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ORIGINAL INVESTIGATION

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Dose-response curves and time-course effects of selected anticholinergics on locomotor activity in rats

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Abstract *Rationale:* In order to facilitate direct comparisons of anticholinergic drug effects on activity, nine drugs were tested in one laboratory using a standardized procedure. *Objective:* The present study compared the effects of aprophen hydrochloride, atropine sulfate, azaprophen hydrochloride, benactyzine hydrochloride, biperiden hydrochloride, diazepam, procyclidine hydrochloride, scopolamine hydrobromide, and trihexyphenidyl hydrochloride on activity levels in rats. *Methods:* Both fine motor activity (reflecting smaller movements) and ambulatory activity (reflecting larger movements) were recorded for 23 h following drug administration in food-restricted rats. All drugs were administered during the light period of the photocycle. *Results:* Atropine, azaprophen, biperiden, scopolamine, and trihexyphenidyl increased both ambulations and fine motor activity significantly during the first hour post-injection, but the increased activity levels returned to vehicle control levels within 2–6 h post-injection. Benactyzine and procyclidine only increased fine motor activity significantly above vehicle control levels and activity levels returned to vehicle control levels within 2–3 h. Finally, aprophen and diazepam generally did not increase measures of activity significantly above vehicle controls at the dose ranges examined. *Conclusions:* Based on potencies relative to scopolamine, the potency of the drugs could be ranked as follows: scopolamine > trihexyphenidyl > biperiden > azaprophen > procyclidine > benactyzine > atropine > aprophen. The comparison of drug effects on activity may be useful in selecting anticholinergic drug therapies with a minimal range of side effects. In addition, these data may reduce the number of anticholinergic drugs that need to be tested in comparison studies involving more complex behavioral tests.

Key words Locomotion · Activity · Dose-response · Time-course · Anticholinergic drug · Rat

Introduction

The central cholinergic system is involved in the mediation of many behaviors, including learning and memory. Cholinergic deterioration is thought to play an important role in the cognitive deficits associated with old age and dementia (Dunnett and Fibiger 1993). The cholinergic hypothesis of memory is supported in part by studies demonstrating that altering cholinergic transmission significantly changes performance on learning and memory tasks (see Blokland 1996, for review). For example, in a paper that Hagan and Morris (1988) cite as "mark[ing] the beginning of modern psychopharmacological research on cholinergic drugs," Macht (1924) reported that atropine disrupted performance in a circular maze. However, disrupting cholinergic function can also produce significant changes in attention, sensation, and motor function that may in turn affect performance on measures of learning and memory (Hagan and Morris 1988; Blokland 1996). Consequently, it is also important to understand the effects of cholinergic disruption of these processes.

One simple measure of behavioral function in animal models that has proven useful in determining the psychopharmacological effects of drugs is the analysis of general locomotor activity (Kelley 1993). General locomotor activity levels are sensitive to drugs and are an established index used in assessing the behavioral and toxico-

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logical effects of drugs on motor function (Reiter and MacPhail 1979). Studies of motor function have been used successfully to screen the effects of drugs that affect the cholinergic system. General locomotor activity can be depressed following the administration of acetylcholine (Herman et al. 1972), anticholinesterases such as physostigmine (Frances and Jacob 1971), and direct-acting agonists such as arecoline (Pradhan and Dutta 1971). In contrast, classic cholinergic antagonists like scopolamine and atropine generally increase measures of activity in many species, including rats (Walters and Block 1969), mice (Bushnell 1987), and cats (Beleslin et al. 1986). Similarly, azaprophen, benactyzine, biperiden, and trihexyphenidyl have also been found to increase locomotor activity (Walters and Block 1969; Witkin et al. 1992) in rats.

Because the measurement of locomotor activity is relatively simple, it has been measured in many ways ranging from observational methods to computer-based automated systems (Reiter and MacPhail 1979; Sanberg et al. 1985; Kelley 1993; Brudzynski and Krol 1997). The introduction of computer-based automated and video-analysis systems has further increased the sensitivity of behavioral measurement and expanded the capability to analyze locomotor behavior (Brudzynski and Krol 1997). However, a standard protocol does not exist for measuring activity levels. Methodological differences including trial length, the types of dependent variables recorded, time of day, ambient temperature, illumination, extraneous odors, rearing conditions, and handling history can all affect behavioral outcomes (Beninger et al. 1985; Brudzynski and Krol 1997). In addition, an animal's age, gender, species, or even strain can affect activity levels (Kelley 1993). As a result, it is difficult to compare the effects of multiple drugs on locomotor activity when data have been collected in different laboratories using a wide range of species and methods.

