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Comparison of the ability of (+)-amphetamine and caffeine to produce environment-specific conditioning

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Abstract. Animals with a history of receiving psychomotor stimulants in a specific environment show enhanced activity when injected with saline and placed there. In the present study, a Pavlovian paradigm was used to compare the unconditioned and conditioned activity effects of (+)-amphetamine (0.1, 0.5, 1.0, and 5.0 mg/kg), caffeine (0.1, 1.0, 10.0, and 30.0 mg/kg), and a saline group (n's = 6–12). Rats experienced conditioning days with either drug or saline injected IP prior to a 60-min session in the activity monitor and the alternate saline or drug injected in the home cage following the session. On test days, all animals received saline in the activity monitors. Results revealed that amphetamine produced environment-specific conditioning in a dose-dependent manner; previous experience with 0.5, 1.0, and 5.0 but not 0.1 mg/kg in the activity monitor resulted in conditioned activity. A caffeine dose of 10.0 mg/kg produced stimulant effects on conditioning days and previous experience with the 1.0, 10.0, or 30.0 mg/kg dose in the activity monitor led to conditioned activity on test days. However, on test days the control groups as well as the 30.0 mg/kg experimental group showed significantly reduced activity as compared to the saline group. Thus, it appeared that caffeine produced hypoactivity 23 h after injection. Amphetamine produced conditioning in a dose-dependent manner, and the appearance of significant unconditioned activity during conditioning sessions was not necessary or sufficient to produce a conditioned effect. For caffeine there was some evidence of environment-specific conditioning, but it appears that between-group differences for caffeine may be accounted for by hypoactivity 23 h following injection.

Key words: (+)-Amphetamine – Caffeine – Environment-specific conditioning – Dopamine

Since the time of Pavlov there have been many reports of a so-called placebo effect in animals and humans after drug taking has ceased. Thus, Tatum and Seevers (1929) found that after repeated cocaine (3.0 mg/kg) injections in dogs, saline produced a 3–5 min period of marked activity similar to that seen following cocaine. Ross and Schnitzer (1963) administered amphetamine (3.0 mg/kg) intraperitoneally (IP) to rats for 1 week in three treatment groups; drug-tested, drug-not tested and untreated-tested. When all rats received the untreated-tested condition, the drug-tested group demonstrated significantly more locomotor activity. This was one of the first experiments to show that the association of drug administration with a specific test environment was an important procedure for establishing "placebo" effects.

Since then many experiments have demonstrated environment-specific conditioning of the locomotor enhancing properties of stimulants. Pickens and Crowder (1967) administered amphetamine (1.5 mg/kg) to rats randomly assigned to four treatment groups: drug immediately before placement in an activity apparatus (conditioned stimulus, CS), drug 30 min before the CS, drug immediately after the CS, and saline before the CS and drug after the session in the home-cage. Results showed that when all animals received saline prior to the session the greatest activity was seen in the two groups that previously received amphetamine before placement in the activity apparatus. Post et al. (1981) conditioned rats with cocaine (10.0 mg/kg) or saline and found that animals which had experienced cocaine in the test environment had significantly higher activity scores than animals which had previously experienced saline in that environment. Thus, environment-specific conditioning is demonstrated when a CS previously associated with a physiological drug experience is able to elicit a behaviour similar to that elicited by the drug itself (Eikelboom and Stewart 1982). There is now evidence suggesting that the establishment of conditioning with amphetamine and cocaine may be mediated by the central neurotransmitter dopamine (DA) (Beninger and Hahn 1983; Beninger and Herz 1986).

Another group of stimulant drugs, the methylxanthines, including caffeine, do not seem to affect DA activity directly (Modrow et al. 1981; Katims et al. 1983). Xanthines may produce their stimulant action by inhibiting cyclic nucleotide phosphodiesterases (Butcher and Sutherland 1962). A more recent explanation for the mechanism of their stimulant effect is that xanthines inhibit adenosine receptors, including those modulating catecholaminergic pathways. A suppression of natural inhibition results, producing an overall excitation effect (Daly et al. 1981).

