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Sensitization and Individual Differences to IP Amphetamine, Cocaine, or Caffeine Following Repeated Intracranial Amphetamine Infusions

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HOOKS, M. S., G. H. JONES, B. J. LIEM AND J. B. JUSTICE, JR. *Sensitization and individual differences to IP amphetamine, cocaine, or caffeine following repeated intracranial amphetamine infusions.* PHARMACOL BIOCHEM BEHAV **43**(3) 815–823, 1992.—Rats that have a high locomotor response to novelty (HR) sensitize more readily to IP-administered amphetamine than rats with a low locomotor response (LR) to novelty. This experiment compared sensitization in HR and LR rats following amphetamine (3.0 μg/side for 5 days) infused bilaterally into either the nucleus accumbens (NACC), ventral tegmental area (VTA), or the medial frontal cortex (MFC). The subsequent locomotor response to IP-administered *d*-amphetamine sulfate (1 mg/kg), cocaine HCl (15 mg/kg), and caffeine benzoate (20 mg/kg) was also examined. No differences were observed between HR and LR rats following amphetamine infusion into either the MFC, NACC, or VTA. However, HR rats showed greater locomotor activity compared to LR rats following either IP amphetamine, cocaine, or caffeine for subjects cannulated in the NACC, MFC, or the VTA. Repeated infusions of amphetamine into the VTA increased the locomotor response to both IP amphetamine and cocaine, but not to IP caffeine, while repeated infusions of amphetamine into the NACC or MFC had no effect on locomotor response to any drug subsequently administered IP. The results support previous findings that changes induced by intra-VTA infusions, but not intra-NACC or MFC infusions, of amphetamine induce sensitization to IP-administered amphetamine and cocaine. Findings from the present experiment indicate the ability of the dopamine cell body region, but not the dopamine terminal fields, to produce locomotor sensitization to amphetamine and cocaine. The results from the present experiment also indicate the lack of localization to one of studied regions of individual differences. Further, it appears that more than dopamine is involved because both dopaminergic-dependent and -independent stimulant drugs produce individual differences.

Locomotor activity Sensitization Amphetamine Individual differences Novelty Nucleus accumbens Ventral tegmental area Medial frontal cortex Cocaine Caffeine

RESPONSE to novelty has been shown to predict both the initial locomotor response to amphetamine (11,32) and the rate at which rats sensitize to low locomotor-producing doses of amphetamine (11,12). Subjects that show a high locomotor response in a novel environment [high responders (HR)] show a larger initial locomotor response to amphetamine and develop locomotor sensitization more rapidly following repeated amphetamine than subjects that have a low locomotor response to a novel environment [low responders (LR)]. Recent evidence from our laboratory (13) and others (7,33,38) suggested this may be due to differences in the reactivity of the mesolimbic dopamine system. HR rats exhibit a larger increase in extracellular dopamine in the nucleus accumbens (NACC) than LR rats following cocaine administration (13). In addition, HR rats show a higher turnover in the NACC and frontal cortex dopamine following exposure to novelty (33). These data support the hypothesis that variation in mesolimbic dopamine is responsible for the observed individual differences between rats (32).

Repeated systemic administration of amphetamine produces pronounced behavioral sensitization that includes increased levels of locomotor activity and more intense behavioral stereotypy (1,6,35,37). Repeated infusions into the ventral tegmental area (VTA) of enkephalin (18) or amphetamine (22) also produce increased locomotor responses to subsequent systemic administration of amphetamine. The change

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in behavior is likely due to changes in mesolimbic dopamine because acute administration of systemic amphetamine or cocaine increases extracellular levels of dopamine in both the NACC (13,31,36,39) and VTA (2,21). In addition, increased extracellular dopamine has been shown after repeated amphetamine administration IP (36) and repeated infusions of neurotensin and enkephalin analogs in the VTA (20) compared to acute administration. Variation in the mesolimbic dopamine system may also be responsible for the differing rates of locomotor sensitization between HR and LR rats (11).

While direct infusions of amphetamine into the VTA produce sensitization to IP administration of drugs, the infusions themselves do not produce increases in locomotor activity as NACC amphetamine infusions do. It has been shown that while infusions of amphetamine into the medial frontal cortex [MFC; (5)] and VTA (22) do not elicit changes in locomotor activity infusions into the NACC of amphetamine produce marked enhancement of locomotor activity and affect other types of behavior (4,24,25,42). Variation in the reactivity of the dopaminergic system in these regions could therefore contribute to variation in vulnerability to drugs of abuse. Other evidence in support of the possible role for mesolimbic dopamine in individual differences is that previous experiments have shown a correlation between locomotor response to novelty and locomotor response to acute infusion of amphetamine in the NACC (11). Another psychomotor stimulant, cocaine, when infused into the NACC produces greater locomotor activity in HR compared to LR rats (10). Differences between shocked and nonshocked rats (28) and socially normal and deprived rats (14) have also been shown following amphetamine infusion into the NACC. These data provide further evidence of the likely role of the mesolimbic dopamine system in individual vulnerability to psychomotor stimulants.

This experiment was designed to determine the role of the NACC, VTA, and MFC in the individual differences in responsiveness between rats to stimulant drugs. The experiment analyzed the locomotor effects of direct infusions of amphetamine into these regions and the effect of subsequent systemic administration of amphetamine, cocaine, and caffeine.

