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Effects of TAK-637, a tachykinin receptor antagonist, on lower urinary tract function in the guinea pig

Takayuki Doi [a,*], Izumi Kamo [a], Shigemitsu Imai [a], Satoshi Okanishi [a], Takenori Ishimaru [b], Yoshinori Ikeura [a], Hideaki Natsugari [a]

[a] *Pharmaceutical Research Division, Takeda Chemical Industries, 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan*
[b] *Discovery Research Division, Takeda Chemical Industries, Ibaraki 300-4293, Japan*

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Abstract

The effects of TAK-637 ((*aR*,9*R*)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7*H*-[1,4]diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione), a novel tachykinin NK_1 receptor antagonist, on the micturition reflex in guinea pigs were studied in comparison with those of anti-pollakiuria agents. Cystometry was performed under urethane anesthesia. TAK-637 increased the volume threshold with a minimum effective dose of 0.03 mg/kg, i.v. without affecting voiding pressure. Oxybutynin, tolterodine, propiverine and inaperisone also increased the volume threshold in urethane-anesthetized guinea pigs, but they decreased voiding pressure, although the effect of propiverine was not statistically significant. A structurally unique tachykinin NK_1 receptor antagonist, (±)-CP-99,994 ((±)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine), increased the volume threshold with a minimum effective dose of 0.3 mg/kg, i.v. TAK-637 increased the volume threshold with a minimum effective dose of 0.01 mg/kg, p.o. in unanesthetized guinea pigs. These results indicate that TAK-637 may be useful as pharmacotherapy for detrusor overactivity without decreasing voiding pressure or causing voiding difficulties.

Keywords: TAK-637; Non-peptide tachykinin NK_1 receptor antagonist; Micturition reflex; Urinary tract, lower

1. Introduction

The tachykinins constitute a mammalian family of neuropeptides, including substance P and neurokinin A and B. Tachykinins bind to three receptors, termed tachykinin NK_1, NK_2 and NK_3 receptors. Substance P has the greatest affinity for the tachykinin NK_1 receptor, whereas neurokinin A and neurokinin B have the greatest affinity for tachykinin NK_2 and NK_3 receptors, respectively. These neuropeptides are known to be involved in a variety of biological activities, such as pain transmission, neurogenic inflammation and smooth muscle contraction and relaxation, and their antagonists have long been considered as potential therapeutic drugs for a variety of diseases, and especially as potential analgesics (Otsuka and Yoshioka, 1993). In spite of the fact that many substance P receptor antagonists have been described, specific clinical indications have not yet been established, although anti-emetic and, recently, anti-depressant effects have been confirmed in animals and humans (Bountra et al., 1993; Tattersall et al., 1993; Kris et al., 1996; Kramer et al., 1998).

Since the discovery of the first non-peptide tachykinin NK_1 receptor antagonist, CP-96,345, by a group at Pfizer (Snider et al., 1991), more than 20 selective new non-peptide tachykinin NK_1 receptor antagonists, starting with RP-67580 (review; Betancur et al., 1997), have been reported upon. We also have described a series of highly potent and orally active non-peptide tachykinin NK_1 receptor antagonists (Natsugari et al., 1995; Ikeura et al., 1998).

The micturition reflex consists of a series of well-coordinated reflexes, and there is no doubt that the sensory systems of the lower urinary tract play a pivotal role in normal as well as pathological micturition (De Groat, 1975; McMahon, 1986). Pharmacological experiments have indicated that substance P-containing or capsaicin-sensitive afferent fibers constitute an important sensory arm of the micturition reflex pathway (Holzer-Petsche and Lembeck, 1984; Maggi and Meli, 1986). The spinal intrathecal injec-

* Corresponding author. Tel.: +81-6-6300-6113; fax: +81-6-6300-6306.
E-mail address: Doi_Takayuki@takeda.co.jp (T. Doi)

