Pharmacology Biochemistry & Behavior, Vol. 32, pp. 309–315. Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Physostigmine-Insensitive Behavioral Excitatory Effects of Atropine in Squirrel Monkeys[1]

J. M. WITKIN,*† R. A. MARKOWITZ† AND J. E. BARRETT†

**Preclinical Pharmacology, Addiction Research Center, P.O. Box 5180*
National Institute on Drug Abuse, Baltimore, MD 21224
and †Department of Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, MD

Received 24 March 1988

WITKIN, J. M., R. A. MARKOWITZ AND J. E. BARRETT. *Physostigmine-insensitive behavioral excitatory effects of atropine in squirrel monkeys.* PHARMACOL BIOCHEM BEHAV 32(1)309–315, 1989.—Lever press responses of squirrel monkeys were maintained under a multiple schedule in which the first response after 3 min produced either food or electric shock depending on the prevailing stimulus. Atropine sulfate (0.3–3 mg/kg, IM) given immediately before experimental sessions disrupted the temporal pattern of responding and produced dose-related decrease in rates of food- and shock-maintained responding. Increases in responding occurred when 1 mg/kg atropine was given 1 to 12 hr prior to experimental sessions. A maximal increase of 200% of control rates was seen following the 2-hr pretreatment. Qualitatively similar effects were obtained with scopolamine suggesting that the time-dependent increases may be a general consequence of muscarinic receptor blockade. Response patterning changes and response rate increases were also produced by coadministration of atropine and physostigmine both given immediately before the session. Increases in rates of responding have also been observed previously after administration of atropine with rate-decreasing doses of the direct-acting muscarinic agonist oxotremorine. Physostigmine did not reverse the rate increases or the alteration in temporal patterning produced by the 2-hr atropine pretreatment; rate decreases induced by immediate pretreatment with atropine were blocked by physostigmine. Thus, the response rate-decreasing effects of atropine were distinct from its rate-increasing effects. Whereas the rate-decreasing effects of atropine appear to involve muscarinic receptors, increases in responding may not. Such nonmuscarinic behavioral excitatory actions of atropine may be expressed when the muscarinic-related decreases are blocked by physostigmine or oxotremorine, or when the decreases are overridden by excessive nonmuscarinic stimulation, perhaps triggered by time-dependent changes in acetylcholine turnover associated with atropine.

Atropine Scopolamine Physostigmine Time-course Drug interactions Lever-pressing Squirrel monkeys

ATROPINE is the prototype muscarinic antagonist whose pharmacological actions have been used to define muscarinic receptor-mediated drug effects (4,15). Physostigmine (eserine) is a classical, reversible cholinesterase inhibitor which increases levels of acetylcholine at cholinergic receptor sites. In theory and in practice in experimental animals and humans, the two compounds are antagonists (6, 11–13, 15). Atropine is the primary drug used in the emergency treatment of poisoning by cholinesterase inhibitors.

Under certain conditions atropine and physostigmine do not interact in a completely antagonistic fashion. Witkin (18) reported that in squirrel monkeys (*Saimiri sciureus*) both atropine and physostigmine, given separately, produced decreases in rates of lever-pressing maintained under a schedule of shock postponement. When atropine was administered either prior to or after physostigmine, the rate-decreasing effects of physostigmine were reversed. However, at relatively high physostigmine doses, responding was increased to 170% of control levels in atropine-treated monkeys. Thus, despite the rate-decreasing effects of either drug alone, behavioral excitatory effects were seen when the drugs were coadministered. Since physostigmine can have actions in addition to those at muscarinic receptors blocked by atropine [cf. (11)], the effects of the selective, direct-acting muscarinic agonist, oxotremorine, were also studied under these conditions (18). As with physostigmine, oxo-

[1]Research was conducted in compliance with the Animal Welfare Act, and other Federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the *Guide for the Care and Use of Laboratory Animals*, NIH publication 85-23. Some of the experiments reported here were conducted in the Physiology and Behavior Branch, Department of Medical Neurosciences, Walter Reed Army Institute of Research, Washington, DC. Portions of this research were funded by USAMRDC contract number 83MM3513. Preliminary results were presented in abstract form in Fed. Proc. 44:897; 1985. We thank R. Alvarado-Garcia for expert technical support and Donna Shelton and Margaret Hawkes for help in preparation of the manuscript.

tremorine decreased response rates when given alone. In conjunction with rate decreasing doses of atropine, however, response rates were increased to 180% of control values. Thus, any nonmuscarinic actions of physostigmine not shared by oxotremorine do not appear to be relevant to the response rate increases.