METHOD

Subjects

Male Wistar rats (Harlan, NACC, $n = 38$; VTA, $n = 38$; MFC, $n = 39$) weighing 290–350 g at the time of surgery were used in the experiment. Rats were group housed six per cage on a 12 L : 12 D cycle (lights on 0700–1900 h) with free access to food and water. Subjects were handled on 2 consecutive days prior to their first exposure to the test cages. Testing was conducted between 0800–1700 h.

Apparatus

Plexiglas photocell cages (39 × 25 × 24 cm) were used to measure locomotor activity. Each cage was equipped with two parallel, horizontal, infrared beams. Beams were 2 cm above the floor and spaced equally along the long axis of the cage. A locomotor count was registered by an IBM computer following interruption of alternate beams. Each cage was supplied with white noise to prevent disturbances from the outside environment. Illumination was provided by a light on the roof of each photocell cage (12).

Drugs

For intracranial administration, amphetamine (*d*-amphetamine sulfate, 3 μg/0.5 μl, Sigma Chemical Co., St. Louis, MO) was dissolved in artificial cerebrospinal fluid (CSF) and infused in a volume of 0.5 μl/side. CSF consisted of 0.13 M sodium chloride, 0.98 mM magnesium chloride, 2.65 mM potassium chloride, 1.2 mM calcium chloride, 0.25 mM ascorbic acid, and 10 mM glucose. The pH was adjusted to 7.3 with 0.1 M NaOH. For IP administration, amphetamine (*d*-amphetamine sulfate 1 mg/ml, Sigma), cocaine (cocaine HCl, 15 mg/ml, NIDA, Rockville, MD), and caffeine (caffeine sodium benzoate 20 mg/ml, Sigma) were dissolved in 0.9% saline and administered in a volume of 1 ml/kg in the test cage. All doses are expressed as weight of salt.

Surgical and Infusion Procedures

Rats were anesthetized with 50 mg/kg IP sodium pentobarbital (Nembutal) and placed in a stereotaxic frame. Bilateral stainless steel guide cannulae (22 g) were implanted to access either the NACC (AP +3.4 from bregma, L ±1.7, V −3.5 from dura with the incisor bar set at +5 mm), the VTA (AP −3.2, L ±0.5, V−7.6 from dura with the incisor bar set at +5 mm and the cannulae rotated 10°), or the MFC (AP +4.5, L ±0.7, V − 1.0 from dura with incisor bar set at 5 mm) (30). The guide cannulae were secured in place with the use of skull screws and dental cement. Removable stylets (31 g) were placed in the guide cannulae. Intramuscular penicillin (60,000 U) was administered immediately following surgery. A recovery period of 7–8 days was allowed following surgery before the initial exposure to the test cage.

Intracerebral infusions were made bilaterally via 30-ga infusion cannulae that protruded 1 mm below the guide cannulae. The infusion cannulae were attached via plastic (PE10) tubing to 10-μl syringes mounted on a Razel (Stamford, CT) infusion pump. The infusions (2 × 0.5 μl) were delivered simultaneously over a 45-s period with an additional 1-min diffusion period allowed to elapse before withdrawing the infusion cannulae. Subjects were held lightly in a towel during the infusions.

Behavioral Procedure

Two days before the initial drug treatment, subjects were placed in individual photocell cages for a 3-h period. Subjects were divided into HR or LR based upon whether their locomotor activity scores for the first hour were above or below the

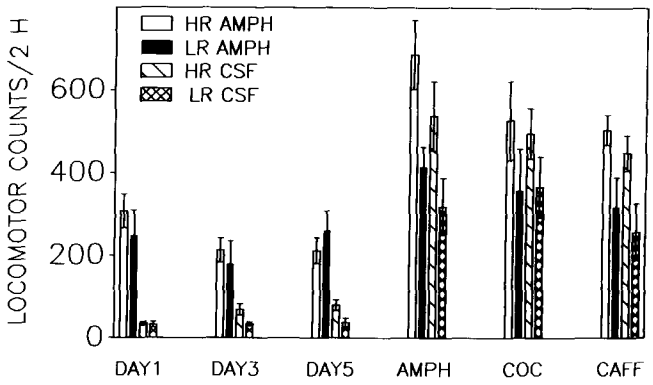

FIG. 1. Total locomotor counts for amphetamine infusions into the NACC and subsequent administration of amphetamine, cocaine, and caffeine IP (HR = 19, amphetamine infused = 10, CSF infused = 19, amphetamine infused = 9, CSF infused = 10). Vertical bars represent SEM.

