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Changes in d-Amphetamine Elicited Rotational Behavior in Rats Exposed to Uncontrollable Footshock Stress

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CARLSON, J. N., S. D. GLICK AND P. A. HINDS. *Changes in d-amphetamine elicited rotational behavior in rats exposed to uncontrollable footshock stress.* PHARMACOL BIOCHEM BEHAV **26**(1) 17–21, 1987.—Male and female rats, selected on the basis of their rotational behavior in response to d-amphetamine, were exposed to either escapable footshock stress, inescapable footshock stress or no stress and were then given a shuttlebox escape task on the subsequent day. Following testing, the magnitude and direction of the animals' rotational responses to d-amphetamine were determined again. Inescapable footshock stress induced a selective change in the direction and intensity of rotational behavior that was dependent upon the subjects' sex and preexisting rotational bias. Right-rotating males and left-rotating females shifted their directional bias toward the opposite side, while left-rotating males and right-rotating females displayed increased rotation in their pre-stress direction. Significant correlations were also noted between the intensity of pre-stress rotational behavior and performance on the shuttlebox shock escape task. The results are discussed with respect to stress' actions on the mesocortical dopamine system and how this system's sex-dependent asymmetrical organization may subserve part of the organism's general reaction to uncontrollable stress.

Rotation d-Amphetamine Stress Meso-cortical Dopamine Shock escape Brain asymmetry

NUMEROUS studies in recent years have shown that normal rats rotate (turn in circles) in response to dopaminergic drugs. This behavior is characterized by a normally consistent left or right directional preference and is thought to be mediated by lateralized functioning of nigrostriatal dopaminergic pathways [14]; endogenous asymmetries in striatal dopamine (DA) content [11], release [27] and uptake [30] have been demonstrated.

Data from this laboratory have recently shown pronounced differences in rotational behavior between left- and right-biased rats in response to an acute dose of cocaine [12]. Right-rotating female rats rotated much more than left rotators while left-rotating male rats rotated much more than right rotators. These findings were in sharp contrast to those obtained with d-amphetamine (d-A) where no significant rotational differences between left- and right-biased rats of either sex were found. In a subsequent study [13], sensitization (i.e., an increased drug response with repeated administration) to the rotational effects of these drugs was evaluated and it was shown that a single dose sensitization occurred much more readily with cocaine than with d-A. These findings suggested that while the two drugs had been shown to be similar in many of their neurochemical and behavioral effects (see [26]), some differences must exist in their actions. A possible locus for these differences was suggested by findings indicating that, while both drugs activate dopaminergic pathways in general, d-A preferentially activates nigrostriatal neurons [5] and cocaine preferentially affects mesocortical neurons [16].

Various stressors will enhance the neurochemical and behavioral effects of d-A [2]. MacLennan and Maier [23] have shown that an important aspect of this enhancement is the degree to which the animal can control the stressor, since exposure to uncontrollable but not an identical pattern of controllable footshock stress potentiates the stereotypic behavior normally elicited by d-A. In another context, uncontrollable stress exposure has been shown to retard performance in a subsequent situation where stress control is possible [25] and part of this retardation has been suggested to involve alterations in DA function (see [1]). Uncontrollable footshock stress has been shown to selectively activate mesocortical DA neurons [7, 17, 33] while leaving nigrostriatal neurons essentially unaffected. Thus, footshock stress and cocaine apparently share a commonality of action on mesocortical DA neurons. Cocaine-like effects on rotational behavior might therefore be produced by a combination of uncontrollable stress and d-A. In the present study, the effects of footshock stress on changes in the rotational behavior elicited by d-A were evaluated. As a means of relating these rotational changes to performance deficits induced by

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uncontrollable stress, an assessment of shock escape behavior, following stress, was also included.

METHOD

Subjects

The subjects were naive male and female Sprague-Dawley derived rats obtained from Zivic-Miller Laboratories (Allison Park, PA), approximately 90 days old at the start of the experiment. They were distributed into 16 groups (N=8–25) on the basis of sex, rotational bias and treatment. Animals were housed individually, were maintained on a 12 hour light/dark cycle, and had food and water continuously available.