The behavioral excitatory effects of these drug combinations cannot be unambiguously interpreted from the data reported by Witkin (18). Although high doses of oxotremorine and other muscarinic agonists can have toxic effects that are unresponsive to muscarinic blockade (20), the response rate increases observed (18) could have been due to nonmuscarinic actions of either atropine or of physostigmine that were unmasked in the presence of the other compound [cf. (17,19)]. However, under the shock-postponement schedule, neither atropine, physostigmine, nor oxotremorine consistently increased response rates when given alone. In contrast to these effects, we have observed time-dependent response rate increasing effects of atropine under schedules of food or electric shock presentation. The present study was designed to characterize these rate increases and to provide a more detailed understanding about their relationship to the behavioral excitatory activity of physostigmine-atropine combinations in squirrel monkeys.

METHOD

Subjects

The experiments were conducted with ten mature male squirrel monkeys (*Saimiri sciureus*) housed in individual cages in rooms in which light, temperature, and humidity were controlled. Fresh water was continuously available with fruit provided daily. The animal's daily food intake was restricted until body weights gradually stabilized at 80–85% of their free-feeding values. This weight was effective for establishing food as a reinforcer to maintain responding without compromising the health of the animals.

Apparatus

Experiments were conducted with monkeys seated in specially designed primate chairs. These chairs were constructed of clear smooth Plexiglas and allowed minimal, comfortable restraint of the animal at the waist. A response lever (BRS/LVE, No. 121-05, Beltsville, MD) was mounted on the panel of the chair facing the monkey. Each depression of the lever with a force exceeding 20 g (0.2 N) was recorded as a response and produced the operation of a relay mounted on the rear of the front panel. Three pairs of colored lamps mounted behind the front panel could be illuminated for use as discriminative stimuli for controlling different behavioral performances. Food presentation consisted of a 300 mg BioServe banana-flavored pellet delivered to a receptacle directly in front of the monkey. Shock delivery consisted of a 200 msec pulse (650 V AC, 60 Hz) delivered through variable series resistance to brass electrodes resting on a shaved distal section of the monkey's tail. The tail was held motionless by a stock. Shock intensity (3–5 mA) was adjusted to control characteristics of performance such as rate of responding to make shock-maintained performances comparable to those maintained by food. During daily sessions, the seated monkeys were placed in individual light- and sound-attenuating enclosures. These enclosures were well ventilated and white noise was present to further mask extraneous sounds. Experimental events were controlled and recorded either by electromechanical switching circuitry, by a PDP-8 computer operating under the Super-Sked control system or a PDP-11/73 computer utilizing SKED-11 behavioral software.

Multiple Schedule of Food or Shock Presentation

Responding under a schedule in which behavioral performances were maintained by either food or electric shock delivery, each under the control of different visual stimuli, was established over a series of training phases (2, 7, 22). Initially, a shock-avoidance schedule was in effect when white lights were illuminated. Each response under this procedure postponed the delivery of scheduled shock for 25 sec; shocks recurred every 5 sec in the absence of responding. When responding stabilized under the avoidance schedule, such that steady rates of responding were maintained and few or zero shocks were presented, the avoidance schedule was replaced by a fixed-interval (FI) 3-min schedule of response-produced shock. Under the FI schedule, the first response to occur after 3 min produced shock. Once responding was maintained by the schedule of shock delivery, an FI schedule of food delivery was introduced in alternate segments of the experimental session when red lights were illuminated. Under the final multiple schedule, responding in the presence of the white lights was maintained by shock delivery and responding in the presence of red lights was maintained by food delivery. Both of these schedules were 3 min in duration and were separated by a 60-sec timeout during which all lights in the chamber were extinguished and responding had no scheduled consequences. Under both the food and shock schedule, if no response occurred between minutes 3 and 4, that component terminated automatically without food or shock (60-sec limited hold). This procedure ensured exposure to both schedule components in the event that a drug produced selective decreases in performance during only one of the components. Experimental sessions consisted of 7 or 10 cycles of each FI component and were approximately 60 min.

