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Changes in Spontaneous Behavior in the Dog Following Oral Administration of L-Deprenyl

E. HEAD AND N. W. MILGRAM[1]

Life Sciences Division, Scarborough Campus, University of Toronto, 1265 Military Trail Road, Scarborough, Ontario, Canada M1C 1A5

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HEAD, E. AND N. W. MILGRAM. *Changes in spontaneous behavior in the dog following oral administration of* L-*deprenyl.* PHARMACOL BIOCHEM BEHAV **43**(3) 749–757, 1992.—An open-field activity test was developed for studying the effect of a single oral dose (range of 0.1–5 mg/kg) of L-deprenyl on spontaneous behavior in the dog. A computer program was used to quantify observations of locomotor activity, directed sniffing, urination, grooming, inactivity, jumping, rearing, and vocalization during a 10-min baseline and posttreatment session. Three dose-dependent behavioral changes were observed: an overall decrease in directed sniffing, an increase in total locomotor activity in females, and a decrease in frequency of urination in males. These effects were only seen at the dose levels of 2 mg/kg or higher. Computer-assisted tracings of behavioral patterns showed increased stereotypical behavior and decreased exploratory behavior at the high-dose levels. These behavioral effects are most likely due to either increased levels of phenylethylamine resulting from inhibition of monoamine oxidase B and/or the production of amphetamines as a result of the metabolism of L-deprenyl.

L-Deprenyl Dog Spontaneous activity Phenylethylamine Amphetamine

L-DEPRENYL is an irreversible inhibitor of monoamine oxidase B (MAO-B) (26), which is widely used as an adjunct to L-dopa in the symptomatic treatment of Parkinson's disease (5,6,16,22,28,50). Recent evidence suggests that it also has prophylactic benefits (52). Patients receiving L-deprenyl report feelings of arousal, mood elevation, insomnia, and euphoria (16,40). Alzheimer's patients treated at similar dose levels show a decrease in depression, anxiety, tension, and retardation and an increase in activity and social interaction (51). High doses are useful in treating depression and lead to an improvement in overall anxiety and depression scores (11,30–32). Depressed patients also report insomnia, increased energy, reduced appetite, and increased aggressive feelings (11,29,30,41). Normal subjects given L-deprenyl show changes in sleep patterns but little effect on mood (53).

There have been surprisingly few behavioral studies with animals administered L-deprenyl. Studies with rats have reported increased behavioral activity (9,26,27). However, the effect was only at high doses (10 mg/kg or higher). L-Deprenyl is a specific MAO-B inhibitor in rats only at low doses; at high doses, there is also inhibition of the A form (38). In studies using doses that are selective for MAO-B, L-deprenyl did not produce changes in activity in mice and rats except when used in combination with phenylethylamine (PE) (9, 35,54). Another effect of low doses is an increase in sexual behavior in young and aged male rats (24,25).

The present study was aimed at characterizing some of the behavioral effects of L-deprenyl in the dog. Dogs were studied as part of an ongoing project aimed at evaluating possible veterinary applications for deprenyl in pet dogs. In addition, because L-deprenyl is primarily used clinically in Parkinson's patients it is important to study its action in animal models other than the rodent. For example, compared to the rat neuromelanin granules in the dog substantia nigra are five or more times larger (13). Because our primary aim was to evaluate the effect on spontaneous behaviors, and because there is evidence of species-specific effects [e.g., in the monkey, L-deprenyl causes a dose-dependent decrease in vocalization (34)], we developed a modified open-field procedure (17). Dogs were placed in a test room for 10-min periods and a computer program was used to continuously monitor total movement, urination, sniffing, grooming, inactivity, rearing, jumping, and vocalizing.

METHOD

Subjects

The study was performed on 22 beagles (12 female, 10 male) obtained from Marshall Farms (North Rose, NY) and 5 mixed-breed dogs (2 male, 3 female) obtained from Laka Biological Supply (Basille-le-grand, Quebec). All but two animals had been in the colony for at least 6 months; those two had arrived 1 month prior to the experiment. Beagles ranged in age from 1.5–10 years, while the ages of the mixed-breed

[1] To whom requests for reprints should be addressed.

