Pharmacology Biochemistry and Behavior, Vol. 65, No. 1, pp. 53–59, 2000

0091-3057/00/$–see front matter

PII S0091-3057(99)00186-0

Kappa Opioid-Induced Diuresis in Female vs. Male Rats

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Received 5 January 1999; Revised 29 April 1999; Accepted 4 June 1999

CRAFT, R. M., C. M. ULIBARRI AND D. J. RAUB. *Kappa opioid-induced diuresis in female vs. male rats.* PHARMACOL BIOCHEM BEHAV **65**(1) 53–59, 2000.—κ Opioid agonists may produce dissimilar discriminative and analgesic effects in female vs. male subjects. The present study was conducted to determine whether a prototypic physiological effect of κ agonists—diuresis—also differs between the sexes. When data were not corrected for individual differences in body weight, the κ agonists U69,593 (0.03–3.0 mg/kg), U50,488 (0.3–10 mg/kg), (−)-bremazocine (0.001–0.1 mg/kg) and (−)-pentazocine (1–10 mg/kg), as well as a nonopioid diuretic, furosemide (1–10 mg/kg) produced significantly greater diuresis in normally hydrated, age-matched males than females; however, there was no sex difference in the diuretic effect of butorphanol (0.3–3.0 mg/kg), or in the antidiuretic effect of the μ agonist morphine (1.0–5.6 mg/kg, in water-loaded rats). In contrast, when data were corrected for individual difference in body weight, U69,593, U50,488, (−)-bremazocine, (−)-pentazocine, and furosemide produced nearly equivalent diuresis/kg in females and males, whereas butorphanol produced slightly greater diuresis/kg, and morphine produced significantly less antidiuresis/kg, in females than males. U69,593-induced diuresis was highly similar in males and females of similar body weight (i.e., different ages). U69,593 effects were dose-dependently antagonized by the κ antagonist nor-binaltorphimine in both sexes, indicating a common, κ receptor-mediated mechanism of action. (−)-Bremazocine was slightly more potent in suppressing vasopressin in 24-h water-deprived males than females. These results suggest that the greater diuretic effects of κ receptor-selective opioid agonists in male rats are primarily due to males' larger body size (greater body water) relative to age-matched females, but may also be attributed to slightly greater vasopressin suppression in males. © 1999 Elsevier Science Inc.

Sex differences Gender Kappa opioids Diuresis Morphine

SEVERAL investigators have shown that there are sex differences in analgesic effects of opioid agonists that have κ receptor-mediated activity, in humans (9,10), rats (1,3), and mice (14), although the direction of these sex differences may be species, assay, and drug dependent. Additionally, males are more sensitive than females to U69,593's discriminative stimulus and diuretic effects (4). These studies suggest that males and females may respond differently to several behavioral and physiological effects of κ opioid agonists.

The purpose of the present study was to determine whether female and male rats respond differently to a variety of κ agonists on diuresis, a prototypic κ receptor-mediated effect (15, 16). To determine whether the sex difference in U69, 593's diuretic effect that we observed in a previous study (4) is common to all opioids with κ agonist activity, five opioid agonists that vary in selectivity for (and efficacy at) the κ receptor were examined in the present study, and their effects were compared to those of a relatively μ-selective agonist, morphine, and a nonopioid, loop diuretic, furosemide (21). Age-matched adult male and female rats differ significantly in body weight, and Leander (18) showed that in males, bremazocine's diuretic effect is positively correlated with body weight. Thus, diuresis was analyzed both uncorrected and corrected for body weight of the individual rat. Moreover, basal plasma vasopressin (AVP) is significantly higher in male than female rats (25), and kappa agonists can produce diuresis by inhibiting AVP release (18,19); thus, AVP was also measured in a separate group of rats, to determine whether bremazocine differentially inhibited AVP in males vs. females. Finally, receptor mediation of U69,593's diuretic effects was confirmed by administering U69,593 in combination with the κ receptor-selective antagonist, nor-binaltorphimine (nor-BNI) (22,24).

