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# Behavioral Effects of d-Amphetamine and Apomorphine in the Hamster[1]

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PETERSON, M. E. AND L P MORIN *Behavioral effects of d-amphetamine and apomorphine in the hamster* PHARMACOL BIOCHEM BEHAV **20**(6) 855–858, 1984 —The effects of d-amphetamine sulfate (0–50 mg/kg) and apomorphine HCl (0–12 mg/kg) on several hamster behaviors were studied Gnawing, grooming, sniffing, locomoting, circling, rearing, and back arching were measured by direct observation during the period 25–44 min after drug injection Large doses of d-amphetamine produced significant decreases in grooming and rearing, but significantly increased circling, back arching, sniffing, or gnawing were not affected Large doses of apomorphine produced significant increases in gnawing and decreases in sniffing, but did not affect grooming, rearing, circling, or back arching. In general, response to either drug was highly variable The results are discussed in comparison with published data from rats

Hamsters Amphetamine Apomorphine Behavior Dose-reponse

CENTRAL catecholamine pathways are thought to be involved in the regulation of motor activity [11,12]. Amphetamine and apomorphine alter the activity of catecholamine systems [10, 15, 16] and stimulate various categories of stereotyped behavior in a wide variety of species. In rats, amphetamine- and apomorphine-induced stereotypy is characterized by continuous licking, sniffing, and gnawing [9,23]. In mice, apomorphine elicits cage climbing, sniffing, and biting [20]; face washing and stereotypic locomotor patterns are commonly seen in gerbils given amphetamine [6]. Chewing movements are seen in apomorphine-induced stereotypy in the guinea pig [14] and amphetamine-induced stereotypy in the cat is characterized by "looking" behavior and head movements [8].

Our preliminary observations with resting hamsters tested during the day in their home cages revealed that after any of several amphetamine doses (up to 30 mg/kg), the animals would simply return to sleep. This contrasted with the dramatic behavioral effects expected following amphetamine and apomorphine treatment of rats. Similarly, larger than expected amphetamine doses are apparently necessary to modify hamster sexual behavior [4]. Therefore, the present study sought to examine the relationship between doses of two dopamine agonists, amphetamine or apomorphine, on hamster behavioral responses in an effort to determine sensitivity to the drugs.

## METHOD

### *Subjects*

Intact male hamsters weighing 90–130 g (Charles River-Lakeview) were housed individually under a 14 hr light, 10 hr dark cycle (light 0800–2200) with free access to food and water. Room temperature was 21±2°C.

### *Apparatus*

The test apparatus consisted of a bipartite Plexiglas-walled enclosure with a hardware cloth floor. Each of the two observation compartments measured 61×46×46 cm. The floor of each compartment was divided by green lines into a grid of 11.5×11.5 cm squares. Two red 25-watt incandescent bulbs mounted 56 cm above the floor of the observation compartments illuminated the test arena. Each animal was given a one minute exposure to the test arena on each of the three days preceding the onset of testing.

Prior to testing, all animals were randomly assigned to one of five dosage groups. In Experiment 1, the doses of d-amphetamine sulfate administered were 0, 5, 10, 20 and 50 mg/kg (N=7 per dose). The drug was dissolved in normal saline. New animals were used in Experiment 2 and the doses of apomorphine HCl administered were 0, 1, 3, 7 and 12 mg/kg (N=8 per dose). Apomorphine was dissolved in normal saline. In each experiment, a drug dose was adminis-

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tered intraperitoneally to each animal per group and each animal was injected only once. The observer was blind to the dose level per individual animal at the time of testing

*Behavioral Observations*

Seven behaviors were monitored during the observation phase of the experiment

| | |
|---|---|
| Gnawing | Biting of the cage floor, generally creating a clearly audible scratching noise |
| Grooming | Repeated rubbing of the animal's fore or hind legs against its body or any contact of the mouth with another part of the animal's body |
| Sniffing | Head directed downward, nose at approximately grid level and nose roving over cage floor |
| Locomoting | Use of all four limbs to move the center of the body across a grid demarkation line |
| Circling | Rotating through an angle of 360° with minimal hind leg movement |
| Rearing | Supporting the body with rear legs |
| Back arching | Rapid convex arching of the back |

Only on behavior could be recorded at a time. Therefore, by definition, the behaviors were mutually exclusive.

Gnawing, grooming sniffing, locomoting, circling, and rearing were included because they were readily observable in the hamster and had been described as amphetamine-sensitive behaviors in other rodent species [13, 20, 23] Back arching was included among the observed behaviors because, during preliminary work, it was observed in some hamsters injected with high (50 mg/kg) doses of amphetamine, but never in undrugged animals The preliminary observations failed to provide clues that other behaviors should also be measured

All tests were conducted between 1240 and 1700 hr. A single observation session consisted of injecting and observing two animals, each from a different drug treatment group. Twenty minutes after injection, the animals were placed in the test apparatus one in each observation compartment. After five minutes adaptation to the arena, the 19 min test session began. The timing of the behavioral tests was chosen to coincide with the general post-drug period during which maximal or near maximal effects persist in several species [6, 12, 13, 21, 24]. Each test minute was divided into two 30 sec observation periods. During the first, observations were continuously made of one animal and then of the second animal during the second period Observations were entered via a keypad into a computer in real-time. Data were irretrievably lost from three animals because of equipment failures during Experiment 1

