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Individual Differences in Amphetamine Sensitization: Dose-Dependent Effects

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HOOKS, M. S., G. H. JONES, D. B. NEILL AND J. B. JUSTICE, JR. *Individual differences in amphetamine sensitization: Dose-dependent effects.* PHARMACOL BIOCHEM BEHAV **41**(1) 203–210, 1992.—Rats were screened for locomotor activity in a novel environment and divided into high (HR) or low (LR) responders based on whether their locomotor score for the first hour was above or below the median. In the first experiment, HR and LR rats were compared for their locomotor response following repeated administration of either 0.0, 0.5, 1.0, or 1.5 mg/kg d-amphetamine sulfate (AMPH). Injections of either 0.5 or 1.0 mg/kg AMPH produced higher locomotor activity in HR rats than in LR rats. Furthermore, there was a correlation between the locomotor response to novelty and the response to either 0.5 or 1.0 mg/kg AMPH. In addition, whereas both groups of rats developed the same degree of sensitization to 0.5 mg/kg AMPH, only the HR rats developed pronounced sensitization to repeated administration of 1.0 mg/kg AMPH. When both HR and LR were considered, there was a significant correlation between response to novelty and the extent of sensitization to the locomotor-stimulating properties of 1.0 mg/kg AMPH. There were no differences in locomotor activity or sensitization between HR and LR rats following the highest dose of AMPH (1.5 mg/kg). In a separate experiment, HR and LR rats were compared for locomotor activity following a series of intracranial infusions of AMPH. There were no overall differences in locomotor activity between the HR and LR groups following AMPH infusions into either the nucleus accumbens (NACC) or the anterior dorsal striatum (ADS). However, the locomotor activity scores in the novel environment significantly correlated with the locomotor response to 3.0 μg AMPH infused into either the NACC or ADS. These results suggest that the locomotor response to novelty can predict both the initial locomotor response and degree of locomotor sensitization following low but not high doses of AMPH. In addition, variations in the NACC and/or the ADS may play a role in these individual differences.

Locomotor activity Sensitization Amphetamine Individual differences Novelty Nucleus accumbens Striatum Rat

THE behavioral and neurochemical responses to drugs of abuse, such as amphetamine (AMPH), show considerable variation between individual subjects (6). Previous experiments have demonstrated that a rat's locomotor response to a novel environment predicts AMPH self-administration behavior (6,20). Subjects who show a high locomotor response in a novel environment (high responders: HR) rapidly acquire and maintain low-dose AMPH self-administration, while subjects who have a low locomotor response to the novel environment (low responders: LR) do not readily acquire AMPH self-administration. It has also been demonstrated that the locomotor response to novelty is a good predictor of the locomotor response to psychomotor stimulant drugs including AMPH and cocaine (8, 9, 20).

Pronounced behavioral sensitization, including increased levels of locomotor activity and more intense behavioral stereotypy, is evident following repeated administration of AMPH (1,24). A relationship between the rate at which animals sensitize to the locomotor effects of peripheral AMPH administration and the response to novelty has been observed in two previous experiments (8,20). One study (20) showed that following repeated treatment with a high locomotor-producing dose of AMPH (1.5 mg/kg), the difference in locomotor activity between HR and LR rats was abolished, while a study from this laboratory (8) demonstrated that repeated administration of a low locomotor-producing dose of AMPH (0.5 mg/kg) enhanced the difference in locomotor activity between HR and LR rats. This apparent inconsistency may reflect dose-dependent differences between HR and LR rats.

Both humans and many species of animals undergo pronounced behavioral changes following repeated use of AMPH. While rats show increases in locomotor activity and stereotypic behavior following repeated AMPH, humans can develop drug-associated paranoid psychosis (5, 28, 30). The symptoms of this psychosis are very similar to paranoid schizophrenia (34). There is considerable variation between individuals in the development of these types of behaviors (5,24). It has been suggested that the development of paranoid psychosis is due to relatively permanent neural changes following AMPH exposure (24). Physical and psychological stress has been shown to precipitate psychotic episodes in AMPH addicts (31,32). This suggests that stress and AMPH may act on similar neuronal pathways in humans. Responses to novelty may provide a model for predicting the vulnerability to develop paranoid psychosis since both exposure to novelty (21) and amphetamine (13,16) activate similar neural

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circuits and are considered to act as stressors (2,16).

