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Attenuation of the effects of amphetamine on the activity of rats following amygdala lesions

SHERWOOD O. COLE
Rutgers University, Camden, New Jersey 08102

The hypermotility effects of d-amphetamine (1.0 mg/kg) are attenuated in male albino rats with lesions of the dorsomedial amygdala, but not in the amygdala-sham or normal-control animals. An analysis of the intrasession adaptation functions of the groups suggests that the attenuation is due to an inhibition of the disorienting action of the drug.

Although the hypermotility effects of amphetamine are well established (Cole, 1967), the brain mechanisms involved in the mediation of such an action are less clearly understood. Lesions of the septal area alter significantly (exaggerate) the action of amphetamine on general activity (Carey & Salim, 1970). Since Stein and Wise (1969) have demonstrated that amphetamine produces a release of norepinephrine from the amygdala and since Cole (1973) has reported an attenuation of amphetamine anorexia following amygdala lesions, amygdala structures may also play a role in mediating the action of the drug on activity. The present study was undertaken to investigate this possibility.

METHOD

Subjects

Ten amygdala-lesion (A-L), 10 normal-control (N-C) and 6 amygdala-sham (A-S) male albino rats of the Charles River strain served as subjects. Animals were housed individually in plastic cages in a temperature controlled laboratory under a regular 12-h light–12-h dark schedule and had continuous access to Purina laboratory chow and water throughout the study. Animals in all three surgical groups had served previously as subjects in a drug-feeding study and a reactivity-to-light study and were approximately 175-180 days old at the time of the present experiment.

Surgical Procedure

In the A-L group, bilateral electrolytic lesions (2 mA anodal dc current for 20 sec) were produced stereotaxically with monopolar stainless steel electrodes, insulated except at the tip, while the animals were anesthetized with Nembutal sodium (50 mg/kg). A rectal cathode completed the circuit. Stereotaxic coordinates for the amygdala were –0.5 mm posterior to bregma, ±4.0 mm lateral to midline, and –8.0 mm vertical depth (Skinner, 1971). The A-S operation was the same as above, except that no current was passed following electrode placement. Surgery was performed when the animals were approximately 120 days old.

Activity Apparatus

Standard shuttleboxes, housed in a soundproof walk-in chamber, were used for testing. Each shuttlebox consisted of two 24 x 21 cm compartments, which were separated by a central divider with a 9 x 9 cm door, allowing freedom of access to either side. Contact points under four corners of the grid floor of the shuttlebox provided a measure of the number of crossings from one compartment to the other (measure of activity). Neither food nor water was available in the apparatus, and the boxes were covered with black-cloth material during testing to eliminate the diffused lighting in the walk-in-chamber.

Testing Procedure

Since animals in all three surgical groups had completed four 50-min sessions in the apparatus as part of a previous reactivity-to-light study, no further adaptation to the shuttlebox was provided. One week following the last of these previous sessions, animals in all three surgical groups (A-L, A-S, N-C) were assigned randomly to one of two d-amphetamine conditions (0.0 or 1.0 mg/kg d-amphetamine SO_4 in 1 cc/kg 0.9% NaCl) and administered a single 60-min activity test in the apparatus under the appropriate drug dose. For each subject, the total number of crossings between compartments and the number of crossings for successive 10-min periods of the 60-min test were determined. All subjects were injected ip 30 min prior to testing.

Following completion of the experiment, the A-L and A-S animals were sacrificed and perfused with 37% formaldehyde solution; the brains were then extracted and sectioned (40 micra) for staining.

RESULTS AND DISCUSSION

At the time of testing, the mean body weights of the A-L, A-S, and N-C groups were 445, 452, and 455 g, respectively. Since the group weights did not differ significantly ($F < 1.00$), the activity data were analyzed without statistical adjustment.