*Statistical Treatment*

A Kruskal-Wallis one-way analysis of variance by ranks was performed for each of the seven behaviors to determine whether there exists a significant difference across dosage groups. If a significant effect appeared, Mann-Whitney U tests were used to compare experimental with vehicle control groups

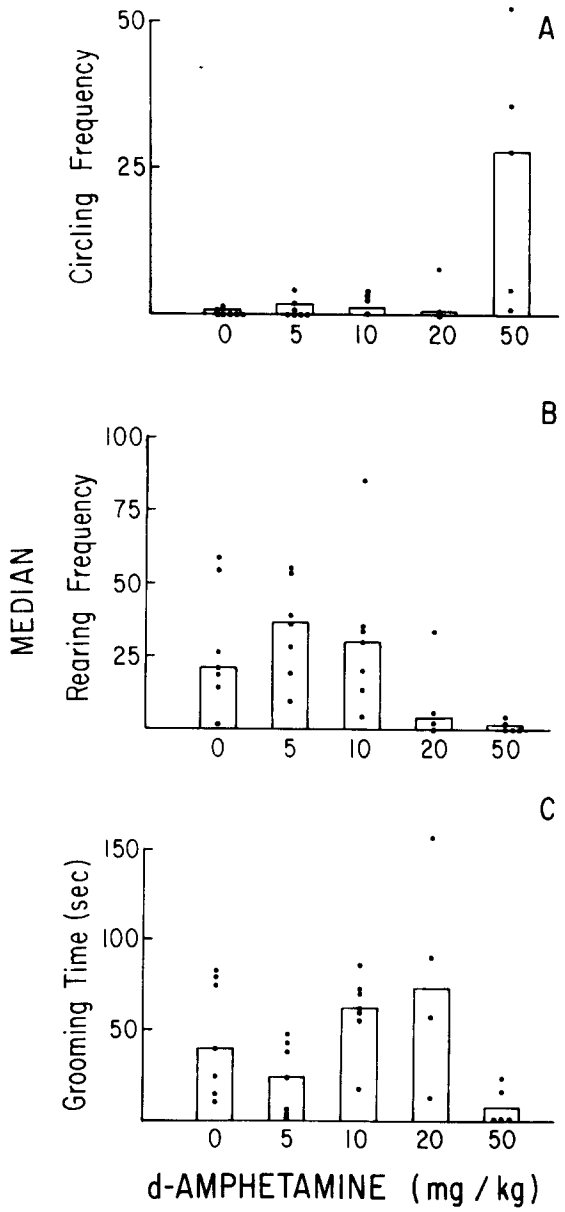


FIG 1 Median levels of (A) circling, (B) rearing and (C) grooming by male hamsters in response to different doses of d-amphetamine sulfate Dots indicate individual responses

## RESULTS

*Experiment 1*

*Circling* Amphetamine affected circling levels ($H=42.48$, $p=0.001$, Fig 1A). The 50 mg/kg group displayed significantly higher circling than the other four groups ($U=2$, $p=0.005$ in each case).

*Rearing.* Significant effects on rearing were produced by amphetamine ($H=13.10$, $p=0.02$, Fig. 1B). Rearing was highly suppressed in the 50 mg/kg group ($U=3$, $p=0.009$) and

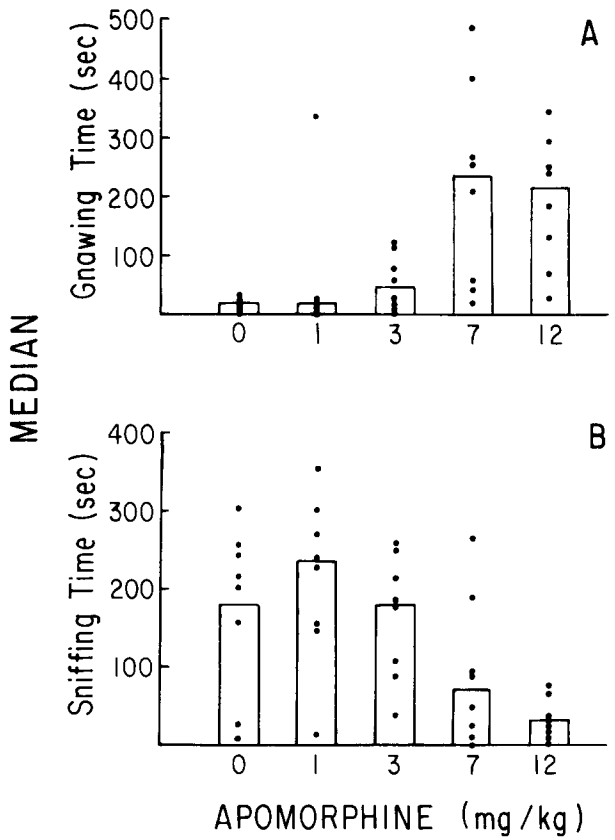


FIG 2 Median levels of (A) gnawing, and (B) sniffing by male hamsters in response to different doses of apomorphine HCl Dots indicate individual responses.

mildly, but not significantly, suppressed in the 20 mg/kg group ($U=7$, $p=0.115$).