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METHOD

Subjects

Subjects were gonadally intact, female and male Sprague–Dawley rats (bred in house from Taconic stock, Germantown, NY), 3–5 months old at the beginning of testing, except where indicated otherwise. Most rats had been used previously as vehicle control subjects in an analgesia experiment, completed at least 1 week before the beginning of the present study. Additionally, rats in the antagonist experiment had been tested for analgesia with 1.0 mg/kg SC U69,593, once/week for 4 weeks (part of a different experiment) prior to testing in the present experiment. Rats were housed in same-sex pairs (in 30 × 35 × 17.5-cm cages), with males and females in separate, adjacent rooms, except during testing. Food and water (except where indicated otherwise) were available ad lib except during testing. Animal quarters were maintained at 21.5 ± 1.0°C, on a 12 L:12 D cycle, with lights on at 0700 h.

Surgery

Each rat used in the antagonist experiment was implanted with an intracerebroventricular (ICV) cannula. Rats were anesthetized with 0.25 ml/100 g body weight Equithesin (active ingredients: pentobarbital sodium and choral hydrate) IP, and placed in a stereotaxic apparatus (Stoelting Instruments, Wood Dale, IL); 0.1 ml of 10 mg/ml lidocaine hydrochloride was administered intradermally at the site of incision, 1–2 min prior to incision. A 22-gauge stainless steel guide cannula (Plastics One, Roanoke, VA) was then implanted into the right or left lateral ventricle using the following coordinates: −0.9 mm A/P, ±1.6 mm L/M, and −3.6 mm D/V, with lambda and bregma in the same horizontal plane. Following surgery, penicillin (11,000 units/kg) was administered IM.

Diuresis Procedure

To test diuretic effects of drugs, normally hydrated rats were used; (−)-bremazocine was also tested in 24-h water-deprived rats, so that its effects on urination and AVP could be compared. To examine morphine's antidiuretic effects, tap water was administered PO (2 ml/100 g body weight) to each rat immediately before testing.

Immediately after receiving a single dose of drug (or vehicle), rats were placed into standard operant chambers for 2 h (κ agonists, furosemide) or 1 h (morphine) (13). Urine was collected in a stainless steel pan under the wire mesh chamber floor, and measured to the nearest 0.05 ml. In general, each rat was tested with all doses of a single agonist plus vehicle,