Analysis of the mean total number of crossings between compartments for the three surgical groups under the two drug conditions demonstrated a significant surgery effect ($F = 6.06$, $df = 2/20$, $p < .01$), a significant drug effect ($F = 55.70$, $df = 1/20$, $p < .01$), and a significant Surgery by Drug interaction ($F = 3.85$, $df = 2/20$, $p < .05$). A further analysis indicated that the A-L 10.13, $df = 1/16$, $p < .01$) and from the combined N-C and A-S groups ($F = 11.01$, $df = 1/22$, $p < .01$); however, the N-C and A-S groups were not themselves significantly different. Since the baseline conditions (0.0 mg/kg) of the three surgical groups did not differ ($F < 1.00$), it is apparent that the significant Surgery by

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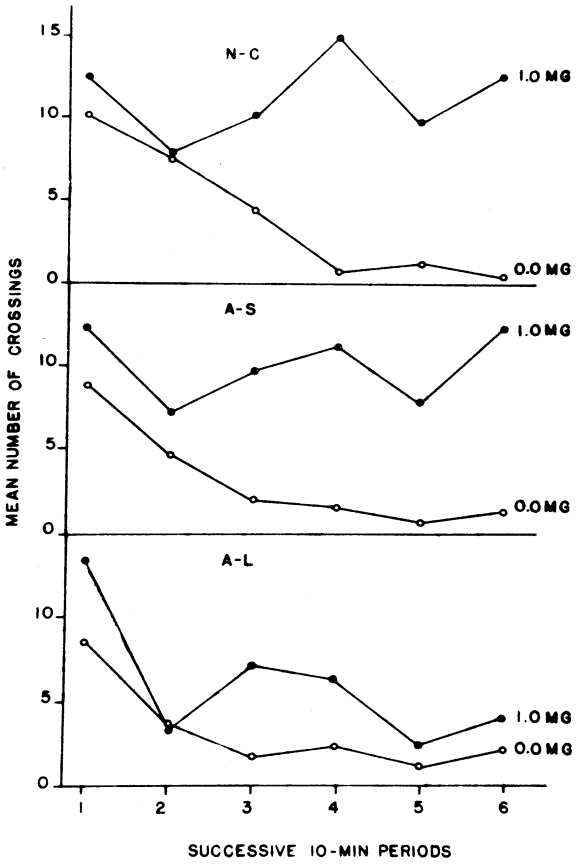

Figure 1. Mean number of crossings between compartments during successive 10-min periods of test session by normal-control (N-C), amygdala-sham (A-S), and amygdala-lesion (A-L) groups after receiving 0.0 or 1.0 mg/kg d-amphetamine.

Drug interaction was due to an attenuation of the effects of amphetamine (1.0 mg/kg) in the A-L group in comparison to the effects of the drug in the other 2 groups.

The mean number of crossings for successive 10-min periods of the 60-min test for the three surgical groups under the two drug conditions is summarized in Figure 1. Analysis of these data demonstrated a significant difference in the trends of the two drug conditions (0.0 and 1.0 mg/kg) in the N-C group (Drug by Successive Period interaction [$F = 5.75$, $df = 5/40$, $p < .01$]) and in the A-S group (Drug by Successive Period interaction [$F = 2.74$, $df = 5/20$, $p < .05$]). However, the trends of the two drug conditions in the A-L group were not significantly different (Drug by Successive Period interaction [$F < 1.00$]). Thus, animals under the 1.0 mg/kg dose condition in the A-L group (but not animals under the same dose condition in the N-C and A-S groups) appear to adapt within the session about as readily as do animals under the 0.0 mg/kg condition.

Histological examination of the 10 amygdala-lesion brains indicated that all animals sustained bilateral damage to the dorsomedial portion of the amygdala, although, in some instances, the damage also extended slightly more posterior into prehippocampal structures. A lesion representative of this group is reconstructed in Figure 2. Histological examination of the six amygdala-sham brains indicated that the bilateral tips of the electrode tracts were generally in the same dorsomedial region of the amygdala as were the lesions.

