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Research Report

Time-dependent effects of amphetamine on feeding in rats

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ABSTRACT

Following administration of a moderate dose of amphetamine, rats appear to pass through a sequence of physiological/psychological states, including stimulant and depressant states. The present research evaluated whether these states could be inferred from time-dependent changes in feeding-related measures. Male rats were housed in individual stations (light–dark 12–12 h, free access to water) where, at 3-h intervals, they could respond for food for 1 h. The work requirement was fixed ratio 1, and each lever press produced six 94-mg food pellets. When the pattern of responding for food stabilized across the light–dark cycle, a series of 6 or 7 tests was run. During each test, rats received a saline treatment (1.0 ml/kg, subcutaneously) followed by a 48-h monitoring period, and then they received an amphetamine treatment (2.0 mg/kg, subcutaneously) followed by a 72-h monitoring period. Different groups were treated at either light onset or light offset. Lever presses and head-in-feeding-bin responses were monitored throughout these tests. Administration of amphetamine at light onset and at light offset produced cumulative food intake functions having four regions: post-treatment hours 1–6 (hypophagia), 7–12 (normal intake), 13–27 (hypophagia), and 28 and beyond (normal intake). The sequence, duration, and quality of the amphetamine-induced changes in food intake resembled those formerly seen in cue state and activity, and provided further evidence of a transient withdrawal state 20–24 h post-amphetamine treatment.

1. Introduction

Amphetamine, a psychostimulant, produces activating effects in the short term (the first several or so hours post administration). These short-term effects and the mechanisms that mediate them have been extensively studied. Amphetamine and related compounds are used recreationally in part because of such effects (reviewed in Berridge, 2006; Robinson and Berridge, 1993; Segal and Kuczenski, 1994).

Amphetamine produces additional time-dependent effects during the first day or so following administration. Investigations of the effects of amphetamine on cue state and on activity have provided good evidence for this. Barrett, Caul and colleagues have examined the impact of amphetamine on cue state in a series of drug discrimination studies involving amphetamine and haloperidol (Barrett et al., 1992, 2005; Caul et al., 1996, 1997; Stadler et al., 1999). By "cue state," Barrett, Caul and colleagues meant the distinguishable internal sensations present at a particular time following drug treatment. In one study, rats treated with 10 mg/kg amphetamine responded on an amphetamine-paired lever 4 and 6 h after treatment, on amphetamine- and haloperidol-paired levers equally 8, 12, and 16 h after treatment, on a haloperidol-paired lever 20 and 24 h after treatment, and again on each lever equally 32 h after treatment (Barrett et al., 1992). White and colleagues have examined the impact of amphetamine on activity. Rats treated with 2.0 or 4.0 mg/kg amphetamine were hyperactive 1 to 6 h after treatment, normally active 7 to 18 h after treatment, hypo-

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active 19 to 24 h after treatment, and again normally active 25 h after treatment (White and White, 2006).

Changes in cue state and activity appear correlated across time, and the changes may signify the presence of different amphetamine-induced states. An amphetamine-like cue state and hyperactivity from hours 1 to 6 post-treatment indicate the presence of a stimulant state, whereas a haloperidol-like cue state and hypo-activity from hours 19 to 24 post-treatment may indicate the presence of a withdrawal state. The withdrawal state may be preceded by a latent state, when measures only appear to normalize, and it may be followed by a recovery state, when measures actually do normalize. Withdrawal is comprised of a constellation of symptoms (Barr and Markou, 2005), and one way to bolster the claim that withdrawal is present at a particular time is to show that other symptoms indicative of withdrawal are also present at that time. One characteristic symptom of withdrawal from amphetamine is diminished food intake (hypophagia).

The purpose of this study was to see whether amphetamine altered food intake in a time-dependent manner comparable to that observed for cue state and activity. We were particularly interested in determining whether amphetamine produced hypophagia during the same interval that it reportedly produced a haloperidol-like cue state and hypo-activity.