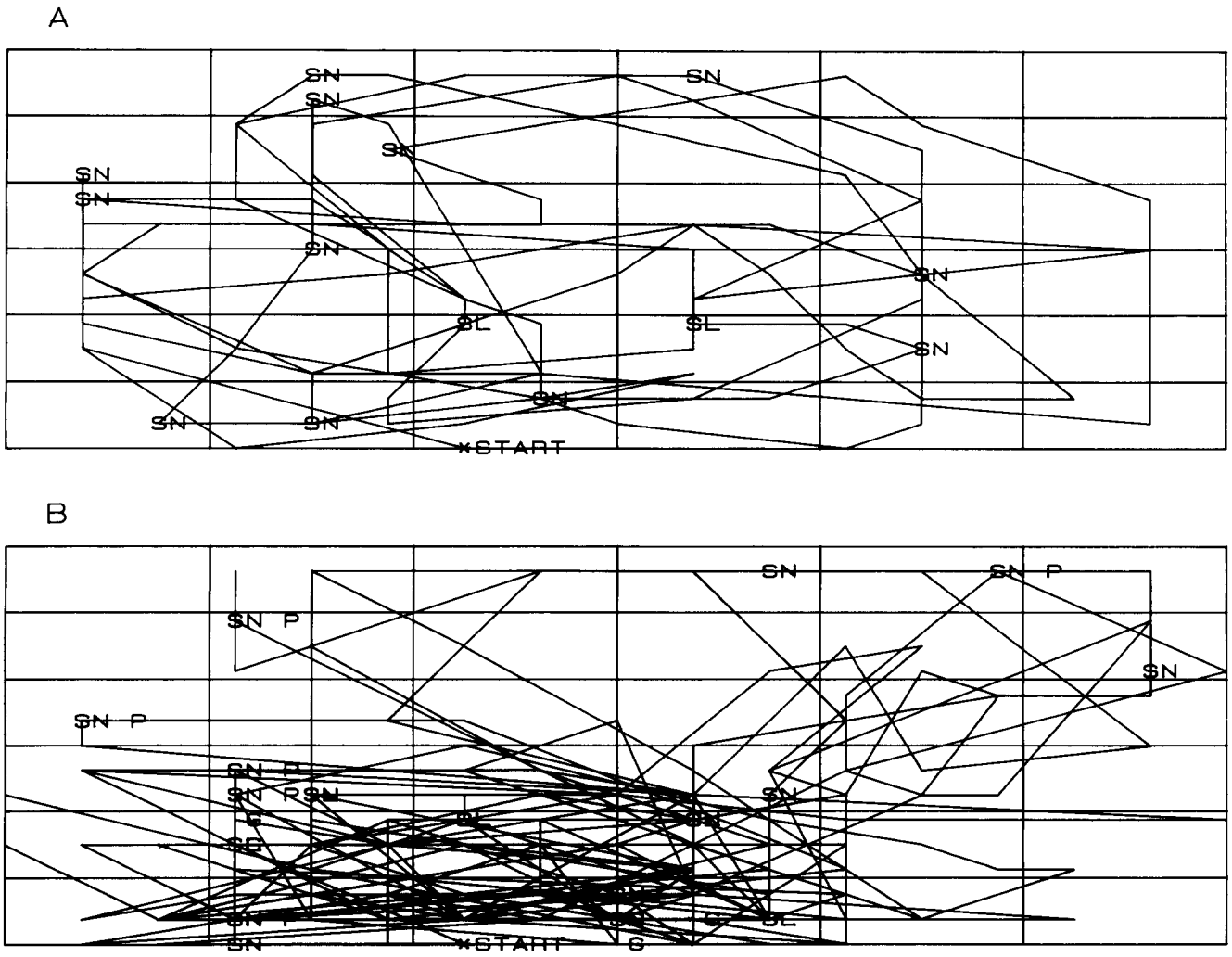

FIG. 1. Computer-assisted reproduction of pattern of spontaneous behavior observed in two dogs during baseline test. (A) is from a mixed-breed dog, while (B) is from an old male beagle. Symbols illustrate location of observed behavior. The line drawing shows all locomotor movements made during the session. The figure illustrates the kinds of individual differences typically observed. (P), urination; (SN), sniffing; (SL), sleep; (G), groom.

dogs were estimated on the basis of dentition by the staff veterinarian to range from 6–10 years.

Animals were individually housed in 1.07 × 1.22-m pens and were maintained on a 12 L : 12 D cycle. The humidity was kept at 40–60% and the temperature at 22–24°C. Pens were washed daily between 8:00 and 10:00 a.m., during which time animals were exercised for 15 min. Water was available continuously from an automatic watering device. Animals were given approximately 300 g Purina Dog Chow for 1 h daily from 2:30–3:30 p.m.

Test Procedures

Animals were placed in a standard testing room, 3.66 × 3.66 m containing a sink, cupboard, and an examining table. The floor was marked into 61 × 61-cm squares with black electrical tape to assist in localizing the spatial position of the animal. Prior to each test session, the floor was thoroughly cleaned with a detergent solution to prevent a behavioral re-

TABLE 1

TEST-RETEST CORRELATIONS FOR ACTIVITY MEASURES

Behavioral Measure	Correlation
Grooming (time)	0.8724*
Total distance (ft)	0.8699*
Urination (frequency)	0.7481*
Sleep (total time)	0.7943*
Sniffing (frequency)	0.5598
Jumping (frequency)	0.9454*
Vocalization (frequency)	0.7785*
Rearing (frequency)	0.7064†

$N = 15$.
*$p < 0.001$ (one tailed).
†$p < 0.01$ (one tailed).