The locomotor response to a novel environment (13,17) and to amphetamine (13, 16, 17, 25) has been shown to be dependent upon mesolimbic dopamine, as large 6-hydroxydopamine (6-OHDA) lesions of this pathway decrease the behavioral response to novelty and to AMPH. In addition, increases in dopaminergic activity have been observed following both exposure to novelty (21) and to amphetamine (25). As many of the behavioral responses to AMPH and novelty are strongly dependent upon dopaminergic mechanisms of the nucleus accumbens (NACC) and striatum (14,16), the differences between HR and LR rats may be due to variations in the responsiveness of these two structures.

Conventional stressors such as footshock are known to enhance the locomotor response to systemic administration of AMPH (2,7). This effect is thought to be due to increased sensitivity of NACC dopaminergic mechanisms (24,25). This view is supported by the fact that prior exposure to stress also increases the locomotor response to infusions of AMPH directly into the NACC (11,18). Changes in NACC and striatal dopamine levels have also been observed after stress and chronic drug administration (4, 24, 25). These data provide evidence that the striatum and NACC are two possible regions from which individual differences in the response to psychomotor stimulants could originate.

The purpose of the present experiments was to determine if the differences in sensitization between HR and LR rats are dose dependent and if the differences are related to the responsiveness of the striatum and/or the NACC.

METHOD

Subjects

In all experiments, male Wistar rats (SASCO, Experiment 1 n=64; Experiment 2 n=34) weighing 290–340 g were used. Rats were housed four per cage on a 12-h light-dark cycle (lights on from 0700–1900 h) with free access to food and water. Subjects were handled for approximately 5 min on two consecutive days prior to their first exposure to the test cages. Testing was conducted between 0800–1700 h.

Apparatus

Plexiglas photocell cages (39 cm long × 25 cm wide × 24 cm high) 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.

EXPERIMENT 1: REPEATED IP AMPHETAMINE

The first experiment was designed to determine the relationship between the locomotor response to a novel environment and locomotor sensitization to various doses of systemically administered AMPH. Several doses of AMPH that primarily produce locomotor activity were used to determine whether individual differences in sensitization are dose dependent.

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 high responders (HR) or low responders (LR) based on whether their locomotor activity scores for the first hour were above or below the median locomotor activity for the subject sample (8,20). Rats were assigned to one of four groups to receive repeated administration of either vehicle, 0.5, 1.0, or 1.5 mg/kg of d-amphetamine sulfate (Sigma Chemical Co.). Each drug group contained 16 rats (HR=8, LR=8). Drugs were administered in a volume of 0.1 ml per 100 g in 0.9% saline. Drug groups were balanced according to the locomotor response to novelty and to body weight.

Subjects were not tested the day before the initial drug treatment. On test days 1, 3, 5, 7, and 9, the rats were weighed and 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 injection. On test days 2, 4, 6, and 8, animals received the appropriate dose of amphetamine in the home cage to minimize environmental conditioning (8). Drugs were administered by a researcher unaware of the experimental conditions.

Data Analysis

Locomotor activity counts were subjected to analysis of variance (ANOVA). 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 AMPH-induced activity.

RESULTS

The screening for locomotor response to the novel environment resulted in a classification of two groups, HR (91 ± 4, mean ± SEM) and LR (53 ± 2), with a different locomotor response during the first hour of exposure, $F(1,56)=90.10$, $p<0.0001$. However, both groups of animals did habituate to the test cage, and they did not differ in locomotor activity during the 30 min prior to drug administration on any test day, $F(3,56)=0.53$, n.s.

AMPH administration (Fig. 1) increased locomotor activity in a dose-dependent manner, $F(3,56)=20.69$, $p<0.0001$. Post hoc analysis revealed a significant increase in locomotor activity following the 0.5-mg/kg ($p<0.01$), 1.0-mg/kg ($p<0.01$), and the 1.5-mg/kg ($p<0.01$) doses of AMPH compared with the saline control group. HR rats showed a greater locomotor response for the 2-h period following AMPH compared to LR rats, as demonstrated by a significant main effect of Novelty group, $F(1,63)=6.54$, $p<0.02$. In addition, there was a Novelty group × Dose interaction [$F(1,63)=2.86$, $p<0.05$, Fig. 1]. There were no differences between HR and LR rats following saline administration [$F(1,14)=0.27$, n.s., Fig. 1]. Figures 2, 3 and 5 show a more detailed analysis of these effects including the time-course of locomotor activity.