Apparatus

Rotation was measured individually in one of eight identical cylindrical (30 cm dia. × 30 cm) Plexiglas rotometers. Each rotometer was equipped with a flexible wire harness which was tightened around the subject's abdomen and was connected to a shaft which activated a photoelectric position sensing device that differentiated between incomplete (90–270°) and full (360°) left and right turns [11].

Footshock stress was administered in one of three identical cylindrical operant chambers which measured 30.0 cm dia. and 30.0 cm high and were constructed of clear Plexiglas. The floors were composed of 0.4 cm diameter aluminum rods spaced 1.75 cm apart through which scrambled AC electric shock was delivered by a Coulborn E13-16, series regulated, controlled current shock source/distributor equipped with a DC milliammeter/full wave rectifier, which indicated current delivered to the experimental subject. Each chamber contained a standard 2.75×1.0 cm rat lever which projected 2.2 cm into the chamber and was located 5.2 cm above floor level.

Three identical shuttleboxes were used for the shock escape test. Each was 45.7 cm long, 24.5 cm high, and 21.6 cm wide. The side walls and door were constructed of aluminum and the ceiling of Plexiglas. The floor was constructed of aluminum rods 0.6 cm in diameter spaced 2.2 cm apart through which shock was delivered as above. The chamber was divided in half by an aluminum wall which had a 10.8 cm high by 6.35 cm wide opening at the center at floor level. A cue light was centered 20.3 cm above the grid floor on each end wall. Photocells were located 4.5 cm above the grid floor and 8.0 cm from the end wall and were used to monitor the subject's location in the chamber. The shuttleboxes and the operant chambers were housed in sound and light attenuating boxes which were equipped with a house light and a ventilating fan. The control of experimental events and the recording data were accomplished with an interface and microcomputer system connected to each apparatus.

Drug Dosage

On the basis of previous studies, dosages of d-amphetamine sulfate were chosen to produce maximal acute rotational effects. They were 1.25 mg/kg for female rats [20] and 1.56 mg/kg for male rats. These dosages have also been shown to produce equal brain drug levels in males and females [4]. The injection volume was 1.0 ml/kg and the vehicle was normal saline.

Procedure

T1 rotation—day 1. Animals were individually tested for d-A induced rotation for one hour in the middle of the light cycle, immediately following an intraperitoneal drug injection. Data were collected as turns in the dominant direction of rotation, turns in the non-dominant direction, and the net magnitude of rotation (the difference between full turns in the dominant and non-dominant direction). An additional measure of rotation strength that is independent of total rotations was computed as "percent preference." It was calculated as:

$$\frac{\text{rotations in the preferred direction} \times 100}{\text{total rotations}}$$

For purposes of analysis, these data were normalized using an arcsine transformation and multiplied × 10.

Stress treatment—day 7. Six days following this treatment, animals were assigned to one of four stress condition groups and were placed in the operant chambers and exposed to one of the 4 stress conditions. Subjects in the controllable stress (ESC) group were given 80 trials of shock, of 0.8 mA intensity on a random time 60 second (RT 60) schedule, which could be escaped with a bar press response. In order to facilitate acquisition of the response, each of the first 20 shocks could be terminated by the performance of a single bar press (FR 1) while the remainder required 2 bar presses (FR 2). Shock would terminate automatically after 30 sec upon shock termination failure. Paired with each animal in this group was an animal that received shock that was identical in duration and temporal patterning to that of its partner