TABLE 2

CORRELATION MATRIX OF DIFFERENT MEASURES USED IN ACTIVITY TEST

	Correlations						
Behavioral Measure	Urine	Sniffing	Groom	Inactive	Rearing	Vocal	Jump
Distance	0.0563	0.2942	−0.2411	−0.6357*	0.1565	0.1998	0.4102
Urination frequency		0.0057	−0.1601	−0.1987	−0.1408	−0.2071	−0.1475
Sniffing frequency			−0.0968	−0.3586	0.1819	−0.0183	−0.1175
Time spent grooming				0.0169	−0.0784	0.1260	−0.0602
Time spent inactive					−0.2509	−0.1829	−0.1114
Rearing frequency						0.2254	0.1856
Vocalization frequency							0.1083
Jumping frequency							

$N = 30$.
*$p < 0.001$ (one tailed).

sponse to the odor of other dogs. Observations were recorded from an adjoining room through a glass window. All testing was done by the same technician. Data acquisition was controlled by software written in the ASYST programming language (Asyst Software Technologies). Prior to the start of each session, an outline of the test room was drawn on the screen and the cursor was positioned to the start point. All movements of the dog could then be followed using a mouse. Feedback was provided by the monitor, which displayed the pattern traced with the mouse. At 2-s intervals, the current x,y coordinate position of the animal in the room was stored in a data file. Other behaviors were recorded by pressing seven function keys that were programmed for: 1) exploratory sniffing—sniffing directed at a specific object or location and intended to provide a measure of general exploration; 2) inactivity, which included sitting, resting, and sleeping; 3) vocalization, defined in terms of discrete episodes rather than single barks; 4) jumping; 5) rearing; 6) urination; 7) grooming. For the measures of inactivity and grooming, both the frequency of occurrence and total time were recorded.

One group of 15 animals was given a control session 3–4 weeks before the start of the experiment that was used to assess test-retest reliability. For the experiment, each animal was tested twice: first, 2 h following administration of an empty capsule and 1 week later a second test 2 h following administration of deprenyl.

To obtain equal numbers of animals per dose, eight animals were randomly selected for retesting at either of two doses: 3 or 5 mg/kg. In each case, there was a minimum 3-week washout period between tests (49,54). In the data analysis, these animals were treated as independent cases.

The crystalline form of the drug was placed in gelatin capsules (Parke-Davis #2) and administered orally after animals had been fasted for 18–20 h. Dose levels of L-deprenyl were: 0.1, 0.25, 0.75, 1.25, 2.0, 3.0, and 5.0 mg/kg. Five animals were treated at each dose, and selection of animals was done in a manner that counterbalanced for sex, age, and breed such that each group included one of each: young male, old male, young female, old female, and one mixed-breed animal.

Statistical analysis was carried out with the use of analysis of variance (ANOVA) procedures employing the SPSSPC statistical package. Main effects of dose levels and interaction effects of sex and age were of interest. Cochrane's univariate homogeneity of variance test was also applied to ensure the assumptions for ANOVA were met. The assigned scores in testing drug effects were difference scores calculated by the subtraction of baseline scores from treatment scores. The level of significance was set at 0.05.

RESULTS

Baseline Activity

Test-Retest Reliability. To obtain a qualitative assessment of behavior, the movement pattern reconstructions were made by a plotter and taken from the raw data files collected during the test session. There were surprisingly large differences in the activity patterns shown by different subjects (Fig. 1). Not only were there differences in locomotor movement but also in the frequency of occurrence of other recorded activities. Thus, only some dogs showed frequent vocalization and only some frequent urination. To determine the extent to which such differences reflected individual differences in behavior patterns, correlation coefficients were determined for each of the measures between the two baseline sessions for 15 animals. The results shown in Table 1 illustrate that there were high positive correlations for every measure, and all but one were significant at the 0.01 level.

Interitem Correlations. To determine the interrelationship between the items, correlations were determined between each

TABLE 3

BASELINE ACTIVITY SCORES AS A FUNCTION OF SEX (MEANS AND SD)

Measure	Males (n = 13)	Females (n = 17)
Grooming (seconds)	4.57 ± 7.54	13.69 ± 38.56
Total distance (ft)	1,133.1 ± 669.7	1,141.6 ± 419.0
Urination (cases)	2.54 ± 2.73	0.71 ± 0.85*
Inactivity (seconds)	69.1 ± 105.6	20.2 ± 46.3†
Sniffing (cases)	10.0 ± 5.12	13.53 ± 6.66‡
Jumping (cases)	1.38 ± 4.11	2.41 ± 4.8
Vocalization (cases)	3.77 ± 5.28	4.71 ± 5.43
Rearing (cases)	2.15 ± 3.99	4.64 ± 4.98

*$t = 2.67, p = 0.012$.
†$t = 1.71, p = 0.098$.
‡$t = 1.87, p = 0.07$.