After exposure to AMPH, there were no differences between drug treatment groups in the initial 1 h of habituation to the test cages on test days 3, 5, 7, and 9, $F(1,56)=1.02$, n.s., indicating a lack of environmental conditioning.

Figure 2 shows the time course of the results following administration of 0.5 mg/kg AMPH. HR rats had substantially higher locomotor activity than LR rats following this dose of AMPH, $F(1,14)=7.26$, $p<0.01$. Subjects showed a development of sensitization to this dose of AMPH, $F(4,56)=4.03$, $p<0.01$, but there were no differences between HR and LR rats, as revealed by the fact that there was no Novelty × Days interaction, $F(4,56)=0.18$, n.s. Least-squares analysis revealed a correlation between locomotor response to novelty and the loco-

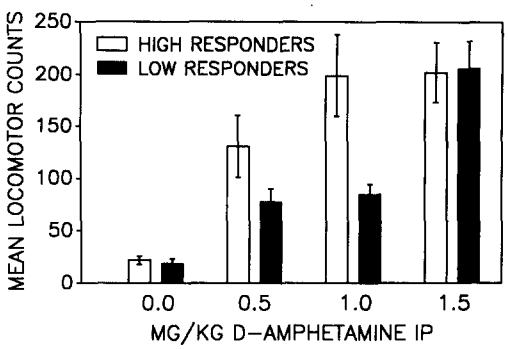

FIG. 1. Mean total locomotor counts following drug administration (n = 16 per dose; HR = 8, LR = 8) for days 1, 3, 5, 7, and 9. There was a dose-dependent increase in locomotor activity following AMPH ($p<0.0001$). In addition, there was a Novelty group × Dose interaction ($p<0.05$). The vertical bars represent the standard error of the mean.

motor response to 0.5 mg/kg AMPH (r = .64, $p<0.01$, not shown).

The results for locomotor activity following the 1.0-mg/kg AMPH administration are depicted in Fig. 3. HR rats had higher locomotor activity than LR rats following administration of 1.0 mg/kg AMPH, $F(1,14) = 5.60$, $p<0.05$. Subjects developed significant locomotor sensitization to AMPH, as revealed by a main effect of Days, $F(4,56) = 10.56$, $p<0.0001$. Figure 3F shows how this sensitization differed between the two Novelty groups, as indicated by a Novelty × Days interaction, $F(4,56) = 5.97$, $p<0.0001$. When analyzed separately, the HR rats demonstrated locomotor sensitization, $F(4,28) = 10.40$, $p<0.0001$, while the LR rats showed no sensitization, $F(4,28) = 1.07$, n.s. Least-squares analysis revealed that the locomotor response following the initial exposure to AMPH did not correlate with response to novelty (r = .27, n.s.), but locomotor activity on test day 9 did correlate with the locomotor response to novelty (r = .84, $p<0.0001$). The change in a subject's locomotor activity following repeated exposure to 1.0 mg/kg AMPH was related to the response to the novel environment, as revealed by a correlation between the locomotor response to novelty and the change in activity scores from days 1–9 (r = .79, $p<0.0005$, Fig. 4).

There were no differences between HR and LR rats following administration of 1.5 mg/kg AMPH [$F(1,14) = 0.02$, n.s., Fig. 5]. However, there was a change in locomotor activity with repeated administration of this dose of AMPH, as revealed by an effect of Days, $F(4,56) = 3.02$, $p<0.025$. This effect was characterized by an increase in locomotor activity from day 1 to day 3 and then a gradual decline in locomotor scores probably due to the development of other stereotyped forms of behavior.