The results of the present study suggest that the dorsomedial region of the amygdala participates in the central mediation of the hypermotility effects of amphetamine and may be one of several target sites for the drug's action underlying such behavior. The present findings in combination with the previously observed exaggerated action of amphetamine on activity following septal damage (Carey & Salim, 1970) suggest the need for a "systems" view of central substrates underlying the drug's action on such behavior. Amygdala lesions in the present study involved areas adjacent to the stria terminalis, with some efferent fibers of this tract terminating in the ventral or precommissural area of the septum (see review by Lammers, 1972); thus, it is possible that such amygdalo-fugal projections provide some basis for an interaction of the dorsomedial amygdala and septal area in mediating the action of amphetamine on activity. The specific functional features of such a system, however, may differ markedly, since dorsomedial amygdala damage attenuates the action of the drug on activity while septal damage exaggerates such an action.

The results of the present study also suggest one

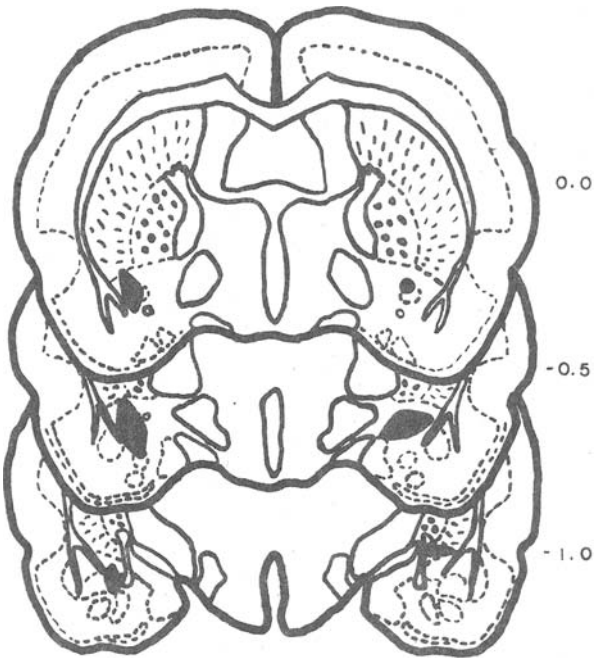

Figure 2. Reconstruction of dorsomedial amygdala damage representative of that observed in the lesion group. Reconstruction is adapted from Skinner (1971).

interpretation of the hypermotility action of amphetamine and how dorsomedial amygdala damage may alter this action. Since the animals under the 1.0 mg/kg d-amphetamine dose condition in both the N-C and A-S groups did not appear to adapt within the 60-min test session as did the animals under the 0.0 mg/kg dose condition, one might interpret the hypermotility action of the drug in the present context as a kind of "disorienting effect" of increased arousal. The attenuation of the hypermotility action of amphetamine in the A-L group might then be viewed as an inhibition of such a disorienting effect (produced by lesion destruction of the target site), allowing the animals under the 1.0 mg/kg dose condition to adapt within the session in a manner typical of the nondrugged animals (0.0 mg/kg dose condition).

REFERENCES

Carey, R. J., & Salim, A. P. Changes in d-amphetamine reactivity resulting from septal forebrain injury. Physiology and Behavior, 1970, 5, 133-136.

Cole, S. O. Experimental effects of amphetamine: a review. Psychological Bulletin, 1967, 68, 81-90.

Cole, S. O. Changes in amphetamine anorexia following amygdala lesions in rats. Proceedings of the 81st Annual Convention, APA, 1973, 1043-1044.

Lammers, H. J. The neural connections of the amygdaloid complex in mammals. In B. E. Eleftheriou (Ed.), *The neurobiology of the amygdala*. New York: Plenum Press, 1972.

Skinner, J. E. *Neuroscience: A laboratory manual*. Philadelphia: Saunders, 1971.

Stein, L. & Wise, D. Release of norepinephrine from hypothalamus and amygdala by rewarding medial forebrain bundle stimulation and amphetamine. Journal of Comparative and Physiological Psychology, 1969, 67, 189-198.

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