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Effects of Chronic Amphetamine in BALB/cBy Mice, a Strain That is not Stimulated by Acute Administration of Amphetamine

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LOGAN, L., T. W. SEALE, W. CAO AND J. M. CARNEY. *Effects of chronic amphetamine in BALB/cBy mice, a strain that is not stimulated by acute administration of amphetamine.* PHARMACOL BIOCHEM BEHAV **31**(3) 675–682, 1988.—The effects of d-amphetamine and methylphenidate on locomotor activity of BALB/cByJ mice were evaluated. d-Amphetamine had no effect or inhibited locomotor activity at acute doses of up to 10 mg/kg while methylphenidate stimulated locomotor activity at acute doses between 10 and 32 mg/kg. The dose-response curves for methylphenidate and d-amphetamine appeared to be quantal in nature. During a 21-day chronic treatment with 10 mg/kg d-amphetamine no evidence of tolerance to the depressant effects of relatively high doses of d-amphetamine was observed. However, a 3.2 mg/kg dose of d-amphetamine, which acutely inhibited locomotor activity, was found to stimulate locomotor activity following chronic amphetamine treatment. Doses of methylphenidate which acutely stimulated activity were without effect in mice chronically receiving amphetamine. Although the mechanism underlying these behavioral effects has yet to be established, our results indicate that inherent alterations can differentially affect both acute and chronic susceptibility to the behavioral effects of amphetamine and methylphenidate. Use of such altered strains of mice can be especially revealing of subtle behavioral effects brought about by chronic drug treatment which are not readily demonstrated following acute administration of amphetamine.

BALB/cByJ Inbred mice Locomotor activity d-Amphetamine Chronic treatment Methylphenidate

AN interesting feature of the pharmacology of d-amphetamine is the sensitization of behavioral responsiveness upon repeated exposure to the drug. This phenomena has recently been reviewed (15). Behavioral sensitization has been reported to occur with several monitored behaviors and following a variety of injection schedules. The pertinent feature of sensitization is that an enhanced response to d-amphetamine is seen days to weeks following the initial dose or doses of d-amphetamine. The enhanced response may be an increase in the intensity of the behavior, decreased time to onset or shift to the left of the dose response curve. There is an apparent sensitization of dopaminergic receptor systems and the possible mechanisms underlying the phenomenon of sensitization have been discussed (15). The timing of d-amphetamine administration as well as the dosage may influence the behavioral and neurochemical consequences of repeated d-amphetamine exposure (5, 12, 15).

Inbred strains of mice have provided evidence for genetically determined differences in responsiveness to d-amphetamine. The majority of these studies have utilized locomotor activity as the monitored behavior. The A/J strain of mice shows greater stimulation of locomotor activity when given d-amphetamine than the C57BL/6J and DBA/2J strains of mice (3). It was shown in a later study that the drug-induced increases in activity in these three strains were inversely proportional to the control level of activity (2). The stimulant effects of d-amphetamine were augmented by presession foot shock in the A/J and DBA/2J strains, while in the C57BL/6J strain the effects of d-amphetamine were slightly reduced (2). The C57BL/6By strain has been shown

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TABLE 1
DOSING SCHEDULE AND THE NUMBER OF MICE RECEIVING EACH DOSE

	Acute Injection			Chronic Injection*				
	Week 1	Week 2	Week 3	Day 6	Day 12	Day 15	Day 18	Day 21
Saline	12	12	12	12	12	—	11	6
d-Amphetamine								
0.01	—	6	—	—	—	—	—	—
0.03	—	6	6	—	4	—	—	—
0.10	6	—	6	6	4	—	—	—
0.32	6	—	6	—	4	—	6	—
1.0	6	—	6	6	4	—	6	—
3.2	6	—	6	—	4	32	6	—
10.0	6	—	6	—	—	—	—	—
Methylphenidate								
0.3	—	6	—	—	—	—	—	—
1.0	—	6	—	6	—	—	—	4
3.2	—	6	—	—	—	—	—	4
10.0	6	—	—	6	—	—	—	6
32.0	—	6	—	—	—	—	—	4