Certain amphetamine administration regimes, such as regimes involving chronic escalating doses, have been used to produce a relatively prolonged condition that has been likened to depression (Barr and Markou, 2005). In contrast, in this research, a moderate dose of amphetamine, 2.0 mg/kg, was repeatedly administered at intervals of at least 5 days, a regime that is better suited to produce a transient withdrawal. Short-term effects of amphetamine on food intake have been extensively studied, whereas longer-term effects have not been. When longer-term effects have been studied, investigators have tended to measure total intake at the end of a long interval such as 24 h (Chen et al., 2001). In order to enhance the opportunity to identify time-dependent changes, we assessed the effects of amphetamine on intake frequently and over a long interval. In particular we allowed rats to lever press for food pellets at meal opportunities that began every 3 h and that were 1 h in duration, and we monitored responding and food intake for 3 days following amphetamine administration. The effects of a drug depend in part on when it is administered in the light–dark cycle (Davies and Wellman, 1991; Reinberg, 1999). To evaluate whether changes could be observed that were independent of administration time, we examined the effects of treating different groups at light onset and at light offset.

2. Results

2.1. *Acquisition*

Groups of eight rats were treated at either light onset or light offset of the 12–12 h light–dark cycle during testing. The groups were not tested until they showed stable responding on the feeding schedule. The feeding schedule allowed animals to respond for food for 1 h every 3 h. During a feeding hour, a lever press could result in a "package" of six 94-mg pellets (Fixed ratio 1, FR1, or "ratio"). The lever press produced the first pellet, and an animal had to place its head in the feeding bin to produce subsequent pellets in the package. Both groups of rats adjusted to the feeding schedule in a similar manner, and so acquisition data will be shown only for the group eventually treated at light offset during tests.

Fig. 1 shows the mean number of ratios the animals completed across days of exposure to the feeding schedule (Training days). The number of ratios completed increased from days 1 to 3, decreased from days 3 to 16, but did not differ from days 16 to 20, $F(7,19)=29.012$, $p<.0001$ and Fisher's PLSD post hoc tests. In summary, performance was stable after 15 days of training.

2.2. *Testing*

Animals received a series of 5-day tests. On day 1, different groups were treated, at either light onset or light offset, with saline (Sal). On day 3, they were treated, at the same times, with 2.0 mg/kg amphetamine (Amp). Feeding opportunities were scheduled as before. Fig. 2 shows the mean number of ratios each group completed on each day of each test. The upper panel shows results for the group treated at light onset. An ANOVA produced a significant effect of Test, $F(6,42)=5.035$, $p<.001$, a significant effect of Test day, $F(4,28)=51.448$, $p<.0001$, and a significant interaction, $F(24,168)=1.762$, $p<.05$. Fisher's PLSD for the main effect of Test day indicated that fewer ratios were completed on the day of amphetamine administration than on any other day, p values $<.05$, but that no other days differed. Fisher's PLSD for the main effect of Test indicated that more ratios were completed during Test 1 than during other tests, p values $<.05$. An ANOVA based on the data of the group treated at light offset (Fig. 2, lower panel) produced a significant effect of Test, $F(5,35)=7.814$, $p<.0001$, and of Test day, $F(4,28)=36.146$, $p<.0001$. Fewer ratios were completed on the day of amphetamine administration than on other days, and more ratios were completed during Tests 1 and 2 than during the other tests (Fisher's PLSD, p values $<.05$). Overall, for treatment at both light onset and light offset, fewer ratios were completed on the day of amphetamine administration, and more ratios were completed during the earliest tests.

Fig. 3 shows the number of ratios each group completed at each meal opportunity during the 2-day period following saline

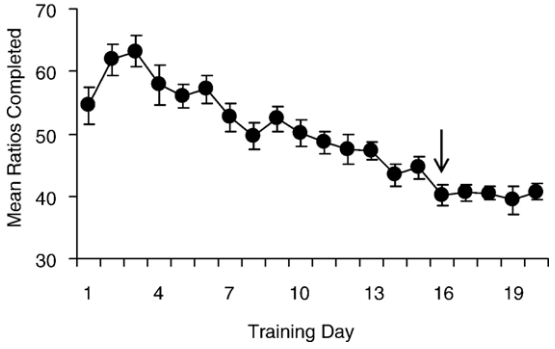

Fig. 1 – Mean ratios completed across acquisition days for the group treated at light offset. 1-h meal opportunities, during which each lever press produced 6 pellets (fixed ratio 1), were scheduled at 3-h intervals. Arrows indicate training days from which performance on the measure was stable.