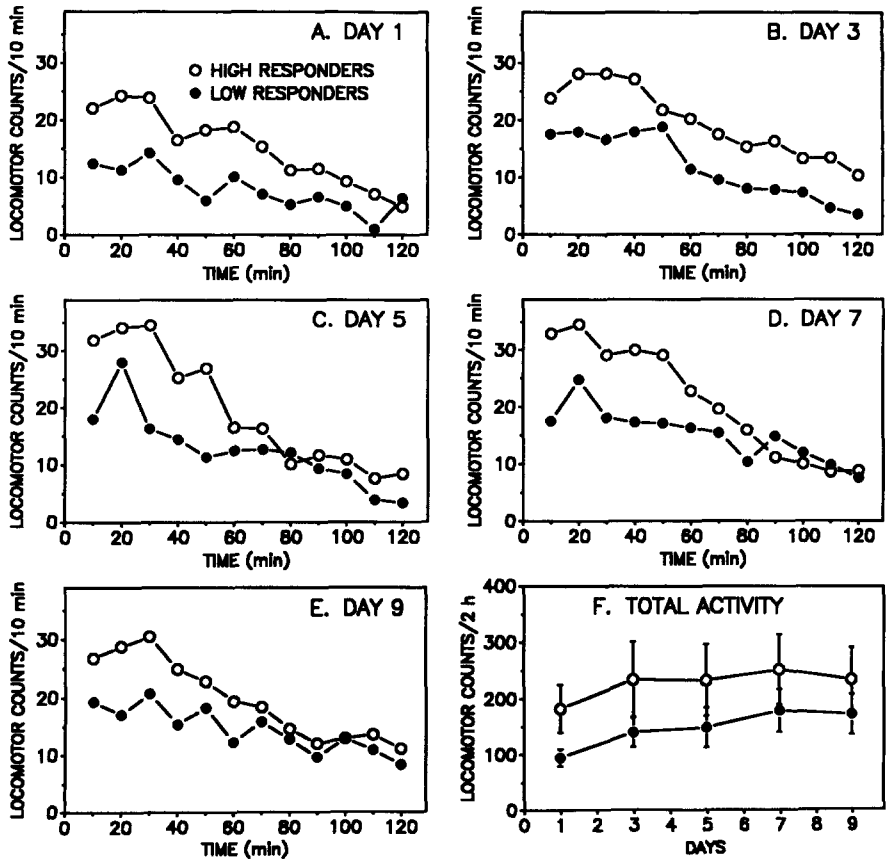

FIG. 2. Effects of 0.5 mg/kg AMPH administration on locomotor activity in high (HR, n = 8) and low (LR, n = 8) responders on test days 1, 3, 5, 7, and 9. Panel (F) depicts the total locomotor activity for each 2-h session. There was an overall difference between high and low responders following amphetamine administration ($p<0.01$). The vertical bars represent the standard error of the mean.