The purpose of the present study was twofold. First, the study determined dose–response curves for the effects of eight anticholinergic drugs (aprophen, atropine, azaprophen, benactyzine, biperiden, procyclidine, scopolamine, and trihexyphenidyl) on activity levels. Testing all of the drugs in the same laboratory using a standardized procedure also allowed for the direct comparison of the drug effects on activity. In addition, the time course data were collected over 23 h to assess the duration of drug effects. Second, all of the drugs have been shown to be effective in blocking or terminating soman-induced seizures (Capacio and Shih 1991) and are candidate anticholinergics that are under consideration for use by the United States Army to either supplement or replace diazepam as an anti-convulsant against soman-induced seizures. As such, diazepam's effects on activity were also measured. The intent with all drugs was to continue the dose–response curves until significant behavioral effects were achieved and/or doses were more than one log unit greater than ED_{50} values for preventing soman-induced seizures (Capacio and Shih 1991).

Methods

Animals

Twenty-four male Sprague-Dawley rats (Charles River Laboratories, Raleigh, N.C.) were maintained at a body weight of 350 g through restricted post-session feeding of ProLab rodent chow (approximately 10 g per day for the duration of the experiment). Subjects were provided with a continuous supply of water and were housed individually in transparent acrylic cages (47.5 cm length × 25.5 cm width × 20 cm depth) with shredded paper bedding, a wire lid, and a filter cover. The environmental room housing the animals was maintained on an alternating 12-h light/12-h dark cycle with lights turned on at 0600 hours.

Apparatus

Activity was monitored using a Photobeam Activity System (San Diego Instruments, San Diego, Calif.) with 12 home-cage activity units attached. Each home-cage unit consisted of an animal's home cage that was placed within a frame containing four photobeams (spaced approximately 8.5 cm apart). Photobeams were adjusted individually by targeting each rat's body at mid flank. The frames were connected to an interface and control board that was coupled to a personal computer. The personal computer served as the control unit, ran the activity software, and collected data.

Testing procedure

Each subject was placed in a home-cage unit and allowed to habituate to its new surroundings for 1 week prior to the onset of the experiment. Subjects were handled, weighed, and restrained daily during the habituation period in order to minimize the effects of subsequent handling on activity levels.

The subjects were weighed and fed between 1430 hours and 1530 hours daily, injected on Tuesdays and Fridays between 1515 hours and 1530 hours, and cages and water bottles were changed on Wednesdays and Saturdays between 1430 hours and 1530 hours throughout the duration of the experiment. The data collection software was started at approximately the same time every day (1530 hours) to minimize circadian variation of activity and electronically recorded the number of photobeam breaks that occurred every 5 min during the ensuing 23 h. Activity counts were broken down into two categories. "Fine movements" included repeated breaks of the same photobeam, whereas "ambulations" included breaks of alternate photobeams. Thus, ambulations represent larger locomotor movements, reflecting subject movements of greater distance, whereas fine movements represent smaller movements, reflecting scratching, grooming, or the performance of stereotypic movements in front of a single photobeam.

Drug testing

Drug administration began following the initial 1-week habituation period. Thursdays served as non-injection control days, with drug or vehicle administration on Tuesdays and Fridays. Aprophen hydrochloride, azaprophen hydrochloride, biperiden hydrochloride, and trihexyphenidyl hydrochloride were obtained from the Department of Experimental Therapeutics, Walter Reed Army Institute of Research. Atropine sulfate, benactyzine hydrochloride, diazepam, and procyclidine were purchased from Sigma Chemical Company (St. Louis, Mo.), and scopolamine hydrobromide was purchased from Research Biochemicals International (Natick, Mass.). Drug doses were injected intraperitoneally in a volume of 1 ml/kg, 15 min prior to the onset of the session. Rats were returned to their home cages after injections.

