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Research report

Estrogen facilitates and the kappa and mu opioid receptors mediate antinociception produced by intrathecal (−)-pentazocine in female rats

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HIGHLIGHTS

- Intrathecal (−)-pentazocine produces thermal antinociception in female rats.
- Estrogen facilitates the antinociceptive effect of pentazocine.
- KOR or MOR mediates the antinociceptive effect of pentazocine.
- Blockade of MOR prolongs the antinociceptive effect of the highest dose of pentazocine.

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ABSTRACT

Pentazocine, a mixed-action kappa opioid receptor (KOR) agonist, has high affinity for both KOR and the mu opioid receptor (MOR), and has been shown clinically to alleviate pain with a pronounced effect in women. However, whether local application of pentazocine in the spinal cord produces antinociception and the contribution of spinal KOR and MOR in mediating the effect of pentazocine in female rats remain unknown. Also, it is not known whether pentazocine-induced antinociception in females is estrogen-dependent. Hence, we investigated whether intrathecal (i.t.) (−)-pentazocine produces thermal antinociception and whether estrogen modulates the drug effect in female rats. Only the highest dose of pentazocine (500 nmol) was effective in producing antinociception in ovariectomized (OVX) rats. In contrast, pentazocine produced antinociception in estradiol-treated ovariectomized females (OVX+E) rats with the lowest effective dose being 250 nmol. KOR or MOR mediated the effect of the lowest effective dose in OVX+E rats; however, MOR blockade extended the KOR-mediated effect of 500 nmol pentazocine in both groups. In normally cycling females, the 250 nmol dose was effective in producing antinociception at the proestrous, but not at the diestrous stage of the estrous cycle. Thus, estrogen facilitates and KOR or MOR mediates the antinociceptive effect of i.t. (−)-pentazocine in female rats. Selective doses of (−)-pentazocine, with or without MOR blockade, may have a therapeutic benefit.

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1. Introduction

Women experience a higher prevalence of numerous chronic pain conditions, such as fibromyalgia, migraines, temporomandibular joint pain, and irritable bowel syndrome [1–5]. We [6–8] and others [9–11] have demonstrated previously that activation of opioid receptors produces antinociception that is modulated by estradiol and testosterone.

Mixed-action kappa opioid agonists, such as pentazocine, nalbuphine, and butorphanol, given systemically, have been shown to produce significant analgesia in women following removal of the third molar tooth [12–14] or when pain was induced experimentally [15]. Experimental data collected from animal studies have demonstrated that mixed-action kappa opioid agonists, administered systemically, produce antinociception [16–18]. Pentazocine displays binding affinity to both KOR and MOR [19,20]. Using MOR knockout mice and MOR antagonist, the antinociceptive effect of pentazocine has been shown to be mediated by MOR [21,22]. In this study, we used (−)-pentazocine since it has been shown to produce opioid receptor-mediated antinociception [17,18,21,23]. (+)-pentazocine binds to the sigma 1 receptor and

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inhibits antinociception [23], but racemic (±)-pentazocine (Talwin) produces analgesia in humans and rodents when administered systemically [12,23,24]. However, (±)-pentazocine administered intrathecally in rats did not produce antinociception using the tail flick nociceptive assay [25]. Because previous research did not delineate whether spinal KOR or MOR mediated the antinociceptive effect of (−)-pentazocine, we examined if pentazocine delivered intrathecally in females produces antinociception and the contribution of spinal KOR and MOR in mediating its antinociceptive effect. In addition, previous research from our laboratory [7] demonstrated that activation of KOR by a selective kappa opioid agonist, U50-488H, produced estrogen-dependent antinociception and antihyperalgesia. Hence, we also sought to determine whether estrogen is required for the antinociceptive effect of pentazocine.

The design of the study is as follows: first, we investigated whether (−)-pentazocine produces antinociception and the role of exogenous estradiol in modulating its effect in OVX animals using an acute thermal nociceptive tail flick assay. Subsequently, by using normally cycling females at proestrous (high levels of estrogen) and diestrous (low levels of estrogen) stages of the estrous cycle, we assessed whether the fluctuation in the endogenous levels of estrogen play a role in modulating the antinociceptive effect of pentazocine. Finally, we evaluated the contribution of spinal KOR and/or MOR in mediating the antinociceptive effect of various doses of pentazocine.

