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BRIEF COMMUNICATION

Individual Differences in Locomotor Activity and Sensitization

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HOOKS, M S , G H. JONES, A D SMITH, D B NEILL AND J. B JUSTICE, JR *Individual differences in locomotor activity and sensitization* PHARMACOL BIOCHEM BEHAV **38**(2) 467–470, 1991.—Male rats were screened for locomotor activity in a novel environment and divided into high (HR) and low (LR) responders based on whether their locomotor activity score for the first hour was above or below the median locomotor activity for the subject sample. Subsequently, the locomotor response to repeated administration of either amphetamine (AMPH, 0 5 mg/kg), cocaine (10 mg/kg), scopolamine (0 5 mg/kg) or saline was monitored in separate groups of HR and LR rats HR rats had significantly higher overall activity scores than LR rats for all 3 drugs. Both HR and LR rats developed tolerance at the same rate to repeated scopolamine administration. In contrast, only HR rats showed pronounced sensitization to the locomotor stimulating properties of AMPH and a direct correlation was evident between the locomotor response to novelty and the magnitude of sensitization These results suggest that an individual's response to a novel environment can, to a certain extent, predict drug-induced locomotor activity and that individual differences in the response to novelty and sensitization to AMPH may result from individual variations in a common neural mechanism.

Individual differences Locomotor activity Sensitization Tolerance Amphetamine Cocaine Scopolamine Novelty Rat

THERE are noticeable differences in the amount of drug exposure required for individual animals and humans to become addicted (11). Furthermore, the behavioral and neurochemical responses to drugs of abuse, such as cocaine and amphetamine (AMPH), show considerable variation between individual subjects (3). It has recently been shown that the rate at which rats acquire AMPH self-administration and the level of locomotor activity induced by the drug are related to an individual's locomotor response to a novel environment (3,13). Rats that show the higher response to novelty exhibit higher locomotor activity following AMPH and acquire self-administration more readily than rats with lower activity levels. High responding rats are also reported to show greater elevations in plasma corticosterone than low responding rats on exposure to a novel environment (13), and although differential responsiveness to stress may be an important component, the possible factors underlying these individual differences are not fully understood.

The current experiment was designed to examine whether the locomotor response to novel stimuli can predict the level of locomotor activity induced by AMPH and cocaine, which predominantly act through dopaminergic mechanisms, and scopolamine (SCOP), an anticholinergic drug. The locomotor hyperactivity produced by cocaine and AMPH is dependent on the functional integrity of the mesolimbic dopamine pathway (7,8). However, the increases in activity following SCOP are not influenced by disruption of nucleus accumbens dopamine (6). Therefore, the response to these drugs should provide additional information as to the possible neural basis for individual differences.

Repeated administration of AMPH can result in pronounced sensitization to the behavioral effects of the drug, including increasing levels of locomotor activity and more intense behavioral stereotypy (15). This phenomenon also shows large variations between individuals and can apparently be predicted from the initial response to the drug (17). Sensitization to psychomotor stimulants may play an important role in an individual's propensity to self-administer these drugs (13) Therefore, an additional aim of this experiment was to determine the predictability of individual differences in sensitization (or tolerance) to these drugs from the locomotor response in a novel environment

METHOD

Subjects

Male Wistar rats (SASCO, n = 64) weighing 290–350 g were

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housed four per cage on a 12-h light-dark cycle (lights on from 07 00–19.00 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 08.00–17 00 h.

Apparatus

Locomotor activity was measured in Plexiglas photocell cages (39 cm long × 25 cm wide × 24 cm high). Each cage was equipped with two parallel horizontal infrared beams, 2 cm above the floor, spaced equally along the long axis of the cage. Interruption of alternate beams resulted in a locomotor count that was registered by an IBM computer. Illumination was provided by a light on the roof of each photocell cage.

Drugs

D-Amphetamine sulfate, cocaine hydrochloride and scopolamine hydrochloride (Sigma Chemical Co., St. Louis, MO) were dissolved in 0.9% saline and injected IP in a volume of 0.1 ml/100 g.

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 (HR) and low (LR) responders based on whether their locomotor activity scores for the first hour were above or below the median locomotor activity for the subject sample (13). Rats were randomly divided into four groups to receive either d-amphetamine sulfate (0.5 mg/kg), cocaine hydrochloride (10 mg/kg), scopolamine hydrochloride (0.5 mg/kg) or saline (n = 16 for each drug; HR = 8 and LR = 8). Doses of drugs were chosen to produce similar locomotor activation on the first day of drug treatment.