Each drug was studied in a single group of rats (n=6) with each dose (see Table 1 for dose ranges) and vehicle administered twice. The order of doses was random except that all subjects in a group

received the same dose on any particular day, all doses were administered once prior to each replication, and the next dose was administered only after behavior returned to baseline. Some groups received more than one drug (see Table 1 for drug sequences), but the next drug was not administered until behavior returned to baseline. Biperiden, diazepam, and trihexyphenidyl were dissolved in a mixture of 50% physiological saline, 40% propylene glycol, and 10% ethanol. The remaining drugs were dissolved in physiological saline. All drug doses were prepared on the day of the first determination and were frozen until the second determination. Dose–response curves were continued until significant behavioral effects were achieved and/or doses were more than one log unit greater than the ED_{50} values for preventing soman-induced seizures. Doses higher than 17.0 mg/kg atropine were not administered because a rat died after receiving that dose. Due to a technical error, the last drug studied (diazepam) was only administered to a dose of 10 mg/kg, not quite a full log unit greater than the 1.5 mg/kg anti-convulsant ED_{50}.

Statistical analyses

Data for the dose–response curves were collected during the first hour post-injection and were presented graphically in Fig. 1 and Fig. 2 as a percentage of non-injection baseline control to facilitate visual comparisons between drugs. Analysis of variance was used to determine the overall significance of dose–response functions. Where significant overall effects were obtained, post-hoc comparisons were preformed using Dunnett's *t*-tests to compare each drug dose to the appropriate vehicle control using non-transformed data. In addition, the dose generating the highest level of activity during the first hour was subjected to further analysis to characterize the time course of that effect. A repeated-measures (one within, one between) analysis of variance was used to examine the time-course data. This analysis was conducted on mean activity counts during 10-min intervals for the first 2 h (Fig. 3) and for mean activity counts during each hour for 23 h following drug administration (Fig. 4). Activity counts following drug administration were compared with mean counts during the same interval following vehicle using repeated *t*-tests.

Table 1 The ED_{50} doses required to increase ambulations and fine motor activity to 50% of the maximum increase for the anticholinergic drugs tested. Potencies relative to scopolamine are presented in parentheses. *ID* ED_{50} doses were indeterminate because dose ranges tested did not produce significant increases

Drug (Dose range mg/kg)	ED_{50} (mg/kg) Ambulations	ED_{50} (mg/kg) Fine motor activity
Aprophen hydrochloride (0.56–17.0)[a2]	ID	ID
Atropine sulfate (1.0–17.0)[a1]	3.05 (0.039)	1.97 (0.061)
Azaprophen hydrochloride (0.56–10.0)[b2]	1.68 (0.071)	1.38 (0.087)
Benactyzine hydrochloride (0.1–5.6)[a3]	ID	1.86 (0.065)
Biperiden hydrochloride (0.1–10.0)[c1]	1.18 (0.102)	1.30 (0.092)
Diazepam (0.3–5.6)[c2]	ID	ID
Procyclidine hydrochloride (0.1–5.6)[b3]	ID	1.74 (0.069)
Scopolamine hydrobromide (0.056–1.0)[b1]	0.12 (1.000)	0.12 (1.000)
Trihexyphenidyl hydrochloride (0.1–10.0)[d]	0.75 (0.160)	1.13 (0.106)

[a–d] Drugs that each group of rats (n=6) received
[1–3] Sequence drugs were presented

Results

Ambulations: dose–response curves

Atropine ($F_{5,30}$=7.63, P<0.0002), azaprophen ($F_{5,30}$= 3.26, P<0.02), biperiden ($F_{5,30}$=5.82, P<0.001), scopolamine ($F_{5,30}$=2.91, P<0.03), and trihexyphenidyl ($F_{5,30}$= 4.285, P<0.005) significantly increased ambulations above vehicle in a dose-dependent fashion (Fig. 1). Post-hoc comparisons indicated that the higher doses (*shaded* in Fig. 1) of atropine, azaprophen, biperiden, scopolamine, and trihexyphenidyl significantly increased ambulations relative to their appropriate vehicle controls (P<0.05, Dunnett's *t*-test). The remaining drugs did not increase ambulations significantly in a dose-dependent fashion.

