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AMPHETAMINE REWARD IN THE MONOGAMOUS PRAIRIE VOLE

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Abstract

Recent studies have shown that the neural regulation of pair bonding in the monogamous prairie vole (*Microtus ochrogaster*) is similar to that of drug seeking in more traditional laboratory rodents. Therefore, strong interactions between social behavior and drug reward can be expected. Here, we established the prairie vole as a model for drug studies by demonstrating robust amphetamine-induced conditioned place preferences in this species. For both males and females, the effects of amphetamine were dose-dependent, with females being more sensitive to drug treatment. This study represents the first evidence of drug reward in this species. Future studies will examine the effects of social behavior on drug reward and the underlying neurobiology of such interactions.

Keywords

drug abuse; addiction; conditioned place preference; attachment; social bonding; monogamy

There are many factors that contribute to drug abuse. Included among these are genetic predisposition and drug availability, variables that have been well modeled with traditional laboratory rodents and that have been shown to greatly influence drug seeking behavior [1, 18,22,59]. However, there are other complexities known to influence drug taking in humans, such as social environment [31]. This variable is more difficult to study in the laboratory because traditional rodent subjects do not exhibit social organization analogous to that shown by humans [4]. Studies in non-human primates demonstrate the importance of social hierarchy on drug taking [39]. However, primate experiments are not practical for most laboratories and therefore understanding the neurobiology of interactions between social behavior and drug abuse would be greatly facilitated if it were studied in rodent models. Here, we have taken an initial step toward this end by establishing a highly social rodent species, the monogamous prairie vole (*Microtus ochrogaster*), for drug studies.

The prairie vole is a powerful model for studies of social attachment [13,23]. Males and females of this species show preferential mating with one partner [20], exhibit high levels of parental behavior [36–38,43], and form enduring pair bonds, which are maintained even if one member of the pair is lost [57]. Pair bond formation is routinely studied in the laboratory by using a partner preference test [60,61] and such studies have provided excellent insight into the neural regulation of pair bonding [62]. In particular, recent studies have shown that pair bond formation and maintenance critically depend on key components of brain reward circuitry,

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including the nucleus accumbens and ventral pallidum [2,3,24,33–35]. These brain regions are critical for processing information about other natural rewards, such as food and sex [9,29, 46,47], and this circuitry is a primary target of all drugs of abuse [42].

Given that pair bonding and drug reward involve the same neural systems, there is likely to be significant interaction between social behavior and drug seeking. To facilitate investigation of these interactions we have established the prairie vole as a viable model for drug studies by establishing amphetamine (AMPH) induced conditioned place preferences (CPP) in this species. Our data show that AMPH dose dependently induced CPP in both males and females, and that females are more sensitive to drug treatment. These findings provide the foundation for future studies focused on the interaction between pair bonding and drug reward.

Materials and Methods

Animals

Subjects were sexually naive male (n = 37) and female (n = 36) prairie voles from a laboratory breeding colony. At 21 days of age, subjects were weaned and housed in same-sex sibling pairs in plastic cages (12cm high × 28cm long × 16cm wide). Water and food were provided *ad libitum*, a 14:10 light-dark cycle was maintained, and the temperature was approximately 20° C. All subjects were between 80–120 days of age when tested and weighed between 35–50g. Experimental procedures were approved by the Animal Care and Use Committee at Florida State University and were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23).

Conditioned place preference

Subjects were initially pre-tested in a 2-chambered place preference apparatus for 30 min. This apparatus consisted of a black plastic cage (20 × 25 × 45 cm) with a solid metal lid and an otherwise identical white plastic cage (20 × 25 × 45 cm) with a wire mesh lid. The wire mesh lid permitted more light into the white cages compared to the solid metal lids used for black cages, which created a darker environment. At the start of the pre-test, one half of the subjects were initially placed in the white cage, the other half were initially placed in the black cage (this same procedure was used at the start of the CPP test). Cages were connected by a plastic tube (7.5 × 16 cm) that allowed the animal to move freely between the two chambers. Cage crosses and time spent in each cage were measured by photobeam breaks with a locomotor analysis program (Ross Henderson, FSU). The objective of the pre-test was to determine whether there was an inherent preference for either the black or white cage. Surprisingly, pilot tests with males suggested that this species preferred the white cage. We therefore attempted to reverse this preference by pairing the black cage environment with AMPH; i.e. a biased test.

