



Research paper

Oxytocin mediates copulation-induced hypoalgesia of male rats

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HIGHLIGHTS

- Ejaculation was dispensable for copulation-induced hypoalgesia in the rat.
- Intracerebroventricular administration of an oxytocin antagonist exerted little influence on sexual behavior of male rats.
- Elevated pain threshold by copulatory behavior is suppressed by the block of oxytocin receptors.

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ABSTRACT

Copulatory behavior has been reported to raise the pain threshold in male rats. In this study, we examined the effect of copulatory behavior with or without ejaculation on pain threshold measured by electrical shock via an electrode attached to the tail. It was demonstrated that ejaculation is not necessary to raise the pain threshold in male rats. In addition, we examined whether oxytocin, a hypothalamic neuropeptide, was involved in copulation-induced hypoalgesia. Sexually experienced males were subjected to stereotaxic implantation of a guide cannula targeting the lateral ventricle. After the recovery period, half of the males were intracerebroventricularly treated with an oxytocin antagonist (OTA, 100 ng d(CH₂)⁵1,Tyr(Me)²,Thr⁴,Orn⁸,Tyr-NH₂29]-vasotocin/1 μL saline) and the remaining half were administered saline without anesthesia. Fifteen minutes later, half of each group were given sexual behavior with receptive females. We found no effect of OTA on sexual activity. Immediately after ejaculation, pain threshold was measured. While raised pain threshold was observed after sexual behavior in saline-treated males, no change in pain threshold was found in OTA-treated males even after copulation. The results suggest that central oxytocin mediates copulation-induced hypoalgesia in male rats.

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1. Introduction

Sexual behavior is believed to be mediated by activation of both the sympathetic and parasympathetic autonomic nervous systems. Penile erection is controlled by the parasympathetic nervous system [3], while ejaculation is controlled by the sympathetic nervous system [2,28,29]. An early study demonstrated that non-specific arousal provoked by painful stimuli promotes copulatory behavior in male rats [5,8]. Presumably, the phenomenon may be mediated by activation of the autonomic nervous systems.

Activation of the autonomic nervous system induced by sexual behavior conversely affects the pain threshold. Hypoalgesia was

reported in male rats following copulatory behavior [13,16,37]. In female rats, although no change in pain threshold was observed just immediately after sexual behavior, hyperalgesia was found 10 min later [10]. This result appears to contradict potent analgesia observed during mechanical stimulation of the uterine cervix [21,32]. Because the relationship between sexual behavior and pain threshold is very complicated, little is known about the underlying neural mechanism involved in the raised pain threshold observed in male rats following sexual activity. Therefore, in this study, we aimed to investigate the physiological background of copulation-induced hypoalgesia in male rats.

We postulate the involvement of the oxytocin neural system. In recent decades, oxytocin has attracted a great deal of attention from researchers because it mediates the neural regulation of a variety of social behaviors, including copulation. Although a previous study observed that administration of an oxytocin antagonist did not exert a crucial influence on sexual behavior, local injection

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of oxytocin per se into the preoptic area increased intromission ratio (number of intromissions/total number of mounts) and shortened the post-ejaculatory refractory period in male rats [14]. While male copulatory behavior greatly depends on sexual experience, it is reported that sexual experience enhances the expression of oxytocin receptors in the preoptic area [15]. In addition, infusion of oxytocin into the third ventricle induces spontaneous penile erection without sexual stimulus [3,4,25], suggesting that penile erection occurs as a consequence of activation of the oxytocin neural system by sexual stimuli derived from receptive females [30]. Projection of parvocellular oxytocinergic neurons in the paraventricular nucleus of the hypothalamus to the thoracic and upper lumbar spinal cord has been suggested to regulate not only penile erection [6,39] but also nociception [22,26]. Thus, we hypothesized the involvement of the oxytocin neural system in copulation-induced hypoalgesia.

In this study, we first determined whether ejaculation is indispensable for copulation-induced hypoalgesia. During copulation, heart rate increases and peaks at ejaculation. However, heart rate is suppressed within 1 min after ejaculation [38], indicating the shift in dominance of the sympathetic to the parasympathetic during postejaculatory period. Second, we examined if blocking oxytocin receptors following intracerebroventricular administration of an oxytocin antagonist could prevent the increment of pain threshold after copulatory behavior in male rats.

2. Materials and methods

2.1. Animals

Adult male and female Long-Evans rats (8 weeks old, 220–260 g BW) were purchased from the Institute for Animal Reproduction (Ibaraki, Japan). All animals were housed one per cage under a controlled temperature ($23 \pm 2^\circ\text{C}$) and reversed light/dark illumination (lights off from 1100 h to 2300 h) with free access to food and water. Behavioral tests were conducted in the dark phase of the illumination cycle. The experiments all adhered to the Guidelines for the Care and Use of Laboratory Animals of Nippon Medical School and were approved by the Committee for Animal Experimentation of Nippon Medical School.