TABLE 4

BASELINE ACTIVITY SCORES AS A FUNCTION OF AGE (MEANS AND SD)

Measure	Young Beagles (n = 10)	Mature Beagles (n = 14)	Pound Dogs (n = 5)
Grooming (seconds)	22.73 ± 49.1	3.85 ± 1.28	1.80 ± 2.8
Total distance (ft)	1,188 ± 537	1,291 ± 353.6	536 ± 179.1
Urination (frequency)	1.30 ± 1.95	1.71 ± 1.54	0.6 ± 0.89
Inactivity (seconds)	365.5 ± 50.8	0.161 ± .060	116.5 ± 107.8
Sniffing (frequency)	13.40 ± 5.97	12.71 ± 6.64	6.60 ± 3.43
Jumping (frequency)	4.20 ± 6.43	0.86 ± 2.93	1.00 ± 2.24
Vocalization (frequency)	6.90 ± 5.09	2.86 ± 5.08	4.00 ± 5.66
Rearing (frequency)	6.10 ± 5.38	2.86 ± 4.38	1.20 ± 1.79

pair of measures. The correlations were based upon data from 30 animals and are summarized in Table 2. The only significant correlation was a negative relationship between inactivity and total locomotion.

Sex Differences. Table 3 provides a summary of the baseline data broken down by sex. The only difference that achieved statistical significance was in frequency of urination, $t(28) = 2.70$, $p < 0.012$: Male dogs were more likely to urinate in the test room than were females.

Age Differences. To test for age effects, young beagles (1.5–2.2 years) were compared to old beagles (6–10 years). The mixed-breed dog data was excluded to remove any variability due to breed. In addition, one beagle was removed from the data analysis because its age was unknown. The only significant result, surprisingly, was that young beagles spent a significantly greater amount of time inactive, $t(23) = 2.47$, $p < 0.021$. These data are summarized in Table 4. Table 4 also shows that mixed-breed dogs tended to show less total movement (distance) than beagles. It was not clear, however, whether this was an age or breed effect.

Effect of L-Deprenyl

Three measures—locomotion, sniffing, and urination—were sensitive to L-deprenyl. For locomotion, a two-way ANOVA revealed a significant dose × sex interaction, $F(6) = 2.63$, $p < 0.046$. The origins of this can be seen in Fig. 2; females showed increased locomotion at doses of 3