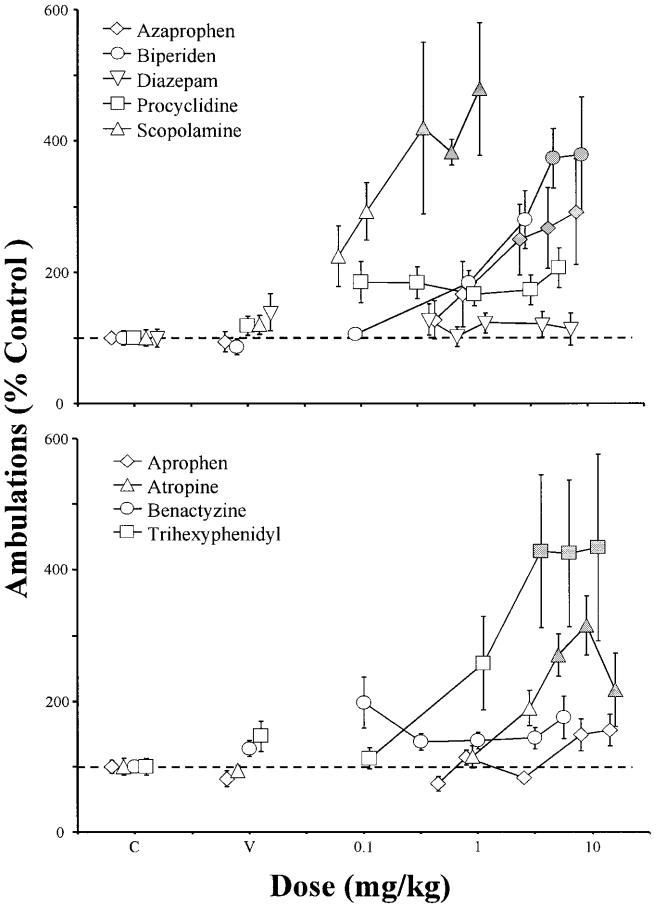

Fig. 1 Dose–response curves for ambulation levels (1 h post-injection) expressed as a percentage of control (±SEM) under control (*C*), vehicle (*V*), and various doses of nine anticholinergic drugs. Vehicle and drug points represent double determination. Control points were taken from the non-injection control days (Thursday). *Points* have been displaced slightly along the ordinate. The *dashed line* represents control levels (100%) and *shaded points* differ significantly from the appropriate vehicle control

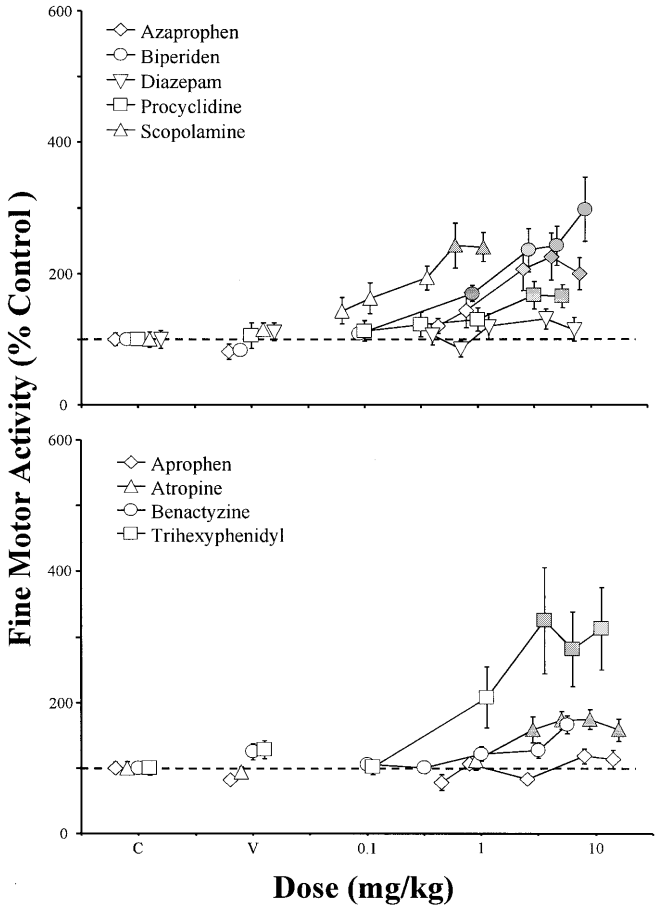

Fig. 2 Dose–response curves for fine motor activity levels (1 h post-injection) expressed as a percentage of control (±SEM) under control (*C*), vehicle (*V*), and various doses of nine anticholinergic drugs. The plotting characteristics are the same as in Fig. 1

