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6. Laboratory red light intensity was 1.1 lux, which was provided by a red LED array on the laboratory ceiling and a 25-W red bulb directed away from the rat cages. Because positions of control and melatonin-injected rats had been determined randomly, there was no systematic variation in illumination intensity between the groups. Food was replenished three times a week at injection time. Cages were cleaned fortnightly just before injection time. Water was provided through a nipple at the back of cages from a common container that was refilled monthly.
7. Melatonin (Sigma) was dissolved in 2 percent alcohol and 0.01*M* acetic acid, then brought to isotonicity by sodium chloride. The dosage (1 mg/kg), although high compared to endogenous levels in the pineal gland, was based on previous behavioral, biochemical, and entrainment studies employing similar dose levels [A. J. Kastin, M. C. Miller, L. Ferrell, A. V. Schally, *Physiol. Behav.* **10**, 399 (1972); P. C. Datta and M. G. King, *Pharmacol. Biochem. Behav.* **11**, 172 (1979); F. Anton-Tay, C. Chou, S. Anton-Tay, R. J. Wurtman, *Science* **162**, 277 (1968); Gwinner and Benzinger (*10*)]. Circulating melatonin is rapidly metabolized by the liver [I. J. Kopin, C. M. B. Pare, J. Axelrod, H. Weissbach, *Biochim. Biophys. Acta* **40**, 377 (1960)]. Because the effects of melatonin appear to depend upon its ability to reach certain brain areas, the systemic dose of melatonin required to produce a given effect may be much greater than the level of endogenous melatonin that normally produces this effect [F. Anton-Tay, *The Pineal Gland* (Churchill Livingstone, Edinburgh, 1971), pp. 213–227].
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## Coping and the Stress-Induced Potentiation of Stimulant Stereotypy in the Rat

Abstract. *It has been shown that stressed rats display increased stereotypy in response to a subsequent amphetamine challenge. Evidence is presented showing that stress potentiates cocaine stereotypy as well. These effects of stress were found to be particular to stress that could not be controlled in that rats receiving an identical amount of stress from footshock, but allowed to control its duration, displayed no more stereotypy than did nonstressed rats. These findings have implications for the role of stress and coping in amphetamine and cocaine psychoses, endogenous psychoses, and some forms of schizophrenia.*

A psychosis brought on in humans by chronic consumption of large doses of amphetamine resembles paranoid schizophrenia (*1*), and both are blocked by neuroleptic treatment (*2*). Amphetamine and other stimulants elicit stereotyped behaviors in animals that increase gradually with chronic administration (*3*), are blocked by neuroleptic treatment (*4*), and may be analogous to behavior seen in amphetamine psychosis (*3*) and schizophrenia (*3, 5*). These findings indicated that these effects of amphetamine and other stimulants might serve as useful models of endogenous psychoses (*3, 5*), stimulant-induced psychoses (*3, 5, 6*), and some forms of schizophrenia (*5, 6*).

Stress can precipitate schizophrenic episodes (*7*) and reinstate amphetamine psychosis in abstinent individuals in remission (*8*), and it is capable of making rats more sensitive to the stereotype-inducing effects of amphetamine (*9*). Such sensitization to amphetamine seems to be general (footshock, food deprivation, and repeated sessions of mild tail pressure are all effective) (*9, 10, 11*) and may operate through the mesolimbic and mesocortical dopamine systems—systems implicated in schizophrenia (*12*) and amphetamine psychosis (*13*)—and not the nigrostriatal dopamine system (*10, 14*). Footshock has also been shown to alter dopamine turnover in the same two systems but not the nigrostriatal (*15*). Because of the similarity in the neurochemical effects of stress and stimulants, it was suggested that the psychotogenic effects of stimulants may be caused by their stress-mimicking effects (*16*). It has also been reported that repeated stress and a series of amphetamine injections cause the same degree of sensitization to amphetamine (*9*).

Although the sensitization to amphetamine caused by stress may be a useful animal model for the role of stress in stimulant-induced psychoses, endogenous psychoses, and some schizophrenias, not all high-risk patients develop schizophrenia when stressed (*17*). The ability to cope with stress may be a major factor mediating the interaction of stress and schizophrenia (*17–20*), a proposal supported by findings that schizophrenia patients in remission who use coping responses, such as social withdrawal, in stressful situations relapse less than those who do not (*21, 22*). We found that rats exposed to footshock become sensitized to both amphetamine and cocaine only if they cannot cope with or control the shock.

