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Effects of apomorphine on mating behavior, flank marking and aggression in male hamsters

Molly M. Hyer, Laura M. Rycek, Owen R. Floody *

Department of Psychology and Program in Animal Behavior, Bucknell University, Lewisburg, PA 17837, United States

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ABSTRACT

In male rats, the dopamine agonist apomorphine (APO) generally facilitates copulatory behavior. However, disruptive effects of high APO doses have been reported. These have been interpreted in diverse ways, as products of a dopaminergic system that inhibits sexual behavior or as consequences of APO's stimulation of competing responses. To test the generality of these effects, we observed APO's impact on copulatory behavior in male hamsters. Several effects were observed, all attributable to a relatively high dose and involving the disruption of male behavior. More unexpectedly, APO treatment caused males to attack estrous stimulus females in the course of these tests. To clarify these effects, we observed the effects of APO on flank marking, a type of scent marking closely allied to aggression and dominance in hamsters. Treatment reliably decreased the latency of marking. It also increased the rate of marking when appropriate measures were taken to prevent this effect from being obscured by drug-induced cheek pouching. Together, these results confirm and extend APO's well-known ability to increase aggression. Further, they suggest that APO-induced aggression can intrude into other contexts so as to disrupt, or possibly facilitate, other forms of social behavior.

1. Introduction

Dopamine (DA) is widely considered to be one of the most influential neurotransmitters in the control of male-typical mating behavior (reviews in Bitran and Hull, 1987; Hull and Dominguez, 2007; Meisel and Sachs, 1994). This view is supported by many forms of evidence, including correlations of central dopaminergic activity with sexual stimulation or performance (Hull et al., 1993, 1995; Tsai et al., 2006), responses to central applications of dopaminergic drugs (Hull et al., 1986), and the effects of lesions specific to dopaminergic neurons (Bazzett et al., 1992). But some of the earliest and most important evidence of this type emerged from descriptions of the behavioral effects of systemic treatment with the nonselective DA receptor mimic apomorphine (APO).

The effects of APO on male sexual behavior have been the focus of many studies (Agmo and Fernández, 1989; Arteaga et al., 2002; Butcher et al., 1969; Clark and Smith, 1987; Paglietti et al., 1978; Scaletta and Hull, 1990; Tagliamonte et al., 1974). These describe a preponderance of facilitory effects, justifying the common characterization of DA and dopaminergic systems as net facilitators of male behavior (e.g., Bitran and Hull, 1987; Hull and Dominguez, 2007; Meisel and Sachs, 1994). At the same time, these studies are limited in two respects. First, nearly all have focused on male rats, leaving the role of DA in other species less clear. Second, studies of the responses to varying doses of APO have sometimes described both facilitory and disruptive effects. In many, but not all, cases these seem to assort by dose, with relatively low doses tending to facilitate and some higher doses tending to disrupt (e.g., Clark and Smith, 1987). These contrasting effects have led to some uncertainty regarding DA's role in male behavior (e.g., Bitran and Hull, 1987; Clark and Smith, 1987; Meisel and Sachs, 1994). To a large extent, this controversy has been resolved by the other forms of evidence described earlier. Nevertheless, the reasons for APO's sometimes contrasting behavioral effects are of interest and remain less than completely clear.

These limitations could be related in the sense that uncertainty regarding some of APO's actions could reflect the concentration of past research on rats: The factors explaining these contrasting effects at the two ends of the dose–response curve could be clearer in other species. It was partly to test this possibility that we sought to describe the effects of systemic APO treatment on mating behavior in male hamsters.

2. Experiment 1: Apomorphine and copulatory behavior

Male hamsters and rats share a basic copulatory pattern characterized by a single intravaginal thrust per intromission, multiple intromissions prior to ejaculation, and the potential for multiple ejaculations during a sexual interaction (Dewsbury, 1975). At the same time, male-typical sexual behavior in these species differs both behaviorally and neurochemically.

* Corresponding author. Tel.: +1 570 577 1432; fax: +1 570 577 7007.
E-mail address: ofloody@bucknell.edu (O.R. Floody).

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Behavioral differences are evident on many of the measures commonly used to describe male performance, including the latencies to mount, intromit and ejaculate (Dewsbury, 1979; Floody, 2011a; Pfaus et al., 1990; Sachs, 1978). Other differences emerge from the studies that have used factor analysis to describe patterns of interindividual correlation suggestive of basic processes underlying the behavior (Dewsbury, 1979; Floody, 2011a; Pfaus et al., 1990; Sachs, 1978). Though factors focused on the initiation and efficiency of copulation have been described in both hamsters and rats, these factors seem to be defined differently in the two species. Further, a factor emphasizing the rate of performance is a prominent feature in rats but seems absent from the factor structure of hamsters.

On the neurochemical level, the role of acetylcholine (ACh) has been studied in both rats and hamsters. In rats, responses to systemic treatment with a muscarinic agonist such as oxotremorine suggest for ACh a quite specific role in the control of intromission frequency and ejaculation latency (e.g., Ahlenius and Larsson, 1985; Retana-Marquez et al., 1993). In contrast, similar treatments seem to produce much broader effects in hamsters, involving changes in most of the common measures of male behavior (Floody, 2011b).