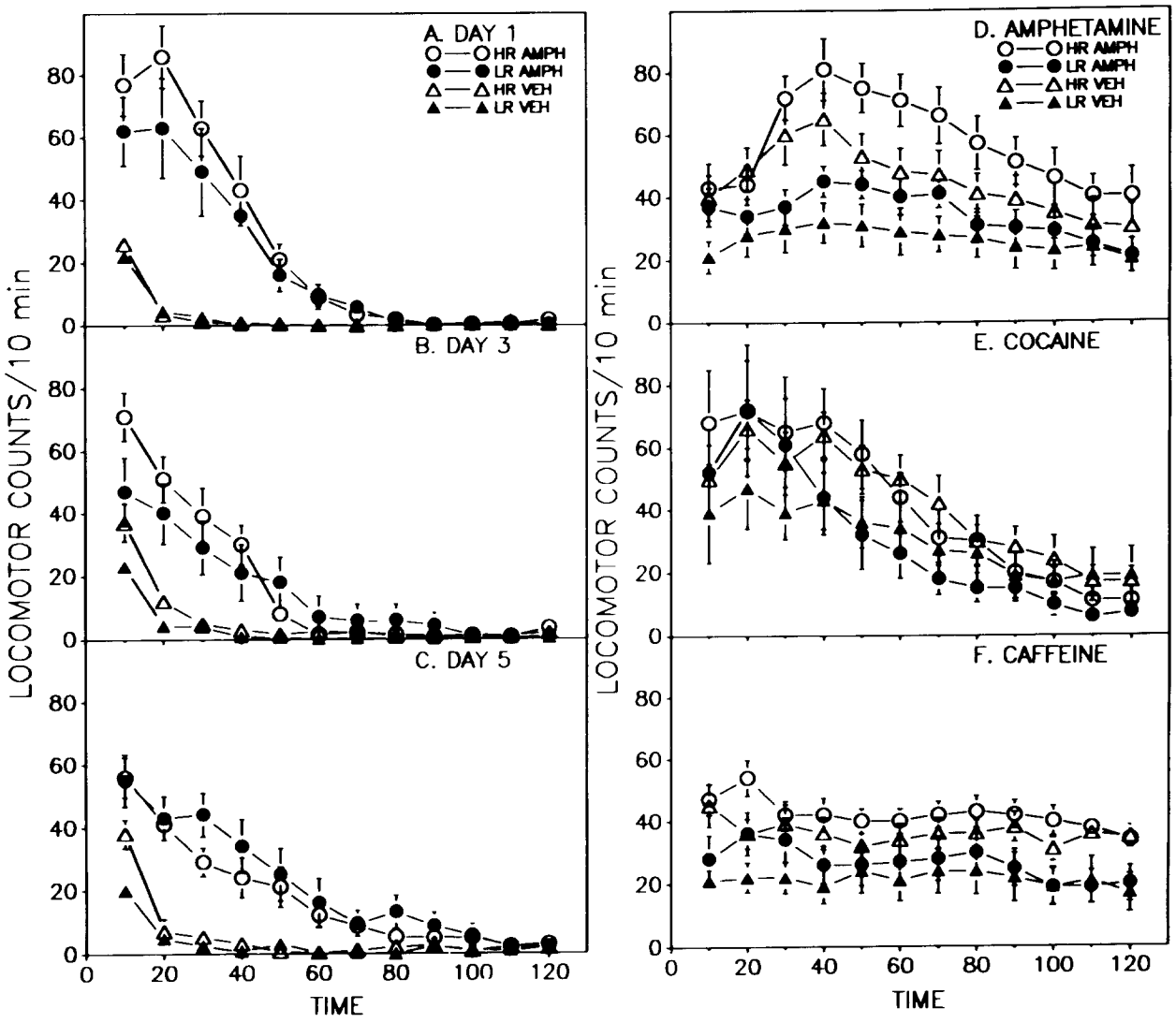

FIG. 2. Effects of amphetamine infusions into the NACC and subsequent administration of amphetamine, cocaine, and caffeine IP. Intra-NACC infusions of amphetamine produced an increase in locomotor activity compared to CSF infusions ($p < 0.0001$) but no difference between HR and LR rats. While amphetamine ($p < 0.0025$), cocaine ($p < 0.05$), and caffeine ($p < 0.005$) produced an overall difference between HR and LR rats, only amphetamine produced a novelty × time interaction ($p < 0.0001$). Vertical bars represent SEM.

median locomotor activity for the subject sample (12). Rats were assigned to one of two drug groups to receive repeated administration of either 0.0 or 3.0 μg/side of amphetamine. Each group was composed of half HR rats and half LR rats. Drug groups were counterbalanced according to the locomotor response to novelty and body weight.

Subjects were not tested the day before the initial drug treatment. On test days 1, 3, 5, 7, 9, 11, 13, 15, and 17, rats were placed in the photocell cage for a 1.5-h habituation period prior to drug administration. Locomotor activity was measured for an additional 2 h after each drug administration. On test days 1, 3, and 5, rats were infused bilaterally with amphetamine (3.0 or 0.0 μg/side) in the test cage. On days 2 and 4, animals received the appropriate dose of intracranial amphetamine in the home cage to minimize possible environmental conditioning. All subjects received 0.9% saline (1 ml/kg) on test days 7, 11, and 15 in the test cage. On test day 9, all rats were administered IP 1 mg/kg amphetamine. All rats received 15 mg/kg cocaine IP in the test cage on test day 13. Rats received IP 20 mg/kg caffeine in the test cage on test day 17. No testing was performed on subjects on days, 6, 8, 10, 12, 14, and 16.

Histology

At the completion of testing, subjects were anesthetized with 400 mg chloral hydrate and perfused transcardially with 50 ml saline followed by 50 ml formalin (10%). Following fixation, coronal sections (75 μm) were cut on a freezing microtome and each section through the area of interest and associated structures was mounted on a glass slide and stained with thionin. Cannulae placements were determined by a researcher unaware of experimental conditions.

Data Analysis

Locomotor activity counts were subjected to analysis of variance (ANOVA). The intracranial data was analyzed with a three-way ANOVA with two dependent variables, drug infused intracranially and novelty group, and one within-subject's factor, day of drug treatment. The IP data was analyzed with a three-way ANOVA with two dependent variables, drug infused intracranially and novelty group, and one within-subject's factor, IP challenge drug. Where appropriate, post-hoc comparisons were made using Newman-Keuls analysis. Least-squares linear regression was conducted to examine the relationship between locomotor activity in a novel environment and drug response.