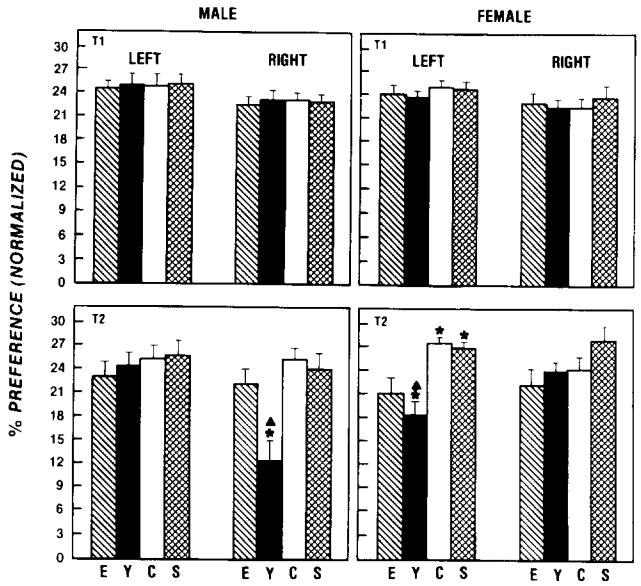

FIG. 1. The effect of various conditions of stress on rats' percent rotational direction preference in response to d-amphetamine. Panels depict the percentage of turns in the T1 preferred direction, before (T1) and following (T2) stress exposure. Bars represent mean (±SEM) transformed (arcsine × 10) percentages. Abbreviations: E—escapable stress/shuttlebox stress (ESC), Y—inescapable stress/shuttlebox stress (YOK), C—no stress (CTL), S—shuttlebox stress only (SCT). LEFT—T1 left rotation preference. RIGHT—T1 right rotation preference. *significantly different from T1 preference (Newman-Keuls Test). ▲Significantly less than T1 preference (*t*-tests).

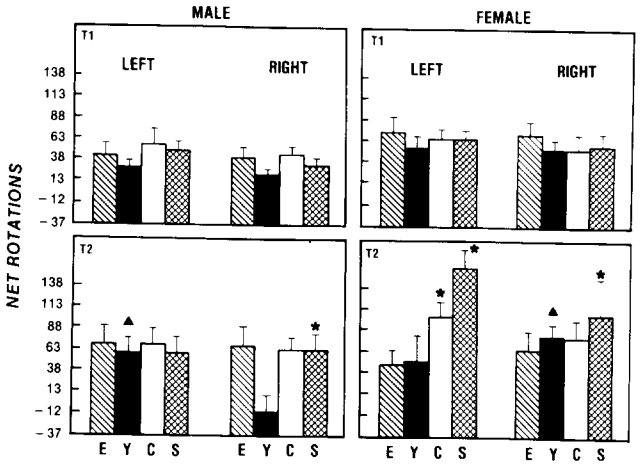

FIG. 2. The effect of various conditions of stress on rats' net rotations in response to d-amphetamine. Panels depict the number of net turns in the T1 preferred direction, before (T1) and following (T2) stress exposure. Negative numbers refer to net rotations in the T1 non-preferred direction (see text). Bars represent mean (±SEM) net rotations. Abbreviations: E—escapable stress/shuttlebox stress (ESC), Y—inescapable stress/shuttlebox stress (YOK), C—no stress (CTL), S—shuttlebox stress only (SCT). LEFT—T1 left rotation preference. RIGHT—T1 right rotation preference. *Significantly different from T1 net rotations (Newman-Keuls Test), ▲Significantly greater than T1 net rotations (*t*-test).

but which it itself could not terminate (YOK). Animals in two non-stressed control groups, (CTL) and (SCT) were each placed in the chamber for a time period that was equal to that of one of the ESC/YOK pairs and not shocked.

Shuttlebox test—day 8. Twenty-four hours after the stress manipulation, the shuttlebox escape test was conducted for subjects in groups ESC, YOK and SCT, while animals in group CTL were placed in the shuttlebox for an equivalent time period and not shocked. Tested animals were placed in the shuttlebox and given 60 trials of 0.6 mA grid shock (RT 60) which could be terminated by the execution of the required response. The shock automatically terminated if a response had not occurred after 30 sec from its onset. In order to facilitate learning of the response, during the first 5 trials the rat was required to cross from one side of the shuttlebox to the other (FR 1). For the remaining 55 shocks, an FR 2 schedule was in effect and the animal had to cross from one side to the other and then back in order to terminate the shock. Data were collected as escape latency, i.e., the amount of time between shock onset and shock termination.

T2 rotation—day 8. Within two hours of the end of the shuttlebox test, all animals were placed in the rotometers and again tested for d-A elicited rotational behavior (T2) as described above. Net rotations were now calculated as: (turns in the T1 preferred direction − turns in the T1 non-preferred direction) with negative values indicating a change in the direction of net rotations. Percent preference was calculated as:

$$\frac{\text{rotations in the T1 preferred direction} \times 100}{\text{total rotations}}$$

TABLE 1

PEARSON CORRELATION COEFFICIENTS BETWEEN T1 NET ROTATIONS AND MEAN SHUTTLEBOX ESCAPE LATENCIES OF LEFT AND RIGHT BIASED MALE AND FEMALE RATS EXPOSED TO VARIOUS STRESS CONDITIONS

Group	Bias	Males	Females
Escape	Left	−0.447*	0.025
	Right	−0.356	−0.182
Yoked	Left	−0.533†	0.457*
	Right	0.594†	−0.249
Stress Control	Left	0.021	−0.015
	Right	0.143	−0.230

Significant probability levels: *$p<0.05$, †$p<0.01$.

