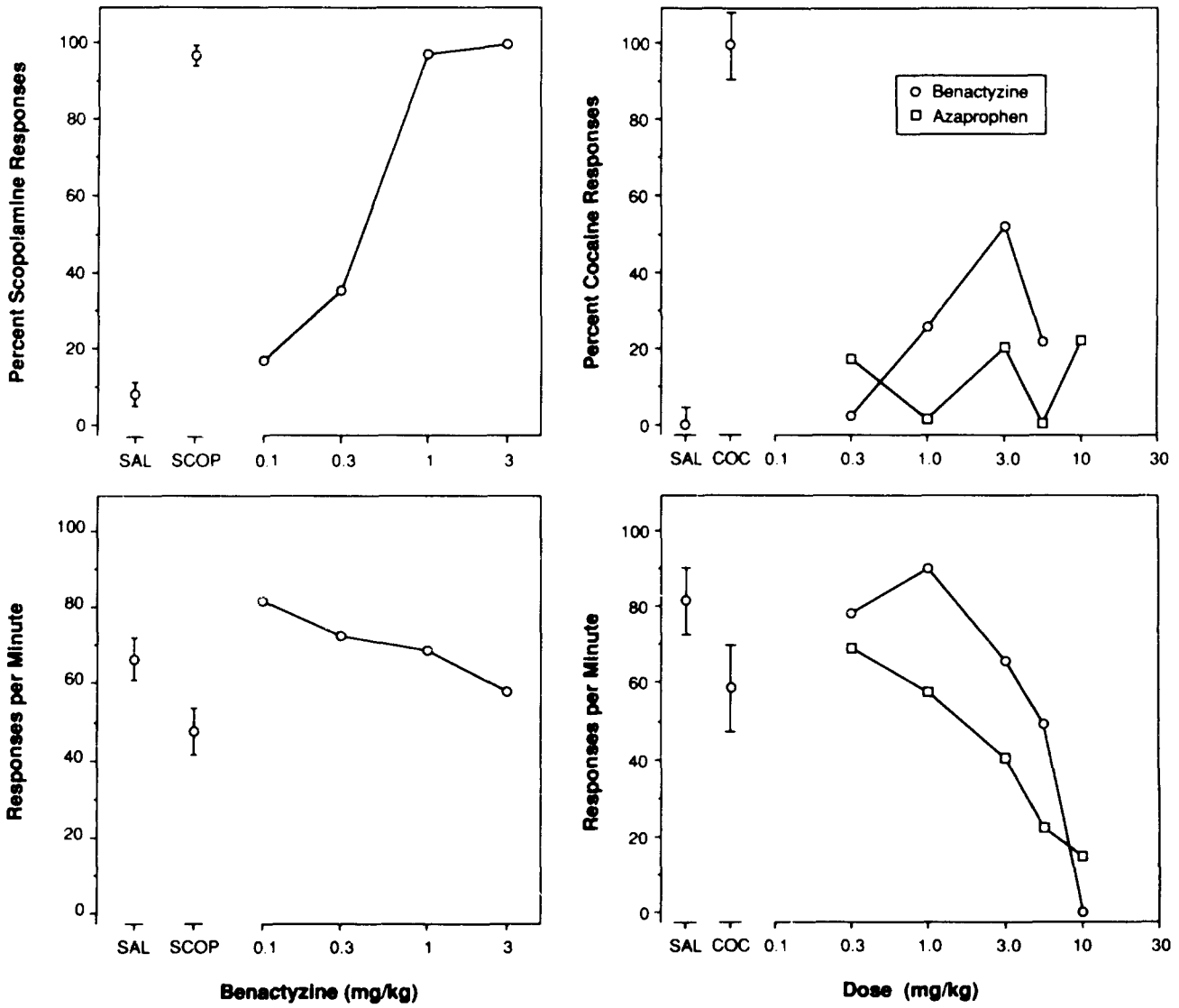

FIG. 3. (Left). Effects of benactyzine in rats trained to discriminate 0.056 mg/kg scopolamine from saline. Points above SAL represent effects of saline ± SEM; points above SCOP represent effects of 0.056 mg/kg scopolamine ± SEM. Each point represents the mean of 11 rats. (Right). Effects of benactyzine and azaprophen in rats trained to discriminate 10 mg/kg cocaine from saline. Points above COC represent effects of 10 mg/kg cocaine ± SEM. Each point represents the mean of 4–10 rats.