Subjects were not tested the day before the initial drug treatment On test days 1, 3, and 5, the rats were weighed and placed in the test cages for a 90-min habituation period prior to drug administration. Locomotor activity was measured for a further 2 h after each injection. On test days 2 and 4 animals received the appropriate drug in the home cage. Drugs were administered by a researcher unaware of the experimental conditions. The order of testing each day was counterbalanced so that equal numbers of HR and LR rats were tested in each session.

Locomotor activity counts were subjected to analysis of variance (ANOVA) (18). Where appropriate, post hoc comparisons were made using Newman-Keuls analysis. A least-squares linear regression analysis was conducted to examine the relationship between locomotor activity in a novel environment and drug-induced activity.

RESULTS

As expected, on the day animals were screened for their locomotor response to the novel environment HR (mean counts = 119 ± 4) and LR (mean counts = 72 ± 2) were significantly different during the first hour of exposure, $F(1,56) = 32.89$, $p<0.0001$. However, subjects did show habituation to the test environment and on test day 1 HR and LR rats also did not differ in any drug group for the first hour in the photocell cages HR and LR rats also did not differ in activity scores for the 30 minutes immediately preceding drug treatment on any test day, $F(3,56) = 0.42$, n s.

Differences between HR and LR rats were dependent upon drug administration as revealed by a significant Group × Drug interaction, $F(3,56) = 5.19$, $p<0.004$. ANOVA indicated that HR and LR rats did not differ following saline on any test day, $F(1,14) = 0.002$, n.s. (Fig 1). There was no correlation between a subject's locomotor response to novelty and that following saline ($r = 29$).

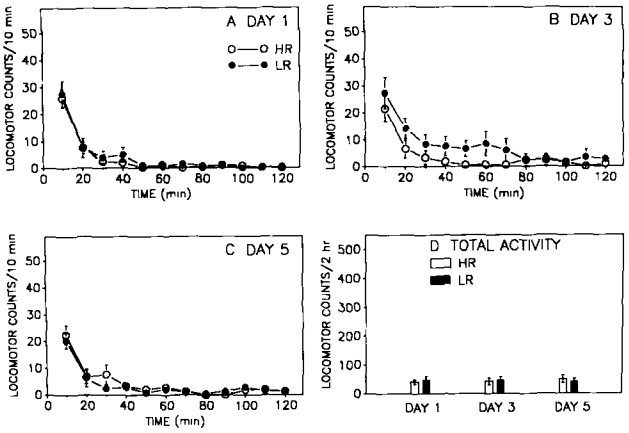

FIG 1 Locomotor activity following saline administration in HR and LR rats A, B, and C show the locomotor activity scores on test days 1, 3, and 5, respectively D shows the total counts for each two-hour test period Error bars represent S E M There were no differences between HR and LR rats following saline administration

The results for locomotor activity following AMPH, cocaine and SCOP are shown in Figs 2–4. The rats in the HR group that received AMPH had substantially greater activity scores than LR rats, $F(1,14) = 10.99$, $p<0.006$. AMPH-treated subjects showed pronounced sensitization to the locomotor stimulating properties of the drug, when HR and LR were treated as a single group, $F(2,28) = 7.38$, $p<0.003$. Post hoc comparisons indicate that amphetamine-induced locomotor activity was greater on day 5 than on both day 1 ($p<0.01$) and day 3 ($p<0.05$).

Strikingly different profiles were seen in the HR and LR rats with repeated AMPH injection, $F(2,28) = 5.31$, $p<0.02$ (Fig. 2).

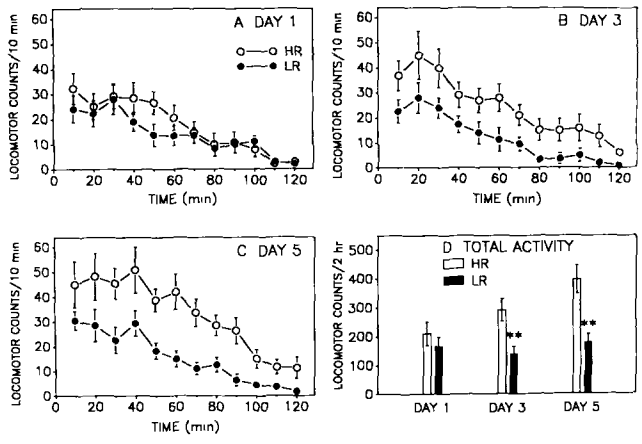

FIG 2 Locomotor activity following AMPH (0 5 mg/kg) administration in HR and LR rats A, B, and C show locomotor activity scores on test days 1, 3, and 5, respectively D shows the total counts for each two-hour test period Error bars represent S E M HR rats showed significantly more AMPH-induced locomotor activity than LR rats ($p<0.006$) and differentially sensitized to the locomotor stimulating properties of the drug ($p<0.02$) **$p<0.01$, represents significant difference between HR and LR rats

