circulating factor of splenic origin or elicited by some factor of splenic origin.

In conclusion, our study suggests that the CXBK may be specifically defective in the μ-receptor-mediated analgesia, whereas, the beige mouse is defective in analgesia mediated by both μ- and κ-opioid receptors due to an unknown cause. Although the analgesic defect in the beige mouse lacks opioid receptor subtype specificity, this strain may be useful for understanding the mechanism of analgesia at the molecular level, because the defect is associated with one gene mutation.

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Antidiuretic effect of bremazocine and U-50,488 in rats after α_2-adrenoceptor blockade

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Abstract—The role of α_2-adrenoceptors and κ-opioid receptors in urination was studied in rats. In water-loaded rats (40 mL kg^{-1} p.o.) the κ-opioid agonist bremazocine (0·05–0·2 mg kg^{-1} i.p.) induced a dose-related diuretic response in the second hour after administration, but had no effect in the first hour. When rats were pretreated with the α_2-adrenoceptor antagonist idazoxan (1 mg kg^{-1} s.c.), bremazocine induced a dose-related antidiuretic response in the first hour; thereafter the rats showed an increase of urination similar to that with bremazocine alone. The antidiuretic effect of bremazocine was dependent on the dose of idazoxan with maximal response after 1–3 mg kg^{-1}. Similar results were obtained with bremazocine in the presence of yohimbine (1 mg kg^{-1} s.c.). The antidiuretic profile of bremazocine after idazoxan was shared by U-50,488 (2·5–10 mg kg^{-1} i.p.), although this compound alone at the high dose reduces urine output in the first hour. The antidiuresis induced by bremazocine in the presence of idazoxan in water-loaded rats was completely antagonized by 10 but not 2 mg kg^{-1} i.p. of the opioid antagonist naloxone. Thus, κ-opioid agonists, in addition to their diuretic effect, also produce an antidiuretic response which may be mediated by α_2-adrenoceptors.

κ-Opioid agonists cause marked diuresis in normally hydrated and water-loaded rats (Slizgi & Ludens 1982; Leander 1983a, b; Huidobro-Toro & Parada 1985; Blackburn et al 1986; Leander et al 1987). This effect has been ascribed to inhibition of vasopressin release with a mechanism different from that of the α_2-adrenoceptor agonist clonidine (Slizgi & Ludens 1982; Leander et al 1985, 1987; Blackburn et al 1986; Oiso et al 1988). However, it was recently reported that the diuresis induced by κ-opioid agonists could be antagonized by the α_2-adrenoceptor antagonist idazoxan (Birch & Hayes 1988), indicating that the noradrenergic system may also be involved. Since α_2-adrenoceptors play a significant role in modulating the activity of vasopressin in the kidney (Pettinger et al 1987) and an interaction between α_2-adrenoceptors and κ-opioid receptors has been reported (Jackisch et al 1986; Limberger et al 1986; Ramme et al 1986; Adamson et al 1988), it was of interest to further investigate the role of these receptors in urination in the rat.

Materials and methods

Hydration procedure and animal handling. Male CD-COBS rats (Charles River, Como, Italy), 260 to 320 g, were used. Generally they were used twice, each once a week. The animals were given 12 mL/rat (about 40 mL kg^{-1}) of tap water by gavage 30 min before the dose of bremazocine, then placed in metabolism cages. Cumulative urine volume was recorded hourly for 3–5 h; during which time rats were kept without food but allowed free access to water.

Drugs. Idazoxan hydrochloride (RX781094, Reckitt and Colman, Hull, UK), and yohimbine hydrochloride (Aldrich, Milwaukee, WI, USA) were dissolved in distilled water. Bremazocine hydrochloride (Sandoz, Basel, Switzerland), U-50,488 [*trans*-(±)-3,4-dichloro-*N*-methyl-*N*-(2-(1-pyrrolidinyl)-cyclo hexyl)-benzeneacetamide methanesulphonate hydrate] (Upjohn Company, Kalamazoo, MI, USA) and naloxone hydrochloride (Endo Laboratories, Garden City, NJ, USA) were dissolved in 0·9% NaCl. Drugs were given in a volume of 2 mL kg^{-1} subcutaneously (s.c.) (idazoxan and yohimbine) or intraperitoneally (i.p.) (bremazocine, U-50,488 and naloxone). Doses refer to the salts used.

Statistical analysis. Values are the mean ± s.e.m. Statistical significance was determined using Duncan's test and a P value less than 0·05 was considered to indicate significance.