Cocaine increased responding under the fixed-interval schedule and produced corresponding alterations in the temporal pattern of responding as indicated by the decreases in quarter-life (Fig. 2). Maximal increases in response rate and decreases in quarter-life values after cocaine administration were somewhat less than those of benactyzine but, again, were observed in all animals.

Interactions with Oxotremorine

To evaluate the contribution of muscarinic receptor blockade to the behavioral stimulatory effects of benactyzine, the muscarinic agonist oxotremorine was used. The minimal dose of oxotremorine that affected fixed-interval responding was 0.01 mg/kg, $t(5) = 3.8$, $p < 0.05$. Although the effects of this dose were to reduce responding by 40% of control, the absolute change in response rate was very small (0.035 ± 0.014 vs. 0.023 ± 0.013 responses/s for saline- and oxotremorine-treated rats, respectively). Oxotremorine did not alter the temporal pattern of responding at this dose as indicated by the quarter-life values (Fig. 3, unconnected points above OXO). When given in conjunction with benactyzine, this rate-decreasing dose of oxotremorine completely blocked the benactyzine-induced increases in responding but did not alter the rate decreases produced by benactyzine (Fig. 4, top). Oxotremorine did not restore the benactyzine-induced reductions in quarter-life values to control levels (Fig. 3, bottom). These effects were observed in all animals.

Scopolamine Discrimination

Since benactyzine produced qualitatively distinct effects under the fixed-interval schedule relative to the other antimuscarinics tested, it was of interest to evaluate whether this compound would also produce disparate discriminative stimulus effects in rats trained to discriminate low doses of scopolamine from saline. When 0.056 mg/kg scopolamine was injected, responding occurred almost exclusively on the scopolamine lever (Fig. 3, unconnected point above SCOP). In contrast, saline injections resulted in responses being distributed primarily on the saline-appropriate lever (Fig. 3, unconnected point above SAL).

Benactyzine produced dose-related increases in responding on the scopolamine lever, $F(3,40) = 58.74$, $p < 0.01$. Effects of 1 and 3 mg/kg benactyzine on the distribution of responses did not differ from that of the training dose of scopolamine (Fig. 3, left, top). Under these testing conditions, benactyzine did not have any major effects on response rate (Fig. 3, left, bottom). However, the lowest dose tested (0.1 mg/kg) produced small increases in response rate relative to saline control levels $t(9) = 4.72$, $p < 0.01$.

Cocaine Discrimination

Behavioral stimulation observed under the fixed-interval schedule with both benactyzine and cocaine was not obtained with azaprophen (Fig. 2). Therefore, the effects of benactyzine and azaprophen were further compared in rats discriminating cocaine injections. In this experiment, benactyzine produced dose-dependent increases in responding on the lever correlated with cocaine injections from 0.3 to 3 mg/kg (Fig. 3, right, top). Both 1 and 3 mg/kg produced effects significantly different than saline, and maximal efficacy was achieved at 3 mg/kg. Full substitution for cocaine (>80%) was observed in 6 of the 12 determinations of the effects of this dose, whereas less than 20% cocaine-appropriate responding occurred with