The purpose of the present study was to determine whether caffeine is able to support environment-specific conditioning. Four doses of caffeine were tested and in each case, one group received drug prior to conditioning sessions and saline in the home cage whereas the other group was conditioned with saline and received drug in their home

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cage. For purposes of comparison, four doses of amphetamine were similarly tested in additional group of rats. All groups were compared to a control group receiving saline prior to conditioning sessions *and* in the home cage.

It was hypothesized that amphetamine would produce environment-specific conditioning in a dose-dependent manner. If caffeine produces conditioning, a relationship to dose might also be expected.

Method

Subjects. The experiment was performed on 192 male albino rats of the Wistar strain (Canadian Breeding Farms, St. Constant, Quebec), weighing 225–250 g at the beginning. They were individually housed in wire cages ($18 \times 25 \times 20$ cm high) in a climatically controlled ($21 \pm 1°$ C) environment, kept on a 12 h light-dark cycle (lights on at 0600 hours), with food (Purina rat chow) and water freely available.

Apparatus. Activity was monitored in six Plexiglas chambers ($41 \times 50 \times 37$ cm high) each enclosed in a styrofoam-insulated wooden sound-attenuating box, illuminated by an overhead bulb (2.5 W) and ventilated by a small fan that also provided constant masking noise. Each chamber was fitted with 14 infrared emitters and detectors, eight being spaced at 10 cm intervals along the length of the chamber and six along the width at a height of 5 and 15 cm above the grid floor. This design allowed for an estimate of both horizontal activity (lower beam breaks) and vertical (rearing or jumping) activity (upper beam breaks). Activity was monitored independently in each chamber with the use of a single board microcomputer (Cromemco) with its user interface being a screen or printing terminal. For further details see Beninger et al. (1985).

Procedure. Eight experiments were conducted, during the light portion of the light-dark cycle, four assessing the unconditioned and conditioned activity effects of amphetamine and the other four caffeine. Doses of (+)-amphetamine (Smith, Kline and French) dissolved in saline (0.9% NaCl) were: 0.1, 0.5, 1.0, and 5.0 mg/kg. Doses of caffeine (Sigma) dissolved in distilled water were: 0.1, 1.0, 10.0, and 30.0 mg/kg. For all doses, 24 animals were randomly assigned to an experimental or home cage (H-C) control group, except for the dose of 0.1 mg/kg caffeine where 12 rats were used. There was an additional group of 12 rats termed the saline group.

On conditioning days, the experimental groups received IP injections of drug immediately before a 60-min session in the activity monitor and saline upon return to their home cage. The H-C control groups received saline before placement in the activity monitor and an injection of the corresponding drug upon return to their home cage. The saline group received saline both before sessions and upon return to their home cage. For each experiment (one dose group) both experimental animals and H-C control animals were tested at the same time.

Four conditioning sessions were followed by a test day when all rats received a saline injection prior to placement in the activity monitor and no injection upon return to their home cage. Following two nonexperimental days in the home cage, days 6–9 were the same as days 1–4, and a second test session was carried out on day 10.

Results

For each 10 min of each 60-min session in the activity monitor, two scores were recorded for each rat: total horizontal activity (lower beam counts) and vertical activity (upper beam counts). Activity levels for the drug experimental groups tended to be fairly constant over the 60-min sessions, whereas the H-C control groups showed within-session declines. As a result, significant differences between the experimental and H-C control groups tended to be seen in the latter portion of the session. As representative examples of each drug group, scores across time averaged across conditioning sessions for 1.0 mg/kg amphetamine and 10.0 mg/kg caffeine are shown in Fig. 1. Analyses of variance (ANOVA) revealed significant or near significant group effects [level 1: $F(1, 22) = 4.04$, $P = 0.054$; level 2: ($F(1, 22) = 5.13$, $P < 0.05$] and significant time by group interactions [level 1: $F\ (5, 110) = 3.09$, $P < 0.05$; level 2: $F\ (5, 110) = 2.96$, $P < 0.05$] for both dependent variables for amphetamine (Fig. 1A and 1B). The caffeine groups differed significantly in vertical [$F(1, 22) = 12.40$, $P < 0.01$] but not horizontal activity and a significant time-by-group interaction was seen for horizontal [$F(5, 110) = 2.34$, $P < 0.05$] but not vertical activity (Fig. 1C and 1D). Post hoc comparisons of groups at each time revealed significant group differences primarily in the latter portion of the sessions, as indicated by the asterisks in Fig. 1. Therefore, only the last 30 min of each session were included in all subsequent analyses, the first 30 min being treated as an habituation period. This resulted in fewer interactions in the ANOVAs. Each drug dose was tested in a separate group of animals with its own H-C control group; therefore, each drug dose was treated as a separate experiment and analyses were conducted between each experimental group and its H-C control group. For each drug dose, separate ANOVAs were done for conditioning and test days and for horizontal and vertical activity. In each case, 3-way ANOVAs were carried out with time, day and group as the variables, the former two being repeated measures.

