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Amphetamine and morphine may produce acute-withdrawal related hypoactivity by initially activating a common dopamine pathway

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HIGHLIGHTS

- Longer-term hypoactivity (LH) is a reduction in activity 12–24 h following drug.
- LH is a sign of acute withdrawal.
- Amphetamine (Amph) and morphine (Morph) given every 5 days elicit similar LH.
- The LH elicited by both drugs was blocked by co-administration of a D1 antagonist.
- Amph and Morph elicit some signs of withdrawal via a common dopamine pathway.

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ABSTRACT

Rats given drugs of abuse such as amphetamine or morphine show longer-term effects, that is, signs of acute withdrawal, including hypoactivity, hypophagia, and blunted affect, sometime between 12 and 24 h after treatment. This research explores the possibility that signs of acute withdrawal produced by different drugs of abuse are instigated by overlapping mechanisms. The specific objectives of the research were to see if amphetamine and morphine produced longer-term hypoactivity, and to see if any longer-term hypoactivity elicited by the drugs could be blocked by SCH23390, a dopamine D1 antagonist. Six groups of rats, with eight rats in each group, were exposed to a series of five-day tests. Near light onset of Test Day 1, each animal was given control administrations, consisting of a saline treatment (1.0 ml/kg) followed 30 m later by a saline posttreatment, and locomotor activity was monitored for the next 24 h. On Test Day 3, each animal was given experimental administrations, and locomotor activity was again monitored for 24 h. Each group received only one combination of experimental administrations across tests. Experimental administrations consisted of saline, amphetamine (2.0 mg/kg), or morphine (5.0 mg/kg), followed by saline or SCH23390 (0.05 mg/kg). All administrations were subcutaneous. Amphetamine and morphine produced longer-term hypoactivity, having similar time courses and magnitudes. SCH23390 blocked the longer-term hypoactivity produced by both drugs. Saline and SCH23390 produced no changes in longer-term activity in their own right. The time course of amphetamine-elicited longer-term hypoactivity resembled that of amphetamine-elicited longer-term hypophagia observed in a prior study. Approximately 1/4 of the animals given amphetamine or morphine did not show longer-term hypoactivity ("low withdrawal" rats). Amphetamine and morphine may initiate the cascade of events resulting in signs of acute withdrawal by producing activation in a common pathway that uses dopamine as a neurotransmitter. Different signs of acute withdrawal (hypoactivity and hypophagia) may involve the short-term activation of the same common pathway. Low withdrawal rats may have a different vulnerability to amphetamine and may show differences in drug assessment outcomes relative to animals that manifest distinct signs of acute withdrawal.

1. Introduction

When rats are administered amphetamine (2.0 mg/kg), they show longer-term hypoactivity, a reduction in activity 12 to 24 h later [22,25], and longer-term hypophagia, a reduction in food intake over a similar time period [21]. The longer-term hypoactivity and hypophagia appear to be aspects of an acute withdrawal or "hangover" state, because other measures change during this period in a manner consistent with

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acute withdrawal, including affect [1]. These measures normalize by 24 h after treatment. The similarity in time course of longer-term hypoactivity and of longer-term hypophagia suggests that the two putative indicators of acute withdrawal may share determinants.

The methods used to assess the effects of amphetamine on longer-term activity and longer-term food intake differed in the intermittency with which drugs were administered. In research involving activity as the dependent measure, amphetamine was given repeatedly at periods of 24 or 33 h [22,25], whereas in research involving feeding, drug treatments, including amphetamine, were given at 5-day intervals [21,22,24].

In the present study, amphetamine was given at 5-day intervals, the schedule used in feeding studies. The purpose was to see whether, when schedules of administration were equated, the time course with which longer-term hypoactivity occurred resembled the time course, formerly seen, of longer-term hypophagia. Similarity of time courses under these circumstances would suggest shared determinants of elicitation. Given that longer-term hypophagia could be prevented by administering a dopamine D1 receptor antagonist (SCH 23390) around the time of amphetamine administration [21], we also examined whether D1 antagonist could prevent longer-term hypoactivity. This outcome would provide another form of evidence that the same mechanism was involved in the elicitation of longer-term hypoactivity and hypophagia. A dose of 0.05 mg/kg SCH 23390 was used in the present study, because previously it completely blocked amphetamine hyperactivity, but it did not reduce longer-term food intake when administered by itself [21]. Finally, further goals of this research were to see if morphine, a narcotic, produced similar longer-term hypoactivity, and to see if any longer-term hypoactivity produced by morphine could be prevented by D1 antagonist. These outcomes would suggest that amphetamine and morphine produced some aspects of acute withdrawal via a similar mechanism.

