Mating and social exposure induces an opioid-dependent conditioned place preference in male but not in female prairie voles (*Microtus ochrogaster*)

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**ARTICLE INFO**

Keywords:
- Sexual reward
- Conditioned place preference
- Social cohabitation with mating
- Opioids and voles

**ABSTRACT**

In rodents, sexual stimulation induces a positive affective state that is evaluated by the conditioned place preference (CPP) test. Opioids are released during sexual behavior and modulate the rewarding properties of this behavior. Prairie voles (*Microtus ochrogaster*) are a socially monogamous species, in which copulation with cohabitation for 6 h induces a pair bond. However, the mating-induced reward state that could contribute to the establishment of the long-term pair bond has not been evaluated in this species. The present study aimed to determine whether one ejaculation or cohabitation with mating for 6 h is rewarding for voles. We also evaluated whether this state is opioid dependent. Our results demonstrate that mating with one ejaculation and social cohabitation with mating for 6 h induce a CPP in males, while exposure to a sexually receptive female without mating did not induce CPP. In the female vole, mating until one ejaculation, social cohabitation with mating, or exposure to a male without physical interaction for 6 h did not induce CPP. To evaluate whether the rewarding state in males is opioid dependent, the antagonist naloxone was injected i.p. The administration of naloxone blocked the rewarding state induced by one ejaculation and by social cohabitation with mating. Our results demonstrate that in the prairie vole, on the basis of the CPP in the testing conditions used here, the stimulation received with one ejaculation and the mating conditions that lead to pair bonding formation may be rewarding for males, and this reward state is opioid dependent.

1. **Introduction**

Sexuality is an essential aspect of human social behavior and has important implications for physical and psychological well-being. Thus, sexual behavior enhances the formation of enduring relationships, which increases longevity and contributes to an adequate function of the immune and cardiovascular systems, resulting in lower incidence of psychiatric disorders (House et al., 1988; Kiecolt-Glaser and Newton, 2001). Deeper pair relationships promote health, well-being, survival, and even social success. Furthermore, social exclusion and the loss of a partner result in depression and feelings similar to physical pain (Zivin and Christakis, 2007).

Despite the importance of pair bonding, its mechanisms and possible effects on the central nervous system are not completely understood. This limitation is produced by the high complexity of the human nervous system and ethical concerns, which require the use of experimental models to explore these paradigms in the laboratory. The socially monogamous species *Microtus ochrogaster* (prairie vole) is used to study the neuronal mechanisms involved in pair bonding because of the reproductive strategy of this species. Prairie vole couples cohabitate the nest, defend their territory, and display parental behaviors, thus forming solid family structures [reviewed in (Gobrogge and Wang, 2015; Gobrogge, 2014; Lieberwirth and Wang, 2016; McGraw and Young, 2010)]. Pair bonding is established when a male and a female cohabitate, with mating, for at least 6 h, or when they cohabitate, without mating, for 24 h. In both instances, voles show a clear preference for the mating partner and selective aggression to other males or females (Carter et al., 1995; Insel et al., 1995; Wang et al., 1997; Williams et al., 1992).

Pair bond formation and maintenance critically depend on the activation of brain structures that also regulate other hedonic behaviors such as social attachment, maternal care, and sexual behavior, which were reviewed previously (Burkett and Young, 2012; Numan and Woodside, 2010; Numan and Young, 2016). These brain areas include the olfactory bulbs, medial amygdala, bed nucleus of the stria terminalis, medial preoptic area, dorsal raphe, anterior hypothalamus,
nucleus accumbens, prefrontal cortex, and the mesocorticolimbic system (Amadei et al., 2017; Cushing et al., 2003; Gobrogge and Wang, 2015; Gobrogge, 2014; Johnson and Young, 2015, 2017; Kirkpatrick et al., 1994; Young et al., 2001; Young et al., 2005).