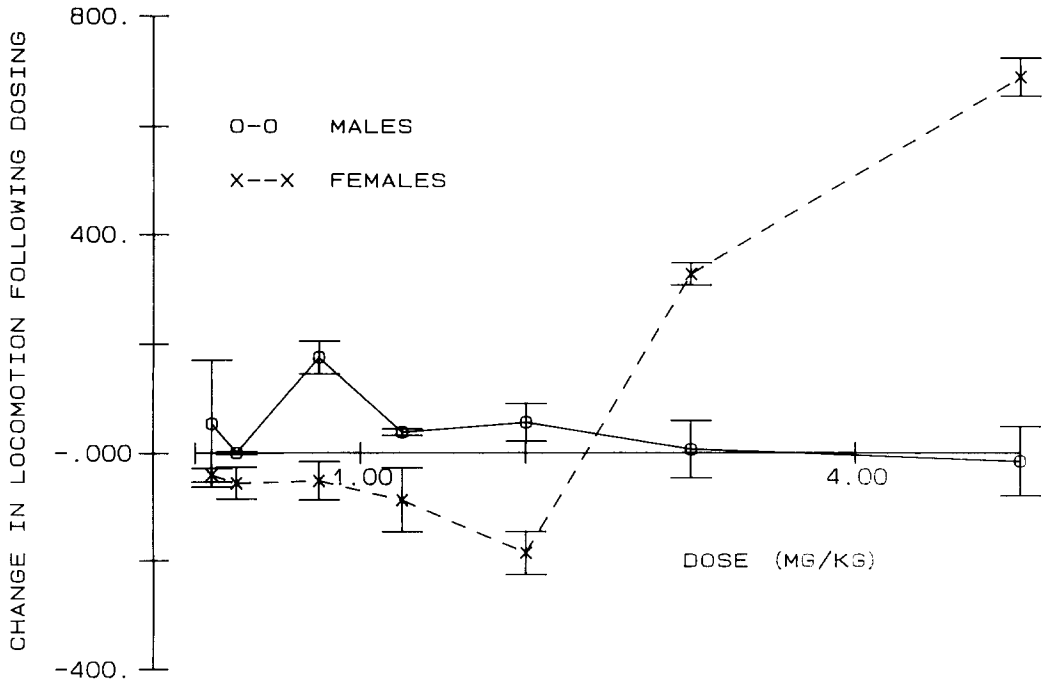

FIG. 2. Difference score calculated by subtracting posttreatment distance score from baseline distance score (change in locomotor activity) on the y-axis is plotted as a function of dose of L-deprenyl. Results for females and males are plotted separately and illustrate a dose-dependent increase in activity in females but not males. Error bars represent standard errors.

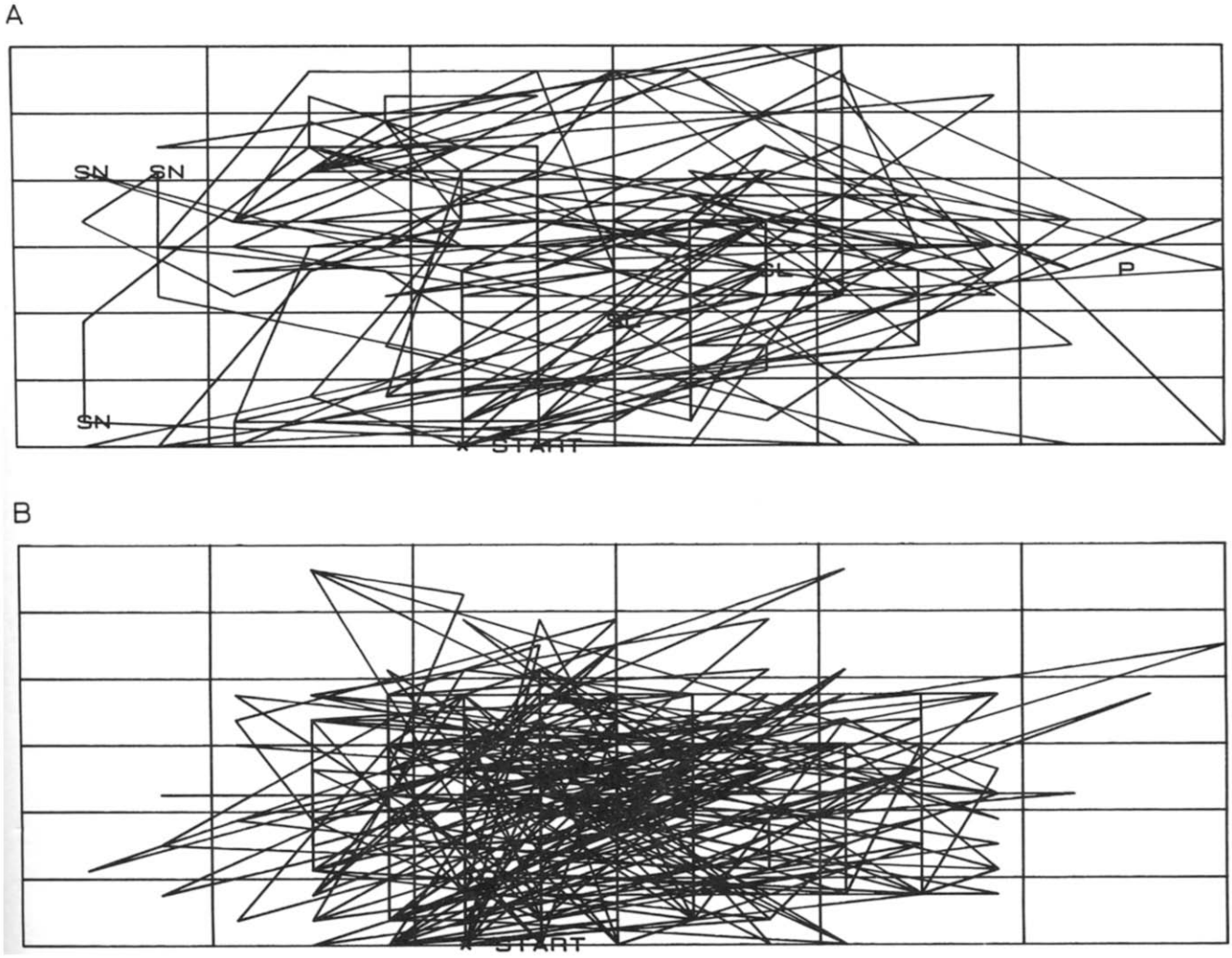

FIG. 3. Baseline (A) and postdrug (B) activity patterns for a female beagle given a high dose of L-deprenyl (5 mg/kg). Symbols are as in Fig. 1. Restriction of movement to one part of the room during the postdrug test is a result of continuous circling behavior. Note also that on the postdrug test there was a decrease in nonlocomotor activities.

and 5 mg/kg while there was no consistent change in males. Examination of activity patterns indicated that the increased locomotion was typically accompanied by a decrease in behavioral variability. The two most dramatic cases were two females that had shown repetitive circling, one of which is shown in Fig. 3. Similar but less dramatic changes in activity patterns at high doses were also noted for males (Fig. 4).