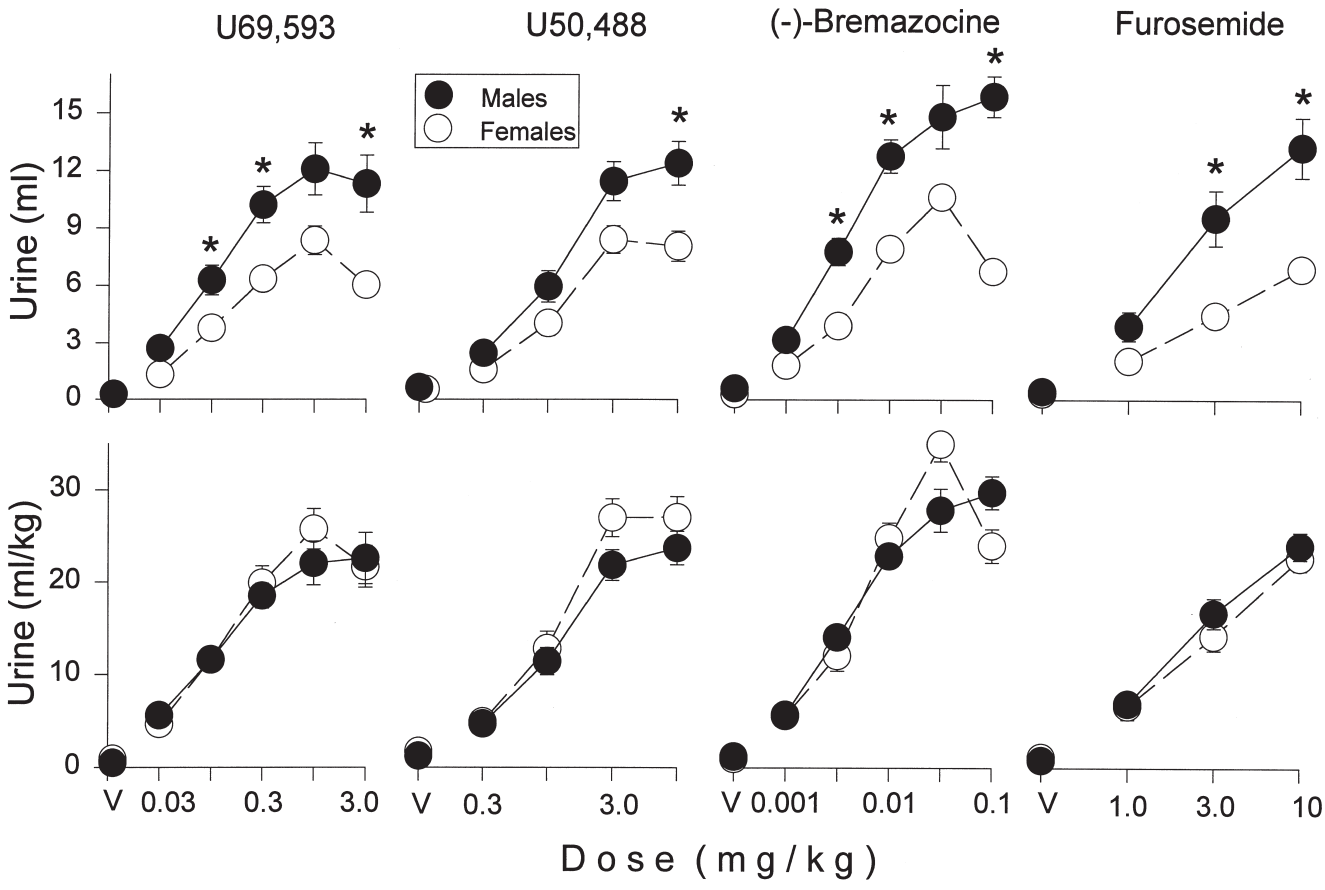

FIG. 1. Diuretic effects of three κ opioid agonists and the nonopioid furosemide, in age-matched, normally hydrated female and male rats. Drugs were administered SC and urine was measured 2 h postinjection. Top panels: data are not corrected for individual differences in body weight (urine in ml). Bottom panels: data are corrected for individual differences in body weight (urine in ml/kg). Abcisscae: dose of drug; V = vehicle. Each point is the mean ± 1 SEM of 9–10 female or male rats. *Urination significantly different between the sexes, $p \leq 0.05$, Bonferroni.

up to two tests/week until all doses were tested; dose order was different for each rat within a sex (but matched between sexes). In the antagonist experiment, rats were tested with a single dose of U69,593 up to twice/week, beginning 4 weeks after ICV nor-BNI administration. Dose order for U69,593 was varied across rats within a sex (but matched between sexes). It has been shown previously that the κ antagonist effects of nor-BNI on tests of antinociception last at least 4 weeks (2,12). To ascertain that nor-BNI was antagonizing U69,593's antinociceptive effects at 4 and 7 weeks postinjection—the interval during which diuresis was examined—some rats were retested on a 52°C hot plate after completing all diuresis tests: 1.0 mg/kg U69,593 was injected SC, and 30 min later the rat was placed on a hot plate; latency to lick a hindpaw or jump off the plate was measured in seconds (45-s cutoff).

Vasopressin Radioimmunoassay

Rats were either water deprived for 24 h or provided with water ad lib. Rats received 0, 0.01, 0.03, or 0.1 mg/kg (−)-bremazocine SC 1 h prior to decapitation. Trunk blood was collected into tubes containing 15 mg EDTA(K_3) in 0.1 ml buffered saline (Sherwood Medical, St. Louis, MO). Tubes were stored on ice until collection of all samples was completed. Cells were pelleted at 3000 rpm for 15 min at 10°C (Beckmann tabletop refrigerated centrifuge). Plasma was carefully removed with a pipette and stored at −70°C until the AVP radioimmunoassay could be performed.

