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Acute withdrawal-related hypophagia elicited by amphetamine is attenuated by pretreatment with selective dopamine D1 or D2 receptor antagonists in rats

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HIGHLIGHTS

- Longer-term hypophagia (LTH) occurred 19-26 hours after amphetamine (AMPH) in rats
- Pretreatment with dopamine D1 or D2 receptor antagonists reduced AMPH-elicited LTH
- Dopamine receptor activation due to AMPH is an early event leading to LTH

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ABSTRACT

After receiving 2.0 mg/kg amphetamine, rats show two phases of reduced food intake, short-term hypophagia, during the first several hours after treatment, and longer-term hypophagia, approximately 19 to 26 h after treatment. The longer-term hypophagia may be an indicator of an acute withdrawal. This study assessed whether D1 and D2 receptor activation were important early events in the elicitation of longer-term hypophagia. Throughout a series of five-day tests, rats could lever press for food pellets for one-hour periods beginning every 3 h. On test day 1, rats were given a saline pretreatment, and 15 min later they were given a saline treatment. On test day 3, they were given a pretreatment of either saline or a selective dopamine receptor antagonist, and 15 min later they were given a treatment of either saline or amphetamine (2.0 mg/kg). In Experiment 1, pretreatments included 3, 12, 31, and 50 μg/kg of the selective D1 receptor antagonist SCH 23390. In Experiment 2, pretreatments included 25, 50, and 100 μg/kg of the selective D2 receptor antagonist eticlopride. Distance moved was monitored for the first 6 h following pretreatment–treatment combinations to obtain an indirect behavioral measure of receptor blockade (antagonist attenuation of amphetamine hyperactivity). Food intake at each meal opportunity was monitored throughout each five day test. Patterns of food intake following day 1 saline–saline and day 3 pretreatment–treatment were compared. The combination saline–amphetamine produced short-term and longer-term hypophagia. Combinations involving antagonist–saline did not produce longer-term changes in food intake. Pretreatment with 12 to 50 μg/kg of SCH 23390 produced substantial blockade of amphetamine hyperactivity and prevented amphetamine-induced acute-withdrawal-related longer-term hypophagia. Eticlopride produced a partial blockade of longer-term hypophagia. Both D1 and D2 receptor activation are required for full expression of longer-term hypophagia following amphetamine administration.

1. Introduction

When rats are administered 2.0 mg/kg amphetamine at intervals of several or more days, they show two phases of reduced food intake (hypophagia) during the 24 h, approximately, after each treatment. The first phase (short-term hypophagia) occurs during the first several hours after drug treatment and is one aspect of the psychomotor stimulant state. The second phase (longer-term hypophagia) tends to be most prominent between, roughly, hours 19 to 26 post-treatment [17,18]. Other motivational and affective impairments are observed during the same time period [2,16,19], and so longer-term hypophagia may be an aspect of an acute withdrawal or "hangover" syndrome. Because the regime described above involves intermittently administering a moderately-high but nontoxic dose, it mimics some features of recreational drug use. A similar regime was employed in the experiments described below.

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In the present study, time-dependent effects will be described in terms of two post-treatment intervals, short-term and longer-term intervals. The intervals are distinguished on the basis of the effects observed in prior studies following 2.0 mg/kg amphetamine [16–19]. The short-term interval includes hours 1–6 post-treatment. The interval is distinguished by biphasic locomotion that peaks above baseline and then returns to baseline. Effects occurring sometime during this interval will be referred to as "short-term effects." One such effect is short-term hypophagia, which occurs during the first several hours of the short-term interval. The longer-term interval includes hours 7–26 post-treatment. Effects occurring sometime during this interval will be referred to as "longer-term effects." Longer-term hypophagia is a longer-term effect that occurs near the end of the longer-term interval.

Amphetamine affects several major neurotransmitters in the brain, including dopamine, norepinephrine, and serotonin. Amphetamine is an indirect agonist of dopamine: Administration of amphetamine results in increased concentrations of dopamine in the synaptic cleft. Dopamine acts at two classes of receptors, the D1-like receptor (D1 and D5) and the D2-like receptor (D2, D3, and D4). The dopaminergic system consists of major pathways that originate in the midbrain and that project to areas including the prefrontal cortex, the dorsal striatum, the nucleus accumbens, and the hypothalamus. Dopaminergic pathways are the primary sites of amphetamine's actions [5]. Many of amphetamine's major short-term effects, including hyperactivity, hypophagia, and reward-related phenomena, depend upon activation of both D1 and D2 receptors [14].