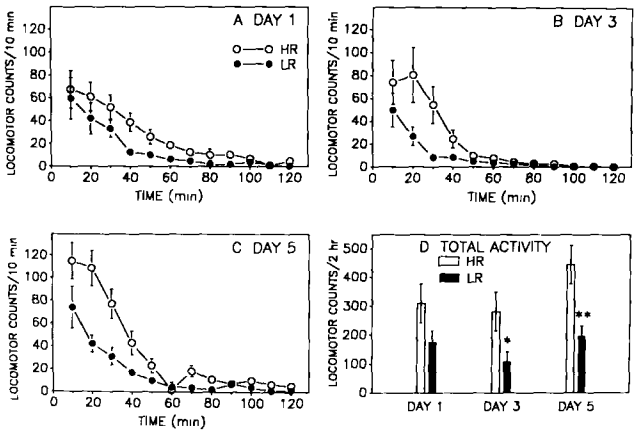

FIG 3 Locomotor activity following cocaine (10 mg/kg) administration in HR and LR rats A, B, and C show locomotor activity scores on test days 1, 3, and 5, respectively D shows the total counts for each two-hour test period Error bars represent S E M HR rats were significantly more active than LR rats following cocaine ($p<0$ 003) *$p<0$ 05 and **$p<0$ 01, represent significant differences between HR and LR rats

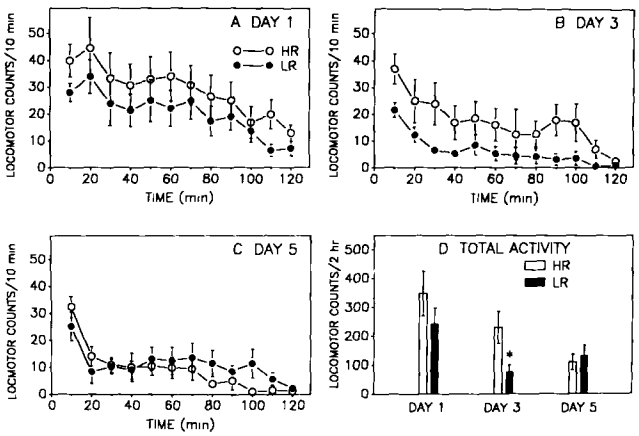

FIG 4 Locomotor activity following SCOP (0 5 mg/kg) administration in HR and LR rats A, B, and C show locomotor activity scores on test days 1, 3, and 5, respectively D shows the total counts for each two-hour test period Error bars represent S E M HR rats were significantly more active than LR rats following SCOP ($p<0$ 04) *$p<0$ 05, represents significant difference between HR and LR rats

Analysis of each subgroup separately revealed that only the HR group showed significant sensitization, $F(2,14)=9.09$, $p<0.003$, with activity scores on day 5 exceeding those on both day 1 ($p<0$ 01) and day 3 ($p<0.05$), whereas the LR group did not show any increase in locomotor activity with repeated AMPH, $F(2,14)=0.89$, ns. As can be seen in Fig. 2C, the elevated locomotor activity in HR rats on day 5 occurred throughout the entire 2-h test period as indicated by a main effect of Group, $F(1,14)=$ 15 03, $p<0$ 002, but no Group × Time interaction, $F(11,154)=$ 1.09, ns. Least-squares analysis revealed that the locomotor response following the initial exposure to AMPH did not correlate with the response to novelty ($r=.24$) However, locomotor activity on test day 5 ($r=.713$, $p=0.002$) and the difference in activity counts between test days 5 and 1 ($r=.56$, $p=0.03$) were related to the subject's response to novelty