Significant main effects of time and day were often observed in the ANOVAs on conditioning days. A significant time effect, a decrease in activity over the 30-min period, was seen in the lowest dose groups on each level of activity for amphetamine and caffeine and never in the highest dose on either level for either drug. These time effects would be computed with the experimental and H-C control groups combined; therefore, a significant effect does not indicate an effect of time due to drug treatment. Time-by-group interactions were rarely seen. Significant effects due to day were also seen (in the experimental and H-C control groups combined) and were observed for almost every drug dose. In each case a downward trend in activity was seen over the first 4 conditioning days with a small increase in activity on the conditioning day that occurred after 2 days off on the weekend followed by a general decline in responding over the next 3 conditioning days (data not shown). The day-by-group interaction was only significant in a small number of cases, as discussed below. Therefore, evaluations of unconditioned drug effects were based on activity over the 8 conditioning days. Occasionally, a time-by-day interaction was seen but no systematic changes were noted. This interaction would also be produced in the ANOVA when both groups were combined. Group effects and interactions involving the group variable are discussed in the following paragraphs.

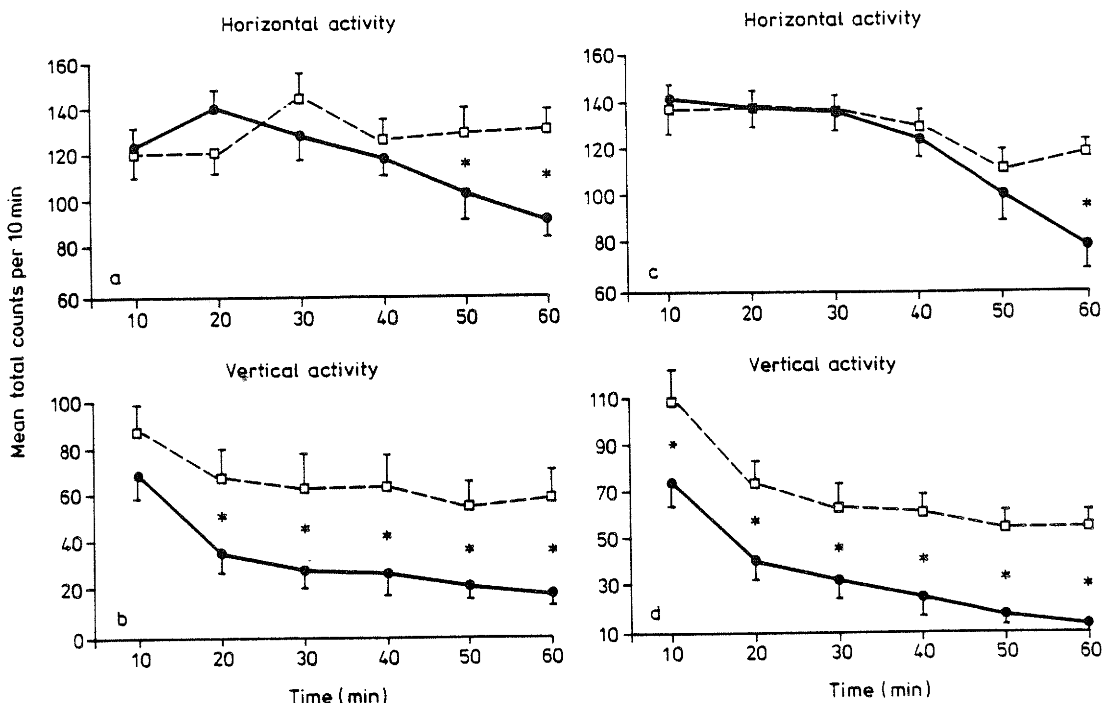

Fig. 1A–D. Representative examples of mean horizontal and vertical activity scores for each 10 min of the 60 min session averaged across 8 conditioning days. **A** and **B** Horizontal and vertical activity, respectively, for the experimental group ($n=12$) that received 1.0 mg/kg amphetamine in the activity monitors (□--) and the H-C control group ($n=12$) that received saline in the activity monitors and amphetamine in the home cage (●—). **C** and **D** Horizontal and vertical activity, respectively, for the experimental group ($n=12$) that received 10.0 mg/kg caffeine in the activity monitors (□--) and the H-C control group ($n=12$) that received saline in the activity monitor and caffeine in the home cage (●—). *Asterisks* indicate significant differences ($P<0.05$) between groups determined using post hoc tests

Mean horizontal and vertical activity counts (per 10 min) for the amphetamine experimental and H-C control groups averaged for 8 conditioning days or 2 test days are shown in Fig. 2A and 2B. Analyses conducted on horizontal activity during conditioning days yielded a significant effect of group for the 1.0 mg/kg dose [$F(1, 22)=10.46$, $P<0.01$]. An interaction of day by group was observed in the 5.0 mg/kg dose group [$F(7, 154)=3.52$, $P<0.01$]. Examination of the data revealed that the 5.0 mg/kg group was more active than the H-C controls during the first 4 conditioning days but that the two groups