SENSITIZATION TO STRESS: THE ENDURING EFFECTS OF
PRIOR STRESS ON AMPHETAMINE-INDUCED ROTATIONAL BEHAVIOR

Terry E. Robinson, Amy L. Angus and Jill B. Becker

Department of Psychology and Neuroscience Laboratory Building
The University of Michigan
1103 E. Huron St., Ann Arbor, MI   48104-1687

Summary

In rats with a unilateral 6-OHDA lesion of the substantia nigra
exposure to footshock or immobilization stress produced a long-
lasting enhancement in the rotational behavior evoked by a sub-
sequent injection of amphetamine. However, the effect was
dependent on the environmental context in which stress was applied.
It is suggested that stress may induce enduring changes in brain
and behavior similar to those produced by psychomotor stimulant
drugs.

The repeated intermittent administration of psychomotor stimulant drugs,
such as amphetamine (AMPH) or cocaine, produces a progressive and enduring
enhancement in many dopamine-mediated behaviors. This phenomenon is known as
behavioral sensitization, or "reverse tolerance" (for reviews see 1, 2, 3).
However, it has been suggested that the behavioral sensitization produced by
stimulants may not be unique to the psychopharmacology of stimulants, but due
to their action as stressors (4, 5, 6). This is because repeated intermittent
stress also produces sensitization-like effects (7, 8). More important,
previous exposure to a variety of stressors (e.g., tail pinch, footshock,
immobilization) enhances the behavioral response to a subsequent injection of
AMPH or cocaine (1, 9, 10).
    In previous studies of stress-stimulant drug interactions behaviors that
can occur in the absence of active locomotion (e.g., stereotyped sniffing,
drinking) were measured to assess the influence of previous stress. Since
stress, and especially footshock stress, often decreases active locomotion (11)
we thought it important to determine if previous stress would also enhance an
AMPH-induced behavior requiring active locomotion. Therefore, we have studied
the effects of footshock or immobilization stress on AMPH-induced rotational
behavior in rats with a unilateral 6-hydroxydopamine (6-OHDA) lesion of the
substantia nigra (12).

Methods

Female Holtzman rats weighing 185-200 g at the time of surgery were
housed singly on a reversed light/dark cycle. Food and water were freely
available. Each rat was anesthetized with sodium pentobarbital 30 min after
pretreatment with desipramine HCl (Merrell-Dow Pharmaceuticals; 13), and a 30
gauge cannula placed into the zona compacta of the right substantia nigra
using standard stereotaxic techniques. To unilaterally destroy the dopamine
(DA)-containing cells on that side 8 μg of 6-OHDA HBr was infused through the
cannula in 4 μl of a 0.9% saline solution that also contained ascorbate (0.1
mg/ml), at a rate of 0.5 μl/min.

After a 1 month recovery period, the animals were randomly assigned to 1 of 5 treatment groups, which will be referred to as the: (1) Shock-Rotometer (SK-R); (2) Shock-Unique (SK-U); (3) Shock-Control; (4) Immobilization (IM); or (5) Immobilization-Control groups. These groups received one of the following treatments on each of 5 consecutive days. Animals in the Shock-Rotometer group (n=20) were placed in automated rotometers similar to those described by Greenstein and Glick (14), but with a flat grid floor through which footshock could be applied. After a 10 min habituation period each rat received 20 min of discontinuous footshock stress (1.3 mA, 0.5 sec duration with 15 sec between shocks), and were then returned to their home cages. Animals in the Shock-Unique group (n=19) were treated exactly as those in the Shock-Rotometer group, except they received footshock stress in a unique environment; i.e., not in the rotometers. The environment in which they received shock was made very distinct from that in which the rotometers were located, including red (vs. white) light conditions, striped (vs. clear) chambers, auditory stimuli (music) and olfactory stimuli ("Jasmine oil"-scented wood shavings). Shock-Control animals (n=13) were also placed in rotometers for 30 min but did not receive any footshock. The rats in the Immobilization (n=20) group were weighed and then individually wrapped in a cloth towel and left in an open area for 3 hours each day. The Immobilization-Control animals were simply weighed on each of the 5 days.

Ten days after the last stress or control treatment each rat was placed in an automated rotometer with a solid flat floor and allowed to habituate for 15 min. Following the habituation period all animals received an i.p. injection of d-amphetamine sulfate (3.0 mg/kg) and rotational behavior recorded during each subsequent 5 min interval for a total of 2.25 hrs.

At least one week after being tested for AMPH-induced rotation, the rats were killed by decapitation, the left and right striata removed and later assayed separately for dopamine (DA) by high performance liquid chromatography with electrochemical detection (15). Only animals that had an 85% or greater DA depletion in the right striatum (relative to the left) and turned ipsiversive were used in the following analysis (see 16 for rationale). The N's given above do not include the six animals that failed to meet this criterion.