Drug Experiments

Sessions were conducted five days a week. Drugs were administered generally on Tuesdays and Fridays, with Thursdays providing baseline control data. During dose-response determination, the order of administration was nonsystematic, although doses at the higher end of the curve were not administered consecutively. Each monkey generally received each dose of drug on at least two test days. Experimental sessions were conducted at the same time every day. During time-course studies, animals were injected in the vivarium at the appropriate interval and then tested at the usual session time. For drug interaction experiments, physostigmine and atropine were both either given immediately before experimental sessions or atropine was administered 2 hr prior to physostigmine and the beginning of the experimental session. Solutions of physostigmine sulfate, atropine sulfate, atropine methylnitrate, and scopolamine hydrobromide (Sigma Chemical Co., St. Louis, MO) were prepared in 0.9% NaCl. Drug doses are expressed as the salt. Drugs were injected into the gastronemious muscle in a volume of 1 mg/kg body weight.

Data Analysis

Response rates and quarter-life values were calculated separately for responding under the food and shock

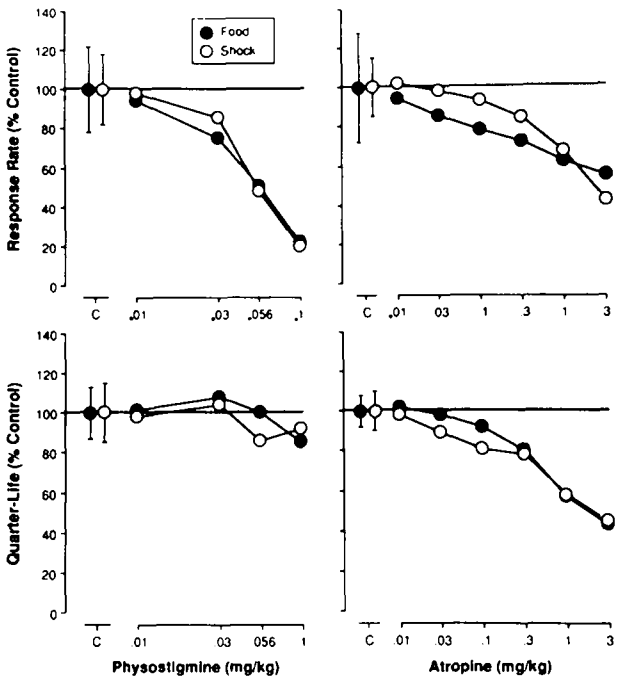

FIG. 1. Effects of physostigmine sulfate and atropine sulfate on two measures of responding under a multiple schedule of food or electric shock presentation. Data are means of at least two determinations in each of 4 monkeys. Vertical lines around control values (unconnected point above c) represent ±1 S.D. of the monkey with the most variable performance.