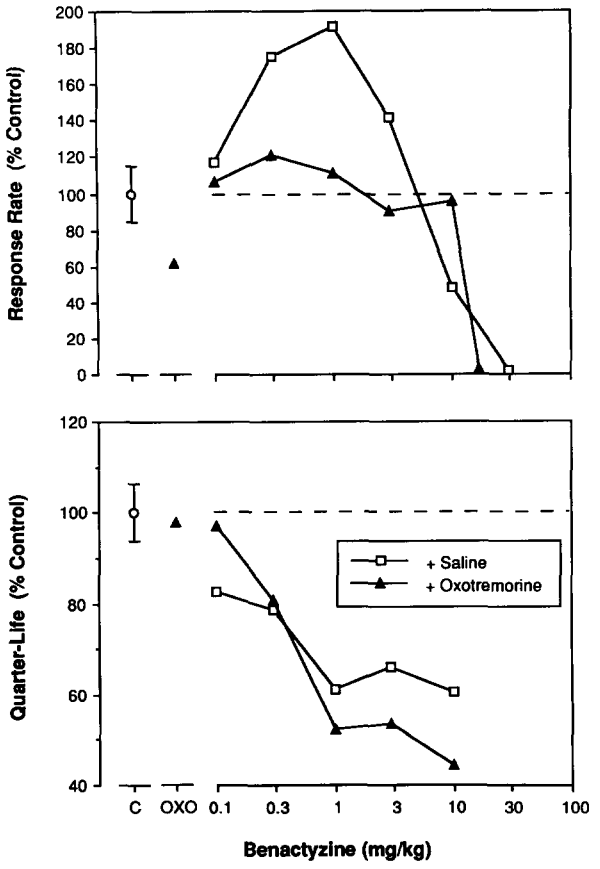

FIG. 4. Effects of benactyzine alone and in combination with 0.01 mg/kg oxotremorine on rates of responding (top) and on the temporal distribution of responses (bottom) under a fixed-interval 5-min schedule of food presentation in rats. Each point represents the mean effect in six rats. Points above C represent control variability ± SEM. Points above OXO represent effects of 0.01 mg/kg oxotremorine alone. Other details as in Fig. 2.

the other determinations. The decreased effect observed at higher doses corresponded to the reduced stimulatory efficacy of benactyzine under the fixed-interval schedule (Fig. 2). In contrast to benactyzine, azaprophen produced non-dose-dependent effects significantly different from saline only at the 10 mg/kg dose, which markedly reduced response rates (Fig. 3, right, bottom).

Locomotor Activity

Further comparisons of the behavioral stimulation induced by antimuscarinics were carried out using locomotor activity. Effects of atropine, benactyzine, and azaprophen on locomotor activity are shown in Fig. 5 (left, top). All these compounds produced small increases in locomotor activity. However, only benactyzine significantly increased overall activity levels, $F(3,32) = 5.51$, $p < 0.01$. Follow-up comparisons indicated that 30 mg/kg benactyzine significantly increased locomotion relative to saline controls ($p < 0.05$, Dunnett's test).

A time course of the locomotor effects at peak doses of all three antimuscarinics are shown in the top right panel of Fig. 5. Rats given saline displayed a time-dependent decrease in

locomotion, $F(5,114) = 5.66$, $p < 0.01$. Administration of atropine (30 mg/kg), azaprophen (10 mg/kg), or benactyzine (30 mg/kg) resulted in relatively constant moderate levels of locomotion across the 60-min test period. Effects of all three drugs were significantly different than saline controls at 60 min postinjection ($p < 0.001$). Benactyzine also produced effects different than saline controls at 40 and 50 min ($p < 0.05$).

Cocaine produced dose-dependent increases in locomotor activity. Doses of 10 and 30 mg/kg cocaine significantly increased locomotion (Fig. 5, left, bottom). These effects were about four times greater than those produced by the antimuscarinics. The effects of cocaine on locomotion across the 60-min test period were also different than that observed after antimuscarinics treatment (Fig. 5, right, bottom). After 30 mg/kg cocaine, locomotor activity was enhanced above saline control values at all time periods. Whereas the antimuscarinics only modestly increased locomotor activity at doses 10-fold higher than those increasing fixed-interval responding (benactyzine), cocaine produced locomotor stimulation and increases in fixed-interval responding at comparable doses (compare Figs. 2 and 5).