*Grooming.* There was a large effect of amphetamine dose on this behavior ($H=13.41$, $p=0.01$; Fig. 1C). Grooming was significantly reduced in the highest dosage group (50 mg/kg) relative to the control group ($U=4$, $p=0.015$).

*Back arching.* Amphetamine did not significantly affect the occurrence of back arching ($H=8.26$, $p=0.10$). Back arching was seen only in the 50 mg/kg group.

*Locomoting, sniffing, gnawing* There was no significant effect of drug treatment on grid cross frequency, time sniffing or time gnawing ($p>0$ 3 in each case)

*Drug lethality* Six of the eight animals in the 50 mg/kg group died within four days of injection One member of the 20 mg/kg group and one member of the 0 mg/kg group also died within four days of injection.

*Experiment 2*

*Gnawing.* Apomorphine dose greatly affected gnawing ($H=18$ 97, $p=0$ 001; Fig. 2A). Large increases were seen in the 7 mg/kg ($U=4$, $p=0.001$) and 12 mg/kg ($U=1.5$, $p=0.001$) groups. A more moderate increase in gnawing was seen in the 3 mg/kg group ($U=15.5$, $p=0.046$).

*Sniffing.* Apomorphine affected sniffing significantly ($H=12.03$, $p=0.02$; Fig. 2B). Sniffing was markedly reduced in the 12 mg/kg group ($U=12$, $p=0.019$).

*Locomoting, grooming, rearing, circling.* Analysis of variance showed no significant effects of apomorphine dose on grooming time, rearing frequency or circling frequency ($p>0.2$ in each case). All groups demonstrated median circling frequencies of zero.

*Back arching* No back arching was observed in any of the animals.

## DISCUSSION

The dopamine agonists, amphetamine and apomorphine, were found to produce several behavioral effects. The dose levels of these two drugs required to produce clear behavioral effects was higher for hamsters than previously reported for rats [9,23], mice [2,22] or guinea pigs [14]. In addition to the apparent dose-response differences between species there were also differences in the direction of change by certain behaviors. For example, d-amphetamine increases gnawing by rats [9,11] (but see [13]), but did not affect this behavior in hamsters. Similarly, there was no observed change in hamster locomoting or sniffing in response to d-amphetamine treatment in contrast to results from rats [13,23].

The principle amphetamine effects observed in hamsters were a decrease in grooming with 50 mg/kg, a marked increase in circling with 50 mg/kg, and a decrease in rearing with 20 and 50 mg/kg. The direction of change of these behaviors in response to amphetamine is generally consistent with data from rats [13, 17, 23]. Only the increased circling can be considered "stereotyped."

The principle apomorphine behavioral effects seen in hamsters were an increase in gnawing with 7 and 12 mg/kg and a marked sniffing decrease with 12 mg/kg. The increase in gnawing with high apomorphine dose is consistent with the rat literature [7,9], although the effective dose is substantially higher for hamsters. Gnawing is a common hamster behavior [18] and can be considered "stereotyped." The decrease in sniffing with a high (12 mg/kg) apomorphine dose in the hamster is contrary to the sniffing dose-response by rats following apomorphine treatment [7,13]. The failure to observe a consistent increase in locomotion with high apomorphine doses in the present study is also inconsistent with data from rats which show that apomorphine has a locomotion stimulating effect [13].

The failure to observe back arching in apomorphine-treated animals and the fact that all animals displaying back arching eventually died suggests that this behavior is produced only by lethal to near lethal doses of amphetamine. Tremor and clonic convulsions have been observed to precede death from amphetamine in rats [3].

Gnawing and rearing were differentially affected by amphetamine and apomorphine. At higher doses, apomorphine produced large increases in gnawing, whereas amphetamine had no significant effect. Rearing was depressed with high doses of amphetamine, but not by apomorphine. These results are consistent with the effects of amphetamine or apomorphine on rat rearing and gnawing [13]. Therefore, the hamster data are consistent with results which suggest different sites of action for amphetamine and apomorphine [5].

In both experiments, there was considerable variation in the behavioral levels displayed by members of the same dosage group. This variability was also evident as performance differences between vehicle control groups of the two experiments (e.g , median sniffing=65 and 180 sec in Experiments 1 and 2, respectively) Similarly, individual hamsters are not consistent in behavioral change after treatment with

different doses of amphetamine (Peterson and Morin, unpublished). Several factors could have contributed to the variability. These include ultradian rhythmicity in general locomotion or in specific components of the behavioral repertoire; ultradian rhythmicity in dopamine receptor binding [19], responsiveness to the drugs or in rates of drug metabolism. Similarly, rapid circadian rhythm changes in drug responsiveness (c.f., [25]) or behavior probability [1] could have introduced large variability into certain behavioral measures. Any one or a combination of these would have tended to obscure a possible relationship between drug dose and behavioral response.

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