*Test days during chronic d-amphetamine (10 mg/kg/day). The day number refers to the day of chronic dosing on which the test is determined. Test injections were also given 7 and 14 days following cessation of chronic d-amphetamine treatment on day 21.

to exhibit increases in locomotor activity with increasing doses of d-amphetamine while the BALB/cBy strain exhibited decreases (11). By the use of a series of recombinant inbred lines derived from BALB/cBy and C57BL/6By strains, responsiveness to the stimulant effects of d-amphetamine was shown to be a polygenetically determined trait (11). The trait of decreased activity in response to d-amphetamine seen in the BALB/cBy strain has been shown to be recessive to the stimulation seen in the C57BL/6 strain (8). The functional basis for such differences in responsiveness to d-amphetamine remains unknown.

In the course of further investigation of d-amphetamine effects on locomotor activity in several inbred strains of mice, we confirmed that the BALB/cBy strain of mice was not stimulated by d-amphetamine and that d-amphetamine administration decreased locomotor activity in this strain. It was of interest to determine what the effects of a chronic course of d-amphetamine administration would be, i.e., whether tolerance to the depressant effects or induction of behavioral facilitation would occur in this strain of mouse which lacks the usual acute responsiveness to d-amphetamine. In this article we report that tolerance to the depressant effects on locomotor activity of a 10 mg/kg dose of d-amphetamine does not develop following up to 21 days of treatment. However, the qualitative effects of d-amphetamine were altered. Instead of its acute depressant action, 3.2 mg/kg d-amphetamine stimulated locomotor activity following chronic dosing. Responsiveness to the stimulatory effects of methylphenidate also changed following chronic d-amphetamine administration but this change was opposite to that of d-amphetamine.

METHOD

Subjects

Ten-week-old male mice of the BALB/cByJ inbred strain, obtained from Jackson Laboratory, Bar Harbor, ME were housed in groups of 6 animals per cage on a continuous 12-hour light-dark cycle under constant humidity and temperature (21–23°C). The designation BALB/cBy will be used throughout this manuscript. Animals were drug naive at the beginning of the study. The litter used aspen wood chips (Sani-chips, P. J. Murphy). Free access to a standard rodent pellet food (Lab/Blox, Wayne) and water was given.

Locomotor Activity Measurement

Locomotor activity was monitored in twelve activity chambers. Each activity chamber consisted of a 2-foot diameter circular arena, 10 in. high, equipped with two photocell detectors. Each detector was illuminated by a 25-W light bulb (General Electric, No. 25R14N) placed outside the arena with the light beam directed through a 1/2 in. hole in the side of the arena. To minimize background light, each bulb was housed in a metal box. The two bulbs were the only source of lighting within the chamber. A Rockwell AIM65 microprocessor system was used for data acquisition. Data for each 1-hour activity session were recorded in six 10-minute interval periods.

Drug Administration and Chronic Dosing Schedule

The following activity monitoring and dosing schedule is summarized in Table 1. d-Amphetamine sulfate (NIDA

Psychotomimetics Committee) and methylphenidate hydrochloride (CIBA-Geigy, Summit, NJ) were dissolved in saline and all injections were given intraperitoneally at a volume of 0.1 ml/10 g body weight immediately prior to the animal being placed in the locomotor activity chamber. Dosages refer to the salt. For four days of the first three weeks the mice were not injected and placed into the locomotor activity chambers for one hour sessions to allow adaptation to the chambers. One group of mice served as saline controls throughout the course of the study. Dose response curves for d-amphetamine and methylphenidate were generated on the fifth day of the first three weeks.

Chronic dosing with 10 mg/kg of d-amphetamine began on the last day of the third week. Daily 1-hour locomotor sessions were conducted during the chronic dosing. On days 6, 12, 15 and 18 of chronic treatment, test doses of d-amphetamine were given to determine the effects of chronic d-amphetamine administration. Test doses of methylphenidate were given on days 6 and 21 of chronic d-amphetamine treatment.

From day 22 to 35 daily injections of saline were given to all mice in the study and activity sessions were conducted. On days 28 and 35 the mice that had been chronically treated with d-amphetamine were given 3.2 mg/kg d-amphetamine. We originally intended to repeat dosing conditions in the same groups of mice, however, mortality of amphetamine-treated mice and the rearrangement of mice to maintain similar group size precluded this possibility.

