Furthermore, CCK receptor antagonists may have therapeutic use in the treatment of various forms of anorexia.

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12. Injection of exogenous CCK produces the opposite effect (*5*).
13. Increased food intake after injection of MK-329 and the weak CCK antagonist proglumide in rats has been observed [G. Hewson, G. E. Leighton, R. G. Hill, J. Hughes, *Br. J. Pharmacol.* **93**, 79 (1988); C. T. Dourish, J. Coughlan, D. Hawley, M. L. Clark, S. D. Iversen, in *Cholecystokinin Antagonists*, R. Y. Wang and R. Schoenfeld, Eds. (Liss, New York, 1988), pp. 307–325; G. Schillabeer and J. S. Davison, *Regul. Pept.* **8**, 171 (1984); R. D. Reidelberger, M. F. O'Rourke, E. Solomon, *Soc. Neurosci. Abstr.* **14**, 1196 (1988)].
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Factors That Predict Individual Vulnerability to Amphetamine Self-Administration

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Clinical observations show that there is considerable individual variability in the response to the addictive properties of drugs. This individual variability needs to be taken into account in animal models of addiction. Like humans, only some rats readily self-administer low doses of psychostimulants. The individual animals at risk can be identified on the basis of their response to environmental or pharmacological challenges. This predisposition to develop self-administration can be induced by repeated treatment with amphetamine. These results may help elucidate the neurobiological basis of addiction liability observed in both rats and humans.

THE ETIOLOGY OF DRUG ADDICTION is largely unknown, although an individual's vulnerability to addiction is one of the main factors that influences the prognosis. As pointed out by O'Brien *et al.* (*1*, p. 329), "Some addicts go for months or years using heroin or cocaine only on weekends before becoming a daily (addicted) user. Others report that they had such an intense positive response that they became addicted with the first dose. . . ." Although the importance of individual differences in humans is well accepted in clinical practice, it has often been neglected in animal studies. Intravenous self-administration (SA), a useful method for analysis of drug-taking behavior in animals, is typically studied after the behavior is well established after prolonged training with relatively high doses of drugs. Although this procedure has provided useful information on the neurobiological substrate of SA (*2*), it has obscured individual differences in vulnerability to the drug. However, during the acquisition of SA, individual differences among rats can be seen if low doses of drug are used. We addressed two questions in this study: (i) Could individual differences in the development of amphetamine SA in rats be predicted by a particular set of traits? (ii) Could these individual differences be modified?

In the first experiment, 30 male Sprague-Dawley rats (280 to 300 g body weight) were separately tested for individual reactivity (locomotor response) in a novel environment (*3*) and after an intraperitoneal injection of *d*-amphetamine sulfate. Novelty-induced locomotor activity was measured every 10 min for 2 hours. Two subgroups of animals were selected on the basis of their level of activity (either below or above the median of the group). Half the animals were classified as low responders to novelty (LRs; $n = 15$) and the other half, with a slower habituation response, were classified as high responders (HRs; $n = 15$) (Fig. 1A) (*4*). The two groups did not differ in other variables such as body weight or health. On the day after exposure to the novel environment, the animals were placed in the same apparatus for a habituation period of 3 hours and then were injected with amphetamine (1.5 mg per kilogram of body weight, intraperitoneally), after which their locomotor activity was recorded for three more hours. Analysis of variance (ANOVA) indicated that the responses of LR and HR

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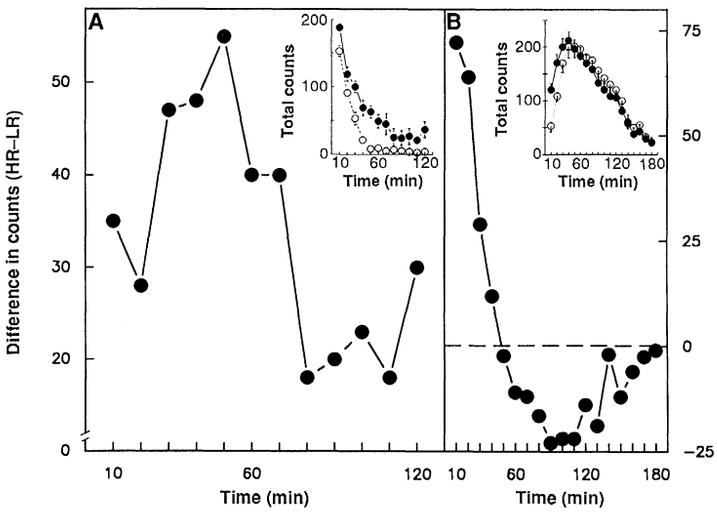