Fine motor activity: dose–response curves

Atropine ($F_{5,30}$=4.48, P<0.004), azaprophen ($F_{5,30}$= 7.08, P<0.0003), benactyzine ($F_{5,30}$=3.13, P<0.03), biperiden ($F_{5,30}$=18.35, P<0.0002), procyclidine ($F_{5,30}$= 4.11, P<0.006), scopolamine ($F_{5,30}$=3.71, P<0.01), and trihexyphenidyl ($F_{5,30}$=11.17, P<0.0002) significantly increased fine motor activity above vehicle in a dose-dependent fashion (Fig. 2). Post-hoc comparisons indicated that the higher doses (*shaded* in Fig. 2) of atropine, azaprophen, biperiden, procyclidine, scopolamine, and trihexyphenidyl significantly increased fine motor activity relative to their appropriate vehicle controls (P<0.05, Dunnett's *t*-test). The remaining drugs did not increase fine motor activity significantly in a dose-dependent fashion.

Ambulations: time-course effects

The time-course effects for the dose of each drug producing the greatest increase in ambulations above vehicle during the first hour post-injection are shown with squares in Fig. 3. Biperiden (10.0 mg/kg) significantly increased ambulations for 6 h before returning to vehicle control levels. Atropine (10.0 mg/kg) and scopolamine (1.0 mg/kg) significantly increased ambulations for 5 h before returning to vehicle control levels. Azaprophen (10.0 mg/kg), procyclidine (5.6 mg/kg), and trihexyphenidyl (10.0 mg/kg) significantly increased ambulation levels above vehicle for 3 h prior to returning to control levels. Aprophen (17.0 mg/kg) and diazepam (0.3 mg/kg) administration significantly increased ambulations above vehicle during the first hour post-injection, but ambulations returned to vehicle levels by the second hour. Finally, benactyzine (5.6 mg/kg) did not increase ambulations significantly above vehicle during the first hour post-injection.

Fine motor activity: time-course effects

The time-course effects for the dose of each drug producing the greatest increase in fine motor activity above vehicle during the first hour post-injection are shown with triangles in Fig. 3. Scopolamine (0.56 mg/kg) significantly increased fine motor activity for 6 h before returning to vehicle control levels. Atropine (10.0 mg/kg) and biperiden (10.0 mg/kg) administration significantly increased fine motor activity above vehicle for 5 h post-injection before returning to vehicle control levels. Azaprophen (5.6 mg/kg) also significantly increased fine motor activity above vehicle levels for 4 h prior to returning to vehicle control levels. Trihexyphenidyl (3.0 mg/kg) and benactyzine (5.6 mg/kg) significantly increased fine motor activity above vehicle for 2 h post-injection. Procyclidine (3.0 mg/kg) increased fine motor activity significantly above vehicle only during the first hour post-injection. Finally, aprophen (10.0 mg/kg) and diazepam (3.0 mg/kg) administration did not increase fine motor activity significantly above vehicle levels during the test period.

Time of peak effect

Time-course data for ambulations and fine motor activity were analyzed further to determine the time of peak effect (Fig. 4). Activity counts during 10-min intervals during the first 2 h following drug administration were compared with the same intervals following vehicle injection. In all cases (except for atropine for fine motor activity at 80 min), peak drug effect occurred within the first hour following the onset of behavioral testing.

Discussion

The effects of aprophen, atropine, azaprophen, benactyzine, biperiden, diazepam, procyclidine, scopolamine, and trihexyphenidyl on fine motor activity and ambulations were examined in the present study. Both activity measures generated stable and reliable baseline patterns under non-injection control and vehicle control condi-