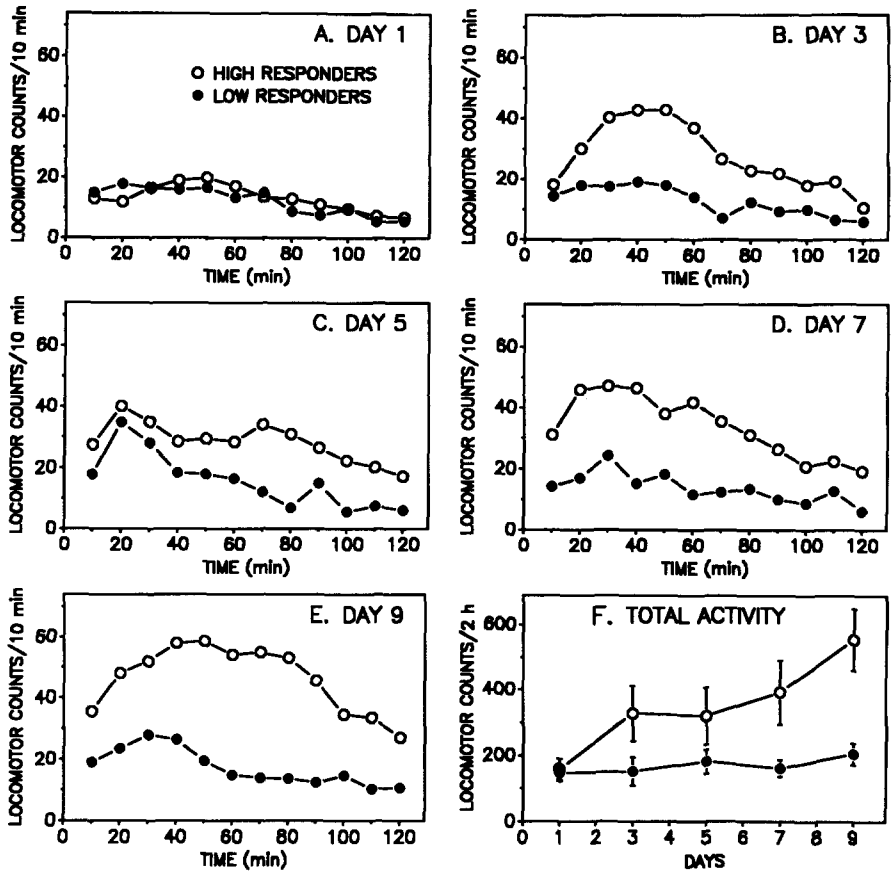

FIG. 3. Effects of 1.0 mg/kg AMPH administration on locomotor activity in high (HR, n=8) and low (LR, n=8) responders on test days 1, 3, 5, 7, and 9. Panel (F) depicts the total locomotor activity for each 2-h session. Following AMPH administration, high-responding rats showed a greater locomotor response than LR rats ($p<0.05$). Only high-responder rats developed sensitization to repeated administration of this dose of AMPH ($p<0.0005$). The vertical bars represent the standard error of the mean.

DISCUSSION

Recently, it has been demonstrated that the level of locomotor activity produced by various locomotor-stimulating drugs can be predicted by an animal's locomotor response to a novel environment (8,20). The present experiments support the results of our previous study (8) in that there are differences between HR and LR rats following exposure to 0.5 mg/kg AMPH. Moreover, the rate at which rats sensitize over a 9-day period to a 1-mg/kg dose of the drug can be predicted by the locomotor response to a novel environment. HR rats displayed a significant increase in locomotor activity following repeated administration of 1.0 mg/kg AMPH. LR rats, however, show no increase in locomotor activity following repeated administration of 1.0 mg/kg AMPH. This indicates that HR rats are more vulnerable to the locomotor-sensitizing properties of AMPH than LR rats at this dose.

Administration of 1.5 mg/kg AMPH produced no differences in locomotor activity between HR and LR rats either acutely or following repeated treatment. The experiment confirms previous studies showing that differences between HR and LR rats are not evident following repeated administration of 1.5 mg/kg AMPH (20). One possible explanation for this lack of differences between HR and LR rats at higher doses of AMPH is that at these doses, locomotor activity is maximally increased. At higher doses of AMPH [e.g., 1.75 mg/kg; (29)], increases in both locomotor activity and stereotypy are exhibited. As forms of stereotypic behavior such as sniffing, licking and biting increase, locomotor activity tends to decrease. Thus there appears to be a certain degree of competition of expression between these behaviors. The more intense forms of stereotypy are also observed with repeated administration of doses of AMPH which do not normally induce these behaviors following acute administration (28). For example, repeated administration of 1.0 mg/kg AMPH over a 15-day period significantly increases behavioral stereotypy (27).

Not only are there no differences in locomotor activity or sensitization between HR and LR rats following the higher dose of 1.5 mg/kg AMPH, but also repeated exposure to this dose of the drug abolishes the differences between HR and LR rats in the acquisition of AMPH self-administration (6,20).

Therefore, it appears that locomotor activity in a novel environment can consistently predict locomotor activity following low locomotor-producing doses of AMPH. There is not the same relationship between the behavioral effects of higher doses of AMPH and the novelty response. These data suggest that differences in the locomotor response to novelty are more likely to be influenced by activity in mesolimbic rather than mesostriatal dopaminergic projections.