We studied the effects of stress on the class of amphetamine-induced stereotypy characterized by sniffing, rearing, and repetitive head movements for several reasons: (i) this class of stereotypy, unlike the biting, licking, and gnawing class, increases with repeated amphetamine administration (*23, 24*) and is thought to operate through the mesolimbic dopamine system (*25*); (ii) others studying the potentiation of amphetamine stereotypy induced by stress have measured this behavior (*9, 10, 11*); and (iii) scores assigned in a preliminary test by observers using a simple rating scale were correlated ($r = .736$, $P < .0001$) with the dose of amphetamine administered (*26*).

Pairs of rats received shocks on three consecutive days. Each session consisted of 180 2.5-mA scrambled grid shocks with 8 seconds between shocks. The rats of a pair received shock separately in identical shuttle boxes (34.5 by 20.5 by 19.5 cm). One rat received controllable shock (CS) and could terminate each shock, which was received by itself and its pairmate, by running through an archway cut in the barrier that divided the shuttle box in two. The rat receiving uncontrollable shock (UCS) had to depend on its CS partner to terminate the shocks. Shocks began at the same time for both rats and terminated for both either when the CS subject ran through the archway or automatically after 5 seconds of shock (< 1 percent of the trials). A third group of rats did not receive shocks.

Twenty-eight hours after the last treatment session the rats received injections intraperitoneally of 4.0 mg of *d*-amphetamine sulfate per kilogram of body weight, and stereotypic behavior was rated by an observer unaware of treatment group (*26*) (Fig. 1). Groups showed essentially no differences in weight at this time. Other rats, treated identically but injected with physiological saline, displayed no stereotypic behavior, as defined by either the amphetamine or the

cocaine rating scales. In agreement with other studies (*9, 10, 11*) of stress-induced potentiation of amphetamine stereotypy in which uncontrollable stressors were used, we found that ratings for UCS rats showed them to be more sensitive to the amphetamine than rats that did not receive shocks. Ratings for CS rats showed them to be less sensitive than the UCS rats and similar to rats that were not shocked, indicating that the provision of a means of controlling the shock eliminates the sensitizing effects of the shock.

In another experiment we further tested the sensitizing effects of shock and the role of its controllability. We used cocaine, whose repeated administration produces a psychosis in humans that is also similar to paranoid schizophrenia (*16, 27*). Rats administered cocaine exhibit stereotypic behaviors and become more sensitive with repeated administration (*28*). The stereotypy is reversed by neuroleptics (*29*) and is thought to be dependent on dopamine (*29*). These stereotypic behaviors are similar but not identical to those elicited by amphetamine (*29*). From preliminary work we developed a rating scale for these behaviors which, when tested, produced ratings that were correlated ($r = .734$, $P < .0001$) with the dose of cocaine administered (*30*). Shocks were administered as in the first experiment, and rats were injected intraperitoneally with cocaine hydrochloride (Merck) (30 mg/kg), 28 hours after the last shock session. The rats were rated for stereotypy after injection (*30*). The three groups showed essentially no differences in weight.

Ratings of stereotypy (Fig. 2) showed a pattern similar to those of the first experiment. Rats that received uncontrollable shock were more sensitive to the effects of cocaine than those receiving no shock. This indicates that stress can potentiate stereotypy elicited by cocaine. The rats provided with a means of controlling the shock were not sensitized.

The difference observed between the CS and UCS rats in sensitization to stimulants cannot be explained in terms of amount of shock received because both groups received the same amount of shock. It appears that coping can play a role beyond that of merely reducing the amount of stressful physical stimuli received. It has been proposed that different individuals react differently (triggered into schizophrenia or not) to the same stressful stimuli, depending on their self-perceived ability to cope with the stressful stimuli (*19*). This sort of influence may be an important determinant of whether exposure to stressful stimuli triggers a schizophrenic episode.

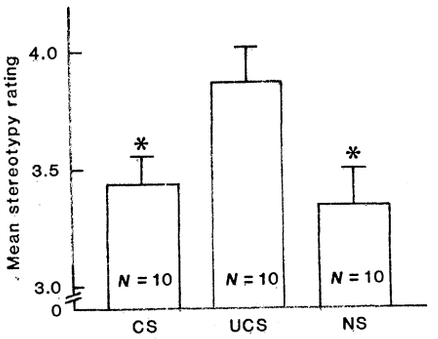


Fig. 1. The mean stereotypy ratings (*26*) (+ standard error of the mean (S.E.M.) for rats receiving amphetamine after three sessions of controllable shock (*CS*), uncontrollable shock (*UCS*), or no shock (*NS*). *$P < .05$, difference from UCS group (Newman-Keuls test).

Our results suggest at least three possible explanations for the differences in sensitization between CS and UCS rats. (i) It is possible that the perception of control over shock somehow prevents sufficient activation of the neurochemical process or processes responsible for the sensitization. The perception of control may alter the animal's perception of the degree of stress so that it falls below a minimum required to activate this neurochemical process or processes. (ii) Stress may produce this neurochemical process or processes only if it is perceived as uncontrollable. (iii) The perception of control may initiate other neurochemical processes that counteract those causing the sensitization.