One day after the pre-test, one half of the subjects received intraperitoneal (IP) injections of saline and was placed in a white cage with a wire mesh lid for two hours. The remaining subjects were given saline with either 0.1, 0.5, 1.0 or 3.0 mg/kg d-amphetamine sulfate and placed in a black cage with a solid metal lid, also for two hours. Conditioning sessions consecutively alternated for 8 days, thus providing 4 associative pairings for saline and AMPH. On the day immediately following the final day of conditioning, subjects in a drug-free state were given access to the place preference apparatus for 30 min. Pre-tests, conditioning sessions, and conditioned place preference tests were all conducted during the light phase; between 10:00 and 14:00h.

Data Analyses

A CPP was defined by the change in duration of the time spent in the AMPH-paired cage before and after conditioning [5]. Here, we present data as percent changes from the pre-test for both

AMPH and saline treatment: total time spent in the AMPH (or saline) cage after conditioning divided by total time spent in the AMPH (or saline) cage before conditioning (i.e. the pre-test), multiplied by 100. Paired samples t-tests were performed to determine whether there were significant differences in time spent in the AMPH-paired cage before and after conditioning. Since an increase in the AMPH-paired cage was expected, one-tailed tests were used to determine p-values.

Results

Consistent with our pilot testing (see Methods), males showed significantly more time spent in the white cage (16.7 ± 1.2 min) compared to the black cage (11.7 ± 1.1 min) following control conditioning with saline injections ($t = 4.29$; $p<0.05$) (Fig. 1a). Thus, the non-preferred cage served as the AMPH-paired environment in subsequent experiments in an attempt to reverse this preference. A low dose of AMPH (0.1mg/kg) resulted in no preference for either environment ($t = 0.78$; $p>0.2$) (Fig. 1a). However, conditioning with higher doses of AMPH (0.5 to 3.0mg/kg), in males, resulted in robust preferences for the drug-paired environment ($t = 2.49$, 2.11, and 4.95, respectively; $p<0.05$) (Fig. 1a).

Female prairie voles showed no inherent preference for either chamber, as there was no preference for either chamber following control conditioning with saline ($t = 0.52$; $p>0.3$) (Fig. 1b). Low dose administration of AMPH (0.1mg/kg) resulted in a trend toward a preference for the drug paired environment ($t = 1.60$; $p = 0.07$), whereas 0.5mg/kg induced a robust CPP ($t = 4.07$; $p<0.05$) (Fig. 1b). Unlike males, higher doses of AMPH (1.0 and 3.0mg/kg) failed to induce CPP ($t = 1.25$ and 0.59, respectively; $p>0.1$) (Fig. 1b).

Given that higher doses of AMPH (1.0 and 3.0mg/kg) induced CPP in males but not females, and the lowest dose of AMPH (0.1mg/kg) appeared to be more effective in females, it would seem that females are more sensitive to drug treatment compared to males. These differences are not due to differences in activity levels since there was no difference between males and females in the number of cage entries in the CPP apparatus (males 22.2 ± 1.4; females 20.1 ± 1.3; mean ± standard error). Further, locomotor activity did not change before and after conditioning for either males or females (Table 1).

Discussion

This study represents the first demonstration of drug reward in the monogamous prairie vole. Similar to other rodent species, AMPH-induced CPP in prairie voles is dose dependent [5, 58]. The majority of studies of AMPH-induced CPP has been conducted with male rats, and these studies show that the most effective doses of AMPH fall between 0.3 and 3.0 mg/kg [25,55], a range consistent with the current results from male prairie voles. For males, the highest dose used (3.0mg/kg) appears to be less effective than median doses (0.5 and 1.0mg/kg). This is consistent with studies showing that higher doses of AMPH are less effective, or in fact, aversive [11].