Plasma levels of AVP were determined using a competitive radioimmunoassay, modified from the method of Glick and Kagan (11). Assay buffer consisted of 0.1 M sodium phosphate, 50 mM NaCl, 0.1% bovine serum albumin, pH 7.6 (28). The standard curve was generated using a stock solution of 1 mg [Arg^8]-vasopressin (Calbiochem, La Jolla, CA) per ml 5% AcOH, diluted in assay buffer at concentrations ranging from 2.5–640 pg/ml. Rabbit anti-AVP serum, goat anti-rabbit IgG serum, and normal rabbit serum (Peninsula Laboratories, Inc, San Carlos, CA) were diluted in assay buffer as specified by the manufacturer. By manufacturer's report, the anti-AVP did not crossreact with oxytocin, vasopressin metabolite neuropeptide, LHRH, ACTH, or met-enkephalin, and had 100% crossreactivity with Arg^8-vasopressin and Arg^8-vasotocin, and 38% with Lys^8-vasopressin. [^{125}I]-Arg^8-vasopressin (New England Nuclear, Boston, MA) was reconstituted in distilled water and stored in 50 μCi/ml aliquots at −70°C.

Standard or plasma (100 μl/tube) was incubated overnight at 4°C in the presence of AVP antiserum and buffer to a final volume of 300 μl/tube. Additional nonspecific binding tubes included only assay buffer, and maximum binding tubes contained buffer and antiserum. [^{125}I]-AVP was added (approximately 12,000 cpm/tube) and incubated overnight at 4°C. Goat anti-rabbit serum (100 μl/tube) and normal rabbit serum (100 μl/tube) were then added to all tubes. Following a 90-min incubation at room temperature, 400 μl of assay buffer was added. Tubes were centrifuged at 3000 rpm (Beckmann tabletop refrigerated centrifuge), supernatant poured off, tubes drained inverted, then counted.

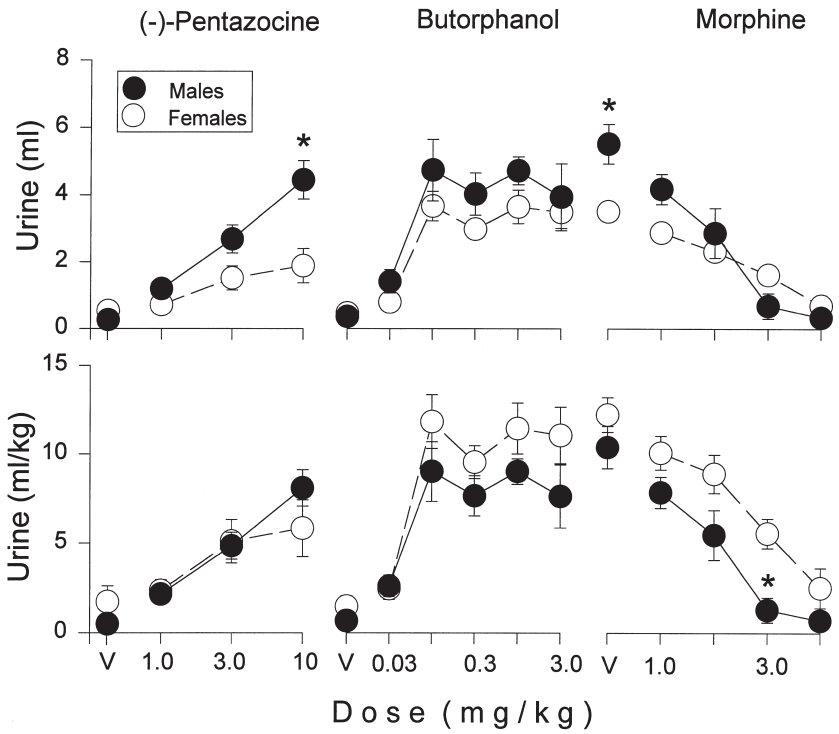

FIG. 2. Diuretic effects of two mixed action (μ/κ) opioid agonists and antidiuretic effect of the mu opioid agonist, morphine, in age-matched female and male rats. (−)-Pentazocine and butorphanol were administered SC to normally hydrated rats and urine was measured 2 h postinjection. Morphine was administered SC to water-loaded rats (2 ml tap water/100 g body weight) and urine was measured 1 h postinjection. Each point is the mean ± 1 SEM of 9–12 female or male rats. Other details as in Fig. 1.

The lower limit of detection of the assay was 0.1 pg/tube. The intraassay and interassay variabilities were 6.4 ± 2.2% and 19.2 ± 7.57%, respectively.