Stereotyped Behavior Evaluation

Assessment of stereotyped sniffing, gnawing and cage climbing was conducted in a wire mesh cage (1/4 inch galvanized hardware cloth, 12×7×7 inches) as we have described previously (17). Cage climbing activity was determined quantitatively by measuring the amount of time an individual had all four feet off the bottom of the cage, i.e., was positioned on the cage side or hanging from the wire on the roof of the cage. Climbing times were determined in 5-minute increments for 30 minutes after the introduction of the animal into the cage. Control values were determined in each mouse prior to IP injections of freshly prepared d-amphetamine solution (10 mg/kg). Measurement of cage climbing activity, sniffing and gnawing stereotyped activities described below were initiated immediately after injection in previously untreated animals. We attempted to objectify the scoring of stereotyped gnawing and sniffing (each scored concurrently with cage climbing) and to assign a numerical score to the behavioral activity according to the following scheme: (0) no stereotyped behavior noted during the scoring interval; no qualitative change from basal activity; (1+) stereotypy present intermittently and infrequently (1/3 of scoring interval); (2+) stereotypy present frequently (2/3 of scoring interval) but not continuously; (3+) stereotypy present in exaggerated form and present continuously during the scoring interval. Animals were scored in 5-minute increments for 30 minutes.

Statistical Analysis

One-hour cumulative locomotor activity counts, cumulative activity counts at each 10-minute time point and 10-minute interval activity counts were compared to respective saline control activity counts by one way analysis of variance (STAT, Matrix Software, Big Rapids, MI). A p value less than 0.05 was considered significant.

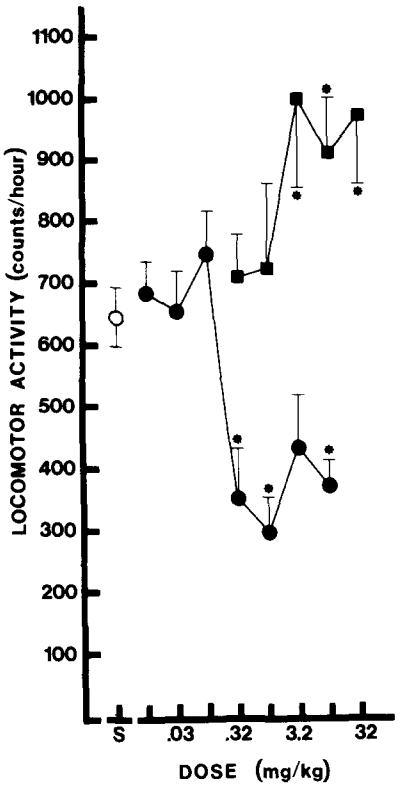

FIG. 1. Dose-response curves for the acute effects of d-amphetamine and methylphenidate on locomotor activity in BALB/cBy mice. The saline point (s) represents the mean 1-hr locomotor activity of 24 observations. The points for the d-amphetamine (●) and methylphenidate (■) doses represent the mean of 6 animals. Vertical lines represent SEM and asterisks denote significant ($p<0.05$) difference from saline data when compared by analysis of variance.

RESULTS

Evaluating Habituation

During initial exposure to the locomotor activity chambers, the BALB/cBy mice showed no evidence of habituation to the chambers based on activity counts obtained from the 12 noninjection days. The mean activity ±S.E.M. of the eight groups of mice on these days ranged from 667±42 to 769±50 activity counts/hr. These values were not statistically different. The 1-hour activity counts of the mice that received saline injections (646±47) on the days of acute drug testing (Table 1) were not significantly different from noninjection values. Also, based upon the interval counts obtained from the first 2 saline injections, the BALB/cBy mice showed no evidence of within session habituation to the activity chamber since the initial 10-min activity values were similar to the terminal 10-minute levels of activity (see control data shown in Fig. 2).