The results for cocaine show a similar profile to those for AMPH (Fig. 3). There were marked differences between HR and LR rats that were administered cocaine as indicated by a main effect of group, $F(1,14)=14.04$, $p<0.003$, and a significant Group × Time interaction, $F(11,154)=7$ 14, $p<0.0001$ (Fig. 3). There was a tendency for rats to sensitize to the locomotor stimulating properties of cocaine, although this did not reach significance, $F(2,28)=3$ 12, $p<0$ 06 While a significant correlation between the response to novelty and locomotor activity following initial exposure to cocaine was not apparent ($r=.48$, $p=0$ 06), locomotor activity following the fifth administration of cocaine did correlate with activity in the novel environment ($r=.69$, $p=$ 0.004)

The HR and LR groups also responded differently to administration of SCOP (Fig 4) As with the two dopaminergic drugs, HR rats showed significantly greater locomotor activity than LR rats, $F(1,14)=5.57$, $p<0.04$. However, in contrast to the AMPH and cocaine responses, SCOP-treated subjects developed a pronounced tolerance to the drug, $F(2,28)=6$ 23, $p<0$ 006, which did not differ between HR and LR rats, $F(2,28)=2.05$, ns Post hoc comparisons indicated that SCOP-induced locomotor activity was greater on day 1 than on day 3 ($p<0$ 05) and day 5 ($p<0.01$) for both groups of animals There was no relationship between SCOP-induced locomotor activity on day 1 ($r=$ 30) or day 5 ($r=$ − 14) with the locomotor response to the novel environment

HR rats in the cocaine group showed greater locomotor activity than LR rats during the first hour of habituation on both day 3, $F(1,14)=13.96$, $p<0.003$, and day 5, $F(1,14)=8.49$, $p<0.02$. This reinstated difference in activity on exposure to the photocell cages did not occur for any other drug treatment group.

DISCUSSION

This experiment demonstrates several important findings. Locomotor activity in a novel environment was predictive of locomotor response to AMPH, cocaine and SCOP. Rats that displayed higher levels of locomotor activity in the novel environment also showed the greater response to all three drugs. A direct correlation between the level of locomotor activity following cocaine and AMPH on day 5 and the locomotor response in the novel environment has also been demonstrated. These results confirm and extend those of previous studies (3,13). The greater responses to both cocaine and AMPH in HR rats are consistent with an involvement of mesocorticolimbic dopamine in the differences between HR and LR rats (13) as the locomotor stimulating properties of AMPH and cocaine depend upon increased dopaminergic transmission in the nucleus accumbens (7,8). However, HR also showed more SCOP-induced locomotor activity which is not affected by dopamine-depleting lesions of the nucleus accumbens (6), thereby implicating the possible involvement of nondopaminergic substrates in these individual differences. There were no differences between HR and LR rats in the response to saline, indicating that the differential drug response is not due to nonspecific effects of the injection procedure

In agreement with previous studies, rats treated repeatedly with AMPH showed pronounced sensitization (15), whereas SCOP-treated animals developed tolerance to the drug (12). However, sensitization to AMPH only occurred in HR rats Large individual variations in sensitization to repeated AMPH have been reported previously (17) and the present results indicate that sensitization to AMPH can, to a large extent, be predicted by the subject's locomotor response to novelty. These data would suggest that common neural mechanisms influence both AMPH sensitization and locomotor activity in a novel environment. Sensitization of the AMPH locomotor response is associated with

increased reactivity of the mesolimbic dopamine pathway (2, 16, 17) and as this projection has been strongly implicated in exploratory behavior (9) these results further support the view that dopamine in the nucleus accumbens may play a role in these individual differences.

The lack of sensitization following repeated cocaine administration is in agreement with previous studies (14). However, although administration of 10 mg/kg cocaine does not induce pharmacological sensitization over this time period, it can result in environmentally induced locomotor activity (14). Evidence for cocaine-induced environment-specific activity was also observed in the current experiment as activity scores in the initial 1 hour of habituation on test days 3 and 5 were higher for cocaine-treated rats than for saline-treated controls.

The origins of these individual differences are not fully understood, and could involve genetic or environmental factors or both. Exposure to stress is known to increase the locomotor stimulating properties of AMPH (4) and HR rats are reported to show a greater elevation in plasma corticosterone than LR rats after exposure to novelty (13) The social environment during early development can also influence the response to stress (1) and to psychomotor stimulant drugs (5) Furthermore, the enhancement of the behavioral effects of psychomotor stimulants by exposure to footshock stress is only present in subjects without environmental control (10). Therefore, differences in AMPH sensitization may represent individual variations in the susceptibility to stress and could have important implications for the relationship between stress, sensitization and the propensity for the self-administration of psychomotor stimulants.

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