Drugs

Morphine sulfate, U50,488 [National Institute on Drug Abuse (NIDA), Rockville, MD] and butorphanol tartrate (Sigma, St. Louis, MO) were dissolved in 0.9% physiological saline; saline served as the control vehicle for these drugs. U69,593 (NIDA) was dissolved in EtOH, to which distilled water was added, for a final ethanol concentration of 9.5%; 9.5% ethanol was used as the control vehicle for this drug. (−)-Bremazocine and (−)-pentazocine (NIDA) were dissolved in lactic acid to which saline was added (pH 5.5); a saline solution of pH 5.5 was used as the control vehicle for these drugs. Furosemide (Sigma) was dissolved in distilled water (pH 8.0); a distilled water solution of pH 8.0 was used as the control vehicle for this drug. All systemic injections were administered SC in a volume of 1.0 ml/kg, except 3.0 mg/kg of U69,593, which was administered in a volume of 3.0 ml/kg (using a 1.0 mg/ml solution) due to solubility limits. Nor-BNI (NIDA) was administered ICV in a volume of 5 μl.

Data Analysis

Urination data were corrected for body weight, in each individual rat for each test (ml urine/kg body weight). A two-way (sex, dose) repeated-measures (dose) ANOVA was then conducted on both raw (ml) and body weight-corrected (ml/kg) urination data. Significance level for all tests was $p \leq 0.05$, or nonoverlapping 95% confidence limits.

RESULTS

Diuretic and Antidiuretic Effects of Opioid Agonists

Male rats weighed significantly more than age-matched females: mean body weights were 536 ± 6 vs. 307 ± 3 g in 3- to 5-month old males vs. females, respectively. However, there were no sex differences in basal, 2-h urine output in normally hydrated rats (Fig. 1, points at "V"). Figures 1 and 2 show that the opioid agonists U69,593, U50,488, (−)-bremazocine, (−)-pentazocine and butorphanol, and the non-opioid furosemide all dose-dependently increased urination in both sexes; furthermore, morphine dose dependently decreased urination in water-loaded males and females (Fig. 2, right panels). Approximate rank order of potency among the drugs that increased urination was (−)-bremazocine > U69,593 > U50,488 ≈ butorphanol > furosemide > (−)-pentazocine. (−)-Bremazocine, U69,593, U50,488 and furosemide also were more efficacious than (−)-pentazocine and butorphanol. Figures 1 and 2 (top panels) show that when data were not adjusted for individual differences in body weight, U69,593, U50,488, (−)-bremazocine, furosemide, and (−)-pentazocine all produced significantly greater urination in males than in females at the higher doses tested. However, when data were adjusted for individual differences in body weight, there were no significant sex differences in the diuretic effects of these five agonists (Figs. 1 and 2, bottom panels). In contrast to these agonists, butorphanol produced only slightly greater urination in males than females when data were not adjusted for body weight differences, vs. slightly greater urination in females than in males (sex: $p = 0.1$) when measured as ml urine/kg body weight (Fig. 2, top middle vs. bottom middle panels). Finally, the μ receptor-selective agonist morphine produced significantly greater decreases in urination in males than in females, per kg body weight (Fig. 2, bottom right panel).

To further examine whether sex differences in diuretic effects of κ agonists could be explained by sex differences in body weight that occur in age-matched rats, female, and male rats of different ages (and, therefore, varying body weights) were tested with 0.3 mg/kg U69,593. Females were 3–9 months old (227–376 g) and males were 2–6 months old (249–694 g). Figure 3 shows that in both male and female rats there was a significant positive correlation between body weight and U69,593-induced diuresis (Pearson $r = 0.829$ and 0.693 in males and females, respectively). There was a slight but nonsignificant difference in slope of the body weight-diuresis function in males compared to females.

Antagonism of U69,593-Induced Diuresis

Figure 4 shows that the κ receptor-selective antagonist nor-BNI produced very similar, dose-dependent, rightward shifts in the U69,593 dose–effect curve in males and females. Similar to Fig. 1, Fig. 4 shows that the sex difference in U69,593-induced diuresis was apparent when raw data were examined (top panel), but not when data were adjusted for body weight differences between females and males (bottom panel). Nor-BNI was also effective in antagonizing U69,593's antinociceptive effects at 4 and 7 weeks postinjection, the interval during which U69,593-induced diuresis was assessed. Rats treated with 0, 1, and 10 μg nor-BNI had mean hotplate latencies of 32.2 ± 5.3, 16.8 ± 3.1, and 10.4 ± 1.6 s, respectively, at 4 weeks postinjection, and 35.4 ± 5.6, 23.8 ± 4.6, and 15.6 ± 5.5 s, respectively at 7 weeks postinjection (no significant difference between the 4- and 7-week hot plate scores in females or males).