Since the mesolimbic dopamine system has been implicated in the mediation of the form of amphetamine stereotypy we studied (*25*) and the stress-induced potentiation of this amphetamine stereotypy (*10, 14*), our data suggest that uncontrollable stress might affect the mesolimbic dopamine system (*15*) but that controllable stress may not. It is possible that the stress-induced potentiation of stimulant stereotypy is at least partially mediated by other systems implicated in stimulant stereotypy and shown to be affected by stress (for example, norepinephrine and serotonin) (*16, 24, 31*).

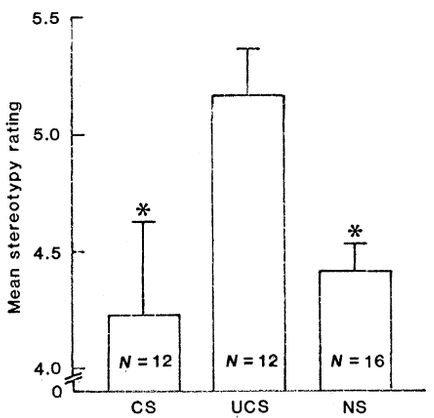


Fig. 2. The mean stereotypy ratings (*30*) (+ S.E.M.) for rats receiving cocaine after three sessions of controllable shock (*CS*), uncontrollable shock (*UCS*), or no shock (*NS*). *$P < .05$, difference from UCS group (Newman-Keuls test).

Our data point to the ability to cope as an important variable in the interaction of stress and the pharmacological effects of both amphetamine and cocaine (*32*). It has been proposed (*9*) that differences in the amount of, or vulnerability to, prior stress experienced by humans may account for the extreme variability in response to amphetamine (*33*). Our data suggest that the ability to cope with prior stress may account for some of this variability and that observed in the response to cocaine (*34*) as well. Our data also suggest that coping may play an important role in the interaction of stress and neurochemical systems thought to be involved in stimulant psychosis and some forms of schizophrenia.

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26. Naive rats (Holtzman, 300 to 400 g) were housed individually in standard wire mesh cages for at least 2 weeks before the beginning of the experiment in order to facilitate stereotypy (*29*). Stereotypy was rated in home cages by an observer (unaware of the rats' group membership) for 1-minute periods at 15, 30, 45, 60, 90, 120, 150, and 180 minutes after injections of *d*-amphetamine sulfate (Sigma) dissolved in physiological saline. In testing the correlation between dose and ratings (slope, .4988; standard error, .503), rats were injected with 3.0 ($N$ = 7), 4.0 ($N$ = 10), 5.0 ($N$ = 8), or 6.0 ($N$ = 8) mg of *d*-amphetamine per kilogram of body weight. The rating scale was: 0, inactive (no movement); 1, intermittent activity; 2, continuous activity; 3, intermittent stereotypy (stereotyped sniffing, rearing, or repetitive head movements); 4, continuous stereotypy over wide area; 5, continuous stereotypy in a restricted area; 6, pronounced, continuous stereotypy in a restricted area (for example, repeatedly falling over from rearing or vigorous sniffing through the same few holes in the cage). No stereotyped biting, licking, or gnawing was observed during any of these experiments.
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30. Rats were rated for 1-minute periods starting 15, 30, 45, 60, and 75 minutes after cocaine hydrochloride injection on the following scale: 0, inactive; 1, intermittent activity; 2, continuous activity; 3, stereotypic rearing; 4, intermittent stereotypic sniffing, repetitive head movements, or both, with periods of nonstereotypic behavior longer than 2 seconds; 5, intermittent stereotypic sniffing, repetitive head movements, or both with periods of nonstereotypic behavior shorter than 2 seconds; 6, continuous stereotypic sniffing, repetitive head movements, or both; and 7, continuous and restricted stereotypic sniffing, repetitive head movements, or both. In testing the correlation between dose and ratings (slope, .0867; standard error, .606), rats were injected with 20 ($N$ = 12), 30 ($N$ = 16), or 40 ($N$ = 12) mg of cocaine per kilogram of body weight.
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32. We do not mean to imply, nor do we suspect, that all forms of coping behavior affect the stress-induced sensitization to stimulants. It is more likely that different coping responses vary in effectiveness.
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35. We thank R. C. Drugan and T. B. Moye for their valuable assistance. This work was supported by NSF grants BNS-78-00508 and RSDA MH-00314 to S.F.