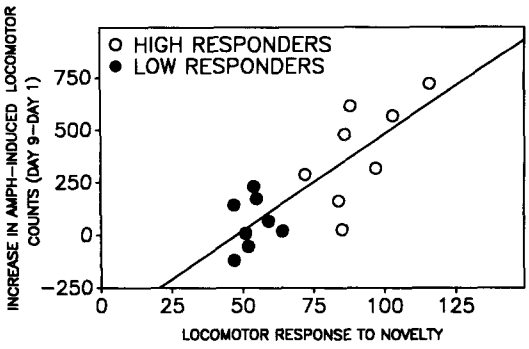

FIG. 4. The correlation of locomotor response to novelty and the change in locomotor activity from day 1 to day 9 for repeated administration of 1.0 mg/kg AMPH ($r = .79$, $p < 0.0005$).

EXPERIMENT 2: INTRACRANIAL AMPHETAMINE

In a second experiment, the locomotor response to intracranial AMPH administration was measured in both HR and LR rats to determine the possible role of the NACC and anterior dorsal striatum (ADS) in these individual differences.

Surgical and Infusion Procedures

Rats were anesthetized with 50 mg/kg IP sodium pentobarbital (Nembutal) and placed in a stereotaxic frame (David Kopf, Tujunga, CA). Bilateral stainless steel guide cannulae (22 gauge) were implanted to access either the NACC, AP +3.4 from bregma, Lat ±1.7, Vert −6.5 from dura with the incisor bar set at +5 mm (19), or the ADS, AP +3.1 from bregma, Lat ±3.0, Vert −3.5 from dura with the incisor bar set at +5 mm (19). The guide cannulae were secured in place with the use of skull screws and dental cement. Removable stylets (31 gauge) were placed in the guide cannulae. Intramuscular penicillin (60,000 units) 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-gauge infusion cannulae which protruded 1 mm below the guide cannulae. The infusion cannulae were attached via plastic (PE10) tubing to 10-μl syringes mounted on a Razel infusion pump (Model A). 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. The subjects were held lightly in a towel during the infu-

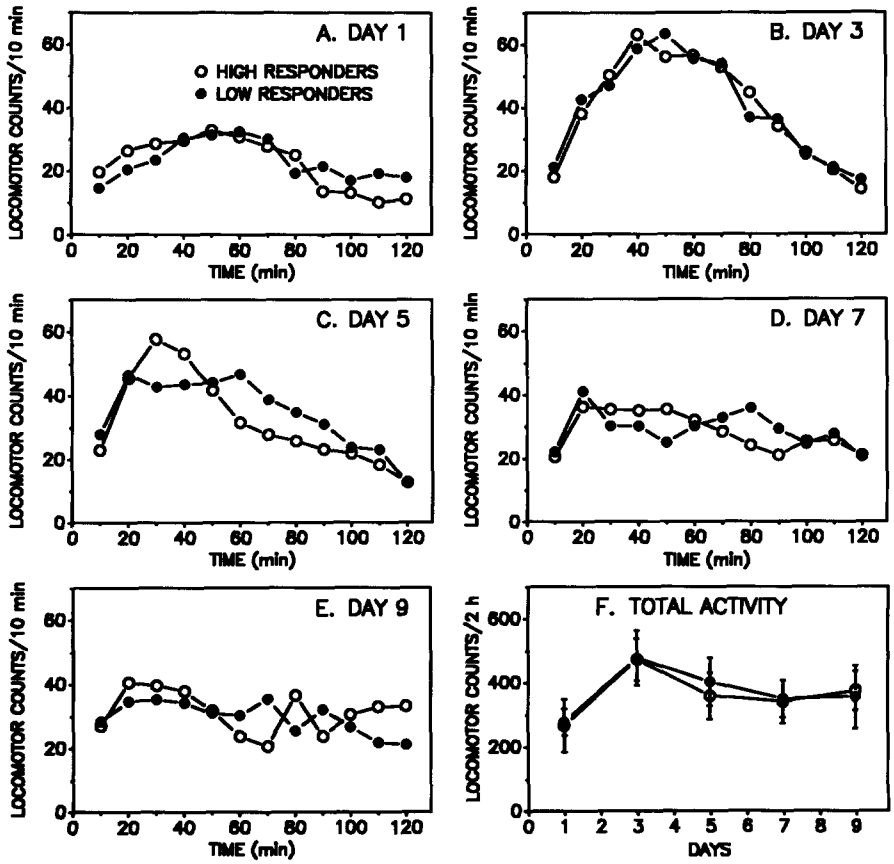

FIG. 5. Effects of the 1.5-mg/kg AMPH administration on locomotor activity in high (HR, n = 8) and low (LR, n = 8) responders on test days 1, 3, 5, 7, and 9. Panel (F) depicts the total activity for each 2-h session. There were no differences between high- and low-responder rats after administration of 1.5 mg/kg AMPH. The vertical bars represent the standard error of the mean.