Results

In water-loaded rats bremazocine 0·05–0·2 mg kg^{-1} i.p. did not affect urine output in the first hour, but dose-related diuresis appeared in the second hour (Fig. 1). Subsequent urine output was close to that of controls. When rats were pretreated with idazoxan (1 mg kg^{-1} s.c.), bremazocine induced a dose-related antidiuretic response in the first hour. In the second hour in rats treated with bremazocine plus idazoxan the increase in urinary output was similar to that after bremazocine alone (see Fig. 1). At 3 h the animals treated with idazoxan plus bremazocine reached the same urine output as those treated with bremazocine alone. Idazoxan alone did not affect urine output. The same profile was observed in normally hydrated rats, although in this condition it was harder to detect antidiuresis (data not shown).

In untreated rats bremazocine (0·1 mg kg^{-1} i.p.) did not affect urine output in the first hour but caused diuresis in the second hour after administration (Fig. 2). In animals given idazoxan 0·1–3 mg kg^{-1} bremazocine caused a dose-related antidiuretic response in the first hour with maximal effect after 1 and 3 mg kg^{-1} of idazoxan. At 3 h rats treated with bremazocine plus idazoxan reached the same urine output as after bremazocine alone. Idazoxan alone at the highest dose tested had no effect on urinary output. In animals given yohimbine 1 mg kg^{-1} s.c. (Fig. 3), bremazocine induced antidiuresis in the first 2 h, then urine output rose to the same level as after bremazocine alone, although more slowly after idazoxan plus bremazocine; at 5 h, urinary output of both groups was similar (urine volume: bremazocine 10·5 mL, yohimbine plus bremazocine 9·8 mL). Yohimbine alone, did not affect urine output. Bremazocine produced antidiuresis when idazoxan was administered 10 min after the κ-agonist (urine volume at 1 h; bremazocine, 0·1 mg kg^{-1} i.p., 4·0 ± 0·5 mL; bremazocine plus idazoxan 1 mg kg^{-1} s.c., 0·7 ± 0·3 mL, $P < 0·01$ from bremazocine alone, means ± s.e.m. $n = 6$).

The effect of U-50,488 alone and in combination with idazoxan in water-loaded rats is shown in Fig. 4. In the first hour U-50,488 did not affect urine output at low dose levels (2·5–5 mg kg^{-1} i.p.) and reduced it at a higher dose (10 mg kg^{-1} i.p.). This initial phase was followed after 2 to 3 h by a marked increase in urine output. In the presence of idazoxan, U-50,488, 2·5–5 mg kg^{-1} induced a dose-related antidiuretic response in the first hour, and at the dose of 10 mg kg^{-1} it had greater antidiuretic effect. Subsequently, the rats treated with idazoxan plus U-50,488 reached the same urine output as after U-50,488 alone. Idazoxan alone did not affect urine output.