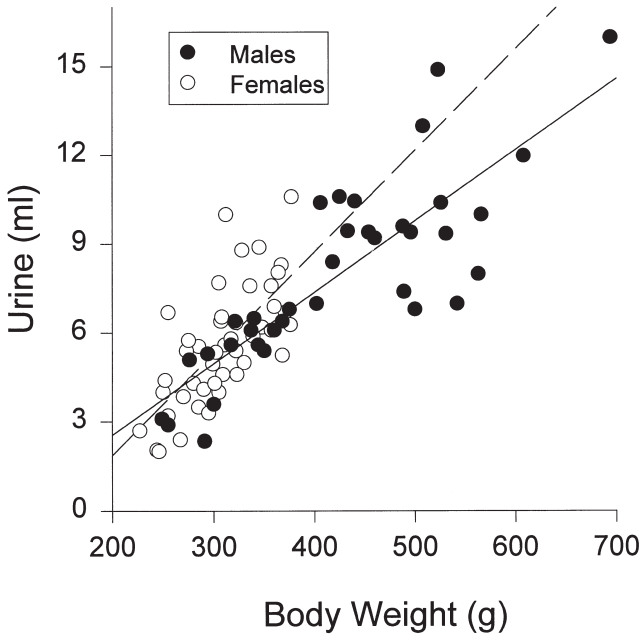

FIG. 3. Diuretic effect of the κ agonist U69,593 in female vs. male rats of different sizes (i.e., different ages). Males ranged from 2 to 6 months old, and females ranged from 3 to 9 months old. A single dose of 0.3 mg/kg was administered SC, and urine was measured 2 h postinjection.

Plasma AVP Levels

Plasma AVP was slightly greater in males than females under both normally hydrated and water deprivation conditions (sex: p = 0.2). Water deprivation significantly elevated plasma AVP in both sexes ($p = 0.005$), but to a greater extent in males than females (134 vs. 165% of normally hydrated control values in females vs. males, respectively). Figure 5 (top and middle panels) shows that, similar to its effects in normally hydrated rats, (−)-bremazocine produced significantly greater urination in water-deprived males than females (sex: $p = 0.03$), but only when data were not corrected for sex differences in body weight. Additionally, (−)-bremazocine produced slightly greater decreases in AVP in males than in females: maximal decreases in AVP occurred at the 0.03 mg/kg dose, to 65 vs. 79% of water-deprived vehicle controls in males vs. females, respectively (Fig. 5, bottom panel, circles). This maximal suppression brought plasma AVP in water-deprived males to well within the control range of normally hydrated males, and nearly so for females (Fig. 5, bottom panel, triangles).