For females, the dose response was shifted leftward, with the lowest dose used (0.1mg/kg) showing a trend toward CPP and higher doses, that were effective in males (1.0 and 3.0mg/kg), failing to induce CPP. This is consistent with previous studies in other species which showed that females were more sensitive to psychostimulants [7,49]. Similar leftward shifts have been shown for AMPH-induced CPP in female mice [16,32] and cocaine-induced CPP in female rats [51]. AMPH and cocaine also cause greater behavioral sensitization as well as greater increases in dopamine release within the striatum and nucleus accumbens in female rats [6]. Our study, therefore, provides additional evidence that females, in general, are more sensitive to drug effects than males [50].

A major contributor to sex differences in psychostimulant sensitivity in rats is serum estrogen levels [12]. Females are most sensitive during estrous and exogenous estrogen also increases AMPH-induced behaviors and AMPH-induced dopamine release in the nucleus accumbens [7,8]. However, prairie voles are induced ovulators [14,27], and have low basal levels of serum and brain estradiol [53]. Low basal estradiol may explain why sex differences in this species are not more pronounced, as it is consistent with studies in rats, showing that while ovariectomized females are still more sensitive to AMPH than males, but the differences are less robust than the ones with intact estrus cycles [8].

Other hormone systems may also contribute to sex differences in the sensitivity to psychostimulants. For example, corticosterone (CORT) plays an important role in mediating drug reward [48] and adrenalectomy removes sex differences in AMPH-induced CPP in rats [51]. Prairie voles have very high levels of serum CORT compared to traditional laboratory rodents [56] and males and females differ significantly in changes in CORT levels in response to a variety of treatments [19]. Further, genetic differences between males and females [17] may also contribute to sensitivity to drug treatment. Future studies are needed to address the underlying biology of sex differences to drug treatment in prairie voles.

Establishing the prairie vole for drug studies provides the foundation for future investigations of interactions between pair bonding and drug reward. While it has been known for over two decades that maternal bonding is dependent on opioid signaling [44], the role of opiates in monogamous pair bonding is largely unknown [54]. However, a detailed understanding of dopamine regulation of pair bonding has emerged [3] and it is very intriguing that pair bonding and self-administration of psychostimulants have similar neural mechanisms [3,52]. This is consistent with the notion that abused drugs potently control behavior because they usurp brain circuitry evolved to mediate behavior essential for survival [10,21,28,41], including social bonding [15,26,45]. In fact, it has been suggested that individuals with impoverished social environments may be more likely to artificially stimulate these neural pathways [40,45] and that social support may reduce addictive urges [44]. This is supported by studies showing that a positive social environment is beneficial for recovery from drug addiction [30,31]. Future studies will directly test if pair bonded voles are ‘protected’ against drug reward and hopefully improve treatment and prevention of drug addiction.