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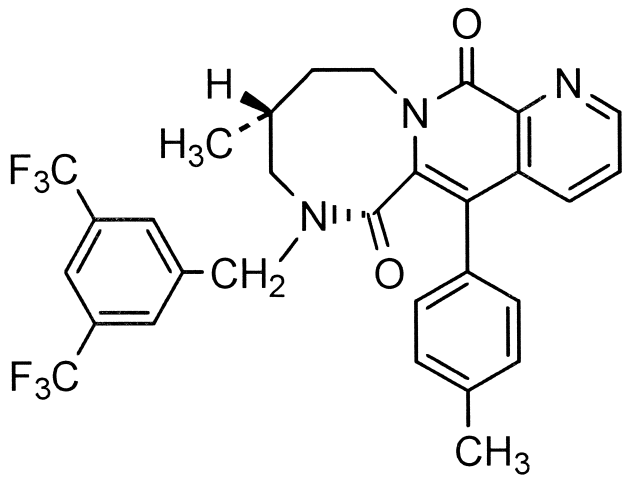

Fig. 1. Chemical structure of TAK-637.

tion of substance P receptor antagonists inhibits the micturition reflex in rats (Lecci et al., 1992, 1993), and the intravesical injection of capsaicin or resiniferatoxin normalizes detrusor hyperreflexia in humans (De Ridder et al., 1997; Lazzeri et al., 1997). Based on these results, substance P receptor antagonists are thought to have the ability to modulate the micturition reflex and to be useful as pharmacotherapy for pollakiuria or incontinence, aiming at sensory functions. The purpose of this study was to determine the effects of TAK-637 ((*aR*,9*R*)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7*H*-[1,4]diazocino[2,1-*g*][1,7]naphthyridine-6,13-dione), Fig. 1) with high affinity (IC_{50} = 0.45 nM) for the tachykinin NK_1 receptors in human IM-9 cells (Ikeura et al., 1998), on the functions of the lower urinary tract in guinea pigs to get an idea of its potential clinical usefulness.

2. Materials and methods

2.1. Increasing effect on the volume threshold in urethane-anesthetized guinea pigs

Male Hartley guinea pigs (250–350 g body weight) were used because the affinity of TAK-637 for the tachykinin NK_1 receptor differs among species, i.e., it has higher affinity for the guinea pig and human tachykinin NK_1 receptor than for the rat tachykinin NK_1 receptor (Natsugari et al., 1999). The animals were anesthetized with an intraperitoneal injection of urethane (1.2 g/kg). Each dose of each test compound was tested with eight animals. The urinary bladder was exposed through an incision in the abdomen. Two 23-gauge needles connected to a polyethylene tube (PE-90) were inserted into the bladder dome: one for the infusion of physiological saline and the other for measurement of intravesical pressure. Before infusion of saline into the bladder, the bladder was always emptied by suction via the polyethylene tube. Warmed saline (39°C) was continuously infused at a rate of 0.3 ml/min using an infusion pump. The volume threshold (volume to which the bladder can be filled before voiding) was measured at least twice before testing. After confirmation of a stable response, the mean value from the last two trials was taken as the control volume threshold, and the volume threshold was then measured 10 min after intravenous injection of the test compound. The micturition pressure was also measured. TAK-637 was dissolved in dimethylsulfoxide (DMSO) as it is insoluble in saline, and was injected in a volume of 0.05 ml/100 g body weight. The other drugs were dissolved in saline and injected in a volume of 0.1 ml/100 g body weight. Statistical analysis was performed by comparing predrug values with postdrug values, using the paired *t*-test.