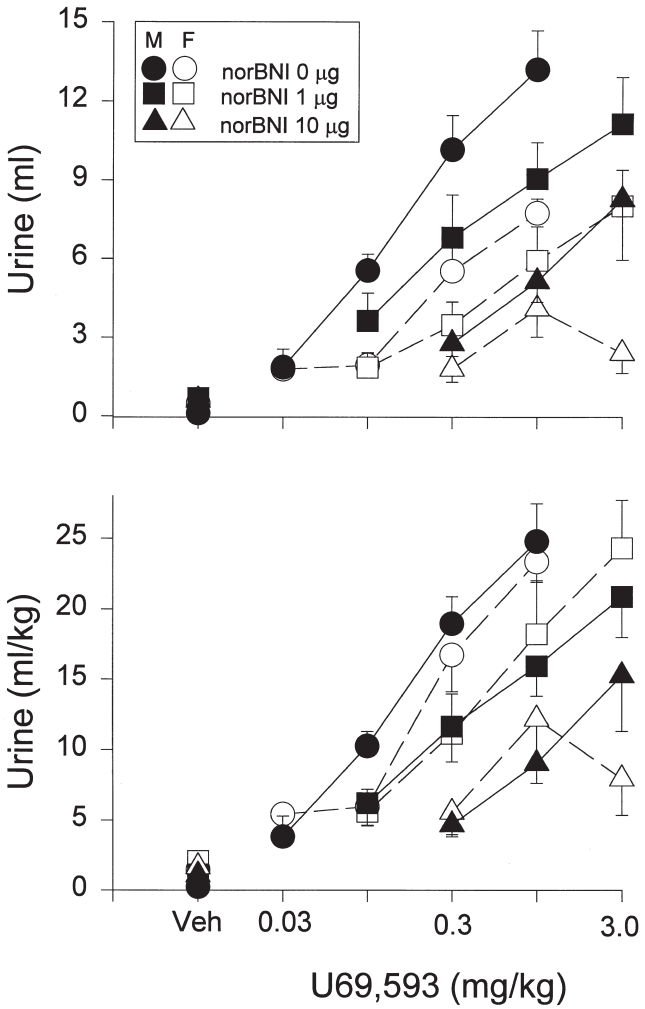

FIG. 4. Antagonism of U69,593-induced diuresis in age-matched, normally hydrated female and male rats. Nor-BNI was administered ICV; U69,593 was administered SC 4–7 weeks later, and urine was measured 2 h after U69,593 injection. Other details as in Fig. 1.

DISCUSSION

In age-matched rats, four of five κ opioid agonists tested and the nonopioid furosemide produced significantly greater diuresis in males than females. However, males also weighed approximately 70% more than age-matched females did, and

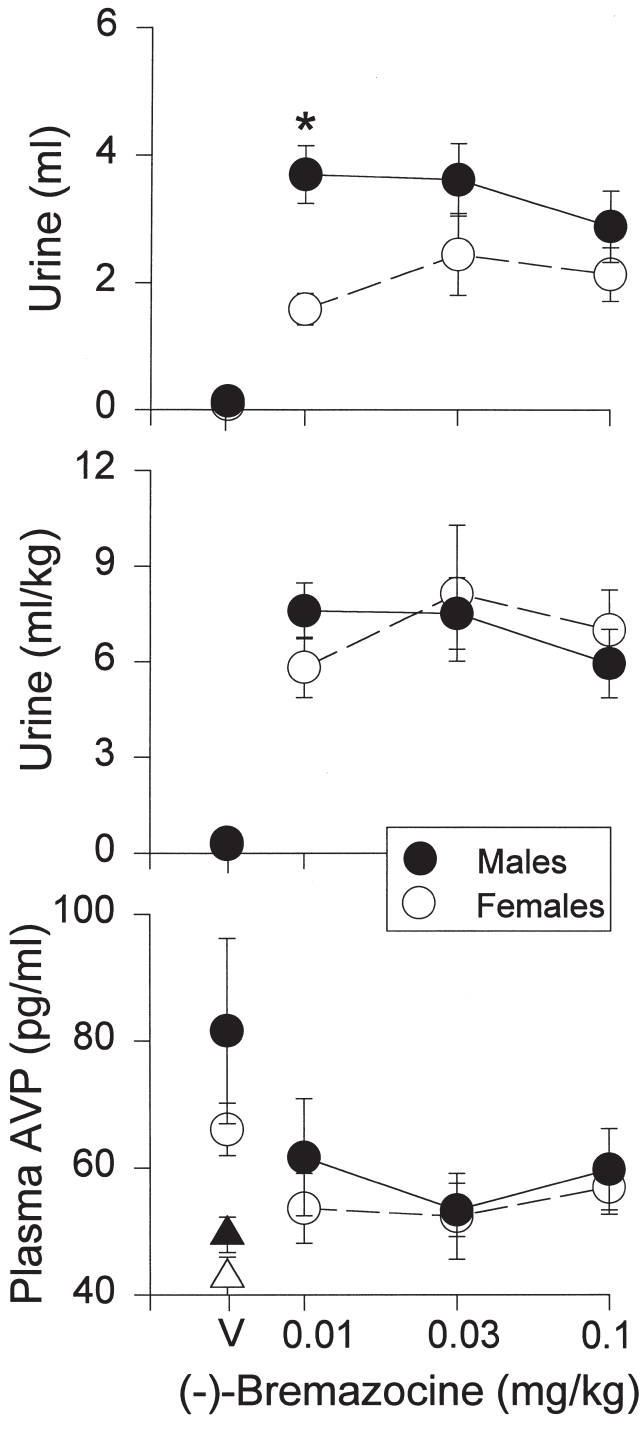

FIG. 5. Effects of (−)-bremazocine on urination (top and middle panels; $n = 10$ rats/sex) and plasma AVP (bottom panel; $n = 4$–7 rats/sex) in 24-h water-deprived female and male rats (circles), and plasma AVP in normally hydrated rats (triangles). Other details as in Fig. 1.