Fig. 1. Difference scores of locomotor activity (**A**) in a novel environment or (**B**) after amphetamine (1.5 mg/kg, intraperitoneally) of rats in the HR group (n = 15) and LR group (n = 15). Raw data are presented in the insets (○) LR; (●) HR. The two groups differed in total locomotor activity in a novel environment [F (1,28) = 18.09; P = 0.0002]. Amphetamine-induced locomotion changed in a different way between the two groups over time [F(17,476) = 2.23; P = 0.003].

groups differed significantly over time [F(17,476) = 2.23; P = 0.003] (Fig. 1B). This difference was most marked in the first 30 min of the test. During this period, the HR group had a higher response to amphetamine. Moreover, for all rats there was a linear relation [y = (0.38 ± 0.18)x + 115.997, P = 0.02] between the amphetamine response over the first 30 min and the locomotor response in the novel environment.

In a second experiment, 40 male Sprague-Dawley rats (280 to 300 g body weight) were first categorized according to their locomotor response to novelty and then tested for acquisition of amphetamine SA. As in experiment 1, groups of HRs (650 ± 51 photocell counts; n = 20) and LRs (373 ± 12 photocell counts; n = 20) were designated. Rats in these groups then received either four injections of d-amphetamine sulfate (1.5 mg/kg, intraperitoneally) separated by 3-day intervals, a procedure that induces a behavioral sensitization (*5*), or saline injections on the same schedule. Thus, the four experimental groups (ten rats per group) were LR saline, LR amphetamine, HR saline, and HR amphetamine. As in experiment 1, HR rats responded faster to the first amphetamine injection than LR rats [F(17,306) = 2; P = 0.01]. A linear relation was again found between the response to amphetamine over the first 30 min and locomotor activity in a novel environment [y = 0.379 ± 0.15)x + 262.111, P = 0.01]. Rats in these two groups also responded differently to the repeated amphetamine injections [F(51,918) = 1.61; P= 0.004]. Although the HR group showed a nonsignificant increase in locomotion with repeated injections, the locomotor response was substantially enhanced in LR rats [F(3,27) = 11.29; P = 0.0001]. The locomotor response of the LR group during the first 30 min of each test showed a progressive increase and reached the level of the HR group by the fourth injection (Fig. 2). Two days after the last injection, all rats were implanted with intravenous cannulas and allowed to acquire amphetamine SA (*6*). Rats in the HR group that had received repeated saline injections acquired SA, whereas saline-treated LR animals did not (Fig. 3A) [F(4,48) = 8.22; P = 0.0001]. Moreover, there was a linear relation between the intensity of amphetamine SA (number of self-injections) over the 5 days [y = (0.23 ± 0.05)x − 53.24, P = 0.001] and the level of reactivity (locomotor activity score) in the novel environment (*7*). In comparison, after the amphetamine sensitization procedure, LR and HR rats did not differ with respect to the acquisition of SA, indicating that the repeated exposure to amphetamine induced the acquisition of SA in LR rats (Fig. 3B).

Our results demonstrate that there are marked individual differences in the development of amphetamine SA. Interestingly, these differences in vulnerability to the drug could be predicted from the behavioral responses to both novelty and single or repeated amphetamine injections. Not only did the LR and HR groups differ in response to these tests, but, regardless of group classification, there was a significant positive correlation between the magnitude of the response to novelty of individual animals and their subsequent response to amphetamine as indicated by locomotion and SA.

Individual differences in the response to novelty were specifically correlated with the intensity of the locomotor response to amphetamine in the first period after injection, and animals with a more rapid locomotor response (HR group) to amphetamine also more rapidly acquired SA. This rapid response may be a characteristic of high vulnerability to drug addiction (*8*). The two groups of rats also responded differently to repeated amphetamine injections. Although the LR rats displayed behavioral sensitization, the HR group did not; in fact, the HR rats behaved as if they had been sensitized.