2.2. Increasing effect on the volume threshold in unanesthetized guinea pigs

Male Hartley guinea pigs (250–350 g body weight) were used. The animals were anesthetized with ether. The urinary bladder was exposed through an incision in the abdomen. A polyethylene tube (PE-90) was implanted in the bladder: one end of the tube was inserted into the bladder and ligated in place, and the other end was tunneled subcutaneously to exit at a site on the dorsal surface of the neck. Potassium penicillin G (10,000 U) was injected intramuscularly to prevent infection. The animals were allowed to recover for at least 2 days before being used in the experiment. Twenty animals were used for each dose of each test compound. Warmed saline (39°C) was infused through the implanted cannula at a rate of 0.1 ml/min, using an infusion pump, to give rise to micturition. The volume threshold was measured three times before drug or vehicle administration and twice 1 h after administration. The first measurement of each series was disregarded because these values were thought to be biased by natural bladder filling. The mean of the last two volume threshold values determined before drug administration was taken as the predrug volume threshold, and the second volume threshold value determined 1 h after drug administration was taken as the postdrug volume threshold. The percentage increase in volume threshold was calculated for each drug-treated as well as vehicle-treated animal. Statistical analysis was performed by comparison with the corresponding vehicle-treated group using the non-parametric Dunnett test. Drugs were suspended in a 0.5% methylcellulose solution and administered orally in a volume of 0.2 ml/100 g body weight.

2.3. Effect on the urethral pressure in urethane-anesthetized guinea pigs

Female guinea pigs (Hartley, 250–300 g body weight) were used. The animals were anesthetized with an intraperitoneal injection of urethane (1.2 g/kg). To record the urethral pressure profiles, a catheter (Groshong® 4Fr.)

connected to a pressure transducer was introduced into the bladder. Saline was constantly infused at a rate of 0.3 ml/min through the catheter, and the bladder pressure was then recorded. The catheter was drawn down the urethra at a rate of 5 mm/min. The maximum pressure throughout the urethra was taken as the urethral pressure. Statistical analysis was performed using the paired *t*-test.

All animal experiments were approved by Takeda's Experimental Animal Care and Use Committee.

2.4. Chemicals

TAK-637, (±)-CP-99,994 · 2HCl ((±)-(2*S*,3*S*)-3-(2-methoxybenzylamino)-2-phenylpiperidine · 2HCl, (±)-CP-99,994), inaperisone hydrochloride (inaperisone) and tolterodine hydrogen tartrate (tolterodine) were synthesized in Takeda's Pharmaceutical Research Laboratories. Oxybutynin hydrochloride (oxybutynin; Kodama), propiverine hydrochloride (propiverine; Taiho) and tamsulosin (Yamanouchi) were extracted from the commercially available tablets in Takeda's Pharmaceutical Research Laboratories. Urethane was obtained from Aldrich. Phenylephrine hydrochloride (phenylephrine) was purchased from Wako.

3. Results

3.1. Increasing effect on the volume threshold in urethane-anesthetized guinea pigs

The mean control volume threshold was in the range of 1.41 to 2.01 ml. Neither DMSO nor saline had any substantial effect on the volume threshold, with 6.3% and 8.2% increases, respectively ($n = 8$). As shown in Fig. 2, TAK-637 dose dependently increased the volume threshold from 0.01 to 0.3 mg/kg, i.v. with a minimum effective dose of 0.03 mg/kg, i.v. The volume threshold was not increased further at doses higher than 0.3 mg/kg, i.v. No overflow dripping or complete loss of the micturiton reflex was observed. Inaperisone, which is a centrally acting muscle relaxant (Morikawa et al., 1992), also increased the threshold with a minimum effective dose of 1.0 mg/kg, i.v. Peripherally acting anti-pollakiuria agents such as oxybutynin (Anderson and Fredericks, 1977), tolterodine (Nilvebrant et al., 1997) and propiverine (Haruno, 1992) increased the volume threshold up to only 50% at their respective non-toxic maximum or tolerable doses.