κ agonist-induced diuresis has been shown to be greater as body weight increases in male rats (18). In fact, when urine output was adjusted for individual differences in body weight, there were no significant sex differences in the diuretic effects of the four κ agonists or furosemide. Moreover, there was a significant positive correlation between body weight and ml urine output in each sex when a range of sizes (ages) was examined. There was also no significant sex difference in κ receptor-selective antagonism of U69,593, and only minor sex differences in the degree to which (−)-bremazocine suppressed AVP. Finally, sex differences in the diuretic effects of a nonopioid, loop diuretic, furosemide—that is, a drug that acts directly on the kidney rather than by suppressing hypothalamic AVP release (21)—could also be attributed to sex differences in body weight. Therefore, the greater diuretic effects produced by most κ agonists in 3- to 5-month-old male rats are most likely due to males' greater size relative to age-matched females.

Butorphanol was the only κ agonist tested that did not produce significantly greater diuresis—in ml urine—in males. Thus, measured in ml urine/kg body weight, butorphanol produced somewhat greater diuresis in females than in males. It is possible that sex differences in μ- rather than κ-agonist activity account for the lack of sex differences in butorphanol's diuretic effects. Butorphanol has μ in addition to κ receptor-mediated activity in the rat (23), mouse (8,26), and human (27). The μ-selective opioid agonist morphine suppressed urination (per kg body weight) significantly more in males than in females. Butorphanol's μ-agonist activity also would be expected to be greater in males than in females, thus limiting its κ receptor-mediated diuresis to a greater extent in males than in females. Alternatively, butorphanol's limited efficacy at the κ receptor relative to agonists like bremazocine (17,19) may have obscured any sex differences in its effects.

The κ receptor-selective antagonist nor-BNI, administered ICV, dose dependently antagonized the diuretic effect of systemically administered U69,593 similarly in males and females. This result indicates that U69,593's diuretic effects are at least partially mediated via centrally located κ receptors in both sexes, as demonstrated previously for males tested with other κ agonists (24).

It has also been shown previously that male rats have higher AVP levels than females do (6,7,25), and that κ agonists produce diuresis by suppressing AVP release from the hypothalamus, in males [e.g., (20)]. The present study confirms that suppression of AVP is a likely mechanism of κ agonist-induced diuresis common to both sexes. The fact that bremazocine was slightly more potent and efficacious in suppressing AVP in males compared to females suggests that sex differences in AVP suppression may also contribute to sex differences in diuretic effects of κ agonists. Thus, the greater diuretic effects of κ receptor-selective opioid agonists in male rats are primarily due to males' larger body size (greater body water) relative to age-matched females, but may also be attributed to slightly greater vasopressin suppression in males.

One discrepancy between the present and previous study is that in our previous study, U69,593 produced significantly greater diuresis in males than in females—even after data were adjusted for body weight (4). The most salient procedural difference between these studies is that in our previous study, U69,593-induced diuresis was not assessed until the U69,593 discrimination study was completed—that is, after administration of U69,593 two to four times/week for approximately 12 months. In contrast, in the present study rats were tested acutely with U69,593. Thus, sex differences in development of tolerance to U69,593 may have produced the considerably larger sex difference in U69,593's diuretic effect observed in our previous study compared to the present one. In support of this argument, urination after 1.0 mg/kg U69,593 in males vs. females was approximately 8.0 vs. 2.0 ml, respectively, in the previous (chronic) study, vs. approximately 12.0 vs. 8.0 ml in the present (acute) study. This cross-study comparison suggests that females may develop greater tolerance than males do to U69,593's diuretic effects. Sex differences in tolerance development to the μ agonist morphine have been described previously (5); further study will be required to determine whether the same is true for κ agonists.

ACKNOWLEDGEMENTS

The authors thank Scott Bernal, Bridget Mathison, and Jennifer O'Rourke for excellent technical assistance.

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