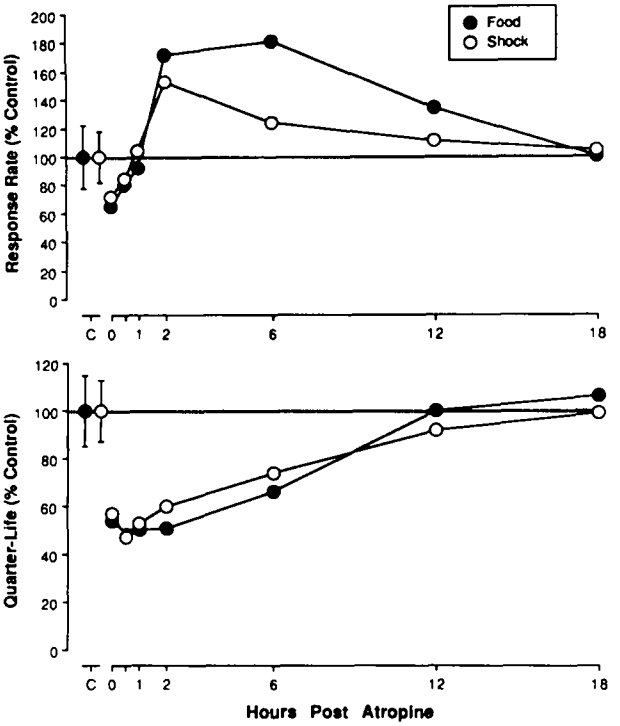

FIG. 2. Time-course of behavioral effects of 1 mg/kg of atropine sulfate. Data are means of single or duplicate determinations in each of 4 monkeys. Other details as in Fig. 1.

schedule. Quarter-life values, which provide a quantitative assessment of the temporal pattern of responding within the fixed-interval independent of response rate, were calculated [cf. (5)]. The quarter-life is defined as the proportion of the interval taken to emit 25% of the total responses within the interval. Quarter-life values can theoretically vary from 0 (negative acceleration in rates across the interval) to 1 (positive acceleration). A quarter-life value of 0.25 indicates linear rates of responding within the interval. Response rates and quarter-life values were calculated separately for each individual monkey. The drug effects for each animal were then expressed relative to their control values. Composite dose-effect functions were constructed by averaging each percentage change across animals. Drug effects were considered significant if they deviated, in individual animals, by at least 2 S.D. from control levels.

RESULTS

Performances under the multiple schedule of food or electric shock presentation were characteristic of those reported previously (2, 7, 22). Responding occurred with increasing frequency across the fixed-interval cycle such that response rates were highest at the end of the cycle where a response produced either food or shock. Response rates were generally higher under the shock schedule than under the food schedule although large variations in rates occurred across animals. For some monkeys, rates of responding maintained by either event were comparable. Under the schedule of food presentation, response rates ranged from 0.23 to 0.59 responses per sec and quarter-life values from 0.46 to 0.67 across monkeys. Under the schedule of shock delivery, response rates ranged across animals from 0.13 to 0.88 responses per sec and quarter-life values from 0.41 to 0.65.

Figure 1 presents the results of acute injections of physostigmine and atropine on performance under the multiple schedule. Physostigmine produced dose-related decreases in rates of responding in both the food and shock components of the multiple schedule. Effects of physostigmine on response patterning (quarter-life values) were variable across subjects but overall physostigmine was without consistent or significant effects. Increased urinary output and emesis were observed at doses above 0.03 mg/kg. These effects were dose-related. Response rate increases were never observed with physostigmine regardless of whether it was given between 0 and 2 hr before experimental sessions.

Response rates were also only decreased when atropine was given immediately prior to the session (Fig. 1). In contrast to physostigmine, quarter-life values were decreased in a dose-dependent fashion by atropine. In some monkeys, atropine occasionally appeared to increase rates of food-maintained responding after 1.0 to 3.0 mg/kg but these increases were short lived (<30 min) and were replaced by pronounced response rate decreases toward the end of the session. In other animals, responding was uniformly decreased across the session.

A time-effect relationship for the behavioral effects of 1 mg/kg atropine is shown in Fig. 2. Atropine was administered at either 0, 0.5, 1, 2, 6, 12, or 18 hr prior to experimental sessions. Immediate pretreatment with 1 mg/kg at-

ropine decreased response rates under both the food and shock schedule. The suppression of food-maintained responding observed when this dose was given immediately before the session was also seen when a 1-hr pretreatment was assessed. After the 1-hr pretreatment, response rates under the food schedule were, in some monkeys, still elevated at the beginning of the session but were decreased progressively toward the last 30 min of the session. Following pretreatment times greater than 1 hr, only marked increases in both food- and shock-maintained responding were seen. The maximum effect was observed following the 2-hr pretreatment and response rates did not return to control values until between 12 and 18 hours had elapsed between drug administration and testing. Quarter-life values showed a progressive regression toward control values with increasing pretreatment times and were not different from control at 12 or 18 hr. Even doses of atropine that depressed rates of responding produced a state of overt behavioral arousal, i.e., hypervigilance and mild hyperreactivity observed by visual inspection of the animals.