The second effect of L-deprenyl was a decrease in the frequency of urination in males after 3 and 5 mg/kg (Fig. 5). A two-way ANOVA yielded a significant decrease in urination, $F(6) = 2.67, p < 0.044$. However, in this test the assumption of homogeneity of variance could not be met. The distribution was negatively skewed because of the low frequency of urination in female dogs.

The third behavior that changed following treatment with L-deprenyl was sniffing frequency, which showed a significant decrease at high dose levels, $F(6) = 3.01, p > 0.028$, in both sexes (Fig. 6).

DISCUSSION

The results show that there is a dose-dependent effect of deprenyl on behavior. At 2 mg/kg or higher, L-deprenyl produced changes in locomotion, urination, and sniffing. An increase in locomotion was seen only in females, a decrease in urination was seen only in males, and, finally, a decrease in sniffing was seen in both sexes. Although there was an increase in locomotion at high doses, this did not appear to reflect increased exploratory behavior. To the contrary, there was a significant dose-dependent decrease in directed sniffing that suggested exploratory behavior was decreased following treatment with L-deprenyl. This distinction between activity and exploration was also indicated in reconstructions of the movement patterns, which showed repetitive circling, most notably from females. This response is characteristic of a behavioral stereotypy that can be defined as abnormal, repetitive, purposeless motor behavior (55).