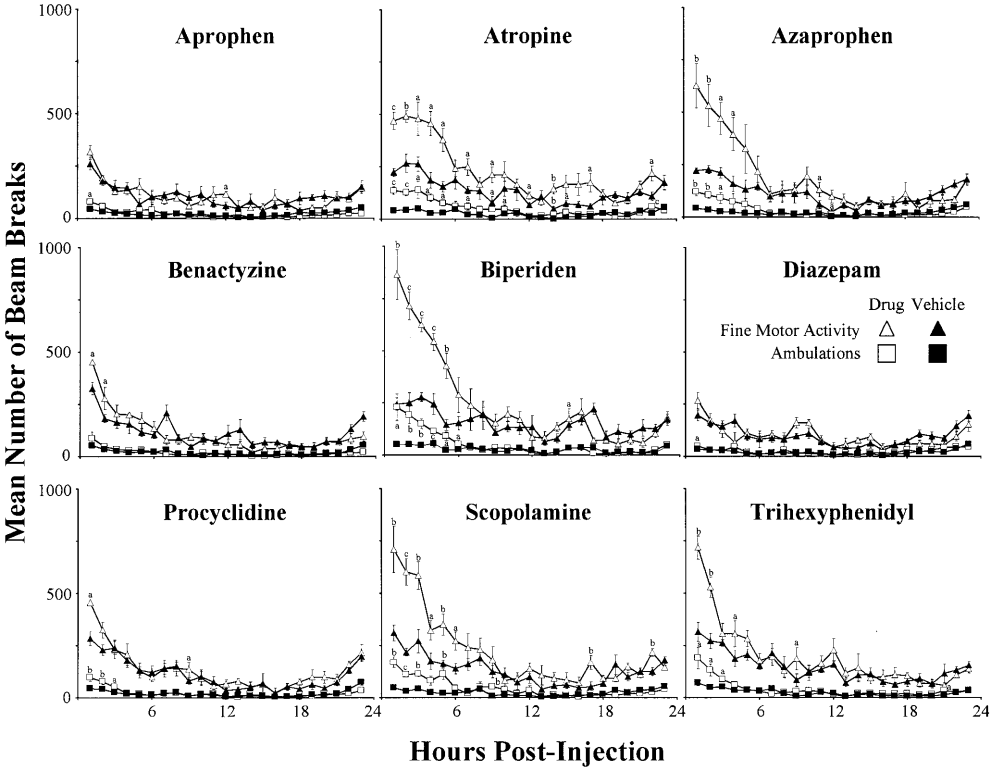

Fig. 3 Time-course data for ambulation (*squares*) and fine motor activity (*triangles*) levels across 23 h, expressed as the mean number of photobeam breaks (±SEM) after vehicle injection (*filled symbols*) and the dose that produced the greatest increase in activity for nine anticholinergic drugs (*open symbols*). Vehicle and drug points represent double determination. [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$