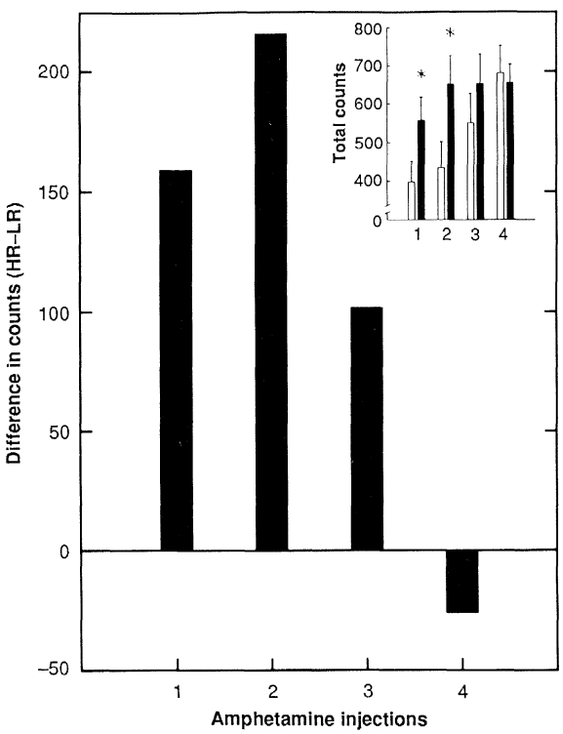

Fig. 2. Effect of amphetamine sensitization on locomotor activity in the LR (n = 10) and HR (n = 10) rats. The difference (HR − LR) in locomotor activity between the two groups (cumulated over 30 min) was abolished by the repeated injections. The insert shows the raw data. *P < 0.05 (ANOVA).

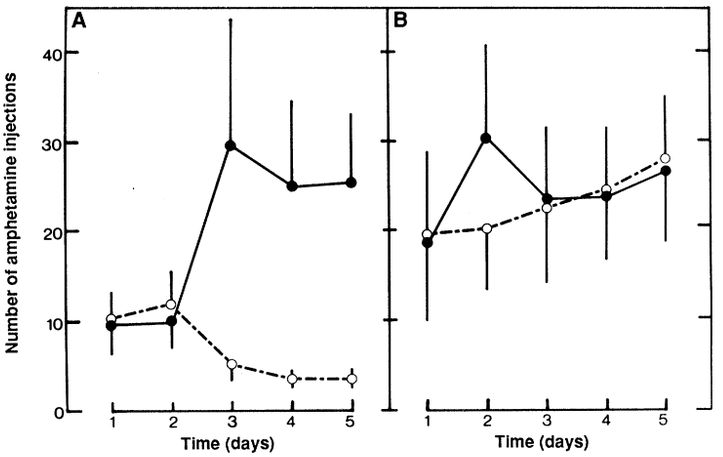

Fig. 3. Acquisition of amphetamine SA of rats in the LR (○) and HR (●) groups after repeated intraperitoneal administration of (**A**) saline or (**B**) amphetamine. After saline treatment, the groups (n = 10 per group) differed in their acquisition of SA both in terms of total amphetamine administered over the 5 days [$F(1,18) = 10.02$; $P = 0.008$] and in terms of the number of injections over the different days [$F(4,48) = 8.221$; $P = 0.0001$]. After amphetamine sensitization, there was no difference between the two groups (n = 10 per group).

Repeated contact with the drug not only eliminated group differences in the behavioral response to amphetamine but also abolished differences in SA. After this procedure, rats in the LR group became more vulnerable to the rewarding properties of the drug. Our results indicate that individual differences in the development of SA behavior can be modified and that previous contact with the drug can enhance subject vulnerability.

Because multiple amphetamine injections produce effects similar to those observed with repeated stress (*9*), exposure to stressful events at some critical period of life might predispose individuals to initiate drug-taking behavior. Also, differences in the locomotor response in a novel environment between the LR and HR groups may be due to differences in the response to stress (*10*), because (i) previous mild stress (such as handling) is enough to enhance exploratory locomotor activity (*11*); (ii) the novel environment is as potent as electric footshock in raising plasma corticosterone levels (*12*); and (iii) we have found that rats with higher responses to novelty (HR group) have higher basal levels of corticosterone as well as higher levels of corticosterone 2 hours after exposure to novelty (*13*). Individual differences in the behavioral response to a single injection of amphetamine can also be ascribed to differences in susceptibility to stress because amphetamine and stress have been shown to have similarities in their behavioral and neurochemical effects (*9*).

Whatever the origin, acquired or inherited, the individual differences observed in our experiments could reflect an intrinsic variation in the neurochemical mechanisms regulating responsiveness to stress or amphetamine. The mesocorticolimbic dopamine system may be involved because dopaminergic neurons are activated by both stress (*14*) and amphetamine (*15*) and play a role in both sensitization (*5*) and SA behavior (*2*).

Our approach represents a first step in the characterization of animals' typologies related to the vulnerability to develop drug-taking behavior. This approach may provide a useful model for investigation of the neurobiological basis of vulnerability to addiction.

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7. Differences between the two groups in SA cannot be accounted for by differences in nonspecific motor activity. Over the entire experiment the number of nose pokes in the inactive hole was equivalent in the two groups.
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