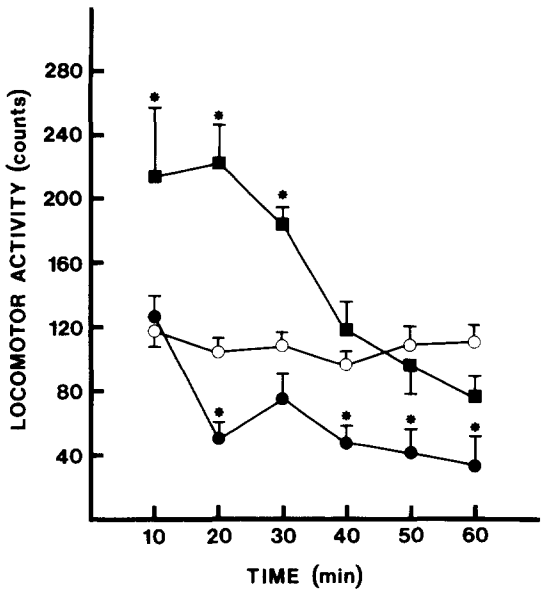

FIG. 2. Effects of 10 mg/kg d-amphetamine (●) and methylphenidate (■) on locomotor activity of BALB/cBy mice. Each point represents the mean locomotor activity of 6 (drug) or 24 (saline) mice during 10-minute intervals of the activity session. Vertical lines represent SEM and asterisks denote significant ($p<0.05$) difference from saline (○) data when compared by analysis of variance.

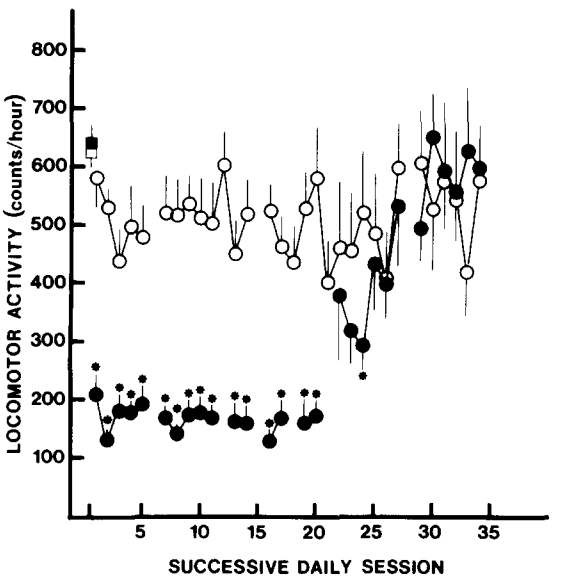

FIG. 3. One-hour cumulative locomotor activity counts of BALB/cBy mice receiving daily saline (open symbols) or 10 mg/kg d-amphetamine (closed symbols) injections. Succession daily session days refer to the day of chronic d-amphetamine treatment as presented in Table 1 and in the Method section. Vertical lines represent SEM and asterisks denote significant ($p<0.05$) difference from saline values. Chronic administration of 10 mg/kg d-amphetamine was discontinued on day 21 and these subjects were given daily saline injections until day 35.

Acute Drug Administration

The results of acute exposure to d-amphetamine and methylphenidate in BALB/cBy mice are shown in Fig. 1. d-Amphetamine doses of 0.01 to 0.1 mg/kg had no significant effect on locomotor activity. Doses of 0.32 to 10 mg/kg d-amphetamine produced significant decreases in locomotor activity to levels that were approximately 60% of control values. The reductions in activity were not clearly dose dependent in the usual manner, but showed a nearly quantal effect, i.e., 0.1 mg/kg was without significant action but a dose of 0.32 mg/kg produced maximal inhibition. The 3.2 mg/kg dose of d-amphetamine did not produce a significant reduction in locomotor activity. In contrast to the depression of locomotor activity seen with d-amphetamine, methylphenidate induced increases in activity at higher doses. Methylphenidate doses of 0.32 and 1.0 mg/kg had no significant effect on locomotor activity. However, locomotor activity of treated animals following doses of 3.2, 10 and 32 mg/kg was significantly higher (approximately 145%) than control values. These increases in locomotor activity were atypically related to dosage since they too appeared quantal, i.e., 1.0 mg/kg produced no effect while 3.2 mg/kg produced a maximal stimulation.