Similar time-dependent effects were observed with scopolamine (Fig. 3). When given immediately before experimental sessions, scopolamine (0.01–1 mg/kg) produced only dose-dependent decreases in responding. A dose of 0.1 mg/kg scopolamine produced decreases in response rates under both food and shock schedules and decreased quarter-life values. These effects were progressively diminished with increases in the pretreatment time. As with atropine, scopolamine increased response rates at some of the longer pretreatment intervals. Although at 1 hr postscopolamine response rates were not different than control, the drug was exerting sizable behavioral effects at this time as evidenced by the marked disruption in the temporal patterns of both food- and shock-maintained behavior (decreases in quarter-life values).

The quaternary analog of atropine, atropine methylnitrate, did not increase response rates when given across a wide range of doses (0.01–5.6 mg/kg) or when given 2 hr prior to testing (data not shown).

Behavioral effects of atropine alone (filled circles) and in combination with physostigmine (open symbols) are presented in Fig. 4. When given alone, immediately before the experimental session, effects of either atropine or physostigmine (unconnected points above P) were generally comparable to those seen in Fig. 1. Both drugs produced dose-related decreases in both food- and shock-maintained response rates. Quarter-life values under both food or shock schedules were markedly decreased by atropine but were only marginally decreased under the food schedule with physostigmine. Atropine (1 mg/kg) given 2 hr prior to experimental sessions produced large decreases in quarter-life values and food-maintained responding was increased 2-fold [filled circles above 1.0 (2 hr)].

The rate-decreasing effects of atropine were prevented by appropriate doses of physostigmine. In addition, at several dose-combinations, response rates were increased above control levels even at doses of either drug which decreased responding when given alone. Increases in rate were dose-dependent and were most pronounced for behavior maintained by food. Maximal increases in food-maintained responding when atropine-physostigmine combinations were administered immediately prior to testing were comparable to those observed when 1 mg/kg atropine alone was given 2 hr prior to testing. Although physostigmine had minimal effects on quarter-life when given alone, when given in conjunction with atropine, quarter-life values were decreased. The effects of 1 mg/kg atropine at the 2-hr pretreatment were unaffected by physostigmine; quarter-life values were still decreased and response rates were increased [unfilled squares above 1.0 (2 hr)]. Thus, although physostigmine reversed the rate-decreasing effects of atropine at the 0-hr pretreatment, it did not alter the effects of atropine on quarter-life values or the increases in food-maintained responding induced by 1 mg/kg atropine observed at 2-hr postinjection.

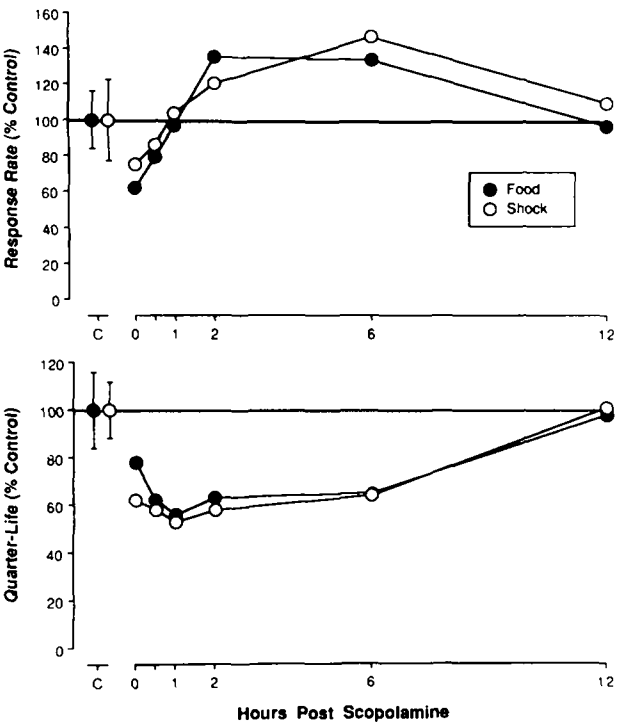

FIG. 3. Time-course of behavioral effects of 0.1 scopolamine hydrobromide. Data are means of single of duplicate determination in each of 2 monkeys. Other details as in Fig. 1.