As stimulus females in sexual behavior sessions described below, all females were ovariectomized under anesthesia using administration of ketamine HCl (25 mg/kg, *im*) and pentobarbital (25 mg/kg, *ip*). The females were treated with estradiol-17 β benzoate (5 μg /0.1 mL sesame oil, *sc*) 2 days before and progesterone (500 μg /0.1 mL sesame oil, *sc*) 3–6 h before use.

All males engaged in sexual behavior three times a week with receptive females prior to the measurement of pain threshold. Males that showed no ejaculation within 60 min were excluded from the subsequent study.

2.2. Effect of copulatory behavior on pain threshold (Experiment I)

Males were grouped into three males based on equivalent sexual activity shown in the 3rd sexual experience session. One of each triplet was randomly assigned to a NoSex group (no sexual behavior, $n = 13$), and the remaining 2 sets of triplets were assigned to M+I (sexual behavior without ejaculation, $n = 18$) or M+I+E (sexual behavior with ejaculation, $n = 18$) groups. Each male of the triplets was separately placed in observation cages. After 5 min acclimation, receptive females were introduced to the cage containing M+I and M+I+E rats, but not the NoSex group. Observation of copulatory behaviors was carried out until one rat was observed to ejaculate; the receptive females was removed from the cages of

M+I and M+I+E. The males which had ejaculated were assigned to the M+I+E group, while rats that did not ejaculate were assigned to the M+I group. Within 3 min after the copulatory session, measurement of pain threshold commenced.

2.3. Measurement of pain threshold

Each male was restrained in an acrylic tube (a restrainer for tail vein catheter, 65 mm in inner diameter). The electrodes which consisted of 9 stainless steel wires 2 mm apart each other sewn onto the fabric was attached around the tail at approximately 10 cm from the base for shock application. Before the wearing, the surface skin of the tail and the electrodes were cleaned with 70% ethanol. One sec shock was generated by the shock generator (ENV-414S, Med Associates, Inc., USA) and the inter-trial interval was longer than 15 s. The measurement consisted of 2 series, ascending and descending, and always started from the ascending series. In the ascending session, the shock started at 0.1 mA, and if no response (body movement or vocalization) occurred, the intensity was increased 0.1 mA in the next trial. When the response occurred, one more shock at the same intensity was applied to confirm the response; the intensity was determined as an ascending threshold. Subsequently, the measurement of the descending series was started at an intensity 0.5 mA higher than the ascending threshold. The shock was weakened 0.1 mA for each trial, and if no response occurred, one more shock at the same intensity was applied to confirm no response; the intensity was determined as a descending threshold. The ascending and descending thresholds were averaged as a pain threshold value for the individual.

2.4. Effect of oxytocin administration on copulation-induced hypoalgesia (Experiment II)

After finishing Experiment I, the experimental males (470–590 g BW) were further subjected to the implantation of a guide cannula that allowed intracerebroventricular administration of a drug without anesthesia for Experiment II. Males anesthetized with ketamine HCl (25 mg/kg; *im*) and pentobarbital (25 mg/kg; *ip*) were placed in a stereotaxic apparatus (the incisor bar was located 3.3 mm below the interaural line). Through a small hole in the skull, a 25 G stainless tube was inserted into the brain 0.5 mm posterior to bregma, 1.5 mm lateral to the midline, and 4.0 mm ventral to the surface of the skull. Three micro screws were placed on the surface of the skull, and covered with dental resin to fix the cannula. After resin was cured, a dummy cannula (30 G stainless tube) was inserted into the guide cannula and covered with paraffin. Animals were allowed to recover for at least a week before experimentation.

2.5. Administration of oxytocin antagonist and sexual behavior

On the test day, the injection of an oxytocin antagonist or saline was carried out without any restriction. The dummy cannula of each male was replaced by an inner cannula (30G) connected to a polyethylene tube (PE50) and 10- μL Hamilton syringe. An oxytocin antagonist (OTA, d(CH₂) 51,Tyr(Me) 2,Thr4, Orn8,Tyr-NH₂29]-vasotocin, 100 ng/1 μL saline, a dose effective for sexual function [14], $n = 11$) or vehicle (1 μL saline, $n = 10$) was injected using a microinjector (0.25 $\mu\text{L}/\text{min}$). The cannula was kept in position for 5 min after infusion, after which the cannula was replaced with the dummy cannula and covered with paraffin.

Thereafter, each male was put into an acrylic observation cage (30 $\times$ 50 $\times$ 40 cm), and allowed 10 min to acclimatize. Seven males from each group were allowed to engage in sexual behavior following introduction of a receptive female. Males were allowed to copulate until ejaculation. The remaining males were left alone for 30 min as a control. Immediately after these sessions, animals were

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