were similar during the last 4 conditioning days producing the interaction. This was confirmed by tests of simple main effects (Winer 1971, pp 544–545) of group at each conditioning day which revealed significant effects on days 2–4 of the 1st week but not during the 2nd week (data not shown). Analyses conducted on vertical activity (Fig. 2B) revealed a significant effect of group for the 0.5 and 1.0 mg/kg doses [$F(1, 22)=6.30$, $P<0.02$; $F(1, 22)=6.52$, $P<0.02$]. An interaction of day by group was observed in the 0.1 mg/kg dose group [$F(7, 154)=4.06$, $P<0.01$]. The 0.1 mg/kg group was more active than the H-C controls during the first 4 conditioning days but the two groups were similar during the last 4 conditioning days. Tests of simple main effects revealed a group difference only on day 2. Analyses of the horizontal activity of the amphetamine groups on test days revealed that the 0.5, 1.0 and 5.0 mg/kg dose groups were significantly more active than their respective H-C control groups [$F(1, 22)=6.53$, $P<0.02$; $F(1, 22)=6.47$, $P<0.02$; $F(1, 22)=4.49$, $P<0.05$, respectively]. There were no significant interactions involving the group variable. Analyses conducted on vertical activity revealed that the 5.0 mg/kg dose group was significantly more active than its H-C control [$F(1, 22)=10.51$, $P<0.01$]. A significant day-by-group interaction was observed in the 0.5 mg/kg dose group [$F(1, 22)=15.32$, $P<0.01$]. Tests of simple main effects showed that there was a significant difference between groups on test day 1 but not on test day 2, revealing the source of the interaction.

Mean horizontal and vertical activity counts (per 10 min) for the caffeine experimental and H-C control groups averaged for 8 conditioning days or 2 test days are shown in Fig. 3A and 3B. Analyses conducted on horizontal activity on conditioning days yielded significant differences between the experimental groups receiving 10.0 and 30.0 mg/kg doses compared to their respective H-C control groups [$F(1, 22)=5.35$, $P<0.05$ and $F(1, 22)=86.20$, $P<0.001$, respectively]. Day-by-group interactions were observed for the 1.0 and 10.0 mg/kg dose groups [$F(7, 154)=2.57$, $P<0.02$ and $F(7, 154)=3.65$, $P<0.01$, respectively]. In the former case the interaction appeared to be produced by a systematic decrease in activity of the control group over days, with little change in the experimental group, and tests of simple main effects revealed that groups differed significantly on the last conditioning day only (data not shown). For the 10.0 mg/kg dose group, although activity counts were more variable, the same general pattern was seen. Tests of simple main effects revealed that the groups differed significantly on days 2, 4 and 7, with the largest difference being on day 7, $P<0.001$. Analyses conducted on vertical activity revealed a significant effect of group for the 10.0 and 30.0 mg/kg doses [$F(1, 22)=21.01$,