The activity obtained during each 10-minute interval of the activity session is shown in Fig. 2. Methylphenidate, 10 mg/kg, produced significant increases in activity in the 1st, 2nd and 3rd intervals while the activity in the last half of the session was comparable to that found in saline-treated animals. Except for the initial interval, activity following 10 mg/kg administration of d-amphetamine was less than that of saline controls with the difference being significant in the 2nd, 4th, 5th and 6th 10-minute intervals.

Chronic Drug Administration

To investigate whether chronic administration of d-amphetamine led to differences in sensitivity of behavioral responses to subsequent doses of d-amphetamine and methylphenidate, we evaluated the effects of a chronic course of d-amphetamine treatment. Since d-amphetamine failed to produce increases in behavior, a dose of 10 mg/kg was selected for chronic dosing. This dose produced large and reliable decreases in locomotor activity. Figure 3 depicts the 1-hr cumulative locomotor activity counts of mice receiving daily saline or 10 mg/kg d-amphetamine injections. The mean±SEM activity counts for the saline group ranged from 605±56 on day 12 to 401±72 on day 21. d-Amphetamine, at a dose of 10 mg/kg, produced a reduction in 1-hr activity counts. No evidence of induction of tolerance to this depressant effect was observed during the 21 days of d-amphetamine administration. The mean±SEM 1-hr cumulative activity of the mice given 10 mg/kg d-amphetamine ranged from 209±35 on day 1 to 125±23 on day 16. Expressed as percent of control activity the range of the d-amphetamine mice was from 41±6 on day 3 to 24±4 on day 16. Over the course of chronic treatment 22 mice from the 10 mg/kg d-amphetamine group and 1 mouse from the saline group died.

Chronic administration of d-amphetamine was discontinued on day 22 and all subjects were given daily saline injections until day 35. Following the discontinuation of d-amphetamine, locomotor activity values of the subjects that received d-amphetamine was comparable to those recorded for animals that had received saline injections. The only significant differences occurred on day 24 when the

TABLE 2

EFFECTS OF d-AMPHETAMINE AND METHYLPHENIDATE ON LOCOMOTOR ACTIVITY AFTER 5 DAYS OF CHRONIC d-AMPHETAMINE TREATMENT

Chronic Treatment	Test Treatment	N	Locomotor Activity: Acute Injection	Locomotor Activity: Chronic Injection (10 mg/kg/day)
saline	saline	6	652(59)[1]	717(78)
saline	1 amphetamine	6	294(61)	302(140)[2]
10amp	saline	5	—	492(83)
10amp	0.1 amphetamine	5	749(70)	388(80)
10amp	1 amphetamine	5	294(61)	191(45)[3]
10amp	1 methylphenidate	5	726(140)	478(54)
10amp	10 methylphenidate	5	916(89)	1150(171)[3]

*Values are mean 1-hr activity counts ± standard error of the mean (SEM).

†$p<0.05$ compared to chronic saline animals given saline by one-way ANOVA.

‡$p<0.05$ compared to chronic amphetamine animals given saline by one-way ANOVA.