RESULTS

Locomotor Activity Following Intra-NACC Amphetamine and Subsequent IP Injections

The results of intra-NACC infusions are depicted in Figs. 1 and 2. Histological verification indicated that four subjects had improper cannulae placement and were therefore excluded from analysis. Following intra-NACC infusions of amphetamine or CSF, amphetamine-treated rats demonstrated a greater locomotor response compared to CSF-treated rats. $F(1, 37) = 53.37, p < 0.0001$ (Fig. 1). Intra-NACC infusions of amphetamine or CSF did not, however, produce differences between HR and LR rats, $F(1, 37) = 0.73$, n.s. In addition, no novelty × amphetamine interaction was revealed by ANOVA either, $F(1, 37) = 0.03$, n.s. There was a correlation between locomotor response to novelty and locomotor response to intra-NACC amphetamine on day 1 ($r = 0.51$, $p < 0.025$) but not on day 3 ($r = 0.34$, n.s.) or day 5 ($r = -0.09$, n.s.).

Following IP-administered amphetamine, there was no difference between rats previously treated with intra-NACC amphetamine or CSF, $F(1, 37) = 2.76$, n.s. (Fig. 1). HR rats did exhibit almost a 70% higher locomotor response to amphetamine administered IP than LR rats, $F(1, 37) = 11.19$, $p < 0.0025$ (Fig. 1), in addition to a novelty × time interaction, $F(11, 418) = 4.04$, $p < 0.0001$ (Fig. 2D). Moreover, there was correlation between response to novelty and to IP-administered amphetamine ($r = 0.62$, $p < 0.0001$). There was also a correlation between locomotor response to IP-administered amphetamine and cocaine ($r = 0.32$, $p < 0.05$) but not caffeine ($r = -0.02$, n.s.).

Following IP-administered cocaine, there were no differences between rats previously infused with amphetamine or CSF, $F(1, 37) = 0.01$, n.s. (Fig. 1). IP cocaine administration did produce a 40% greater locomotor response in HR rats compared to LR rats, $F(1, 37) = 5.23$, $p < 0.05$ (Fig. 1), but no novelty × time interaction, $F(11, 418) = 0.95$, n.s. (Fig. 2E). In addition, there was correlation between locomotor response to cocaine and novelty ($r = 0.59$, $p < 0.0001$), but not caffeine ($r = 0.13$, n.s.).

Caffeine administered IP did not elicit any differences between rats previously infused with intra-NACC amphetamine or CSF, $F(1, 37) = 1.40$, n.s. (Fig. 1). Following caffeine, there was a 65% greater locomotor response in HR compared to LR rats, $F(1, 37) = 10.57$, $p < 0.0005$ (Fig. 1), but no novelty × time interaction, $F(11, 418) = 0.98$, n.s. (Fig. 1F). In addition, there was also a correlation between locomotor response to novelty and locomotor response to caffeine ($r = 0.54$, $p < 0.005$).

Saline administered IP did not produce any differences between rats that had received previous intra-NACC infusions of either amphetamine or CSF, $F(1, 37) = 0.46$, n.s. No differences were observed between HR and LR rats following saline either, $F(1, 37) = 3.32$, n.s.

Locomotor Activity Following Intra-VTA Amphetamine and Subsequent IP Injections

Figures 3 and 4 depict the results of intra-VTA administration of either amphetamine or CSF. There were eight subjects excluded from analysis due to improper cannulae placements. Following intra-VTA infusions, there were no differences between amphetamine- and CSF-treated rats, $F(1, 37) = 1.05$, n.s. (Fig. 3). Moreover, no differences were observed between HR and LR rats, $F(1, 37) = 1.51$, n.s. (Fig. 3), following intra-VTA infusions.

IP administration of amphetamine did produce an 80% greater locomotor response in rats previously infused with intra-VTA amphetamine compared to CSF-treated subjects, $F(1, 37) = 12.97$, $p < 0.005$ (Fig. 3). Amphetamine administered IP also produced a 50% greater locomotor response in HR compared to LR rats, $F(1, 38) = 6.92$, $p < 0.025$ (Fig. 3). There was also a trend for a novelty × infusion group interaction, $F(1, 37) = 3.41$, $p < 0.075$. There was, however, no infusion group × time interaction, $F(11, 418) = 1.19$, n.s., or novelty × time interaction, $F(11,418) = 1.31$, n.s. (Fig. 4D). Correlations between locomotor response to IP-administered amphetamine and locomotor response to novelty ($r = 0.37$, $p < 0.05$) and cocaine ($r = 0.48$, $p < 0.005$) but not caffeine ($r = 0.14$, n.s.) were observed.