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## Prenatal Food Restriction and Subsequent Weight Gain in Male Rats

A report by Ravelli *et al.* (*1*) has stimulated interest in the relation between maternal undernutrition and subsequent obesity in human male offspring. Jones and Friedman (*2*) presented data demonstrating the existence of a similar effect in Charles River male rats. Male offspring of rats restricted to 50 percent of prepregnancy food intake during the first two trimesters of pregnancy had enhanced weight gains and heavier fat pads at 160 days of age than rats born to mothers given free access to food. Here we comment on our attempts to mimic "the Dutch famine effect." Experimentally naïve rats (from Charles River Laboratory) were allowed to mate in our laboratory at St. Lawrence University. The females were then randomly placed in one of three groups: control ($N$ = 7; free access to food), yoked ($N$ = 5; daily feeding restricted to 50 percent of control intake), and 50 percent restricted [$N$ = 6; daily feeding restricted to 50 percent of prepregnancy (PP) intake]. They remained on these diets for the first two trimesters of pregnancy. During the last trimester, all rats were given free access to powdered Charles River Laboratory Chow.

Weight changes during the first two trimesters of pregnancy were control, +81.3 ± 1.8 g (mean ± standard error of the mean); yoked, −5.6 ± 3.6 g; and 50 percent of PP, −40.8 ± 4.3 g. Dams in the yoked and 50 percent PP groups that were given free access to food during the last trimester showed hyperphagia for 1 day [analysis of variance: day 1 refeeding, $F(2, 16) = 4.67$, $P < .05$] and incomplete recovery of body weight. Litter size and weight and gestation period were constant across groups. On day 3 after parturition, litters were culled to six rats (three males, three females). Pups were weaned at 21 days of age and given free access to Charles River rat pellets. They were housed in group cages and exposed to a cycle of 12 hours of light and 12 hours of darkness at 22°C. Food intake was measured over four consecutive 24-hour periods when the pups were 30, 60, and 90 days of age. There were no significant differences in food intake among pups from dams in any of the three groups [$F(2, 41) = 2.36$, not significant (N.S.)]. However, at 120 days of age the body weights of male offspring of dams in the yoked and 50 percent PP groups were lower than the body weights of offspring of control dams. At 160 days of age, epididymal but not retroperitoneal fat pads of offspring of the yoked and 50 percent PP groups weighed less than the corresponding pads of offspring of control dams (see Table 1, experiment 1).

In a second experiment (at the Rockefeller University), we restricted the food intake of one group of pregnant, experimentally naïve Charles River rats to 50 percent of control intake (yoked) for the first two trimesters of pregnancy. Weight changes during the first two trimesters for the control ($N$ = 5) and yoked dams ($N$ = 3) were +80.0 ± 3.5 g and +10.0 ± 3.5 g, respectively. Litter size, weight of the pups, and gestation period did not differ significantly between the two groups. Litters were culled, weaned, and monitored for food intake as in the first experiment. Food intakes did not differ between the two groups [$F(1, 15) = 0.28$, N.S.]. Body weights at 120 days, and epididymal and retroperitoneal fat

Table 1. Mean (± standard error) body weights and weights of epididymal fat pads (EP) and retroperitoneal fat pads (RP) of male pups born to mothers in control, yoked, or 50 percent prepregnancy (PP) groups during the first two trimesters of pregnancy.

| Group | Experiment 1 | | | | Experiment 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Body weight at 120 days* (g) | Weight at 160 days (g) | | | Body weight at 120 days (g) | Weight at 135 days (g) | | |
| | | Body | EP† | RP | | Body | EP | RP |
| Control | 632.9 ± 9.8<br>$N$ = 20 | 683.2 ± 24.5<br>$N$ = 9 | 13.04 ± 1.0<br>$N$ = 9 | 17.91 ± 1.4<br>$N$ = 9 | 554.9 ± 20.8<br>$N$ = 8 | 570.1 ± 18.2<br>$N$ = 7 | 6.42 ± 0.9<br>$N$ = 7 | 10.28 ± 1.7<br>$N$ = 7 |
| Yoked | 580.1 ± 10.8<br>$N$ = 15 | 626.3 ± 12.3<br>$N$ = 8 | 9.04 ± 0.6<br>$N$ = 8 | 13.14 ± 1.8<br>$N$ = 8 | 569.2 ± 10.0<br>$N$ = 9 | 598.4 ± 9.2<br>$N$ = 9 | 5.58 ± 0.4<br>$N$ = 9 | 11.71 ± 1.0<br>$N$ = 9 |
| 50 percent PP | 598.7 ± 18.0<br>$N$ = 14 | 605.7 ± 26.2<br>$N$ = 6 | 11.30 ± 1.1<br>$N$ = 6 | 16.07 ± 2.3<br>$N$ = 6 | | | | |

*Analysis of variance, $F(2, 46) = 4.84$, $P < .05$. †$F(2, 20) = 5.61$, $P < .05$.