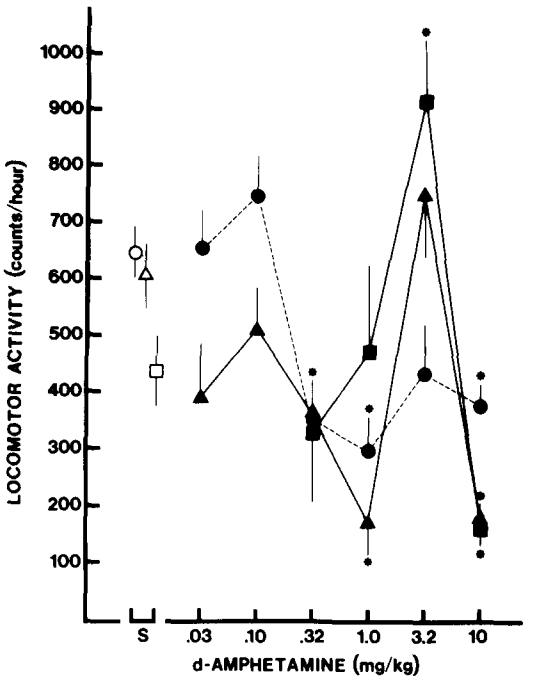

FIG. 4. Dose-response curves for the effect of d-amphetamine on locomotor activity acutely and following daily injections of 10 mg/kg d-amphetamine. Open symbols represent saline effects (○=acute; △=day 12; □=day 18) and closed symbols represent d-amphetamine (●=acute; ▲=day 12; ■=day 18). Vertical lines represent SEM and asterisks denote significant ($p<0.05$) difference from corresponding saline data when compared by ANOVA.

activity observed for the chronic d-amphetamine group was less than that observed for the saline-treated animals.

Results of Test Doses of d-Amphetamine and Methylphenidate

To assess whether chronic administration of d-amphetamine leads to alterations in the efficacy or potency of subsequent d-amphetamine doses, we investigated the effect of various d-amphetamine doses at intervals throughout the chronic treatment. The results of the test doses of d-amphetamine and methylphenidate given on day 6 of chronic treatment are shown in Table 2. The previous results obtained with these doses on acute exposure are shown for comparison. The activity levels of the chronic saline mice given saline were comparable to the results obtained with acute saline injections. The results obtained with 1 mg/kg d-amphetamine in the chronic saline mice were also comparable to the results seen when this dose was given acutely. The activity of the chronic d-amphetamine mice that received saline on day 6 did not differ significantly from that of the chronic saline group. A dose of 0.1 mg/kg d-amphetamine produced a slight decrease in activity of the chronic d-amphetamine mice in contrast to the insignificant changes observed following acute exposure. A 1 mg/kg dose of d-amphetamine produced an approximate 40% decrease in activity and this decrease is comparable to that seen with acute exposure to this dose. The 1 mg/kg dose of methylphenidate had no effect on activity of the chronic d-amphetamine mice while the 10 mg/kg dose of methylphenidate produced a significant increase that was more than double the activity of the respective saline-injected mice. This increase in activity was comparable to that seen on acute exposure to 10 mg/kg methylphenidate.

The effects of six doses of d-amphetamine on locomotor activity of mice that had received chronic d-amphetamine for 11 days are shown in Fig. 4. Since the activity levels following 10 mg/kg d-amphetamine did not appear to vary with chronic exposure, a single time point (day 11) was chosen for inclusion in the dose response curve. Although there was a trend toward reduction in locomotor activity levels following the 0.03 and 0.1 mg/kg doses of d-amphetamine, these changes were not significant. The 0.32, 1.0 and 10 mg/kg doses produced significant reductions in activity. The dose response curve was nonhomogenous in that the 3.2 mg/kg dose of d-amphetamine now had no significant effect on activity rather than reducing activity comparable to the 1.0 and 10 mg/kg doses as was noted on acute exposure to d-amphetamine.

On day 15 the 3.2 mg/kg dose of d-amphetamine was given to all mice to determine if this was a chance occurrence. The activity of the chronic saline mice on day 14 was 519±60. In these mice the activity following the 3.2 mg/kg dose of d-amphetamine was 661±194 and this increase was nonsignificant. In the chronic d-amphetamine mice the activity following the 3.2 mg/kg dose of d-amphetamine was 1057±101 and this increase was significant when compared to the saline group's activity from the previous day. It thus appears that the effect of a 3.2 mg/kg dose of d-amphetamine was reversed from depression to stimulation of locomotor activity.