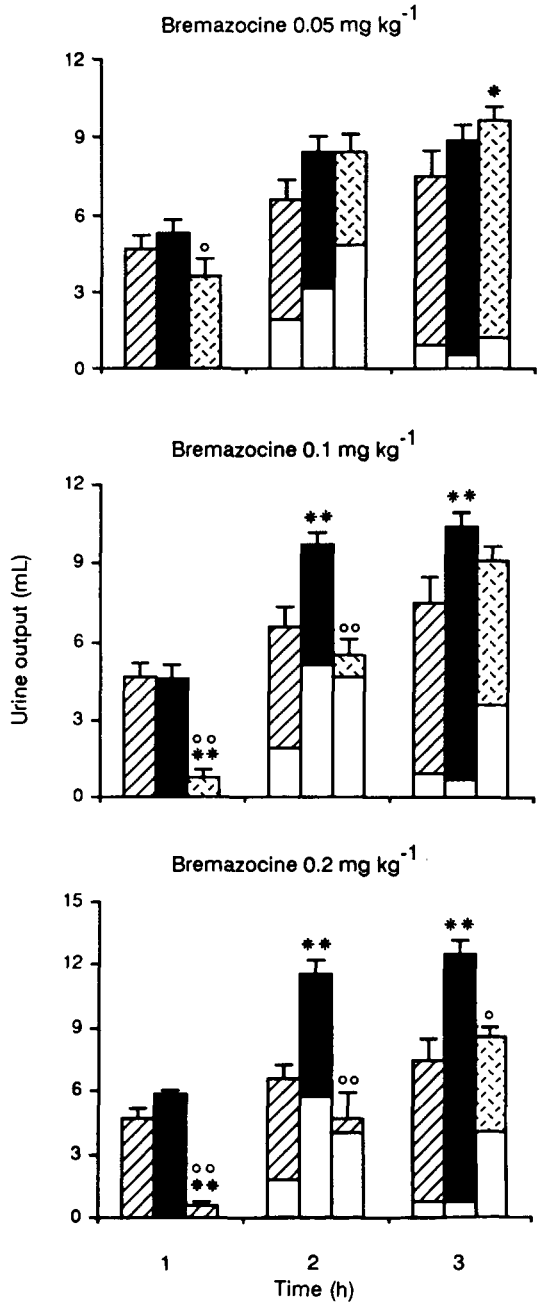

FIG. 1. Effect of bremazocine and idazoxan plus bremazocine on urination in water-loaded rats. Tap water (12 mL/rat p.o.) was given 30 min before bremazocine. Idazoxan (1 mg kg^{-1}) was injected s.c. 15 min before bremazocine i.p. Each column and bar represent the mean ± s.e. of 6–10 animals for drug-free controls (▨), bremazocine (■) and bremazocine plus idazoxan (▩). Open columns represent the increase of urinary output. Idazoxan alone did not affect urine output: 4·5 ± 0·4, 6·1 ± 0·5 and 6·9 ± 0·5 mL at 1, 2 and 3 h, respectively. Significant differences from drug-free controls; * $P < 0·05$ and ** $P < 0·01$, and from the corresponding group of bremazocine without idazoxan; ° $P < 0·05$ and °° $P < 0·01$.

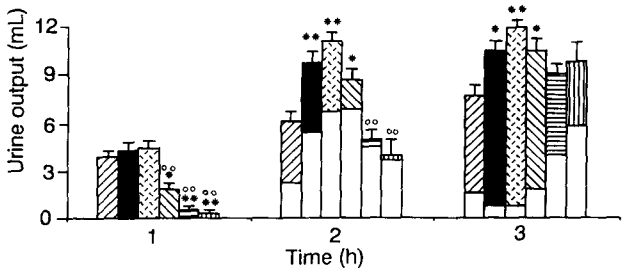

FIG. 2. Effect of bremazocine after different doses of idazoxan on urination in water-loaded rats. Tap water (12 mL/rat p.o.) was given 30 min before bremazocine. Idazoxan (1 mg kg^{-1}) was injected s.c. 15 min before bremazocine i.p. Each column and bar represent the mean ± s.e. of 5–10 rats for drug-free controls (▨), bremazocine (■), bremazocine plus idazoxan 0·1 (▩), 0·3 (▩), 1 (▩) and 3 (▩), mg kg^{-1}. Open columns represent the increase of urinary output. Idazoxan alone at the highest dose reported did not affect urine output: 3·4 ± 0·2, 5·4 ± 0·5 and 6·3 ± 0·4 mL at 1, 2 and 3 h, respectively. Significant differences from drug-free controls; * $P < 0·05$ and ** $P < 0·01$, and from the corresponding group of bremazocine without idazoxan: °° $P < 0·01$.

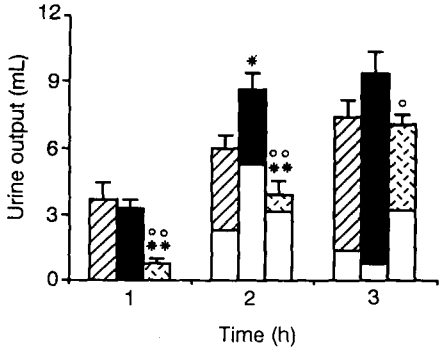

FIG. 3. Effect of bremazocine and yohimbine plus bremazocine on urination in water-loaded rats. Tap water (12 mL/rat p.o.) was given 30 min before bremazocine. Yohimbine (1 mg kg^{-1}) was injected s.c. 15 min before bremazocine i.p. Each column and bar represent the mean ± s.e. of 5–8 animals for drug-free controls (▨), bremazocine (■) and bremazocine plus yohimbine (▩). Open columns represent the increase of urinary output. Yohimbine alone did not affect urine output: 3·3 ± 0·6, 5·8 ± 0·4 and 6·4 ± 0·4 ml at 1, 2 and 3 h, respectively. Significant differences from drug-free controls, * $P < 0·05$ and ** $P < 0·01$, and from the corresponding group of bremazocine without yohimbine: ° $P < 0·05$ and °° $P < 0·01$.