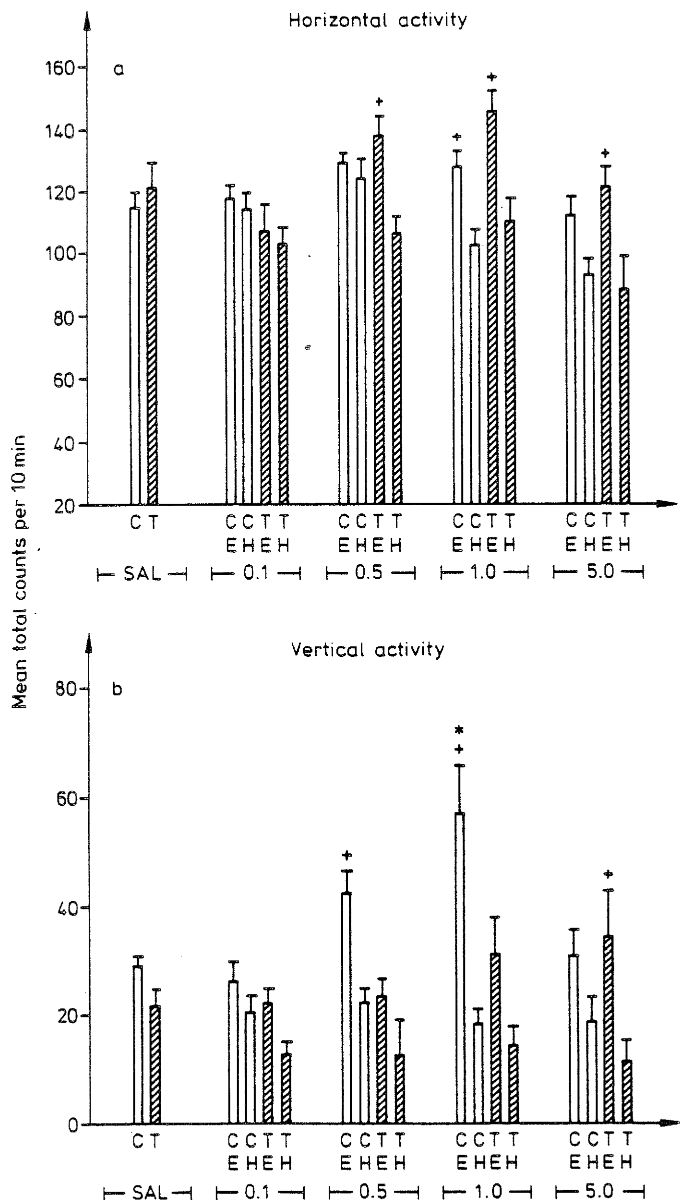

Fig. 2 A, B. Mean (± SEM) horizontal (**A**) and vertical (**B**) activity counts per 10 min for saline (*SAL*), experimental (*E*), and H-C control (*H*) groups, receiving each dose of amphetamine, averaged over 8 conditioning days (*C*) or 2 test days (*T*) and across time for the last 30 min of each session. Note that the scale on the vertical axis differs from for the two panels. +: significantly different from H-C control ($P<0.05$); *: significantly different from saline ($P<0.05$)