On day 18 of the 0.32, 1.0 and 3.2 mg/kg doses of d-amphetamine were repeated in the chronic d-amphetamine mice and these results are shown in Fig. 4. In contrast to the significant reductions in activity seen with 0.32 and 1.0 mg/kg d-amphetamine on day 6, these doses had no signifi-

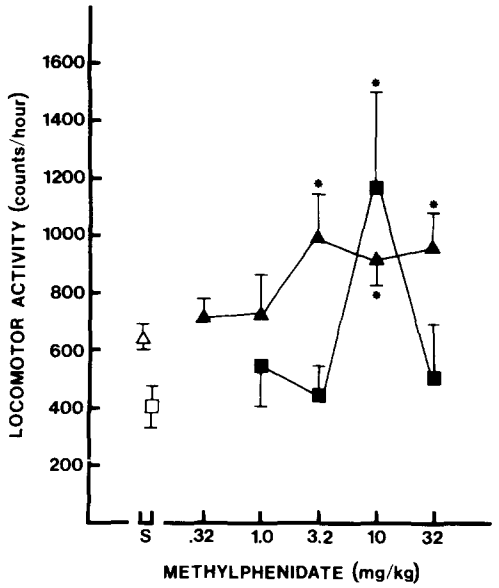

FIG. 5. Effects of methylphenidate on locomotor activity given acutely (▲) and after 21 days (■) of 10 mg/kg/day d-amphetamine. Open symbols represent corresponding saline results. Vertical lines represent SEM and asterisks denote significant ($p<0.05$) difference from saline determined by ANOVA.

cant effect on day 18. The activity of the chronic saline mice on this day was 436±63 and the activity observed following the 0.32 and 1.0 mg/kg doses was 330±122 and 471±154, respectively. The activity of mice receiving 3.2 mg/kg d-amphetamine was more than doubled compared to saline-treated mice with the activity observed being 920±115. This increase was significant.

Four doses of methylphendiate were given on day 21, and their effects before and after chronic d-amphetamine are shown in Fig. 5. The activity of the saline-treated mice on day 21 was lower than the value determined on acute exposure. On day 21 of chronic d-amphetamine treatment, the 3.2 and 32 mg/kg doses of methylphenidate did not produce significant increases in locomotor activity, in contrast to the stimulation seen with these doses on acute exposure. The 10 mg/kg dose produced a significant increase in activity compared to vehicle or to these two doses of methylphenidate. Expressed as a percent of the vehicle-treated control, the relative methylphenidate-stimulated increase in locomotor activity was significantly larger in the chronically-treated mice than in mice receiving and acute dose of methylphenidate (respectively, 295 versus 152 percent).

Chronic administration of d-amphetamine was discontinued on day 22. All subjects then received daily saline injections for two weeks. On days 28 and 35 (7 and 14 days after cessation of d-amphetamine administration), the 3.2 mg/kg dose of d-amphetamine was given to all subjects. In the animals that had received chronic saline, this dose of d-amphetamine had no significant effect on locomotor activity compared to activity of the previous day. Chronically d-amphetamine-treated animals, which had previously been significantly stimulated by this dose of d-amphetamine, no longer showed significant increases in locomotor activity when the chronic dosing had been discontinued for 7 to 14 days.

Results of Stereotypy Assessment

One possible explanation for the significant increase in the locomotor stimulating ability of d-amphetamine subsequent to its chronic administration could involve a differential depression of stereotypy rather than an actual direct enhancement of motor activity. To investigate this possibility, we attempted to determine whether the depression of motor activity was accompanied by a demonstrable increase in stereotyped behaviors. d-Amphetamine doses of 10 mg/kg provided the most interesting activity effects following chronic d-amphetamine administration. This dose given acutely depressed motor activity. For these two reasons, this dose was selected to assess acute induction of stereotypy. Four behaviors were assessed—grooming, stereotyped sniffing, stereotyped biting and stereotyped cage climbing. During the 30-minute test period following drug administration, BALB/cBy mice showed no increase in repetitive grooming behavior, biting behavior or sniffing behavior compared to controls. Fewer than 5 isolated, short-lived (5 seconds) episodes of grooming or biting occurred in control or treated animals during the test period. Sniffing, while nearly continuous in the presence and absence of the drug, showed no stereotyped pattern following d-amphetamine administration. Cage climbing, quantitated in terms of total amount of time spent in the activity during 5-minute intervals or in terms of number of individual episodes of climbing, was not significantly different from control values (3.0±1.5 minutes versus 1.5±0.8 minutes, respectively, in vehicle-treated and amphetamine-treated animals).