Cocaine administered IP also produced 50% greater locomotor activity in subjects previously receiving intra-VTA amphetamine infusions compared to rats that had received intra-VTA CSF infusions, $F(1, 37) = 6.72$, $p < 0.025$ (Fig. 3). HR rats exhibited a 50% greater increase in locomotor activity following cocaine than LR rats, $F(1, 38) = 7.92$, $p < 0.01$ (Fig. 3). There was no novelty × infusion group interaction, $F(1, 37) = 0.55$, n.s., or infusion group × time interaction, $F(11, 418) = 1.41$, n.s. A novelty × time interaction was also not evident, $F(11, 418) = 0.98$, n.s. (Fig. 4E). A correlation existed between locomotor response to IP cocaine and loco-

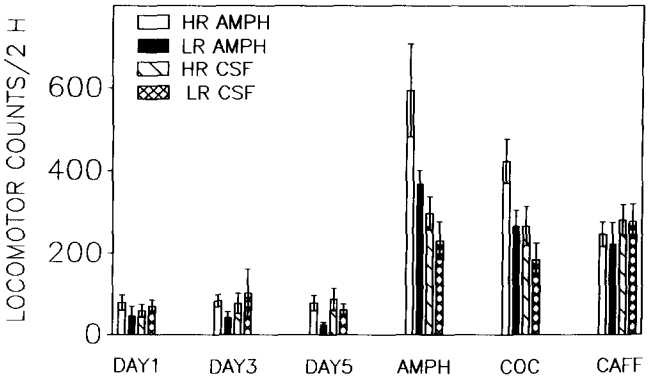

FIG. 3. Total locomotor counts for amphetamine infusions into the VTA and subsequent administration of amphetamine, cocaine, and caffeine IP (HR = 19, amphetamine infused = 9, CSF infused = 10; LR = 19, amphetamine infused = 9, CSF infused = 10). Vertical bars represent SEM.

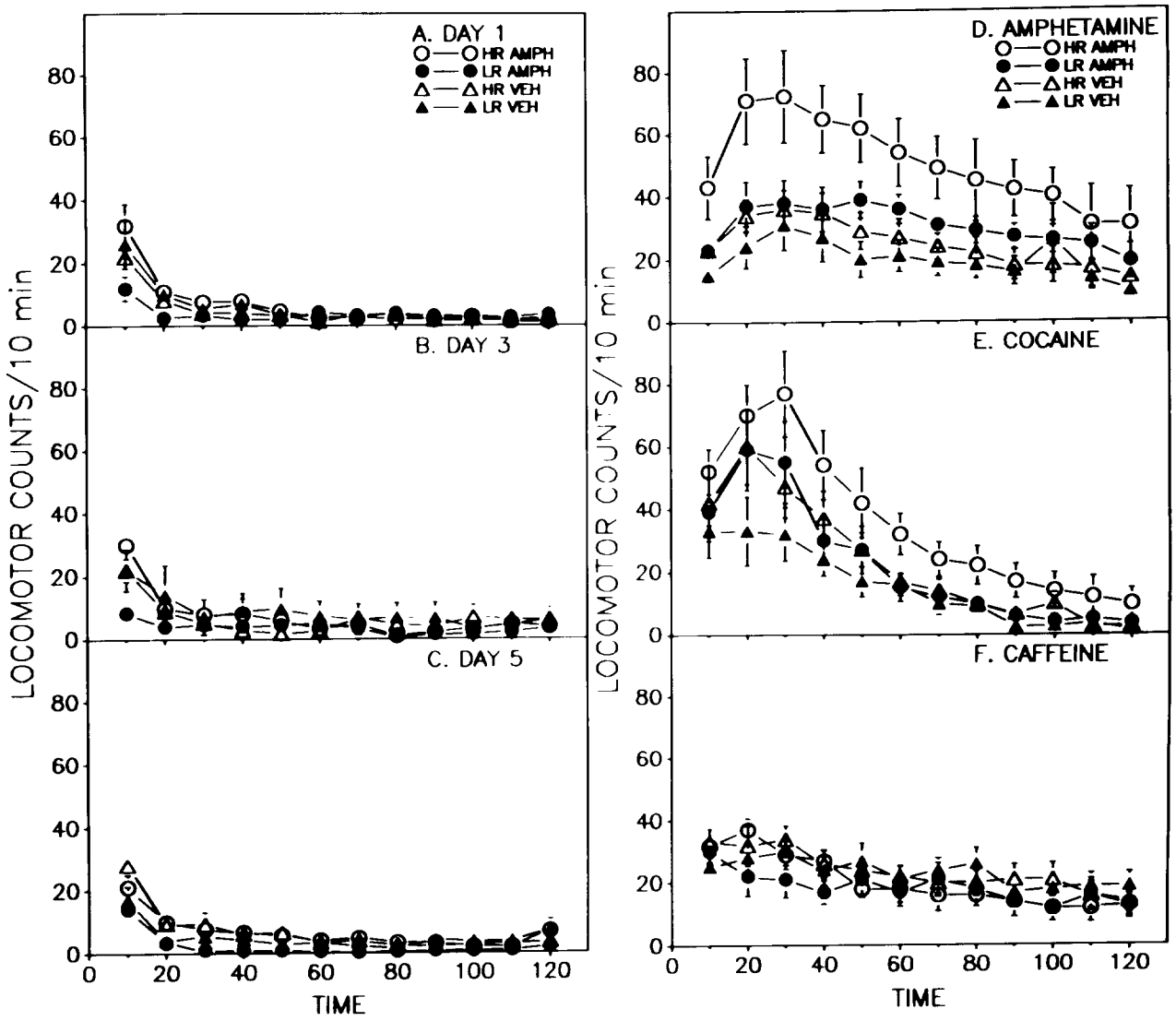

FIG. 4. Effects of amphetamine infusions into the VTA and subsequent administration of amphetamine, cocaine, and caffeine IP. No increase in locomotor activity was produced by intra-VTA infusions of amphetamine. While amphetamine ($p < 0.025$) and cocaine ($p < 0.025$) produced an overall difference between HR and LR rats, caffeine produced a novelty × time interaction ($p < 0.005$). Vertical bars represent SEM.

motor response to novelty ($r = 0.55$, $p < 0.0005$) but not to caffeine ($r = -0.05$, n.s.).