Observations of males also suggested that higher doses

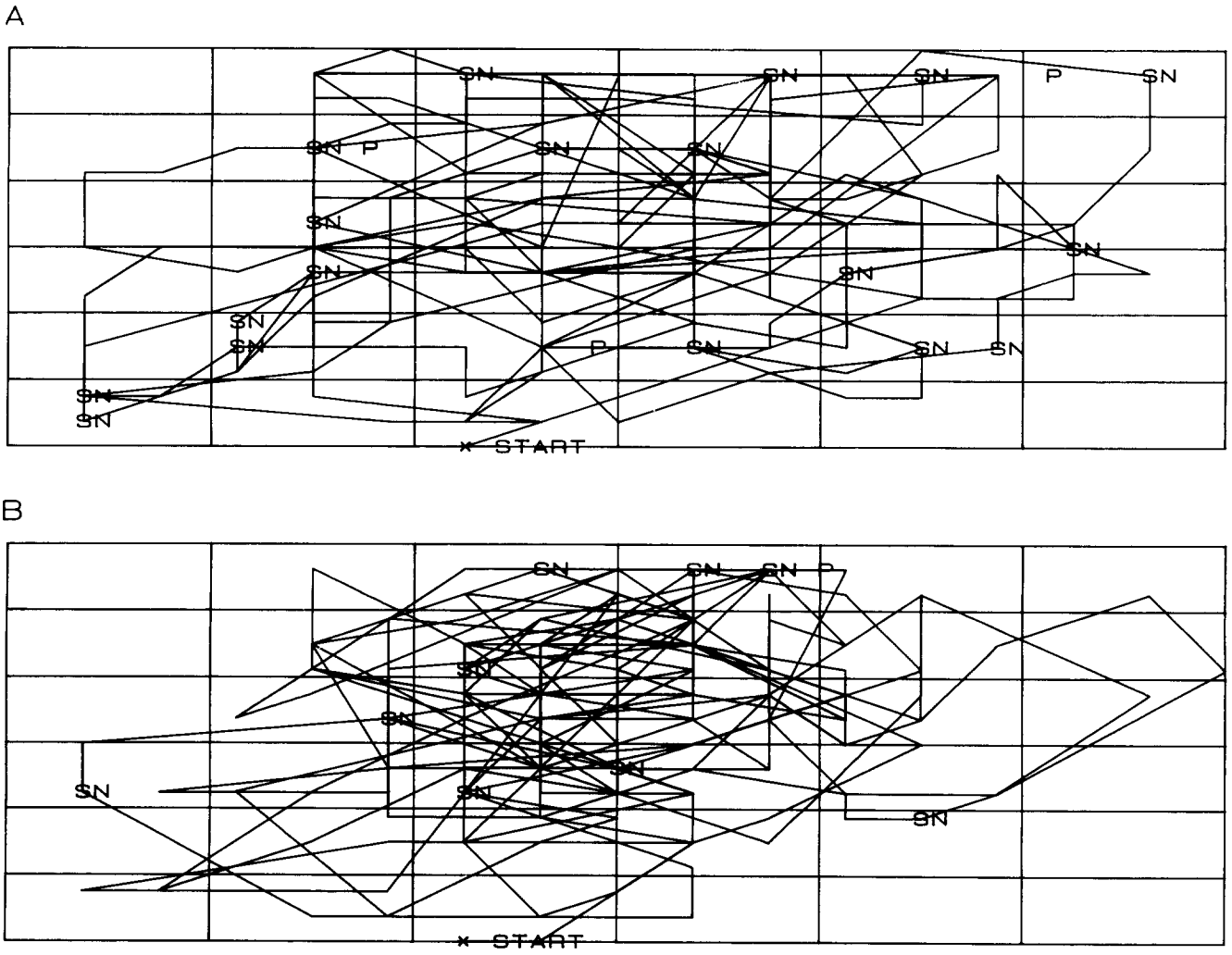

FIG. 4. Reconstruction of movement pattern shown by male beagle prior to (A) and following (B) a 5-mg/kg dose of L-deprenyl. Symbols are as in Fig. 1. Note that following drug movement was restricted to a smaller area of the room. Note also the decrease in frequency of urination and sniffing.

caused a decrease in exploration and other goal-directed activities. At higher dose levels, movement was restricted to a smaller portion of the test room, directed sniffing frequency was decreased, and urination frequency was decreased. The decrease in urination was particularly interesting in light of the role of urination in this species in sexual attraction and territorial demarcation (15).

It is important to emphasize that the test procedure detected behavioral changes because a methodology was developed to sample from a range of normal behaviors rather than activity per se. In most of the work on the effects of L-deprenyl on activity in the rat, activity was measured automatically using a procedure that would not distinguish locomotion from rearing, sniffing, or jumping. Thus, the present results may not be incompatible with data obtained from other species when an automated testing procedure was used.

The pharmacological basis for the changes in spontaneous behavior following L-deprenyl may be explained in three possible ways. First, the behavioral changes may reflect increased striatal levels of PE resulting from inhibition of MAO-B (8,9,44–46,57). It has also been suggested that PE may act as a dopaminergic agonist (1,7,8,12,21,36,37,39). This suggestion is consistent with evidence that both dopamine and PE produce an increase in arousal and activity (9,10,14,33,35). PE causes an early increase in activity and a later stereotypical behavior in the rat (9,33,35) and the mouse (14,20). L-Deprenyl, in conjunction with PE, results in a decreased threshold for PE-induced stereotypy and a prolongation of this activity (9,35,54).

The second possibility is that high doses of L-deprenyl may lead to an increase in brain dopamine levels (18,23,44). If so, this would probably reflect an effect of high doses of L-deprenyl on MAO-A activity. At doses of 1 mg/kg or lower, L-deprenyl causes inhibition of only MAO-B and does not affect brain dopamine levels (N.W. Milgram et al., unpublished data). The effects of high doses of L-deprenyl in the dog are unknown; however, as previously mentioned in the rat, high doses inhibit MAO-A activity (38).

Finally, the behavioral changes may be a response to the metabolites of L-deprenyl, methamphetamine, and amphet-