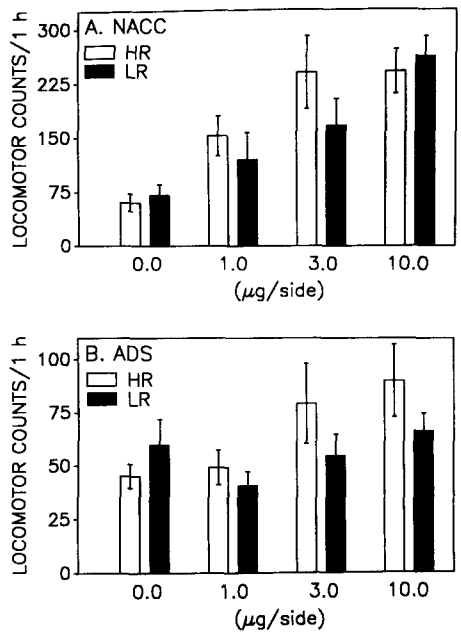

FIG. 6. Effects of AMPH infusion in the nucleus accumbens (NACC: n=9 HR, n=9 LR) on locomotor activity is represented in Panel (A). Effects of AMPH infusion into the anterior dorsal striatum (ADS: HR, n=8; LR, n=8) on locomotor activity are represented in Panel (B). There were no differences between high- and low-responding subjects. The vertical bars represent the standard error of the mean.

sion. D-Amphetamine sulfate was dissolved in artificial cerebrospinal fluid (CSF) consisting 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.

Behavioral Procedure

After recovery from surgery and two days before the initial drug treatment, subjects were placed in photocell cages for a 2-h period and screened for their response to novelty. They were then divided into HR and LR groups as described in Experiment 1. Each rat was assigned to receive a series of d-amphetamine sulfate infusions (0, 1, 3, or 10 μg/side) into either the NACC or the ADS. A Latin-square design was used to determine the sequence of infusions which allowed each rat to serve as its own control. Locomotor activity was monitored for 1 h following each infusion. A 48-h period separated each of the four test sessions in order to ensure recovery from the effects of the drug infusion.

Histology

At the completion of testing, subjects were anesthetized with 400 mg choral hydrate and perfused transcardially with 50 ml of saline followed by 50 ml of 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). 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 AMPH-induced activity.

RESULTS

Figure 6A shows locomotor activity following AMPH infusions into the NACC. Histological verification indicated that 3 of the NACC rats and 1 of the ADS rats had improper cannula placements and were therefore excluded from analysis. There was a significant dose-dependent effect of intra-NACC AMPH on locomotor activity, $F(1,16)=17.33$, $p<0.0001$. Post hoc comparisons revealed that the 1.0 ($p<0.01$)-, 3.0 ($p<0.01$)-, and the 10.0 ($p<0.01$)-μg doses of AMPH produced higher locomotor scores than CSF administration. AMPH infusion produced higher locomotor activity immediately following infusion, as revealed by a Drug × Time interaction, $F(33,528)=3.52$, $p<0.0001$. There were no differences between HR and LR rats following NACC infusion of AMPH, $F(1,16)=0.29$, n.s.

When all subjects were analyzed, there was a correlation between subject's locomotor response to the novel environment and its locomotor response to 3.0 μg AMPH ($r=.52$, $p<0.025$), but not to its response to either 0.0 ($r=-0.15$, n.s.), 1.0 ($r=.23$, n.s.), or 10.0 ($r=.13$, n.s.) μg AMPH.

Increases in locomotor activity following infusion of AMPH into the ADS were dose dependent, as indicated by a main effect of dose [$F(1,14)=5.16$, $p<0.005$, Fig. 6B]. Post hoc analysis revealed a significant increase in locomotor activity following either the 3.0 ($p<0.05$)- or the 10.0 ($p<0.05$)-μg doses of AMPH. There were no differences between HR and LR subjects following ADS infusion of AMPH, as indicated by a nonsignificant effect of Novelty, $F(1,14)=0.79$, n.s.