DISCUSSION

The present experiments describe a time-dependent behavioral excitatory effect of atropine characterized by increases in response rates and disruption in the temporal patterning of responding. The effect can be produced by both appropriate pretreatment with atropine and by coadministration of physostigmine. Behavioral excitatory effects of atropine, as defined here, can be distinguished from the response rate-decreasing effects observed after immediate pretreatment with atropine. Whereas the rate decreases were reversed by physostigmine, the rate increases obtained after pretreatment were unaffected by physostigmine. Further clarification of these results should be obtained through exploration of full dose- and time-effect relationships with atropine alone and in the presence of physostigmine.

Related observations were made in squirrel monkeys responding under schedules of shock-postponement (18). In that study, response rate decreases produced by atropine were reversed by either physostigmine or oxotremorine. Although both physostigmine and oxotremorine also decreased

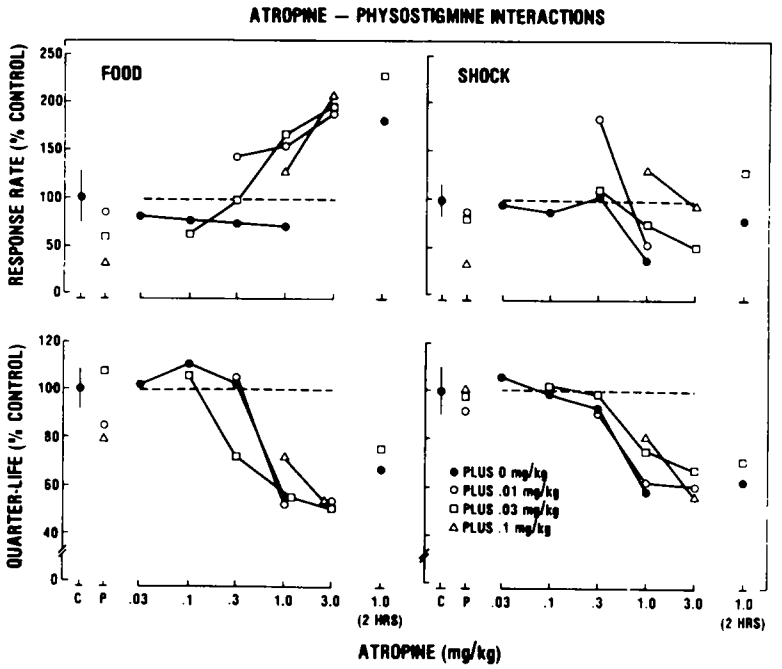

FIG. 4. Effects of atropine sulfate alone (filled symbols) or in conjunction with physostigmine sulfate (unfilled symbols). Effects on responding maintained by food presentation are shown in the left panels; effects on responding maintained by shock presentation are shown in the right panels. Unconnected symbols above P represent effects of physostigmine alone. Unconnected points above 1.0 (2 hr) represent effects of 1 mg/kg atropine given 2 hr prior to experimental sessions either alone or in combination with immediate presession physostigmine. All other points represent effects of the drugs given immediately prior to experimental sessions. Data are means of single or duplicate determinations in 4 monkeys. Other details as in Fig. 1.

responding when given alone, response rates, as in the present study, were increased 2-fold when the drugs were coadministered with atropine. Similarly, Olds and Domino (9) found that although arecoline decreased responding when given alone, rates of responding maintained by electrical brain stimulation were increased when arecoline was administered to scopolamine-treated rats. The relatively restricted actions of oxotremorine at muscarinic receptors make it possible to rule out general cholinergic actions or diffuse properties of physostigmine in producing the rate increases. Direct stimulation of muscarinic receptors in the presence of atropine appears to be sufficient to account for the phenomenon. Taken together, these observations suggest that the rate-decreasing effects of atropine were related to blockade of muscarinic receptors, whereas its behavioral excitatory effects appear to be only indirectly due to this action of atropine. Instead, the response rate increases, as evidenced by their insensitivity to muscarinic agonists, are more properly nonmuscarinic actions of atropine. This nonmuscarinic behavioral exictatory effect may be expressed when the muscarinic receptor-related decreases are reversed by agonists or when the rate decreases are overshadowed by excessive nonmuscarinic stimulation. Further, behavioral exictatory effects may be triggered by time-dependent changes in acetylcholine turnover associated with atropine administration [cf. (10,14)]. The precise nature of these pharmacological actions remains to be determined but may involve nicotinic receptors or changes in dopaminergic transmission as these systems are often recruited by alterations in acetylcholine flux.