Preference data were again normalized using an arcsine transformation and multiplied × 10.

RESULTS

Figure 1 depicts the pre-stress (T1) and post-stress (T2) rotational % preference for animals exposed to the 4 stress conditions with data points representing transformed (arcsine × 10) values. As shown, *a priori* orthogonal tests using *t*-ratios ($p=0.05$, one-tailed see [22]) showed significant reductions in preference among right-biased YOK males and left-biased YOK females. A four-way ANOVA, using pre- and post-stress rotation as a repeated measure, revealed a significant interaction between conditions of sex, T1 preference, stress treatment and time of rotation, $F(3,245)=143.74$, $p<0.001$. Main effects of T1 preference, $F(1,245)=5.11$, $p=0.023$, and stress condition, $F(3,245)=6.55$, $p<0.001$, were also significant. As shown in the figure and confirmed by *a posteriori* Newman-Keuls ($\alpha=0.05$) multiple comparisons (N-K) of the interaction's simple main effects, the interaction was produced by reductions in rotational preference among right-rotating YOK males and left-rotating YOK females; and by increases in rotational preferences among left-rotating CTL and SCT females and right-rotating SCT females.

Figure 2 represents pre-stress (T1) and post-stress (T2) net rotations in the T1 preferred direction for animals in the various groups. As hypothesized, *a priori* Student's *t*-tests ($p=0.05$, one-tailed) revealed increases in net rotations in left-rotating YOK males and right-rotating YOK females. A four-way repeated measures ANOVA yielded a significant, $F(3,245)=3.46$, $p=0.016$, four-way interaction, and main effects for stress condition, $F(3,245)=3.32$, $p=0.020$, and time of test, $F(1,245)=18.64$, $p<0.001$. Multiple comparisons on the simple effects of the four-way interaction also revealed that right-rotating SCT males, left- and right-rotating SCT females, and left-rotating CTL females showed increases in net rotations.

Table 1 lists the Pearson correlation coefficients between net day 1 rotations (T1) and day 8 shuttlebox shock escape performance as indicated by the mean escape latency for the 55 FR 2 trials. Significant inverse relationships, indicating better escape performance with increasing T1 net rotations, are shown for left-rotating ESC and YOK males. Significant positive correlations, indicating poorer escape performance

with increasing net T1 rotations, are indicated for right-rotating YOK males and left-rotating YOK females.

DISCUSSION

Previous studies have shown that exposure to stress will potentiate many of the behavioral actions of d-A [2,23]. The present data suggest that exposure to uncontrollable stress changed d-A elicited rotational behavior in a way that was dependent upon the subjects' sex and pre-stress directional bias with some subjects showing a potentiation of pre-stress rotation and other subjects, a change in direction.

The results indicate that uncontrollable footshock stress, administered before a second exposure to d-amphetamine, modified the direction and intensity of elicited rotational behavior compared to that seen with the first exposure. As hypothesised, this modification was selective in that the rotational preference of right-rotating males was shifted toward the left and that of left-rotating females was shifted toward the right. In addition, the intensity of rotational behavior, as indicated by net rotations, was increased for left-rotating males and right-rotating females. These effects were dependent upon the uncontrollable nature of the footshock (YOK) as they did not occur in animals exposed to an identical pattern of controllable shock (ESC).

Significant increases in both rotational preference and intensity were also seen in groups not exposed to stress (CTL) and in groups exposed only to shuttlebox footshock on day 8 (SCT), indicating sensitization to the rotational effects of d-A. Unexpectedly, animals in the SCT groups, which were included as a control for the effects of day 7 shock, showed the strongest sensitization to the rotational effects of d-A; significant increases in directional preference and rotational intensity were seen in both left- and right-rotating SCT female rats and an increase in intensity was noted in right-biased males. These findings appear to be consistent with previous reports indicating that stressful stimuli will induce sensitization to the behavioral effects of d-A [2]. However, the effects on rotational behavior seen in YOK groups indicate that uncontrollable stress induced selective changes in animals of differing sex and bias.