There was, however, a correlation between an animal's locomotor response to a novel environment and locomotor response to the 3.0-μg injection of AMPH ($r=.65$, $p<0.01$). This trend was also seen for the 1.0-μg dose ($r=.48$, $p<0.06$), but not for the 10.0 ($r=.39$, n.s.)- or 0.0 ($r=-.18$, n.s.)-μg doses.

DISCUSSION

The intracranial data partially support the suggestion that the NACC and ADS play a role in these individual differences. Although no overall difference was observed between HR and LR rats following infusions into either the NACC or ADS, a correlation between locomotor response to 3.0 μg of AMPH and the locomotor response to novelty was observed. The lack of difference between HR and LR rats may be due to the use of the Latin-square design. Differences in nonspecific damage may cause additional variability which may override the individual differences. In addition, with this experimental design, each subject receives several doses of drug which may also mask potential individual differences. Another possible reason is that individual differences are due to variations in many brain regions which combine to yield the overall effect following IP administration. It does appear that variation in the NACC and ADS may contribute to the behavioral differences observed between individual subjects.

GENERAL DISCUSSION

The varying degree of responsiveness both to novelty and to AMPH between individual subjects in the present experiments may originate from either innate or environmental factors or both. For example, different strains of rats (33) or rats exposed to various forms of stress such as foot shock (7), tail pressure (2), food deprivation (3), or social deprivation (10,26) show altered responses to psychomotor stimulants. These alterations in

the response to novelty and to drugs like amphetamine or cocaine may result from changes in common neural mechanisms. It has been suggested, for example, that variations in the responsiveness of the dopaminergic system may play a role (9,20). Previous studies have demonstrated that prior exposure to foot shock (7,30) or social isolation (11) alters subsequent dopaminergic responses. There are also data to suggest that exposure to novelty acts as a mild form of stress (15), and it has been demonstrated that HR and LR rats differ in their NACC and prefrontal cortex dopaminergic responses to a novel environment (21). Moreover, HR rats show a greater increase in NACC dopamine following cocaine than LR rats (9). These findings together with evidence that 6-OHDA lesions (12, 16, 17, 22, 23) of the NACC and ADS reduce the response to psychomotor stimulants and to novelty suggest that variations in these behavioral responses may originate in the dopaminergic projections to these brain regions.

The data from Experiment 2 partially support the suggestion that the NACC and ADS may play a role in these individual differences in locomotor behavior. Previously, studies have demonstrated that infusions of AMPH directly into the NACC and ADS increase locomotor activity in rats (14), and prior exposure to stress can enhance these effects (11,18). For example, foot shock potentiates the subsequent locomotor response to the locomotor-stimulating properties of AMPH infused into the NACC (18), and social isolation increases the locomotor response to low intra-NACC doses of AMPH (e.g., 3.0 μg/side), but not to higher doses [10 μg/side: (11)]. This latter finding is particularly relevant, as isolated rats consistently show a heightened responsiveness to a novel environment (11,26). The data from the present experiments have demonstrated a correlation between response to novelty and to infusions of AMPH directly into either the NACC or ADS. Taken together, these data suggest that activity in these brain regions underlies the responsiveness to novelty and to psychomotor stimulants.

The current results also indicate that the degree to which an individual subject develops sensitization to the locomotor-stimulating properties of AMPH is also related, at least to a certain extent, to the locomotor response to novelty. These findings suggest that the response to novelty may provide an effective screening process for identifying individuals with a vulnerability to exhibit sensitization to psychomotor stimulants. These suggestions appear to have some validity, as recent clinical literature has suggested that individuals with higher levels of novelty-seeking behavior are more likely to develop psychosis and other behavioral disorders than those with low novelty-seeking behavior (5).

Further study is needed to determine the origins and underlying neuronal mechanisms involved in these individual differences, as this may lead to further understanding of the basis for vulnerability to drugs of abuse and the development of some psychopathological disorders.

ACKNOWLEDGEMENTS

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