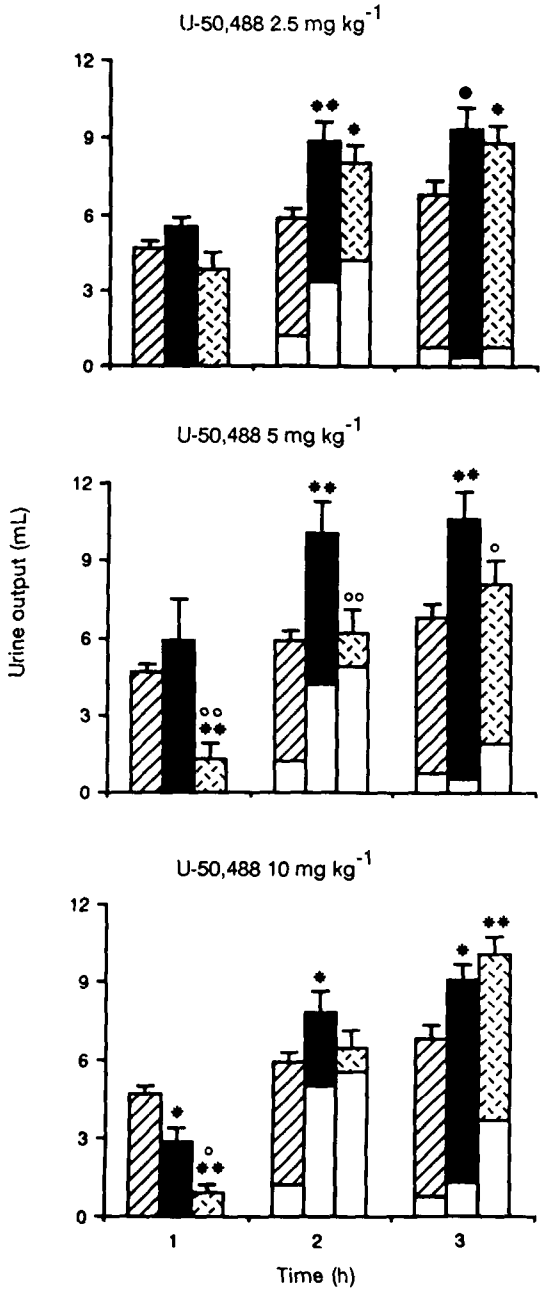

FIG. 4. Effect of U-50,488 and idazoxan plus U-50,488 on urination in water-loaded rats. Tap water (12 mL/rat p.o.) was given 30 min before bremazocine. Idazoxan (1 mg kg^{-1}) was injected s.c. 15 min before U-50,488 i.p. Each column and bar represent the mean ± s.e. of 6–8 animals for drug-free controls (▨), U-50,488 (■) and U-50,488 plus idazoxan (▩). Open columns represent the increase of urinary output. Idazoxan alone did not affect urine output: 4·2 ± 0·4, 5·5 ± 0·5 and 6·6 ± 0·4 mL at 1, 2 and 3 h, respectively. Significant differences from drug-free controls, * $P < 0·05$ and ** $P < 0·01$, and from the corresponding group of bremazocine without idazoxan; ° $P < 0·05$ and °° $P < 0·01$.

Table 1 shows the effect of naloxone on the antidiuretic and diuretic actions of bremazocine alone and in combination with idazoxan. Both in animals treated with bremazocine alone and in those pretreated with idazoxan, naloxone, 2 mg kg^{-1} i.p., failed to antagonize bremazocine-induced diuresis and antidiuresis. However, the dose of 10 mg kg^{-1} of naloxone completely prevented the antidiuretic effect of bremazocine in rats pretreated with idazoxan and partially antagonized the diuretic response of bremazocine alone and in animals pretreated with idazoxan. Naloxone alone or in combination with idazoxan did not affect urine output.

Discussion

Bremazocine and U-50,488 are reported to activate κ-opioid receptors (Romer et al 1980; VonVoigtlander et al 1983; Hayes & Kelly 1985; Corbett & Kosterlitz 1986). U-50,488 has greater selectivity towards κ-opioid receptors than bremazocine (James & Goldstein 1984; Weyhenmeyer & Mack 1985). However, bremazocine is a pure antagonist at the μ and δ opioid receptors in-vivo and in-vitro (Petrillo et al 1984; McKnight et al 1985; Corbett & Kosterlitz 1986; Sheehan et al 1986; Dunwiddie et al 1987). The fact that a high dose of naloxone is required to block

Table 1. Antagonism of naloxone on urinary effects of idazoxan plus bremazocine and bremazocine alone in water-loaded rats. Tap water (12 mL/rat p.o.) was given 30 min before bremazocine. Idazoxan (1 mg kg^{-1}) was injected s.c. 15 min and naloxone i.p. 5 min before bremazocine (0·2 mg kg^{-1} i.p.). Results are the means ± s.e. of 6–12 animals. Significant differences from drug-free controls: * $P<0·05$ and ** $P<0·01$. Significant differences from bremazocine: $^{\circ}P<0·05$ and $^{\circ\circ}P<0·01$. Significant differences from idazoxan plus bremazocine: $^{\bullet}P<0·01$.

