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Addictive agents and intracranial stimulation: Daily amphetamine and hypothalamic self-stimulation

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Twelve rats fixed with chronically indwelling electrodes for stimulation of the lateral hypothalamus were used to test for the effects of daily doses of amphetamine (2 and 4 mg/kg daily for 20 days). The rats' rate of pressing for brain stimulation was observed 1, 4, and 23 h after injections in 5-min sessions. These doses did not reliably increase self-stimulation rates during the times of testing. During the 5 days following termination of injections, pressing rates of rats receiving amphetamine were slightly less than those of rats receiving a placebo.

Amphetamine, at certain doses and regimens of testing, can accelerate pressing for lateral hypothalamic medial forebrain bundle (MFB) stimulation (Stein, 1964). Chronic use of amphetamine presumably produces something approaching psychoses in certain individuals (Bell, 1965; Ellinwood, 1968). Stein and Wise (1971) have suggested that affective psychoses are related to changes in levels of functional norepinephrine of the MFB system. Furthermore, amphetamine is known to increase available norepinephrine of the MFB (Stein & Wise, 1969, 1971). Despite the potentially important relationships among the actions of chronic dosing with amphetamine, adrenergic functions, and the MFB, there have been only limited tests of daily amphetamine and MFB self-stimulation. Consequently, it was decided, while testing the effects of daily injections of morphine on self-stimulation (Bush, Bush, Miller, & Reid, 1976), to test concurrently for the effects of daily injections of amphetamine.

These tests with amphetamine are limited. Only two doses, 2 and 4 mg/kg, were used. These doses were selected because larger doses, when given daily, produce serious debility (West, Hunsicker, Propheter, Taylor, & Reid, 1972). The self-stimulation tests were confined to sessions 1, 4, and 23 h after injections across 20 days and to days immediately before and after days of injections. Because of the limitations of the procedure, this study is only a preliminary study of the effects of chronic dosing of amphetamine on self-stimulation; results suggest that more systematic investigation might be interesting.

METHOD

Subjects

The subjects were 12 adult male Sprague-Dawley rats. Each was fixed, using standard procedures, with a chronically indwelling bipolar electrode. The stainless steel electrodes (Plastic Products ms 303) were insulated except at the cross section of the stimulating tips. The tips were separated from each other only by the width of the insulation.

The sites of intracranial stimulation (ICS) were verified by direct inspection of frozen sections of the subjects' brains and by inspection of photographs of enlarged images of those sections (Guzman, Flores, Alcarez, & Fernandez, 1968). Electrode tips were within the lateral hypothalamus and the primary structure of ICS was the MFB.

Apparatus

The experimental chamber was a Plexiglas box (30 x 25 x 43 cm) equipped with flexible electrode leads allowing free movement of the subjects. A lever extended through one side of the chamber, and its depression resulted in an ICS of 60-Hz sine waves of .5 sec and 25 microamperes, peak to peak.

Procedure

After surgery of fixing electrodes, recovery from surgery spanning at least 5 days, and initial tests to confirm that subjects pressed for ICS, the subjects were tested three times a day. Each of the testing sessions was 6 min: the first 1 min (a warm-up period), during which subjects began pressing, and the last 5 min, during which number of presses was recorded. The three sessions of a day were arranged so that times of testing would correspond to 1, 4, and 23 h after injections.

After subjects' rates of pressing for ICS became somewhat stable during their three daily test sessions, subjects were tested for 5 days to determine baseline rate of pressing. Subsequent to baseline, each of three groups of four subjects was given one of three doses of amphetamine: 0, 2, and 4 mg/kg of amphetamine sulfate. Because of the concurrent injections of morphine among other subjects and because only one saline-placebo group was tested, subjects of 0 mg/kg received subcutaneous injections, matching the injections of morphine, and subjects of amphetamine were injected intraperitoneally. There were 20 daily injections, while daily measures of pressing were taken at the three times after injections, 1, 4, and 23 h. After injections were terminated, there were another 5 days of daily testing with ICS.