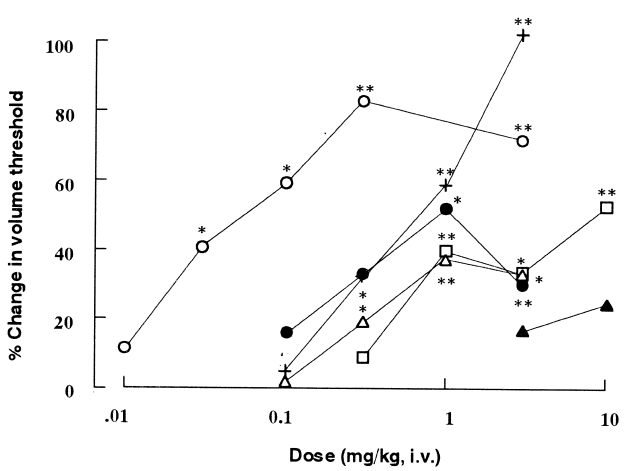

Fig. 2. The effects of various drugs on the volume threshold in urethane-anesthetized guinea pigs. TAK-637 (○), (±)-CP-99,994 (+), oxybutynin (●), tolterodine (△), propiverine (▲) and inaperisone (□) were administered intravenously. Each point represents the mean value for eight animals. $^{*}P < 0.05$; $^{**}P < 0.01$ compared with the predrug value (paired *t*-test). The effects of drugs are expressed as percentage increase in volume threshold compared with the predrug value. The minimum effective dose of each drug was as follows: TAK-637, 0.03 mg/kg; (±)-CP-99,994, 0.3 mg/kg; inaperisone, 1.0 mg/kg; oxybutynin, 1.0 mg/kg; tolterodine, 0.3 mg/kg; and propiverine, > 10 mg/kg.

Table 1
The effects of various drugs on voiding pressure
Pre and post indicate voiding pressure before and after drug administration, respectively. Data are expressed as the means ± S.E.M. for eight animals. Asterisks indicate significant differences from the predrug value.

	Dose (mg/kg, i.v.)	Voiding pressure (mm Hg)	
		Pre	Post
TAK-637	0.01	18.6 ± 0.6	17.6 ± 0.7
	0.03	17.7 ± 1.1	18.7 ± 0.9
	0.1	18.1 ± 0.6	18.9 ± 0.9
	0.3	20.0 ± 1.9	18.5 ± 1.1
	3.0	20.1 ± 1.4	20.2 ± 1.0
(±)-CP-99,994	0.1	22.0 ± 1.1	22.5 ± 1.4
	0.3	21.4 ± 1.3	20.8 ± 1.8
	1	21.7 ± 0.9	19.4 ± 0.7[a]
	3	20.0 ± 0.9	18.4 ± 1.0
Oxybutynin	0.1	18.3 ± 1.2	16.0 ± 0.6
	0.3	18.4 ± 1.0	16.0 ± 0.8[a]
	1.0	18.6 ± 1.2	15.6 ± 0.4
	3.0	22.2 ± 1.4	17.7 ± 1.1[b]
Tolterodine	0.1	19.1 ± 1.0	18.0 ± 1.5
	0.3	19.4 ± 0.9	16.4 ± 1.3[b]
	1	18.7 ± 1.0	15.1 ± 0.2[b]
	3	19.0 ± 1.1	15.5 ± 0.6[b]
Propiverine	3	21.5 ± 1.4	20.0 ± 1.1
	10	20.3 ± 1.5	17.6 ± 0.8
Inaperisone	0.3	20.1 ± 1.0	20.3 ± 1.5
	1	20.3 ± 1.3	16.9 ± 0.9[a]
	3	19.6 ± 1.4	17.4 ± 1.3[a]
	10	20.4 ± 2.0	15.3 ± 1.5[a]

[a] $P < 0.05$; paired *t*-test.
[b] $P < 0.01$; paired *t*-test.

The structurally unique tachykinin NK_1 receptor antagonist, (±)-CP-99,994, qualitatively showed almost the same effect as TAK-637 with a minimum effective dose of 0.3 mg/kg, i.v. These results suggest that tachykinin NK_1 receptors are involved in the mechanism for micturition induced by bladder distension.

The micturition pressure was not altered by DMSO or saline alone: the pre-voiding pressure/post-voiding pressure was 18.7 ± 1.1/20.1 ± 1.2 mm Hg and 21.4 ± 2.1/20.6 ± 1.8 mm Hg, respectively (mean ± S.E.M.; $n = 8$). The voiding pressure was not affected by TAK-637 at any dose tested. On the other hand, the other anti-pol-

lakiuria agents, except for propiverine, significantly decreased the voiding pressure (Table 1). (±)-CP-99,994 significantly decreased the voiding pressure at a dose of 1.0 mg/kg, i.v.