Following caffeine administered IP, there were no differences between rats previously infused with intra-VTA amphetamine or CSF, $F(1, 37) = 1.29$, n.s. (Fig. 3), or between HR and LR rats, $F(1,38) = 0.10$, n.s. (Fig. 3). There was no novelty × infusion group interaction, $F(1, 37) = 0.05$, n.s., or infusion group × time interaction, $F(11, 418) = 0.91$, n.s. There was, however, a novelty × time interaction, $F(11, 418) = 2.72$, $p < 0.005$ (Fig. 4F). No correlation between locomotor response to IP caffeine and locomotor response to novelty ($r = 0.06$, n.s.) was observed.

IP saline administration did not elicit differences between rats previously infused with intra-VTA CSF or amphetamine, $F(1, 37) = 1.75$, n.s. In addition, no differences were observed between HR and LR rats, $F(1, 37) = 0.53$, n.s., following saline.

Locomotor Activity Following Intra-MFC Amphetamine and Subsequent IP Injections

The results of intra-MFC infusions of amphetamine or CSF are depicted in Figures 5 and 6. Histological verification indicated that one rat had improper cannula placement and it was therefore excluded from analysis. There were no differences between rats infused with amphetamine or CSF, $F(1, 38) = 0.30$, n.s. (Fig. 5). No differences between HR and LR subjects resulted from intro-MFC infusion of amphetamine as shown by the lack of a novelty × drug interaction $F(1, 38) = 0.15$, n.s. (Fig. 5).

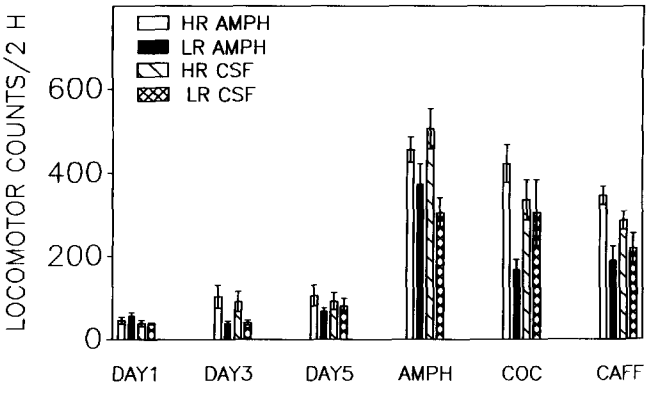

FIG. 5. Total locomotor counts for amphetamine infusions into the MFC and subsequent administration of amphetamine, cocaine, and caffeine IP (HR = 20, amphetamine infused = 10, CSF infused = 10; LR = 19, amphetamine infused = 10, CSF infused = 9). Vertical bars represent SEM.

Amphetamine administered IP did not elicit any differences between rats previously infused with intra-MFC amphetamine or CSF, $F(1, 37) = 0.11$, n.s. (Fig. 5). IP-administered amphetamine did produce a 40% higher locomotor response in HR compared to LR subjects, $F(1, 38) = 11.47$, $p < 0.0025$ (Fig. 5). Following amphetamine, there was no novelty × infusion group interaction, $F(1, 37) = 2.47$, n.s. In addition, there was no infusion group × time interaction, $F(11, 418) = 1.44$, n.s., or novelty × time interaction, $F(11, 418) = 1.29$, n.s. (Fig. 6D). A correlation, however, did exist between locomotor response to IP-administered amphetamine and locomotor response to novelty ($r = 0.38$, $p < 0.025$), cocaine ($r = 0.57$, $p < 0.0001$), and caffeine ($r = 0.49$, $p < 0.0025$).

Following cocaine administered IP, there were no differences between rats previously infused with amphetamine or CSF, $F(1, 37) = 0.20$, n.s. Following IP-administered cocaine, HR rats exhibited a 65% higher locomotor response than LR rats, $F(1, 38) = 7.54$, $p < 0.01$ (Fig. 5). In addition, there was a novelty × infusion group interaction, $F(1, 37) = 4.99$, $p < 0.05$). There was, however, no infusion group × time interaction, $F(11, 418) = 0.37$, n.s., but there was a novelty × time interaction, $F(11, 418) = 3.92$, $p < 0.0001$ (Fig. 6E). Moreover, there was a correlation between locomotor response to IP-administered cocaine and the locomotor response to novelty ($r = 0.54$, $p < 0.0005$), but not caffeine ($r = 0.30$, n.s.).

Caffeine administered IP did not produce any difference between rats previously infused with intra-MFC amphetamine or CSF, $F(1, 37) = 0.28$, n.s. (Fig. 5). There was, however, a difference between HR and LR rats, $F(1, 38) = 15.46$, $p < 0.0005$ (Fig. 5), following caffeine administration. There was no novelty × infusion group interaction, $F(1, 37) = 2.27$, n.s. (Fig. 5), or infusion group × time interaction, $F(11, 418) = 0.54$, n.s. Caffeine did not produce a novelty × time interaction, $F(11, 418) = 1.16$, n.s., in rats that had been MFC cannulated (Fig. 6F). There was a correlation between locomotor response to caffeine and locomotor response to novelty ($r = 0.40$, $p < 0.01$).