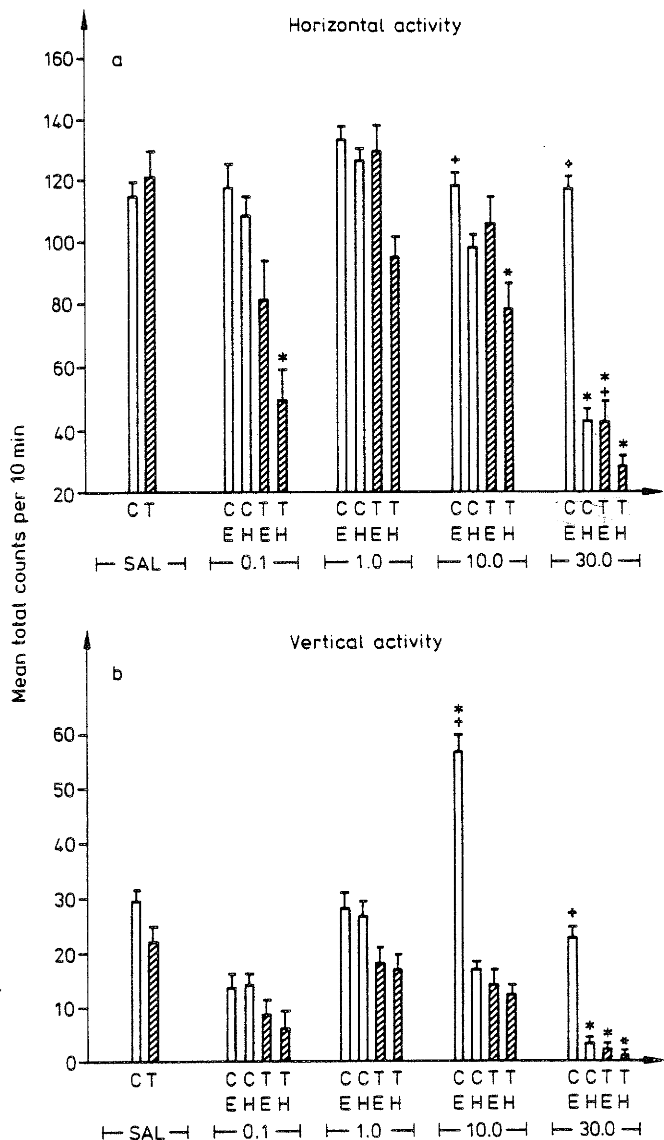

Fig. 3 A, B. Mean (± SEM) horizontal (**A**) and vertical (**B**) activity counts per 10 min for saline (*SAL*), experimental (*E*) and H-C control (*H*) groups, receiving each dose of caffeine, averaged over 8 conditioning days (*C*) or 2 test days (*T*) and across time for the last 30 min of each session. Note that the scale on the vertical axis differs for the two panels. +: significantly different from H-C control ($P<0.05$); *: significantly different from saline ($P<0.05$)

$P<0.001$ and $F(1, 22)=15.87$, $P<0.001$]. An interaction of day by group was observed in the 10.0 mg/kg dose group [$F(7, 154)=6.46$, $P<0.01$]. Examination of the data showed this to be due to a general downward trend in activity in the H-C control group but not in the experimental group, and tests of simple main effects revealed significant group differences on all conditioning days but the first 2. Analyses of horizontal activity of the caffeine groups on test days revealed significantly greater activity for the 30.0 mg/kg dose compared to its respective H-C control group [$F(1, 22)=4.94$, $P<0.05$] with the differences for 1.0 and 10.0 mg/kg approaching significance [$F(1, 22)=4.03$, $P=0.055$ and $F(1, 22)=3.81$, $P=0.06$]. A significant day-by-group interaction was observed in the 1.0 mg/kg dose group [$F(1, 22)=6.58$, $P<0.02$]. This interaction occurred because the group difference on the 1st test day was not significant, whereas it was on the 2nd test day. Analyses conducted on vertical activity did not reveal any significant effects of group, nor were there any significant interactions involving the group variable.

Dose-response effects produced on conditioning or test days were analyzed by conducting ANOVAs on group (saline, the four experimental and the four H-C control groups) for each type of activity for each drug. Results