3.2. Increasing effect on the volume threshold in unanesthetized guinea pigs

As the micturition reflex is sensitive to anesthetics, it is necessary to evaluate the effects of drugs in unanesthetized animals. The mean volume threshold before vehicle administration was between 0.42 ± 0.03 ml and 0.73 ± 0.07 ml (mean ± S.E.M.), and 1 h after vehicle administration, the mean volume threshold ranged from 0.54 ± 0.04 ml to 0.90 ± 0.07 ml (mean ± S.E.M.). TAK-637 significantly increased the volume threshold at more than 0.01 mg/kg, p.o. A ceiling effect was found, and the maximum effect was an about 130% increase in volume threshold (Fig. 3).

TAK-637 (0.03 mg/kg, p.o.) was rather long-acting as is shown in Fig. 4: the volume threshold was significantly increased up to 6 h after administration in comparison with the value in the vehicle-treated group.

Oxybutynin, propiverine and inaperisone significantly increased the volume threshold with minimum effective doses of 10 mg/kg, p.o.

3.3. Effect on the urethral pressure in urethane-anesthetized guinea pigs

Vehicle (DMSO, 0.05 ml/100 g, i.v.) itself had no effect on the urethral pressure: pre-pressure/post-pressure was 10.7 ± 1.3/10.4 ± 1.1 mm Hg (mean ± S.E.M.; n = 7).

For measurement of the increase in urethral pressure induced by α adrenergic stimulation, urethral pressure was

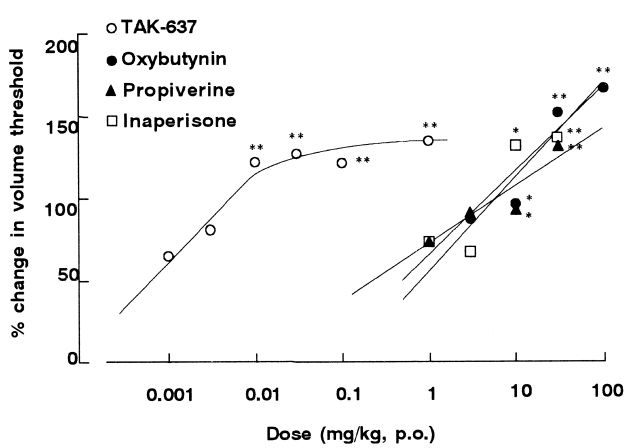

Fig. 3. The effects of various drugs on the volume threshold in unanesthetized guinea pigs. The percentage change in volume threshold was measured in each animal. Drugs were administered orally 60 min before the experiment. Each point represents the mean for 20 animals. The minimum effective dose (at $^{*}P < 0.05$; or $^{**}P < 0.01$; compared with vehicle-treated group; non-parametric Dunnett test) of each drug was as follows: TAK-637, 0.01 mg/kg; inaperisone, 10 mg/kg; oxybutynin, 10 mg/kg; and propiverine, 10 mg/kg.

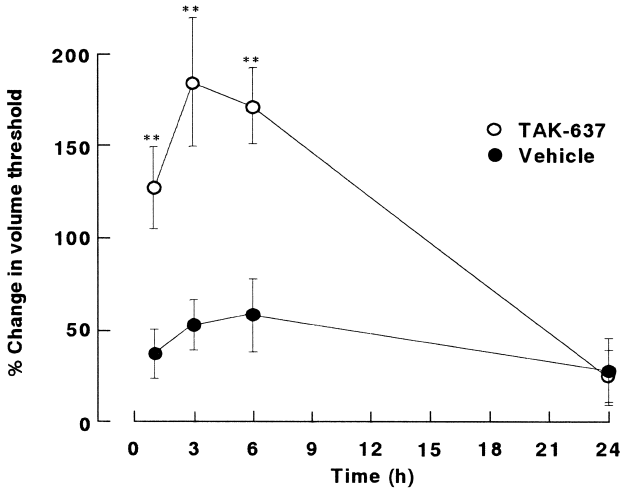

Fig. 4. The time course of the effect of TAK-637 at a dose of 0.03 mg/kg, p.o. The ordinate shows the mean percentage change in volume threshold. The abscissa shows the time after the administration of TAK-637. A significant increase in the volume threshold was observed from 1 to 6 h after administration. $^{**}P < 0.01$ vs. vehicle-treated group (t-test).