Current data do not rule out entirely the possibility that nonmuscarinic actions of either physostigmine or oxotremorine instead of atropine are responsible for the increases in responding when the drugs are combined [see (17–19)]. A related problem was posed by the response rate increases observed in squirrel monkeys after combinations of meperidine and naloxone, but not by morphine and naloxone (22). In that study, increased rates of responding were also observed when meperidine was given alone in morphine-tolerant monkeys permitting the definitive conclusion that nonopioid actions of meperidine and not naloxone were responsible for the behavioral effects observed. Since neither physostigmine nor oxotremorine produce consistent response rate increases in squirrel monkeys [cf. (3,18)], and since appropriate pretreatment with atropine results in rate increases, it seems likely that some nonmuscarinic actions of atropine and not of physostigmine or oxotremorine were initiating the behavioral excitatory effects seen after the drug combination. From this it would be predicted that even immediate presession administration of atropine would produce behavioral excitatory effects in squirrel monkeys tolerant to behavioral effects of muscarinic agonists.

A number of pieces of evidence are available to indicate

that actions of these drugs at peripheral synapses are not sufficient to induce behavioral exictatory effects. Methylatropine does not increase rates or produce dose-related alterations in response patterning [see also (13, 16, 18)]. In addition, combinations of methylatropine with either neostigmine or oxotremorine-M, two quaternary compounds with limited access to the central nervous system after systemic administration, do not significantly increase responding in squirrel monkeys (18).

Although, as discussed above, some exceptions have been noted, atropine and physostigmine or related compounds are generally mutually antagonistic without producing additional effects (see Introduction). Previous studies of interactions of physostigmine and muscarinic antagonists in squirrel monkeys have supported these observations (3,13). In these experiments, however, the range of doses studied may not have been sufficient to observe behavioral excitatory effects. In the study by Chait and Balster (3) the dose of atropine was relatively low (0.1–0.4 mg/kg) and in Vaillant's (13) study, dose-effect functions were not presented for physostigmine in monkeys treated with both methylatropine and scopolamine. Thus, the present findings are not necessarily discrepant, but represent effects not previously explored.

There are some data which further complicate straightforward interpretation of the observed physostigmine-insensitive behavioral excitatory effects of atropine. McKearney (8) reported that atropine increased response rates in a small percentage of squirrel monkeys when administered without any pretreatment. These effects were interpreted as being due to biological differences in sensitivity to rate-increasing effects of antimuscarinic drugs. In the present study, monkeys which did not show increases in overall rates of responding with atropine, showed striking increases after appropriate pretreatment or after physostigmine administration. In addition, in the present study, responding was increased in a few animals on some occasions during the early portions of experimental sessions but was markedly reduced in latter parts of the sessions. If such increasing and decreasing effects of atropine were due to pharmacokinetic processes alone, then appropriate pretreatment with atropine should have resulted in more homogenous response rate changes throughout the session. Likewise, if the response rate increasing effects of atropine were induced simply by a time-dependent process, then manipulation in atropine pretreatment should have produced increases in responding beginning at the appropriate time in the experimental session. However, atropine pretreatment produced rate increases which were seen starting at the beginning of experimental sessions. Thus, the overall behavioral effects seen after atropine administration appear to depend upon a host of factors which are not all clearly delineated.