revealed that in every case there was a significant effect of group [amphetamine conditioning days level 1: $F(8, 99) = 3.08$, $P < 0.01$; level 2: $F(8, 99) = 2.82$, $P < 0.01$; test days level 1: $F(8, 99) = 3.00$, $P < 0.01$; level 2: $F(8, 99) = 2.57$, $P < 0.02$; caffeine conditioning days level 1: $F(8, 87) = 14.18$, $P < 0.001$; level 2: $F(8, 87) = 8.96$, $P < 0.001$; test days level 1: $F(8, 87) = 12.03$, $P < 0.001$; level 2: $F(8, 87) = 3.40$, $P < 0.01$]. Dunnet's post hoc tests ($P < 0.05$) were conducted to determine which groups differed significantly from the saline group. For the amphetamine groups during conditioning, only the experimental group receiving 1.0 mg/kg showed significantly more vertical activity than the saline group; none of the amphetamine groups differed significantly from the saline group in the test. For the caffeine groups during conditioning the experimental group receiving 10.0 mg/kg showed significantly more vertical activity and the H-C control group receiving 30.0 mg/kg showed significantly less horizontal and vertical activity than the saline group. In the test phase, the 30.0 mg/kg experimental group showed less horizontal and vertical activity; the H-C control groups receiving 0.1, 10.0 and 30.0 mg/kg showed less horizontal activity and the 30.0 mg/kg H-C control group also showed less vertical activity than the saline group (Figs. 2 and 3).

Discussion

On conditioning days the amphetamine groups receiving 0.1 and 5.0 mg/kg showed no significant stimulant effect on either horizontal or vertical activity with respect to their H-C controls. The 0.5 mg/kg group showed a stimulant effect on vertical activity and the 1.0 mg/kg group showed a stimulant effect on both measures. Additionally, the 1.0 mg/kg dose produced significantly greater vertical activity than the saline control. The observation of locomotor stimulation with moderate doses of amphetamine is consistent with many previous reports (Isaacson et al. 1978; Schiff 1982). It has also been found that lower doses of stimulants primarily affect rearing activity, whereas higher doses influence both rearing and locomotion (Scheel-Kruger et al. 1977). In the case of 5.0 mg/kg the lack of increased activity may have been due to a high level of stereotypy which has been shown to be inversely related to locomotor activation (Browne and Segal 1977).

On test days, experimental groups previously receiving amphetamine doses of 0.5, 1.0 and 5.0 mg/kg showed environment-specific conditioned horizontal activity. For vertical activity significance was only reached with 5.0 mg/kg. Of particular interest is the dissociation of significant effects between conditioning days and test days for the 0.5, 1.0 and 5.0 mg/kg groups. It seems that a significant unconditioned increase in activity is not necessary to produce the conditioned effect. The observation of environment-specific conditioned activity is consistent with previous reports of this effect following amphetamine (Pickens and Crowder 1967; Beninger and Hahn 1983), cocaine (Post et al. 1981; Beninger and Herz 1986), apomorphine (Schiff 1982) and opiate compounds (Vezina and Stewart 1984).

The general lack of effect of amphetamine on horizontal activity in comparison with the saline group is noteworthy. The activity level of the saline group was considerably higher than typically reported (e.g., Post et al. 1981). However, in the present study animals were not pre-exposed to the conditioning environment prior to testing. Possibly increased exploration due to novelty led to high levels of activity in the saline group and the lack of significant differences observed. Another possibility is that the saline animals showed high activity levels because the large floor area of the activity monitors provided them with their only opportunity to run. The high level of activity in saline groups is consistent with previous data from this laboratory (Beninger and Herz 1986; Beninger et al. 1985). Furthermore, the saline group was tested alone over a 2-week period whereas the experimental and H-C control groups for each dose of amphetamine were tested on the same days. Thus, the activity of the saline group may have been influenced by uncontrolled variables associated with time of testing. Therefore, the H-C control groups may provide the most reliable comparisons for the experimental groups. Although the amphetamine H-C control groups, especially those receiving high doses, appeared to be less active than the saline group, significant differences were not found. Nevertheless it remains possible that part of the environment-specific conditioned effect is due to a decrease in the H-C control groups. The reason for this decrease remains unclear. Perhaps the anticipation of the home cage injection, which immediately followed conditioning sessions, influenced the activity of the H-C control groups. Further studies are required to test this possibility.