RESULTS

Scores in Figure 1 are means of difference scores across 5-day blocks of testing. The differences were obtained by subtracting each subject's mean baseline

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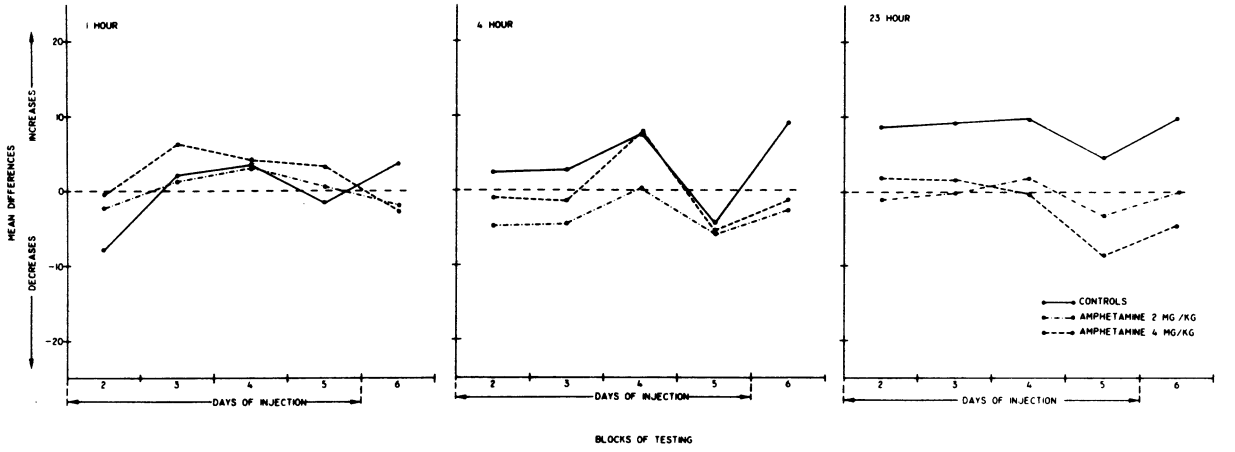

Figure 1. Mean differences from baseline across 5-day blocks of testing. Pressing was measured 1, 4, and 23 h after injections. There were 20 days of daily injections (Blocks 2 through 5 of 5 days each). Block 1 was the baseline to which other blocks were compared. Block 6 scores summarize pressing after injections terminated.

score of either 1, 4, or 23 h from every comparable post-baseline score. These differences were then used to get means of Figure 1 and as the "raw data" for further analyses.

Separate ANOVAs were performed on data of days of injections for each measurement corresponding to 1, 4, and 23 h after injections. These ANOVAs for repeated measures yielded no value indicating reliable differences in pressing among groups (or doses, 0, 2, and 4 mg/kg): $F(2,9)$ for 1-h data = .3; $F(2,9)$ for 4-h = .6; and $F(2,9)$ for 23-h = 1.47; $p > .25$. The Dose by Block interactions were also not reliable sources of variance for any of the three ANOVAs.

An inspection of mean difference scores of the tests following injections (Block 6 scores of each of the three panels of Figure 1) suggests that the responding of rats getting no amphetamine was generally higher than their preinjection scores, while responding of rats getting amphetamine was slightly less than their preinjection scores. To test this proposition, a 3 by 3 ANOVA was performed on the difference scores of Block 6, which resulted in an $F(2,27) = 3.77$, $p < .05$, confirming that the groups of amphetamine pressed less than the controls during tests postinjection.

DISCUSSION

It has been demonstrated that single doses as great as 2 mg/kg of amphetamine do not facilitate self-stimulation, but smaller doses of .5 or 1.0 mg/kg will accelerate pressing for ICS (e.g., Carey, Goodall, & Lorens, 1975). Furthermore, with pressing for ICS and pressing for conventional reinforcers, smaller doses of amphetamine are more likely to increase low rates of responding than high rates of responding (Dews, 1958). Consequently, it was not expected that initial doses of 2 and 4 mg/kg would produce marked increases in our fairly high rates of pressing, 1 h after injections. We were, however, interested in whether or not pressing rates would be modified by doses toward the end of the 20-day injection period. Unlike with high doses of morphine (Bush et al., 1976), daily doses of amphetamine did not eventually lead to marked facilitation of pressing.

Across days of testing, rats having placebo injections typically increase rates of pressing for a fixed ICS. The rats that received a placebo in this study are no exception. The rats receiving amphetamine, however, did not increase their pressing and, in general, decreased slightly their rate of pressing. Because pressing at high rates for near-optimal density of ICS would be less sensitive to modification of the substrate than, for example, less rapid pressing for near-reinforcing threshold ICS, these tests may not be sensitive enough to register the potential reduced reactivity to ICS. Nevertheless, the data do lead to the testable hypothesis that daily amphetamine might lead to reduced pressing for ICS, especially following a series of injections. Such reduced pressing could be an index of modification of the medial forebrain system. In turn, such modification could be part of the syndrome of behavior that accompanies prolonged amphetamine use (Groves & Reber, 1976).

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