Results

The Shock-Control and Immobilization-Control groups did not differ statistically (2-way ANOVA, F values < 1.0), and therefore they were pooled to form one Control (C) group. Fig. 1 shows the number of rotations made during each 5 min interval over the 15 min habituation period and the 2.25 hr period after AMPH administration for these Control animals, and animals in each of the experimental groups. Each experimental group was compared to the Control group using 2-way analyses of variance.

Animals that were previously exposed to footshock in the rotometers (SK-R) did not differ significantly from the Control animals in AMPH-induced rotational behavior, and in fact, made slightly fewer AMPH-induced rotations than Controls (Fig. 1; F = 1.2). The tendancy of animals previously shocked in the rotometers to freeze when subsequently placed in the rotometers is indicated by a decrease in the rate of spontaneous rotation during the 15 min habituation period, relative to Control animals. Shock-Rotometer animals made an average (± S.E.M.) of 2.2 ±0.9, 2.2 ± 0.7, and 1.8 ± 0.6 spontaneous rotations during the three 5 min habituation intervals, whereas Control animals made 5.8 ± 1.2, 4.5 ± 0.8, and 2.6 ± 0.6 rotations (Main effect F = 6.0, p = .019; interaction F = 2.4, p = .10). In contrast, rats that had been previously exposed to immobilization stress (IM vs. C interaction F = 5.9, p < 0.001) or to footshock stress in an unique environment (SK-U vs. C interaction F = 1.9, p = 0.005) made significantly more AMPH-induced rotations than Control animals (Fig. 1). These latter three groups did not differ in their rate of spontaneous rotation during the habituation period. In addition, animals in the Shock-Unique group made more AMPH-induced rotations than those

in the Shock-Rotometer group (F = 2.2, p < 0.001). The significant inter-
actions indicate that the groups did not differ over the entire test session,
but only during peak rotation (approximately 30-50 min after AMPH administra-
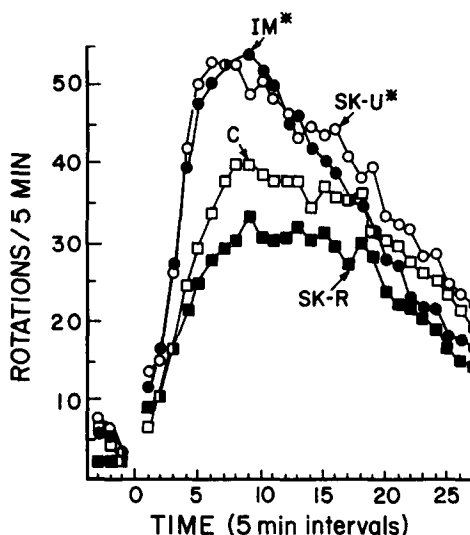tion).

Fig. 1. Average rotations per 5 min interval for control rats (C; see text),
and rats previously exposed to immobilization stress (IM), footshock stress in
the rotometers (Shock-Rotometer; SK-R) or footshock stress in an unique
environment (Shock-Unique; SK-U). One rotation consists of 4 consecutive 90°
turns in the same direction. Both spontaneous rotational behavior during the
15 min habituation period (intervals -3 to -1) and rotational behavior
induced by 3.0 mg/kg of AMPH (intervals 1 to 27) are illustrated. The
asterisks indicate groups that differed from the control group in AMPH-induced
rotational behavior.

Discussion

     The results reported here support earlier claims that prior exposure to
stress, like prior exposure to AMPH, enhances stimulant drug-induced behavior
(1, 4, 9). Furthermore, this phenomenon is not limited to behavior that can
occur in the absence of active locomotion (e.g., stereotypy), but includes
behavior requiring active locomotion. Since these experiments were completed,
Herman et al. (17) reported that footshock stress also enhances the locomotor
response (measured in photocell cages) to AMPH given 24 hr after the last
stress session. However, it should be noted that the environmental context in
which stress is applied can have a large effect on the outcome of these types
of experiments. Environmental context is also an important variable in
studies of behavioral sensitization to AMPH (e.g., 18, 19).
     The fact that stimulants and stress have similar enduring effects on
behavior suggests that they may also have similar enduring effects on brain.
It is known that acute treatment with either stimulants or stress produces
comparable effects on brain activity and the hypothalamo-pituitary-adrenal
axis (reviewed in 1 and 5). Unfortunately, we know little about the long-term
changes in brain produced by either stimulants or stress. However, it has
recently been found that the repeated intermittent administration of AMPH
produces an enduring enhancement in mesocortical DA utilization (20), and this
may be related to the selective enhancement in mesocortical DA utilization

produced by acute footshock stress (21). Future experiments comparing the long-term effects of stimulants and stress on mesotelencephalic DA systems may yield interesting similarities. If both stimulants and stress are found to produce an enduring up-regulation of brain DA systems this may help explain why both are precipitating factors in psychiatric disorders thought to involve brain catecholamine dysfunction (2, 3, 5, 22).

Acknowledgements

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