In the present study, "short-term effects" will be defined as drug-induced changes occurring during the first six hours following treatment. Short- and longer-term effects of morphine on activity have been examined in several studies. In the short-term, morphine produced a biphasic pattern, first suppressing activity for approximately 1.5 to 2 h, and then, after approximately 1 to 1.5 h, enhancing it for 1 to 2 h [9,14]. In the longer-term, high morphine doses (above 40 mg/kg) received daily reduced activity sometime between hours 13 and 24 following administration [5,7,13]. The purpose of the latter studies was to model abuse. The present research used a lower dose (5 mg/kg) more intermittently administered, and it showed a more detailed time course of effects. Some short- and longer-term effects of amphetamine on activity have been discussed previously [22,25] and will not be reviewed here.

Amphetamine is an indirect dopamine agonist that promotes release of dopamine from vesicles and attenuates dopamine reuptake [4,18]. Morphine is a mu-opioid receptor agonist [2,11]. Dopamine antagonists might plausibly be expected to alter effects produced by morphine because dopamine and opioid neurotransmitter systems interact, most familiarly, via the ventral tegmental area (VTA). By binding to mu-opioid receptors in the VTA, morphine inhibits the inhibitory GABA neurons that synapse on dopaminergic dendrites in the VTA, indirectly exciting dopamine neurons, and leading to an increase in dopamine output to the nucleus accumbens (NAc), the prefrontal cortex (PFC), and the amygdala [2,11,16]. Through this shared pathway, amphetamine and morphine could initiate the cascade of events leading to longer-term hypoactivity, and a D1 antagonist could prevent the longer-term hypoactivity produced by either drug.

The procedure used in the present study was similar to that used in prior research involving feeding as the dependent measure [21,23,24]. Rats received a series of five-day tests. At the start of Day 1 of a test, animals received a control treatment, and at the start of Day 3, animals received an experimental treatment such as amphetamine or morphine. Patterns of activity on Day 1 and Day 3 were compared. Each five-day test began with a one-day re-baseline in the eventuality of baseline shifts due to repeated apparatus exposure, to aging, or to drug-induced shifts in food-intake set point [6]. 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 15 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.

Activity was used as the dependent measure because it is sensitive to the effects of drug treatment: An animal accomplishes most functional behaviors (eating, drinking, exploration, etc.) via activity, and the diminution of any functional behavior by drug would probably be reflected in reduced activity. Additionally, activity is potentially informative with respect to antagonist results: A complete blockade of drug-induced longer-term hypoactivity by an antagonist would suggest a blockade of acute withdrawal signs generally, and a normalization of all functional behaviors.

2. Materials and methods

2.1. Animals

The subjects were 48 adult male outbred Wistar rats (Harlan, Indianapolis, IN). Eight rats were in each of six groups. Each group was in a different treatment condition. The six groups/treatment conditions were run one after the other from May 2014 to July 2015. Several shipments of animals were received prior to and during this period. The eight subjects in each group were randomly selected from a recent shipment. After arriving, subjects were housed in pairs in an animal colony in an animal vivarium. This colony was used to house only those groups of animals that were involved in this study. The colony was on a 12–12 h light-dark cycle, and the animals had free access to food (5001 Rodent Diet, Lab Diet) and tap water. A week before the start of a treatment condition, each animal in the group was housed in an individual cage. On each of several days prior to the start of a treatment condition, each animal was briefly handled, weighed, and rubbed on the back of the neck.

2.2. Apparatus

Activity was monitored in one of four stations. Each station consisted of an Activity Test Chamber (Med Associates, ENV-515) placed in a Sound Attenuating Cubicle. Each chamber had clear plastic walls and was 43 cm × 43 cm × 30 cm high. Near the floor of each wall was a strip containing 16 infrared sources or detectors (Med Associates, ENV-258). Each source or detector was spaced 2.5 cm center to center, and strips were positioned so that each source or detector was 3.7 cm above the floor. A plastic insert was placed in an activity chamber before an animal was placed in the chamber. Each insert was approximately 42 cm × 42 cm × 7.3 cm high and had finger holes so that it could easily be inserted or removed. Each of the eight rats in an experimental group was assigned its own insert. Water was available from a bottle secured in a metal holder affixed to a chamber wall. The bottle could contain as much as 300 ml of water. Each chamber could be covered with a removable top that contained ventilation holes.

Each sound attenuating cubicle (Med Associates, ENV-017M-027) consisted of compressed wood and was 73 cm wide by 60 cm deep by 59 cm high. The cubicle and chamber could be illuminated by a low-profile 15-cm long light fixture that was mounted near the top of one cubicle wall. The fixture contained a fluorescent bulb (Lampi, F4T5WW). The light-fixture in each station was connected to an appliance timer that controlled a 12–12 h light-dark cycle within each station. Light-dark cycles in the stations and in the animal colony were synchronized. Each cubicle contained a fan that ventilated the station and masked noises.

Strips containing infrared sources and detectors were connected to a 48 Channel IR Controller (Med Associates, ENV-520). The controller of each station was connected to a computer that ran activity monitoring