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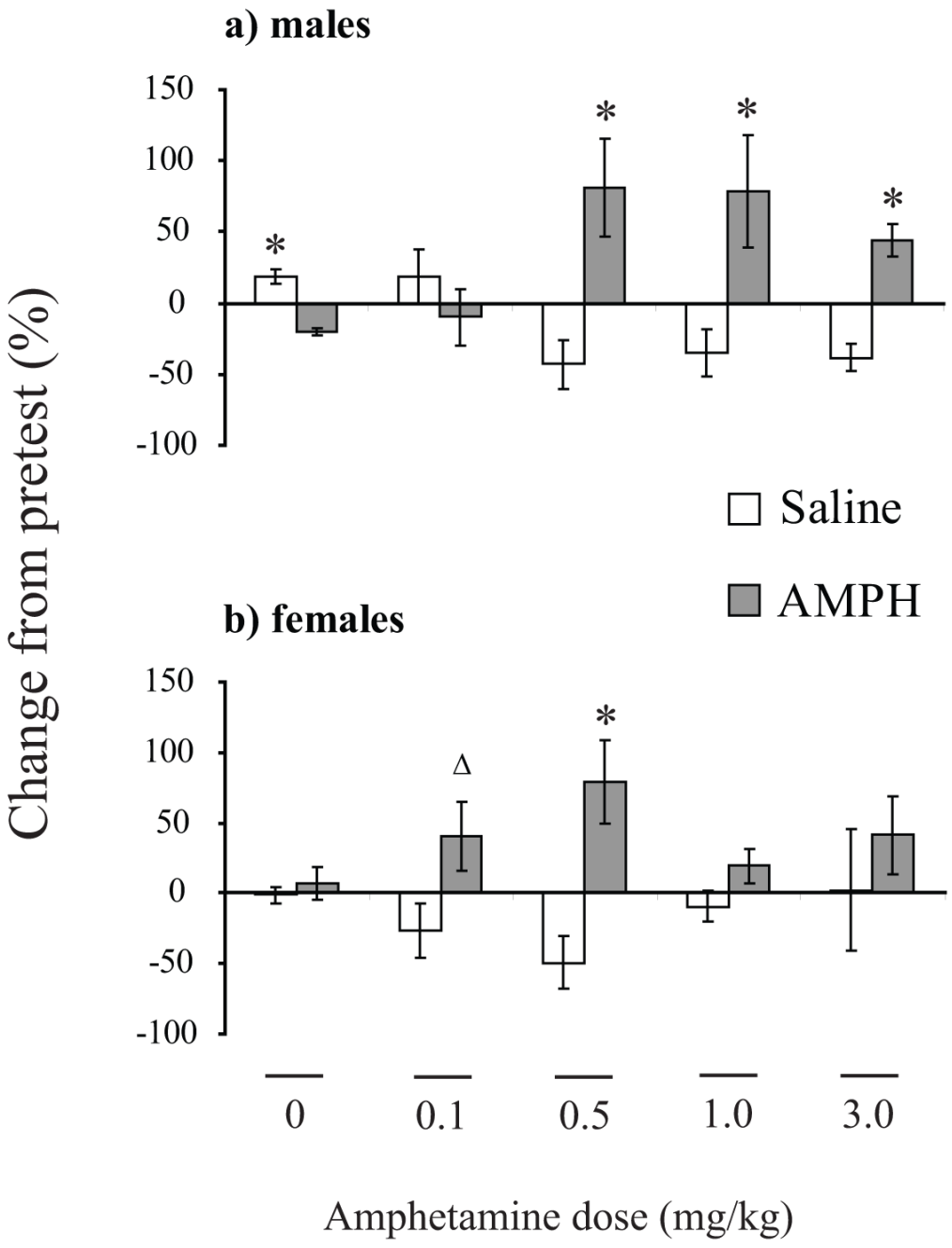

Figure 1.

Amphetamine induced conditioned place preference in male and female prairie voles. a) For males, control subjects (n = 5) showed an inherent preference for the environment that would subsequently serve as the saline environment (open bar). AMPH conditioning at 0.1mg/kg (n = 8) failed to induce CPP. Higher doses (0.5mg/kg: n = 8; 1.0mg/kg: n = 8; and 3.0mg/kg: n = 8) induced robust CPP – animals spent significantly more time in the drug paired environment (filled bar). b) For females, controls showed no inherent environmental preference. Low dose administration of AMPH (0.1mg/kg; n = 8) resulted in a trend toward a preference for the drug paired environment, whereas 0.5mg/kg (n = 8) induced a robust CPP. Higher doses of AMPH (1.0mg/kg: n = 7 and 3.0mg/kg: n = 6) failed to induce CPP. Difference scores were based on

the pre-test data from each individual subject. * = $p < 0.05$; Δ = $p<0.10$; error bars indicate standard error from the mean.

Table 1

Number of cage crosses within a two chambered place preference apparatus prior to conditioning (Pre-test) and after conditioning (CPP). There is no difference in locomotor activity between males and females. There is also no difference in locomotor activity following conditioning for either sex.

AMPH	0 mg/kg		0.1 mg/kg		0.5 mg/kg		1.0 mg/kg		3.0 mg/kg	
	Pre-test	CPP	Pre-test	CPP	Pre-test	CPP	Pre-test	CPP	Pre-test	CPP
Males	23.2±2.4	26.4±2.5	19.8±3.0	19.6±7.5	27.5±3.0	20.4±4.3	23.1±3.0	20.6±3.6	21.0±2.9	22.4±4.6
Females	19.0±5.7	19.9±2.5	24.0±3.1	16.1±2.4	28.0±6.7	16.1±6.1	23.4±3.4	27.9±3.2	12.6±3.4	12.3±1.5