		Cumulative urine output (mL)		
Pretreatment (mg kg^{-1})	Treatment	1 h	2 h	3 h
—	—	5·1 ± 0·6	6·7 ± 0·5	8·0 ± 0·5
Idazoxan	—	4·8 ± 0·6	7·3 ± 0·6	8·5 ± 0·6
Naloxone (10)	—	4·4 ± 0·4	6·1 ± 0·5	7·1 ± 0·4
Idazoxan + naloxone (10)	—	4·5 ± 0·3	7·8 ± 0·5	8·3 ± 0·5
—	Bremazocine	5·6 ± 0·4	11·4 ± 0·4**	12·4 ± 0·5**
Idazoxan	Bremazocine	0·6 ± 0·1**$^{\circ\circ}$	5·0 ± 0·7$^{\circ\circ}$	10·0 ± 0·5°
Idazoxan + naloxone (2)	Bremazocine	1·2 ± 0·4**$^{\circ\circ}$	6·4 ± 0·5$^{\circ\circ}$	9·2 ± 0·8$^{\circ\circ}$
Idazoxan + naloxone (10)	Bremazocine	4·0 ± 0·5$^{\circ\bullet}$	8·5 ± 0·5$^{\circ\circ\bullet}$	9·9 ± 0·7°
Naloxone (2)	Bremazocine	6·0 ± 0·8	11·6 ± 0·9**	12·3 ± 0·9**
Naloxone (10)	Bremazocine	5·3 ± 0·5	9·0 ± 0·8*$^{\circ\circ}$	10·0 ± 0·9°

the antidiuretic effect of bremazocine in the presence of idazoxan is compatible with the interpretation that the effect is κ-receptor mediated. Bremazocine also produces antidiuresis when given before idazoxan which rules out a possible explanation in terms of metabolic or other pharmacokinetic effects of idazoxan. It is possible that bremazocine in the presence of idazoxan produces antidiuresis by inducing hypotension but this seems unlikely for a variety of reasons: in conscious rats bremazocine produced hypertension rather than hypotension (Salas et al 1989); low doses of naloxone (0·1–1 mg kg^{-1}) blocked the pressor response of κ-agonists (Ureta et al 1987; Salas et al 1989) whereas a dose of 10 mg kg^{-1} was required to antagonize the antidiuretic response in the study and the α_2-adrenoceptor antagonist idazoxan and the full κ-agonist U-50,488 had no effect on blood pressure (Ashton et al 1990; Harland & Brown 1988).

Thus, the present findings confirm and extend the observations of Birch & Hayes (1988) in providing evidence of the involvement of an α_2-adrenoceptor component in κ-opioid mediated urinary effects. It has been reported that κ-agonists such as tifluadom, U-50,488 and ethylketocyclazocine produced brief antidiuresis before the diuretic phase (Birch & Hayes 1987; Ureta et al 1987), and the present study indicates that after α_2-adrenoceptor blockade the antidiuretic responses of κ-agonists are enhanced or unmasked, suggesting a close relation between κ-opioid receptors and α_2-adrenoceptors on urination.

In this connection, it has been recently hypothesized that κ-opioid receptors and α_2-adrenoceptors interact in such a way that when α_2-adrenoceptors are blocked, the effects of κ-opioid receptor activation are enhanced or activated (Jackisch et al 1986; Limberger et al 1986; Ramme et al 1986). Therefore, one possible explanation of the present findings is that blockade of α_2-adrenoceptors activates κ-opioid receptors, inducing the antidiuretic response. It is also possible, that the α_2-adrenoceptor antagonists reduce the diuretic effect of κ-agonists and this unmasks an antidiuretic effect. However, more detailed study is necessary before any definite conclusions can be drawn about the mechanisms of interaction between α_2-adrenoceptors and κ-opioid receptors on urination.

In conclusion, the results described here show that κ-agonists, not only have a diuretic effect but also induce an antidiuretic response and that this may be mediated by α_2-adrenoceptors. Independently of the physiological significance of these findings, the present study suggests that κ-opioid receptors play an important role in the control of fluid balance.

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