IP-administered saline produced no differences between rats previously infused with CSF or amphetamine, $F(1, 37) = 0.34$, n.s., or between HR and LR rats, $F(1, 37) = 3.58$, n.s.

DISCUSSION

Individual differences in sensitization following repeated peripheral administration of amphetamine have been recently demonstrated (11,12,32). It has also been shown that repeated amphetamine infusions into the VTA, but not the NACC, elicited sensitization to IP-administered amphetamine and cocaine (21). The data from the present study indicate that repeated intracranial infusions of amphetamine into the NACC, VTA, or MFC do not elicit differences between HR and LR rats. The current experiment did show that amphetamine, cocaine, and caffeine administered IP will elicit differences in locomotor response between HR and LR rats. In addition, repeated amphetamine infusions into the VTA, the dopamine cell body region, produced sensitization to IP-administered amphetamine and cocaine but not caffeine. However, repeated infusions of amphetamine into the NACC and MFC, dopamine terminal field regions, had no effect on subsequent locomotor response to IP-administered amphetamine, cocaine, or caffeine. These results suggest that while one region of the mesolimbic dopamine system may be primarily responsible for producing sensitization, the differences between HR and LR rats do not appear to be as localized in the mesolimbic system.

The data from previous and present work that show IP administration of cocaine and amphetamine producing differences between HR and LR rats in locomotor response (10–13,32,45) agrees with the hypothesis of mesolimbic dopamine being responsible for individual differences (32). However, caffeine in the present experiment and scopolamine in a past experiment (12) also produced differences between HR and LR rats in locomotor activity. These data argue against the sole involvement of mesolimbic dopamine in producing individual differences. Previous work has shown that 6-hydroxydopamine lesions of NACC dopamine greatly attenuate locomotor response to amphetamine and cocaine (16,17,26,27,34) but have no effect on the locomotor response to caffeine and scopolamine (16). This would indicate that an intact dopamine system is not necessary for caffeine and scopolamine to enhance locomotor activity. It is possible that differences in other transmitters in addition to dopamine may be producing the individual differences. This action may be separate or may be due to actions by other transmitter systems such as GABA, acetylcholine, or glutamate on the dopaminergic system.

In agreement with previous work (5,8,22), infusions of amphetamine into the NACC, but not the VTA or MFC, produce increases in locomotor activity. There was not, however, a difference between HR and LR rats in locomotor activity following either acute (11) or repeated infusion of amphetamine into the NACC. This is in contrast with the results following repeated infusions of cocaine into the NACC that did produce differences between HR and LR rats (10). One explanation is differences in dose. A complete dose response with amphetamine yielded a correlation between response to novelty and 3.0 μg amphetamine (11) but not higher or lower doses. The 3.0-μg dose was used in the present experiment and only produced a correlation with response to novelty after acute administration but not repeated infusion in the NACC. The differences in cocaine and amphetamine's actions on neuronal transmitters are also likely to be important. It is established that cocaine not only blocks dopamine uptake but also uptake of serotonin and norepinephrine (29). Amphetamine, on the other hand, increases the release of norepinephrine, serotonin, and dopamine and also inhibits their uptake. In addition, they act on the various neural systems to a different extent (29). These differences may contribute to the variation in response