The significant correlations found between T1 net rotations and shuttlebox performance in the YOK groups suggest that the changes in rotational behavior are related to other findings associated with the effects of uncontrollable stress. Exposure to uncontrollable stress has been repeatedly demonstrated to induce performance deficits in a subsequent situation where stress control is possible [25]. Part of the mechanism for this effect has been shown to involve the induction of post-stress activity changes [19]. Besides showing selective post-treatment rotational activity changes, the present data suggest that the intensity and direction of pre-stress (T1) rotation was related to post-stress shuttlebox performance. Right-rotating males and left-rotating females exhibited poorer shuttlebox performance (longer escape latency) with greater pre-stress rotational intensity; these groups also shifted their rotational preference following stress (T2), with males shifting toward a left bias and females toward a right bias. On the other hand, left-rotating males exhibited better shuttlebox performance when pre-stress rotation was greater and the rotation intensity of these animals was increased following uncontrollable stress (T2). In animals exposed only to shuttlebox stress (SCT), no significant correlations were found. Taken together, these findings indicate that animals of differing sex and rotational bias are differentially sensitive to the performance deficits engendered by uncontrollable stress, and that part of the effect of uncontrollable stress is to shift the animal's rotational bias toward the direction that is predictive of better escape performance.

These changes in rotational bias and intensity induced by uncontrollable stress are in the same direction as those previously found for cocaine and are compatible with our hypothesis that similar neuronal systems subserve both changes. The sex-dependent side effect seen for both treatments may be related to functional asymmetries in mesocortical DA projections that are selectively activated by cocaine and footshock stress. A large body of literature indicates that the frontal cortex may modulate sub-cortical DA function [6, 10, 29]. Cortical ablation studies in rats have shown an enhancement of the locomotor activity induced by amphetamine [18] and an alteration of the response of striatal neurons to amphetamine [34]. DA utilization in the frontal cortex has been shown to be inversely related to the locomotor activity of different mouse strains in an open field [32]. These and other data suggest that the frontal cortex exerts an inhibitory influence on limbic and striatal DA neurons, and their associated behavioral functions, perhaps through a cortico-striatal pathway that may use glutamate as a transmitter [9, 21, 24]. Part of the shock escape and motor deficit caused by exposure to uncontrollable shock may be subserved by activation of the frontal cortex.

Previous work from this laboratory has indicated that the frontal cortical influence on the striatum may be asymmetrical: bilateral frontal cortical lesions in female rats decreased the rotational behavior of right rotators and increased the rotational behavior of left rotators [28]. The results of anatomical studies [8] suggest a sex-dependent difference in the lateralized strength of this influence—the left frontal cortex is thicker in female rats and right frontal cortex is thicker in male rats. A neurochemical asymmetry of the pre-frontal cortex has also been described [31]. The present data indicate that the activation of the frontal cortex by uncontrollable stress has an effect that is opposite to that induced by lesions, i.e., increasing the rotation of right-rotating females and decreasing that of left rotators; and increasing the behavior in left-rotating males while decreasing it in right rotators. Further, if one assumes that left-rotating females and right-rotating males have a stronger overall cortical influence, this would account for the positive correlation between rotational bias and shock escape impairment found with these groups.

The present rotational changes may also reflect an effect of uncontrollable stress on nigrostriatal DA systems directly. While many studies [5, 13, 24] have found an exclusive effect of stress on mesocortical and mesolimbic DA systems, other findings (see [3]) suggest that striatal DA neurons are also responsive to stressful stimuli, and exhibit increased DA release. Whether a stress effect on striatal systems contributes to a lateralized alteration of the nigrostriatal system's response to d-A remains to be established.

The data indicate that footshock stress induces a change in the dynamics and direction of d-A elicited rotational behavior that is dependent both on the preexisting magnitude and direction of rotation as well as the conditions under which the stressor is experienced. They suggest that an organism's reaction to stress may under certain circumstances be subject to wide individual differences; and that part of these differences may be dependent upon an endogenous asymmetrical organization in the central nervous system.

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