DISCUSSION

Consistent with previous findings [cf. (2,23,25)], benactyzine produced a different spectrum of behavioral effects in rats than those observed with atropine. In the present study, benactyzine increased rates of responding and altered temporal patterns of responding, an effect shared by cocaine. Atropine and azaprophen only decreased response rates, and patterns of responding were altered only at relatively high doses. Benactyzine also displayed greater efficacy than azaprophen in substituting for cocaine in rats trained to discriminate cocaine from saline. Atropine has previously been shown to be devoid of cocaine-like behavioral effects under these conditions (4). Although benactyzine only partially substituted for cocaine as reported earlier (4), the maximal effects were comparable to subtype-selective dopamine receptor agonists (26). This comparison emphasizes the significant efficacy of benactyzine in this behavioral assay. Benactyzine has also been reported to produce a different clinical picture at higher doses than that of atropine, but it is difficult with the existing data to be sure that this is not simply a quantitative rather than a qualitative difference [cf. (14)].

Benactyzine, atropine,and aprophen stimulated locomotor activity to about the same degree. Moreover, all the antimuscarinics reduced the normal decline in activity levels that occur over time under nondrug conditions. That these compounds have different effects from classic psychomotor stimulants was evidenced by the enhanced efficacy and varying time course of the locomotor stimulatory effects of cocaine. Furthermore, whereas the antimuscarinics only modestly in-

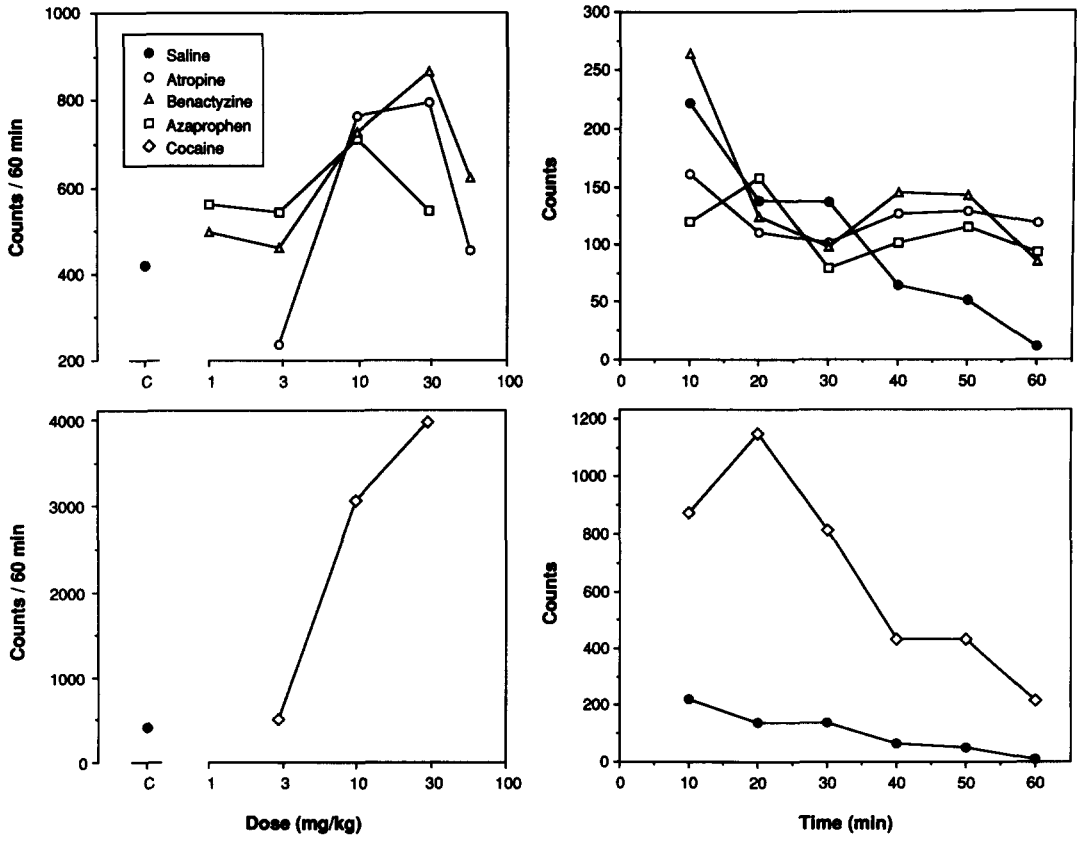

FIG. 5. (Left). Effects of atropine, benactyzine, and azaprophen on total 60-min locomotor activity levels (top) compared to cocaine (bottom). (Right). Effects of the antimuscarinics (top) and cocaine (bottom) across the 60-min observation period. Control variability (saline administration) around the unconnected point above C is encompassed within the diameter of the point. Each point represents the mean effect in at least six rats. Note the different ordinate scales for cocaine.