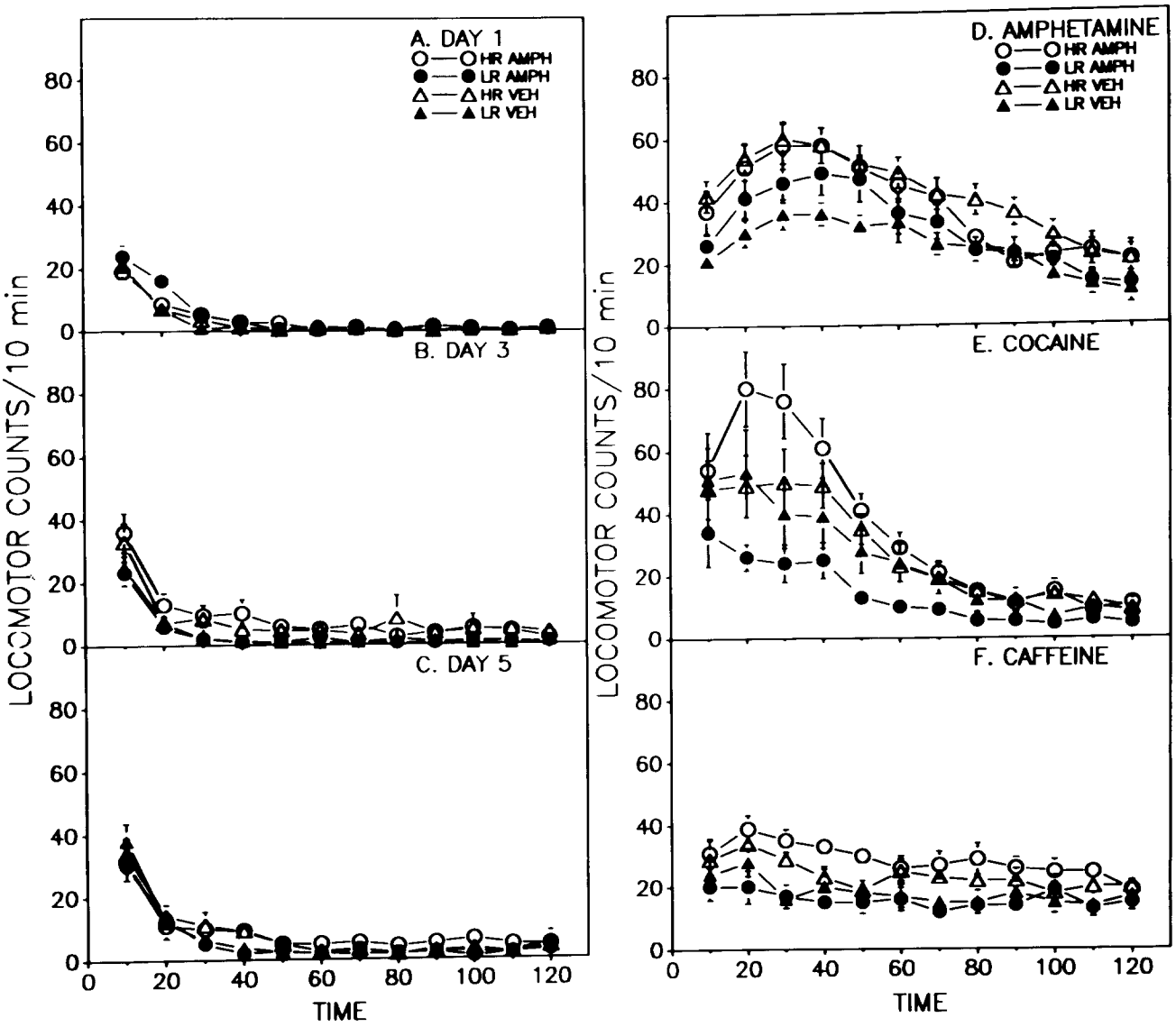

FIG. 6. Effects of amphetamine infusions into the MFC and subsequent administration of amphetamine, cocaine, and caffeine IP. No increase in locomotor activity was produced by intra-MFC infusions of amphetamine. Amphetamine ($p < 0.0025$), cocaine ($p < 0.01$), and caffeine ($p < 0.0005$) produced an overall difference between HR and LR rats. Only cocaine produced a novelty × time interaction ($p < 0.0001$). Vertical bars represent SEM.

to intracranial administration of the two drugs between HR and LR rats.

Repeated infusions of amphetamine into the terminal fields, the MFC and NACC, did not produce increase in locomotor activity to subsequent IP administration of amphetamine, cocaine, or caffeine. However, repeated infusions of amphetamine into the cell body region, the VTA, did produce increases in locomotor activity to a subsequent IP challenge of cocaine and amphetamine but not caffeine. This agrees with previous results (21) that show that infusions of amphetamine into the VTA, but not the NACC, increase the subsequent locomotor response to IP administration of amphetamine and cocaine. In addition, previous experiments have shown that while repeated infusions into the VTA of morphine (43,44) or a specific μ-opioid receptor agonist increase locomotor activity repeated infusions into the NACC have no effect. This increase in locomotor activity may be caused by increased transmission of NACC dopamine because substance P, neurotensin, enkephalin (3), glutamate (20,21), and apamin (41) infused into the VTA increase dopamine turnover in the NACC.

Repeated infusions of neurotensin or the enkephalin analog DAMGO increase extracellular dopamine levels in the NACC compared to acute treatment just as IP amphetamine and cocaine administration do (19,31,36). This may indicate that changes in dopamine transmission in the NACC produced by changes in the VTA are responsible for sensitization. It is also possible that the changes in NACC dopamine may be responsible for individual differences in sensitization because there was a trend toward differences in sensitization between

HR and LR rats following repeated intra-VTA infusions and there is a difference in NACC dopamine between HR and LR rats following cocaine (13).

While repeated infusions of amphetamine into the VTA induced sensitization to IP amphetamine and cocaine, they had no effect on the response to IP caffeine. It has previously been shown that while repeated administration into the VTA of enkephalin analogs produce sensitization to IP amphetamine no change in the locomotor response to caffeine is observed (18). A lack of cross-tolerance between repeated systemic administration of caffeine and amphetamine has also been demonstrated (9). The current experiment provides further evidence that the neurochemical changes elicited by chronic amphetamine do not alter the locomotor response to caffeine. This seems plausible because chronic caffeine administration causes the development of tolerance in locomotor response to future caffeine administration (9) while chronic amphetamine administration causes sensitization in behavioral responses to amphetamine challenge injections (35,37). Repeated amphetamine causes sensitization for only certain types of stimulants and not a general increase in locomotor activity to any form of stimulation (18,22,43).

The current experiment demonstrates the wide range of drugs whose locomotor response to systemic administration can be predicted by response to novelty and how this effect does not appear to be localized in one region of the mesolimbic dopamine system. While response to novelty has consistently predicted vulnerability to the systemic administration of drugs, it cannot as readily predict the response to centrally administered amphetamine. Data from the current experiment and previous experiments (11,13,33,40) indicate that individual differences in vulnerability to psychomotor stimulants do not localize to any of the regions examined. It appears as though either regions not examined, multiple neural systems, or changes in the same system in multiple regions may be producing differences in vulnerability to drugs of abuse. If the underlying neuronal mechanism for this variation can be established, it would aid in the treatment and prevention of drug abuse.

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