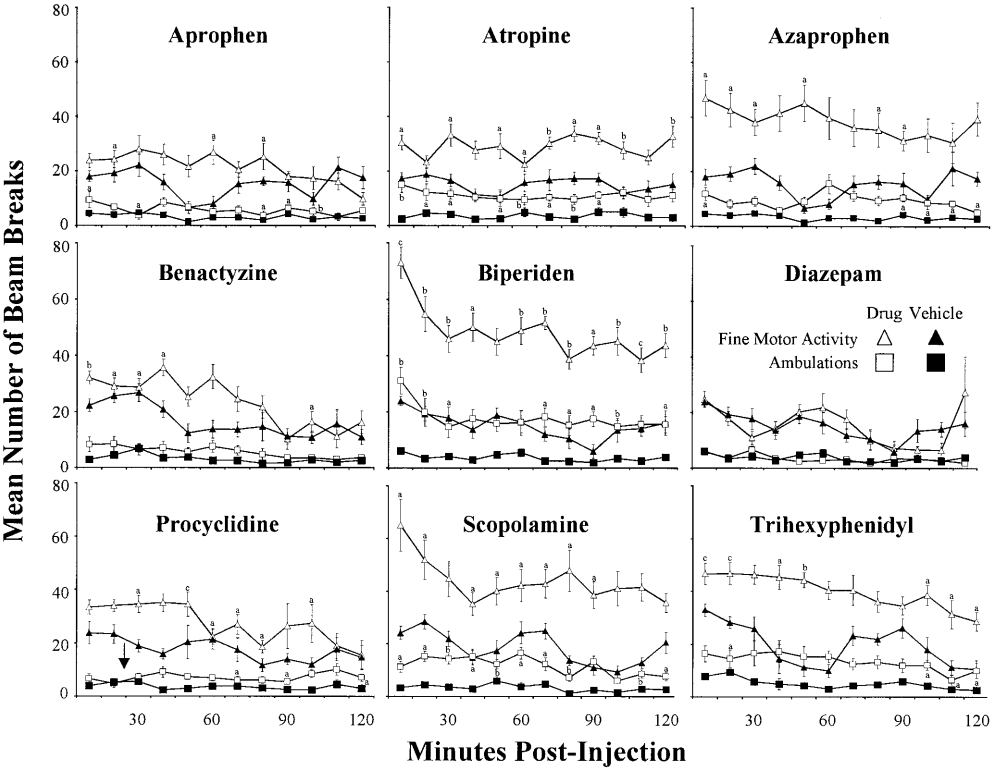

Fig. 4 Time-course data for ambulation (*squares*) and fine motor activity (*triangles*) levels across the first 2 h post-injection expressed as the mean number of photobeam breaks (±SEM) after vehicle injection (*filled symbols*) and the dose that produced the greatest increase in activity for nine anticholinergic drugs (*open symbols*). Vehicle and drug points represent double determination. [a]$P<0.05$, [b]$P<0.01$, [c]$P<0.001$

tions. Fine motor activity levels and ambulations under control conditions were elevated during the first 3–4 h post-feeding, gradually decreased and remained minimal during the subsequent 15 h, and began to increase again during the last 3–4 h prior to feeding (Fig. 3). The patterns of activity seen under baseline conditions in the present study are consistent with the anticipatory activity seen prior to single daily feedings in other laboratories (Reid and Finger 1955; Phillips and Milkulka 1979; Honma et al. 1983).

In general, vehicle injections did not increase ambulations (except for the trihexyphenidyl vehicle) or fine motor activity significantly over baseline controls or change the patterns of activity seen under baseline conditions. In contrast, atropine, azaprophen, biperiden, scopolamine, and trihexyphenidyl significantly increased both measures of activity relative to vehicle controls in dose-dependent fashion at 1 h post-injection. Benactyzine and procyclidine significantly increased fine motor activity, but not ambulations in dose-dependent fashion at 1 h post-injection. Most of the drugs tested continued to increase both fine motor activity (except aprophen and diazepam) and ambulations (except benactyzine) significantly above vehicle beyond the first hour post-injection, but the time of peak effect occurred within the first hour of the test session (except atropine, which occurred within 80 min).

In several cases, drugs had differential effects on ambulations and fine motor activity. For example, smaller doses of atropine, biperiden, and procyclidine were required to significantly increase fine motor activity than to increase ambulations. In contrast, scopolamine was the only drug tested that significantly increased ambulations at a dose smaller than that required to increase fine motor activity. The remaining drugs significantly increased both measures at the same doses. Aprophen, biperiden, diazepam, procyclidine, and trihexyphenidyl also increased ambulations longer than they increased fine motor activity. In contrast, azaprophen, benactyzine and scopolamine increased fine motor activity for a longer duration than ambulations. These findings argue for using ambulations (reflecting subject movements of greater distance) and fine motor activity (reflecting smaller movements in front of a single photobeam) to differentiate between the effects of drugs with similar actions.

The findings from the present study confirm and extend published findings from several laboratories showing that anticholinergic drugs increase locomotor activity in many species. Scopolamine increases activity in rats (Hughes et al. 1975; Stewart and Blain 1975; Geyer et al. 1986; Mueller and Peel 1990; Mathur et al. 1997), mice (Bushnell 1987; Shannon and Peters 1990), and cats (Beleslin et al. 1986). Similarly, atropine increases activity in rats (Pradhan and Roth 1968; Molloy et al. 1986; Witkin et al. 1992) and cats (Beleslin et al. 1986). Both scopolamine and atropine increased measures of activity for a significantly longer period of time than has been reported previously.