Mating-induced pair bonding likely involves reinforcing properties associated with mating. In several mammals including humans, it has been demonstrated that sexual behavior endures and is repeated because it induces a positive affective state. Several research groups including ours have demonstrated that when male and female rats, a species that does not form a pair bond, are able to control (pace) the rate of sexual stimulation, sexual behavior induces a positive affective state, evaluated by the conditioned place preference (CPP) test (Agmo and Berenfeld, 1990; Coria-Avila et al., 2006; Coria-Avila et al., 2005; Martinez and Paredes, 2001; Mehrara and Baum, 1990; Paredes and Alonso, 1997; Pfuss et al., 2012). It is well documented that the release of opioids during sexual behavior contributes to the rewarding consequences of mating. Administration of the opioid antagonist (naloxone) completely blocks the reinforcing properties of mating in male and female rats (Agmo and Gomez, 1993; Coria-Avila et al., 2008; Mehrara and Baum, 1990; Paredes and Martinez, 2001). From the above described data, parsimony will suggest that mating induces a reward state that could contribute to the establishment of the long-term pair bond in the prairie vole.

The opiate system is involved in social attachment, maternal bonding, social learning, and sexual reward (Nelson and Panksepp, 1998; Panksepp et al., 1980). In female voles, the administration of the opioid antagonist naltrrexone blocks the formation of a partner preference. Furthermore, administration of the μ-opioid receptor (MOR) selective antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH2 (CT-AP) into the caudate-putamen (CP) 24 h before cohabitation with a male inhibits the preference for the sexual partner (Burkett et al., 2011). In addition, inhibition of MORs within the dorsomedial nucleus accumbens shell inhibited partner preference formation without affecting mating behavior (Resendez et al., 2013).

We hypothesized that cohabitation with mating for 6 h, which produces pair bonding (Williams et al., 1992), and sexual stimulation until one ejaculation, which is rewarding in male and female rats (Agmo and Berenfeld, 1990; Martinez and Paredes, 2001), will induce a reward state in male and female voles. Because opioids are involved in sexual reward and social attachment, we propose that the positive affective state induced by one ejaculation and 6 h of mating would be blocked by the administration of an opioid antagonist.

2. Methods

Six M. ochrogaster mating pairs were generously donated by Dr. Larry J. Young from his colony at Emory to establish a colony at the Instituto de Neurobiología, Universidad Nacional Autónoma de México. Animals were maintained in a room with controlled light (14:10 light-dark cycle) and temperature (23 °C) conditions. The animals were provided Rabbit diet high fiber 5326 (LABDIET), oats, sunflower seeds, and water ad libitum. Adult males and females (3–4 months old) were used in this experiment. Females were bilaterally ovariectomized under deep anesthesia with a mixture of ketamine (Cheminova, 60 mg/kg) and xylazine (Cheminova, 4 mg/kg), and were allowed to recover from the surgery for 1 week. To induce sexual receptivity, females were injected daily with estradiol benzoate (EB, 0.5 μg/vole, Sigma-Aldrich) for 4 days before the behavioral test. The EB injections continued daily until the end of the CPP tests (12 days total). This treatment consistently induces sexual receptivity in this species (Roberts et al., 1998; Smale et al., 1985). In voles, progesterone is not needed to induce sexual receptivity (Dizzen and Carter, 1979).

All experiments were performed in accordance with the “Reglamento de la Ley General de Salud en Materia de Investigación para la Salud” of the Mexican Health Ministry, which follows NIH guidelines for the use and care of animals in research. The experiments were approved by the Instituto de Neurobiología Animal Care Committee and by the Ethics Committee of the Instituto Nacional de Perinatología. The timeline of the different experiments is depicted in Fig. 1.

2.1. Conditioned place preference (CPP)

The test was performed in a three-compartment acrylic box; the central compartment (22 × 24 × 32 cm) was gray and was connected with the lateral compartments through guillotine doors (23 × 37 × 32). One of the lateral compartments was white and the other was black; thus, the lateral compartments offered distinct color stimuli.

We followed the procedure described by Dr. Wang’s research group with slight modifications (Liu et al., 2011; Young et al., 2011). Briefly, the CPP test includes a pretest, six training sessions, and a test. During the pretest (day 1), each vole was placed at the center of the cage (gray compartment) with the guillotine doors closed. After 1 min of habituation, doors were opened to allow the animals to move freely between compartments for 30 min. The time that voles spent in the white and black compartments was recorded. The compartment where the
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