DISCUSSION

The results of the present study demonstrate that on acute exposure to d-amphetamine, the BALB/cBy strain of mice fails to exhibit increases in locomotor activity. Only decreases in locomotor activity are seen at higher doses of d-amphetamine. These findings confirm the results of other studies which reported that the BALB/cBy strain was not stimulated by d-amphetamine (9,10). Stereotypic behavior was not observed in response to d-amphetamine in this strain, and the decrease in locomotor activity is likely to be a direct effect of d-amphetamine rather than a substitution of one behavior for another. In contrast to the lack of stimulation or a decrease in activity in response to d-amphetamine administration, locomotor activity was increased by the administration of methylphenidate. It should be noted that both the decreases produced by d-amphetamine and the increases produced by methylphenidate did not exhibit clear, graded dose-response relationship. The responses appeared to be quantal in nature.

The finding that d-amphetamine and methylphenidate produce qualitatively opposite activity effects in the BALB/cBy strain is at variance with the results obtained in rats using the drug discrimination paradigm in which methylphenidate generalized to the d-amphetamine cue (7). Thus, our results suggest that the behavioral effects of the two stimulants are separable by mutation. d-Amphetamine and methylphenidate have been reported to differ in their effects on Y-maze activity (9). Differences in response to d-amphetamine and methylphenidate in the intact animal may reflect their differing actions on newly synthesized or storage pools of dopamine (16,19). The unusual inherited difference in response to d-amphetamine and methylphenidate may reflect neurochemical changes occurring at this level.

Although chronic treatment with daily dosing of 10 mg/kg d-amphetamine did not result in the development of tolerance to the depressant effects of this dose, alterations in the dose response curve did occur as the result of chronic administration. The changes in the dose response curve were manifested as the loss of inhibition of locomotor activity at the lower doses and the conversion of a depressant effect of 3.2 mg/kg d-amphetamine into a stimulatory effect. The low dose depression of locomotor activity may be related to activation of presynaptic dopamine receptors and subsequent inhibition of dopamine release (1). Release of serotonin (6) and blockade of serotonin reuptake (14) are among the known effects of d-amphetamine. These actions may be involved in the low dose depression seen with d-amphetamine. The lack of a stimulant effect of acute d-amphetamine doses in the range of 3.2 mg/kg may reflect the mixed stimulant and depressant effects of this dose. As a result of chronic treatment, it appears that tolerance to the initial depressant component occurs. As a result of this tolerance, the stimulant effects occurring at 3.2 mg/kg are now unopposed and, thus, are exhibited. The neurochemical basis for these effects on locomotor activity are at the present unknown.

A potential interpretation of the results is that depression of locomotor activity results from the intrusion of stereotypic behavior on locomotor activity. Selective tolerance to the stereotypic effects would allow an underlying locomotor stimulant effect to be expressed. Since this strain of mice did not exhibit stereotypy in response to d-amphetamine, the development of tolerance to the stereotypic effects of d-amphetamine and unmasking of locomotor stimulation could not explain the behavioral responses we observed.

Chronic treatment with d-amphetamine also produced changes in the methylphenidate dose-response curve. On acute exposure to methylphenidate, stimulation of locomotor activity was seen at the 3.2, 10 and 32 mg/kg doses; after chronic amphetamine only the 10 mg/kg dose of methylphenidate produced stimulation. Thus, chronic d-amphetamine administration appeared to alter the stimulatory effect of methylphenidate.

A survey of the literature revealed few reports of chronic d-amphetamine administration to mice (4, 12, 18). Neurochemical changes reported following chronic administration of d-amphetamine include decreased dopamine content and uptake, increased dopamine content and synthesis, and decreased or increased concentrations of norepinephrine. Due to the differing treatment regimens utilized in these various studies, it is difficult to evaluate the potential for neurotoxicity as the result of the dosing schedule used in our study. However, the return to control levels of locomotor activity following cessation of chronic d-amphetamine treatment suggests that major neurotoxic effects did not occur under our conditions.

The results reported in this study indicate that d-amphetamine and methylphenidate can have opposite acute effects on locomotor activity of BALB/cBy mice. While chronic amphetamine exposure can alter these behavioral effects, it can alter them in opposing ways. Such differences in effects may be related to differing mechanisms of action of the two drugs.

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