The anti-parkinsonian drugs, biperiden, procyclidine, and trihexyphenidyl also increase locomotor activity. Biperiden and trihexyphenidyl significantly increased activity levels in mice at 1.0 mg/kg and were classified as being strongly stimulatory, whereas procyclidine significantly increased activity in mice at 8.0 mg/kg and was classified as being mildly stimulatory (Goldschmidt et al. 1984). Trihexyphenidyl and biperiden also increased activity in cats following intracerebroventricular injection at doses ranging from 0.2 mg/kg to 2.0 mg/kg (Beleslin et al. 1986). In the present study, biperiden, procyclidine, and trihexyphenidyl also increased both measures of activity, but the first effective doses required to elevate ambulations and fine motor activity were generally higher than reported in mice and cats. All three drugs significantly increased measures of activity for longer periods of time (trihexyphenidyl 3–4 h; biperiden 6–7 h; and procyclidine 2–4 h) than has been reported previously.

Benactyzine and azaprophen also have been reported to increase locomotor activity in rats (Witkin et al. 1992). However, Witkin et al. (1992) found that only the highest dose of benactyzine tested (30 mg/kg) produced a significant increase in activity counts. In our hands, azaprophen was more potent than benactyzine and produced a dose-dependent increase in both fine motor activity and ambulations. Furthermore, activity levels remained elevated for 4–5 h following azaprophen injection. In contrast, benactyzine did not increase ambulations or fine motor activity significantly at any of the doses tested. Differences between our findings and those of Witkin et al. (1992) could be due to methodological differences, including the time of day the drugs were administered (0900–1300 hours for Witkin et al. 1992; 1500–1530 hours for the present study) or the length of time elapsing between the injection and the start of the experimental session (30 min for Witkin et al. 1992; 15 min for the present study).

Aprophen, an anti-spasmodic drug which is structurally similar to benactyzine, has had very limited use in both research and treatment (Grauer and Kapon 1996). In the limited research using aprophen, it produced minimal effects on performance in paired discrimination tasks (Grauer and Kapon 1996) and schedule-controlled behaviors (Genovese et al. 1990). Similarly, in the present study, aprophen did not increase either measure of activity significantly at any of the doses tested.

The present findings make it possible to compare the effects of multiple anticholinergic drugs on locomotor activity, a task that would be difficult to do using data collected from several laboratories that employ a wide range of species and methods. Scopolamine was the most potent compound tested, and drug potencies relative to scopolamine are presented in Table 1 for both measures of activity. Based on potency relative to scopolamine, the drugs were ranked as follows: scopolamine > trihexyphenidyl > biperiden > azaprophen > procyclidine > benactyzine > atropine > aprophen.

It is clear from the results of the present study that anticholinergic compounds can have very dramatic effects on locomotor activity. Although it might be considered simplistic or uninformative to study motor activity, changes in motor activity can have important consequences for models of more specific processes, such as learning and memory, reward, or fear responses (Kelley 1993). As such, it is critical to understand how a drug affects a very simple behavior like motor activity before studying the drug in more complex behavioral tests. For example, tests of spatial learning and memory can be conducted in various types of mazes (e.g., radial arm mazes, water mazes, T-mazes) that clearly require motor

activity for their completion. If a drug decreases performance in a spatial learning and memory task, it is important to understand the drug's effects on activity to rule out the possibility that changes in activity, and not deficits in learning or memory, account for decreased performance in the task.

The nine drugs tested in the present study have each been shown to be effective in blocking or terminating soman-induced seizures (Capacio and Shih 1991). Prior to a drug being fielded, however, its efficacy in blocking or terminating seizures must be weighed against any potential adverse effects of the drugs alone on behavior. Examining the relationship between the drugs' effects on behavior and their efficacy in blocking or terminating soman-induced seizures can be useful in selecting the best candidate compounds for advancement in more complex behavioral tests and in non-human primates. For most of the drugs tested, the ED_{50} doses for behavior were higher than the doses required to block or stop soman-induced seizures. Atropine, the only exception, increased behavioral activity at a much smaller dose than required to block seizures. Although biperiden, benactyzine, procyclidine, and trihexyphenidyl affect activity, the ED_{50} doses required to affect activity levels are approximately 5–10 times higher than the ED_{50} doses required to prevent soman-induced seizures. Thus, these compounds would be predicted to be the better choices for pretreatment use as anti-convulsants than atropine, diazepam, or scopolamine, for example, which blocked seizures at doses close to or higher than those required to affect behavior. Thus, biperiden, trihexyphenidyl, benactyzine, and procyclidine warrant further investigation using more complex behavioral measures.

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