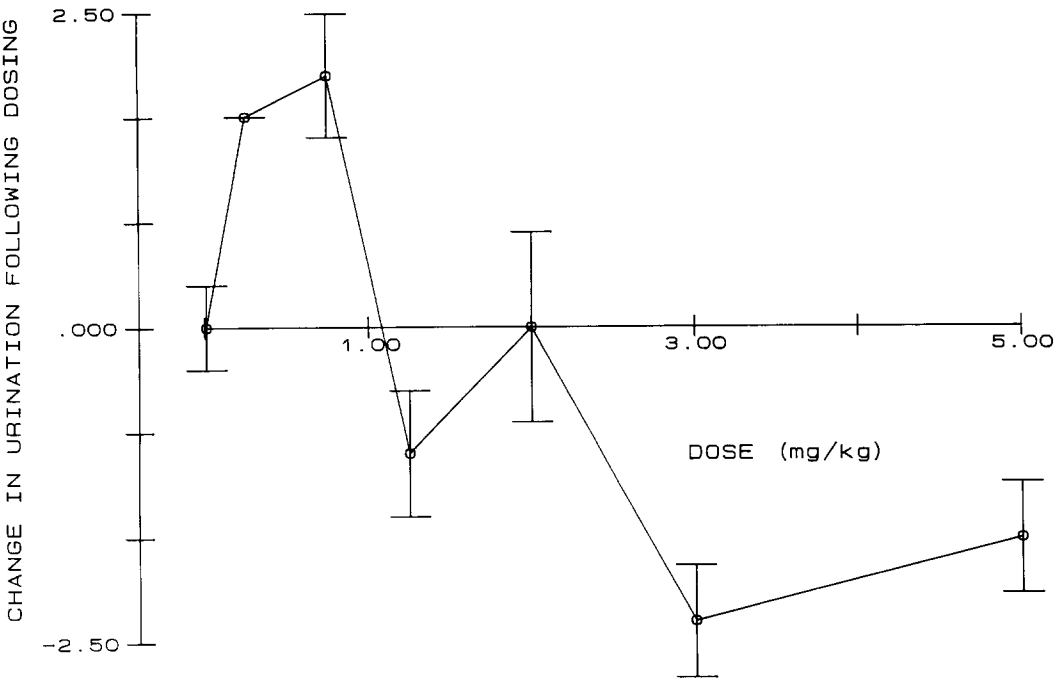

FIG. 5. Effect of L-deprenyl on urination in male dogs. Dose of L-deprenyl is plotted against difference in urination, which was calculated by subtracting baseline from postdrug score. Note decrease in frequency of urination following dosing at 3 and 5 mg/kg.

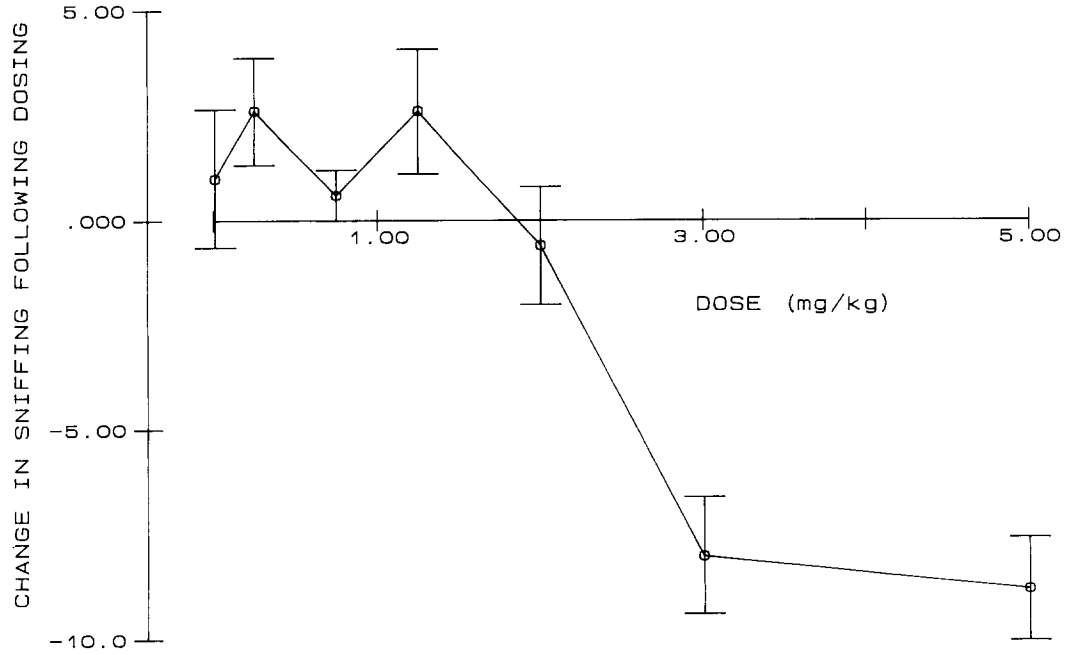

FIG. 6. Frequency of sniffing as a function of dose of L-deprenyl. Data is for both sexes combined. The *y*-axis is difference between baseline and postdrug score. Sniffing was recorded when it was directed toward some object or part of the test room. As shown, high doses of L-deprenyl decreased exploratory behavior.

amine (43,44,58). The behavioral response to amphetamine has been studied in rats (42,48), mice (12,19), and dogs (3,4,55,56) and, characteristically, responses to amphetamine include increases in activity that accelerate into stereotypical behavior. In dogs, these meaningless, repetitive movements are seen as circling, head-bobbing, head-wagging, and freezing (55). Because the amphetamine metabolite of L-deprenyl is the L isomer, the importance has tended to be deemphasized. However, the D and L isomers have been directly compared in the dog and it was found that the D isomer was only about 1.5 times more effective than the L form in inducing stereotypical behavior (55) and in serving as a reward for intravenous self-administration (47). In addition, the L form of amphetamine has proven effective in calming aggressive and hyperkinetic dogs (2). At present, there are no grounds for ruling out any of these three possibilities.

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