Longer-term hypophagia occurs many hours after amphetamine administration, and the phenomenon may have at least two sets of determinants linked by a cascade. The first set of determinants would begin to act immediately after drug receipt and would initiate the cascade. The second set of determinants would be involved in the proximate expression of longer-term hypophagia. In this research, we assessed the involvement of D1 and D2 receptor activation in initiating the cascade that results in amphetamine-induced longer-term hypophagia. Rats were pretreated with different doses of D1 (Experiment 1) or D2 (Experiment 2) receptor antagonist 15-min prior to treatment with 2.0 mg/kg amphetamine. The impacts of these pretreatments on longer-term hypophagia were observed. If D1 antagonist pretreatment were to prevent longer-term hypophagia, then this would suggest that D1 receptor stimulation by amphetamine was involved in initiating the cascade that resulted in longer-term hypophagia. The same was true for D2 antagonist pretreatment. If both D1 and D2 antagonist pretreatment were to prevent longer-term hypophagia, then this would further suggest that a receptor interaction was involved.

Some studies have examined the impact of dopamine antagonists on food intake. Results indicate that D1 and D2 antagonists do not reduce food intake during the longer-term interval, though higher doses can reduce intake during the short-term interval [4,6,10,13]. Zigmond et al. [21] focused on intake shortly after treatment with a dopamine antagonist in combination with amphetamine. They suggested that an optimal level of dopaminergic activity mediated feeding, and that increases and decreases from this optimum following amphetamine, dopamine agonists, dopamine antagonists, and some combinations of dopamine antagonists and amphetamine may disrupt feeding. Very few studies have examined the impact of combinations of dopamine antagonists and amphetamine on feeding over longer intervals. Chen et al. [3] found that pre-treatment with a D1 or D2 antagonist blocked amphetamine-induced reductions in 24-hour food intake. Because intake was measured at only one time point (24 h post-treatment), whether antagonist pretreatment prevented short-term hypophagia, longer-term hypophagia, or both is unclear. To decide the issue measurements must be made at multiple time points during the 24 h interval after treatment, particularly at those times that could reflect short- and longer-term hypophagia.

The present study employed a procedure that measured short- and longer-term effects [17,18]. Throughout a series of five-day tests, rats could lever press for food pellets during one-hour intervals that began every 3 h. Each five-day test began with a two-day re-baseline in the eventuality of baseline shifts due to prolonged housing in the apparatus, to aging, or to shifts in food-intake set point due to repeated drug receipt [7]. Drug was administered at light onset, the start of the inactive period, so that motivational deficits due to amphetamine administration, which tend to be greatest 19 to 24 h post-treatment, would coincide with the active period and so be easier to detect. The beginning of the inactive period is also the time at which recreational drug use presumably peaks in humans.

2. Materials and methods

2.1. Animals

A total of sixteen adult male Wistar rats (Harlan, Indianapolis, IN) were used. The study consisted of two experiments, and each experiment included eight animals. Animals were housed in plastic tubs in a departmental colony having a 12-h light/12-h dark cycle and a temperature of 20–22 °C, and they were adapted to this environment for several weeks prior to the start of their condition. Animals had free access to water and chow (Purina 5001 Rodent Diet, Lab Diet; composition by calories: 30% protein, 13% fat, 57% carbohydrate). Initially, animals were housed in pairs, but a week before the start of their study they were housed individually. Just prior to the start of their study, animals were handled and were pre-exposed in their home cages to the pellets that they would consume during the study. Animals in Experiment 1 weighed between 430 and 520 g at the start of their study, and animals in Experiment 2 weighed between 490 and 600 g.

2.2. Apparatus

Animals learned to lever press for food pellets in four standard operant conditioning stations (Med Associates). Each station contained a retractable lever, a feeder that dispensed 94-mg pellets, and a bin that could be illuminated and that was equipped with a head-in-bin detector.

The animals were tested in one of eight "24-h stations" that were designed for long-term housing. Each station consisted of a sound attenuating, wooden compartment (58 cm × 42 cm × 58 cm high) that enclosed a plastic housing cubicle (40 cm × 20 cm × 40 cm high). Each station contained a response lever, a pellet dispenser, and a food bin similar to those in the operant stations. The lever was situated just below the bin in the left half of one end wall of the cubicle. The right half of the end wall contained a drinking tube that was attached to a water bottle. The floor of each cubicle was a black metal pan. The floor of the pan was covered with black grip tape and contained a thin layer of absorbent micro-waved topsoil. Each compartment had a fan (Sunon, sf11580A) that provided ventilation and that masked noises and a light fixture (Lampi-Pico accent light, 4-W) that produced a 12-h light/12-h dark cycle.

Devices in operant conditioning stations and in 24-h stations were connected to an interface (Med Associates) and a computer. Software (Med Associates) was used to arrange contingencies and monitor lever presses and head-in bin responses.

In the ceiling of each compartment, and centered 50 cm above the floor of each cubicle, was a monochrome infrared camera (Cat eyes, PC184IR). The cameras were connected to a monochrome multiplexer (Robot-Duplex Digital Video Multiplexer, DMV16Q), which combined images from the cameras in each of the stations into one image for quantification. The multiplexer was connected to a monitor (36 cm Trinitron high resolution video monitor, ECM-1402H) and a computer. The computer (Dell, M782p) contained a piccolo frame grabber. An Etho Vision Pro 3.0 Video Tracking, Motion Analysis, and Behavior Recognition System collected and analyzed the data. Each animal was tracked within an area corresponding to the dimensions of the cubicle