As scopolamine produced qualitatively similar time-dependent behavioral excitatory effects as those of atropine, such behavioral excitatory effects may be a general consequence of muscarinic receptor blockade. It is interesting to note in this regard that the benzilate antimuscarinics, benactyzine, aprophen and adiphenine, produced response rate increases in rats when administered immediately prior to experimental sessions. Such increases were not seen with a host of other muscarinic antagonists including atropine (21). Behavioral excitatory effects of these benzilate antagonists but not of atropine or scopolamine were also observed in squirrel monkeys injected immediately before behavioral observation [Galbicka, Markowitz, Barrett and Witkin, unpublished observations, cited in (19)]. It is at present unclear what relationship exists between the response rate increases observed with the benzilate compounds and those seen after appropriate pretreatment with atropine. However, it is compelling to speculate that the behavioral excitatory effects of the antimuscarinics may be predictive of their propensity in man toward effects which include excitement, delirium and hallucinations (1,15).

REFERENCES

1. Abood, L. G.; Biel, J. H. Anticholinergic psychotomimetic agents. Int. Rev. Neurobiol. 4:218–273; 1962.
2. Barrett, J. E. Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or electric shock presentation. J. Pharmacol. Exp. Ther. 196:605–615; 1976.
3. Chait, L. D.; Balster, R. L. Effects of phencyclidine, atropine and physostigmine, alone and in combination, on variable-interval performance in the squirrel monkey. Pharmacol. Biochem. Behav. 11:37–42; 1979.
4. Cohen, S.; Sokolovsky, M. Complexity apparent in muscarinic mechanisms. Trends Pharmacol. Sci. 8:41–44; 1987.
5. Gollub, L. R. The relations among measures of performance on fixed-interval schedules. J. Exp. Anal. Behav. 7:337–343; 1964.
6. Longo, V. G. Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacol. Rev. 18:965–996; 1966.
7. McKearney, J. W. Effects of *d*-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. J. Pharmacol. Exp. Ther. 190:141–153; 1974.
8. McKearney, J. W. Effects of tricyclic antidepressant and anticholinergic drugs on fixed-interval responding in the squirrel monkey. J. Pharmacol. Exp. Ther. 222:215–219; 1982.
9. Olds, M. E.; Domino, E. F. Comparison of muscarinic and nicotinic cholinergic agonists on self-stimulation behavior. J. Pharmacol. Exp. Ther. 166:189–204; 1969.
10. Szerb, J. C. Autoregulation of acetylcholine release. In: Langer, S. Z.; Starke, K.; Dubocovich, M. J., eds. Presynaptic receptors. Oxford: Pergamon Press; 1979:293–298.
11. 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. 7th ed. New York: MacMillan; 1985:110–129.
12. Vaillant, G. E. Antagonism between physostigmine and atropine on the behavior of the pigeon. Naunyn Schmiedebergs Arch. Pharmacol. 248:406–416; 1964.
13. Vaillant, G. E. A comparison of antagonists of physostigmine-induced suppression of behavior. J. Pharmacol. Exp. Ther. 157:636–648; 1967.
14. Vizi, E. S. Non-synaptic interactions between neurons: Modulation of neurochemical transmission—Pharmacological and clinical aspects. New York: John Wiley and Sons; 1984.
15. 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. 7th ed. New York: MacMillan; 1985:130–144.

16. Wenger, G. R. Effects of physostigmine, atropine and scopolamine on behavior maintained by a multiple schedule of food presentation in the mouse. J. Pharmacol. Exp. Ther. 209:137–143; 1979.
17. 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: Ellishorwood Ltd.; 1987:800–813.
18. Witkin, J. M. Central and peripheral muscarinic actions of physostigmine and oxotremorine on avoidance behavior of squirrel monkeys. Psychopharmacology (Berlin), in press; 1989.
19. Witkin, J. M. Behavioral pharmacology of compounds affecting muscarinic cholinergic receptors. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Advances in behavioral pharmacology. vol. 7. Hillsdale, NJ: Lawrence Erlbaum; 1989:in press.
20. Witkin, J. M.; Alvarado-Garica, R.; Lee, M. A.; Witkin, K. M. Nonmuscarinic neurotoxicity of oxotremorine. J. Pharmacol. Exp. Ther. 241:34–41; 1987.
21. 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.
22. Witkin, J. M.; Leander, J. D.; Dykstra, L. A. Modification of behavioral effects of morphine, meperidine and normeperidine by naloxone and by morphine tolerance. J. Pharmacol. Exp. Ther. 225:275–283; 1983.