creased locomotor activity at doses 10-fold higher than those increasing fixed-interval responding (benactyzine), cocaine produced locomotor stimulation and increases in fixed-interval responding at comparable doses. In addition, like other muscarinic antagonists, benactyzine fully substituted for scopolamine in rats discriminating low doses of scopolamine from saline. These results are consistent with observations in rats trained to discriminate higher doses of atropine or scopolamine (19), emphasizing the common antimuscarinics activity of these drugs.

Although oxotremorine blocked the behavioral stimulatory effects of benactyzine, it did not alter the disruption in temporal response patterning typical of stimulant compounds or shift the dose–response curve to the right in the present study. Moreover, increases in fixed-interval responding were not observed with atropine or azaprophen. These results support previous observations suggesting that behavioral stimulatory effects of antimuscarinics may not be due solely to blockade of muscarinic receptors [cf. (15,23)]. However, the pharmacological mechanisms underlying the propensity of benactyzine and closely related diphenyl-substituted antimuscarinics to induce behavioral stimulation are not fully known. Benactyzine differs from atropine or scopolamine along a number of dimensions including indices of central vs. peripheral muscarinic blockade (12), induction of acetylcholine release from rat hippocampal slices (20), and in their nicotinic activity (1). Unlike scopolamine or atropine, benactyzine induces convulsions at higher doses (24). This effect is shared by benztropine (24), a compound that inhibits dopamine reuptake (13,18), produces increases in schedule-controlled responding (16,17), and partially substitutes for cocaine in cocaine-discriminating rats (4). The close structural similarity of benactyzine to that of benztropine, their effects on brain catecholamine levels (15), and their common behavioral effects suggest that dopaminergic systems may play some role in the behavioral pharmacology of these stimulatory diphenyl-substituted muscarinic antagonists.

Azaprophen had behavioral effects that resembled atropine more closely than benactyzine. Azaprophen, like atropine, did not increase response rates under the fixed-interval schedule or produce the same degree of disruption in temporal response patterning as did benactyzine. Azaprophen also did not substitute for cocaine in rats discriminating cocaine in contrast to the partial substitution by benactyzine. Nonetheless, azaprophen, like benactyzine, produced dose-dependent substitution for scopolamine (8), further substantiating the predominant antimuscarinic profile of azaprophen (3,7,25). Due to its potency, efficacy, and lack of behavioral stimulatory effects, it has been suggested that azaprophen may be a useful antimuscarinic devoid of some of the CNS excitation associated with high doses of conventional antimuscarinics (3,25). Recent studies have indicated that azaprophen significantly potentiates the protective effects of physostigmine against the lethal effects of the nerve agent soman at doses devoid of striking behavioral side effects (5).

Although azaprophen, atropine, and cocaine share structural features (Fig. 1), only cocaine produced behavioral excitatory effects in these studies. Thus, the presence of a tropane ring or its isomeric form is not sufficient in and of itself to confer behavioral excitatory effects. Qualitative differences in the behavioral effects of the two diphenyl-substituted antimuscarinics, benactyzine and azaprophen, suggest that the alkyl-ester of benactyzine may be necessary for behavioral excitatory effects in this series of compounds. Support for this conclusion comes also from the rate-increasing effects shared by aprophen and adiphenine (23,25).

In conclusion, the diphenyl-substituted muscarinic antagonist benactyzine possesses a classical antimuscarinic behavioral profile (moderate increases in locomotor activity and scopolamine-like discriminative stimulus effects). Benactyzine also has behavioral excitatory actions similar in some respects to that of cocaine but not typically shared by tropate antimuscarinics such as atropine. The behavioral excitatory effects of these compounds do not appear to be exclusively mediated by functional antagonism of muscarinic receptors. The absence of behavioral excitatory activity associated with the novel aprophen analog azaprophen suggests that the alkyl-ester side chain may be an important determinant of this behavioral effect.

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