Though the data on cholinergic control raise the possibility of other species differences in neurochemical mechanisms for sexual behavior, the existing studies instead emphasize similar, facilitory, responses by male rats and hamsters to DA. Indeed, the one previous study of APO's effects on male behavior in hamsters seems to offer especially clear support for such effects (Arteaga et al., 2002). On the other hand, this study examined the impact of just one, relatively low dose (0.025 mg/kg), whereas most of the uncertainty regarding APO's effects revolves around its dose–response curve, and especially the tendency of low and high doses to sometimes produce opposite effects (e.g., Clark and Smith, 1987). This suggests that further work is required to describe the responses of male hamsters to a wider range of APO doses, such as used in the present study.

2.1. Methods

2.1.1. Animals and drug treatments

The subjects were 18 adult male golden hamsters (*Mesocricetus auratus*, LVG:Lak outbred strain) that averaged 169.9 g in weight (SEM = 5.0) at the time of their first test. These were selected from a larger group of 25 on the basis of their successful completion of 2 screening tests requiring the achievement of ejaculation within 10 min of social contact. The experimental stimuli included 12 adult female hamsters, each of which was bilaterally ovariectomized approximately 3 months before the start of testing. Each animal was housed in a 34×18×18 or 31×21×21 cm stainless steel cage in a colony maintained at 20–25 °C and on a reversed 14:10 light:dark cycle. All had free access to food and water except during tests. All methods were approved by Bucknell University's Institutional Animal Care and Use Committee.

Behavioral tests were conducted weekly. At 15 min before testing, each male received an intraperitoneal (ip) injection containing 0, 0.05 or 0.5 mg/kg of APO (apomorphine hydrochloride hemihydrate, Sigma-Aldrich, Inc) in a volume of physiological saline equal in ml to his body weight/1000. All APO solutions were prepared shortly before use. Each male was tested twice after exposure to each treatment. To determine treatments on the first 3 tests, the 6 possible orders of treatment were randomly assigned to subjects with the constraint that each be equally represented. For each subject, the second series of 3 tests duplicated the first. Tests were staged and scored without knowledge of the treatment.

Each of the stimulus females was ovariectomized under sodium pentobarbital anesthesia (70 mg/kg, ip) supplemented by a subcutaneous (sc) injection of 0.4 mg of butorphanol tartrate (both from Henry Schein, Inc). To ensure sexual responsiveness, each female was primed with two sc injections of gonadal hormone in 0.05 ml of peanut oil, the first at approximately 48 hr before use and containing 10 μg of estradiol benzoate and the second at 4–6 hr before use and containing 500 μg of progesterone (both from Steraloids, Inc).

2.1.2. Behavioral tests

Each test began with the introduction of a male into a 40×20×25 cm glass aquarium. After 1–2 min of adaptation, a female was presented, the timing of the encounter beginning with the first social contact. Tests then normally continued through 2 copulatory series (2 ejaculations plus the first intromission thereafter). However, males sometimes failed to achieve this criterion. Specifically, some tests were terminated when males failed to intromit within 10 min of contact, failed to complete 2 copulatory series within 15 min, or upon the occurrence of a fight. Though encounters with fighting were terminated as quickly as possible, only obvious fights (e.g., as described in Floody and Pfaff, 1977) were scored as such: Males sometimes use relatively gentle bites to inspect or reposition females, but biting of this type was not mistaken for fighting. Fights between hamsters sometimes develop so quickly that it can be impossible to determine the instigator. However, most or all of the fights reported here were initiated by the male: The instigator could be identified in 10 of the 13 fights observed and was the male in each case.

The data collected during each completed test included the timing of the first mount and intromission in each copulatory series, the timing of each ejaculation, and the total numbers of mounts and intromissions in each series. From these scores we derived each of the 14 dependent variables that typically would be used to describe male copulatory behavior in encounters of this length (e.g., Arteaga et al., 2002; Bunnell et al., 1977). This set includes 2 measures that are considered to initiate the interaction and so are not tied to a copulatory series, i.e., mount latency (ML, the delay between the initiation of contact and the first mount), and intromission latency (IL, the corresponding delay for the first intromission). The remaining 12 measures include 6 dependent variables, each of which is defined for each of the 2 copulatory series. These include ejaculation latency (the interval separating the first intromission of a series from the ejaculation that concludes that series, identified as EL-1 for the first series and EL-2 for the second), mount frequency (the number of mounts in a series; MF-1, MF-2), intromission frequency (the number of intromissions in a series; IF-1, IF-2), intromission ratio (the proportion of all mounts and intromissions in a series that are intromissions, or IF/(MF + IF) for the relevant series; IR-1, IR-2), interintromission interval (the average interval separating successive intromissions in a series, or EL/IF for the series; III-1, III-2), and postejaculatory interval (the interval separating the ejaculation of a focal series from the first intromission of the next series; PEI-1, PEI-2). Most of these measures were defined in standard ways (e.g., as in Arteaga et al., 2002; Bunnell et al., 1977). Our few departures from some earlier methods are detailed in Floody (2011a), along with evidence for the validity and reliability of the entire system of observation and scoring. Of special relevance to the present study is the recent successful use of this system in the analysis of cholinergic influences on male behavior in hamsters (Floody, 2011b; Floody et al., 2011).

Dopaminergic agonists are well known to stimulate stereotyped behaviors. In hamsters, the most likely of these to appear over the present range of APO doses is reported to be gnawing (Schnur and Martinez, 1989). To reduce the chances of misinterpreting a change in sexual behavior due to the occurrence of an incompatible stereotyped act, each test cage was provided with a potential stimulus for gnawing (a wooden dowel, 5.6–6.0 cm long, 1.2 cm diameter) and the measures recorded during each test included the male's total duration of gnawing.

2.1.3. Analysis

Our analyses distinguished the likelihood of failing a test from the quality of behavior on successful tests. Treatments were compared for