The results for the caffeine groups on conditioning days showed that with respect to their H-C control groups, doses of 10.0 and 30.0 mg/kg produced significantly greater horizontal and vertical activity. Additionally, the 10.0 mg/kg dose produced significantly greater vertical activity than the saline group. It was also observed that the 30.0 mg/kg H-C control group displayed significantly lower horizontal and vertical activity than the saline group. Thus, the significant difference seen between the 30.0 mg/kg experimental and H-C control groups may be due to the large decrease in activity seen in the latter. To a lesser degree the stimulant effect produced by 10.0 mg/kg on vertical activity may also be due in part to decreased activity in the H-C control group. On test days, significant differences in horizontal activity were observed between the experimental and H-C control groups previously receiving a dose of 30.0 mg/kg and the difference for the 1.0 and 10.0 mg/kg doses approached significance. Relative to the saline group, horizontal activity of the 30 mg/kg experimental group and the 0.1, 10.0 and 30.0 mg/kg H-C control groups was depressed. For vertical activity, the 30.0 mg/kg experimental and H-C control groups showed significantly reduced activity as compared to the saline group.

It is possible that the large decrease in activity in the 30.0 mg/kg caffeine H-C control groups is related to anticipation of the home cage injection, which always occurred shortly after removal from the activity monitor. Of particular relevance to this hypothesis is the observation that the 30.0 mg/kg *experimental* group showed significantly decreased horizontal and vertical activity on test days. Presumably this group would *not* be anticipating a stimulant injection in the home cage and therefore the hypothesis that reduced activity was related to anticipation of the drug injection may be incorrect. Alternatively, it appears that the 30.0 mg/kg dose of caffeine produces hypoactivity 23 h after the drug injection, the usual time of testing. It may be that with repeated dosing, 10.0 mg/kg similarly produces a decrease in activity 23 h following injection. This suggestion is supported by the finding of significant day-by-group

interactions for horizontal and vertical activity in the analysis of these groups and the finding that these interactions were attributable to a decline over days in activity of the H-C group. Furthermore, the 10.0 mg/kg H-C control group showed significantly less horizontal activity than the saline group on test days (Fig. 3A). It is noteworthy that the body weights of the 10.0 and 30.0 mg/kg caffeine groups were not different from those of the other groups throughout the experiment, suggesting that hypoactivity may not have been a result of toxic effects of caffeine. The low dose of 0.1 mg/kg seemed to produce disproportionately decreased activity on test days. However, these were the only experimental and H-C control groups with six rats, and the standard errors were quite large, raising the possibility that the magnitude of decrease in these groups was a result of sampling error. On the other hand, Katims et al. (1983), although observing a stimulant effect in mice given high doses (5.8 and 19.4 mg/kg) of caffeine, found locomotor depression with low doses (1.0 and 1.9 mg/kg).

In light of these considerations, does caffeine produce environment-specific conditioning? Although it appears clear that animals are hypoactive 23 h after injections of caffeine, it is also clear that animals with a history of receiving the drug *in the test environment* (experimental groups) are less hypoactive than H-C controls on drug-free test days (Fig. 3). In the case of 30.0 mg/kg this difference attained significance and it approached significance for 1.0 and 10.0 mg/kg. Thus it appears that there is some conditioning to environments associated with caffeine. This conditioning apparently can counteract to some degree the usual hypoactivity seen 23 h following caffeine treatment.

There is good evidence that the stimulant effects of amphetamine are mediated by DA (Beninger and Hahn 1983; Kuczenski 1983). Some evidence suggests that caffeine may interact with DA systems. Thus, locomotor activity induced by the injection of DA into the nucleus accumbens of reserpine-nialamine pretreated rats is potentiated by caffeine (Anden and Jackson 1975). On the other hand, lesions of the DA pathways projecting into the nucleus accumbens block amphetamine-induced activity but not caffeine-induced activity (Joyce and Koob 1981).

It has been shown that the establishment of conditioned activity to amphetamine-associated environments involves a DA substrate; this may serve as a reliable animal model for the reinstatement of behaviours and physiological states that certain drug environments induce in humans (Crowley 1972; Sideroff and Jarvik 1980). The 23-h hypoactivity shown in the present study with caffeine may be associated with human withdrawal. Further studies are needed to test the ability of specific DA antagonists such as pimozide to block the unconditioned effect of caffeine before a direct DA involvement in its stimulant mechanism can be substantiated.

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