2. Methods

2.1. Animals

Sprague-Dawley female (normally cycling) and ovariectomized (OVX) rats (250–274 g; 3–4 months of age) were purchased from Harlan, Inc., (Envigo) (Indianapolis, IN, USA). The total number of rats used was 122. The rodents were housed in an animal care facility approved by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) at Meharry Medical College with a 12-h light/12-h dark cycle, temperature range between 68 and 70 °F, and provided with ample water and food (Lab Diet Prolab RMH 1000, Prolab Laboratory Animal Diet, Brentwood, MO, USA) ad libitum. Rats were housed three per cage with bedding material of Diamond Soft and Soft Cob (Harlan Teklab, Madison, WI, USA). All experiments were conducted during the light cycle. All experimental protocols were approved by the Institutional Animal Care and Use Committee of Meharry Medical College and conformed to the guidelines established by the National Research Council Guide for the Care and Use of Laboratory Animals and the International Association for the Study of Pain (IASP). All efforts were made to minimize stress to the animals and the number of animals used.

2.2. Intrathecal implantation of cannulae in rats

Using a modified version of the Yaksh and Rudy chronic catheterization protocol [26], a mixture of ketamine (80 mg/kg) and xylazine (4 mg/kg) was employed to deeply anesthetize rats before positioning their shaved heads in a stereotaxic frame. Subsequent to removing the muscle dorsal to the atlanto-occipital membrane, the dura was penetrated to permit insertion of a stretched PE-10 cannula (Intramedics, Clay Adams, Sparks, MD, USA) caudally 8.8–9.0 cm in the subarachnoid space of the lumbosacral segment of the spinal cord. We determined this length to be the most appropriate to achieve the optimal drug effect with the tip of the cannula located in the lumbosacral region. Lastly, the cannula was fastened with dental cement. The dead volume of the cannula was 10 μl. The length of the surgery was 20 min. This surgery was performed during the diestrous phase of normally cycling female animals. In OVX rats, this surgery was performed 2 weeks after the ovariectomy procedure. Pain medication was not administered following surgery to avoid any residual effect that may confound our results. Seven to fourteen days after implanting a cannula, the rats were subjected to behavioral testing. Subsequent to testing, the position of the cannula in the subarachnoid space of the spinal cord was determined by injecting 2% lidocaine, which induced short-lasting hind limb paralysis. Further, after euthanasia, 1% Chicago Sky Blue dye was injected to determine the patency of the cannula, location of the tip, and dye spread along the lumbosacral spinal cord.

2.3. Estrogen replacement

To determine the role of estrogen in females, estradiol benzoate (Sigma Aldrich, St. Louis, MO, USA) (10 μg/100 μl sesame oil; 48 h prior to nociceptive testing) was administered subcutaneously in OVX rats as described previously [6,7,27,28]. The rationale for using this dose of estradiol was that it produced a proestrous-like vaginal cytology as described below.

2.4. Vaginal cytology

Vaginal smears were taken from OVX and OVX+E animals immediately after behavioral testing, stained using hematoxylin and eosin, and examined microscopically to determine diestrous-like (OVX) and proestrous-like (OVX+E) cytology [6,29]. The presence of at least 75% nucleated epithelial cells was indicative of the proestrous-like stage. In normally cycling female rats, two regular estrous cycles were established prior to conducting experiments at proestrous and diestrous stages.

2.5. Tail flick nociceptive testing

This nocifensive assay was conducted as described previously [6,7,30,31]. Rats were restrained in a tail access rodent restrainer (Stoelting, Wood Dale, IL, USA) and allowed thirty minutes to habituate prior to testing. Using an analgesia meter (IITC Model 33T, Woodland Hills, CA, USA), a noxious heat stimulus was applied consecutively at three different positions along the dorsal surface of the tail. Three baseline readings were recorded. The heat intensity was set to generate a baseline tail flick latency (TFL) of 2–5 s. Over an eighty-five minute time period, the TFL was recorded automatically every five minutes. The trigger temperature was set at 32 °C and a commonly used cut-off time at 15 s was employed to prevent tissue damage. A cutoff latency of 15 s or higher is commonly used in the field in rats [6,7,32,33]. During the time course of the experiment, we did not observe any reduction in TFLs below the baseline that could be indicative of hyperalgesia caused by tissue damage in vehicle-treated animals.

2.6. Drugs

(−)-Pentazocine-succinate (125–500 nmol/10 μl), nor-binaltorphimine (nor-BNI) (26 nmol/10 μl) [34], and D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP) (34 nmol/10 μl) [35,36] were administered intrathecally (i.t.) and flushed with 0.9% sterile saline (10 μl). CTAP [10] and nor-BNI [11] were administered five minutes and 18 h, respectively, before pentazocine. Using this time interval (18 h), 26 nmol nor-BNI has been shown to selectively antagonize KOR [11]. Pentazocine was administered at time point zero. The vehicle for pentazocine was sterile water, and for nor-BNI and CTAP, 0.9% sterile saline. The rate at which the drug or vehicle was delivered was 1.5–2 μl/second. Following drug injection, a TFL reading was taken immediately (under 1 min), and plotted as time point zero in the figures. Each rat was tested only once and subsequently euthanized with an intraperitoneal

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