increased in a sustained fashion by continuous intravenous infusion of phenylephrine (9 μg/animal/min). In a pilot study, 20 min after the start of the infusion, the mean blood pressure and the urethral pressure were elevated from 49.0 ± 3.3 to 75.4 ± 2.1 mm Hg and from 13.9 ± 1.3 to 18.0 ± 1.8 mm Hg (mean ± S.E.M.; n = 5), respectively, and thereafter, the values were stable for up to 20 min. Measurement of the pre-control values was started 20 min after the beginning of the phenylephrine infusion, and then the test compound was administered intravenously. Postdrug values were measured 15 min after administration. DMSO (0.05 ml/100 g, i.v.) had no effect on the phenylephrine-induced increase in urethral pressure: pre-pressure/post-pressure was 17.9 ± 0.9/19.2 ± 1.3 mm Hg (mean ± S.E.M.; n = 7). TAK-637 (3 mg/kg, i.v.) had no significant effect on the basal urethral pressure: pre-pressure/post-pressure was 13.0 ± 1.6/12.0 ± 1.4 mm Hg (mean ± S.E.M.; n = 7). The phenylephrine-induced increase in urethral pressure was not affected by TAK-637 (3 mg/kg, i.v.) either: pre-pressure/post-pressure was 16.4 ± 1.0/16.0 ± 0.5 mm Hg (mean ± S.E.M.; n = 7). Tamsulosin (0.001 mg/kg, i.v.), an α_1-blocker (Honda et al., 1985), significantly reduced the pressure: pre-pressure/post-pressure was 20.7 ± 2.7/15.4 ± 1.6 mm Hg (mean ± S.E.M.; n = 10, $P < 0.05$, paired t-test).

4. Discussion

This study was the first to show that a tachykinin NK_1 receptor antagonist increases bladder volume upon systemic administration in guinea pigs, although intrathecal injection of tachykinin NK_1 receptor antagonists has been reported to inhibit the micturition reflex in rats (Lecci et al., 1992, 1993). Most studies on substance P have ad-

dressed the sensory events at the spinal level, especially in reference to pain (review; Otsuka and Yoshioka, 1993). The present experiments also addressed sensory processing, but in reference to micturition and not pain. Evidence has accumulated to show that substance P is involved in the sensory processing of the micturition reflex at the spinal level as follows. (1) Substance P-containing primary afferents have been found in the bladder with their terminals in the spinal dorsal horn at the level corresponding to the sacral micturition center (Jancsó and Maggi, 1987), and substance P binding sites are densely distributed there (Charlton and Helke, 1985; Yashpal et al., 1990). (2) Capsaicin-sensitive afferents play a role in regulating the sensory component of the micturition reflex, probably via substance P-containing afferents (Holzer-Petsche and Lembeck, 1984; Maggi and Conte, 1990). (3) Spinal intrathecal injection of tachykinin NK_1 receptor antagonists inhibits the micturition reflex (Lecci et al., 1992, 1993). (4) The sensory impulses induced not only by physiological stimuli (bladder distension) (Maggi et al., 1986), but also by chemical nociceptive stimuli (Maggi et al., 1984), cause micturiton. All this evidence suggests strongly that substance P-containing primary afferents arising from the bladder convey sensory information to secondary neurons in the spinal dorsal horn, probably via tachykinin NK_1 receptors (Lecci et al., 1992, 1993). Therefore, tachykinin NK_1 receptor antagonists should inhibit the micturition reflex by blocking the transmission of sensory messages from the bladder at the spinal cord level, which provides us with another type of anti-pollakiuria agent which is pharmacologically distinct from antimuscarinic and antispasmogenic drugs.

The tachykinin NK_1 receptor antagonist, TAK-637, showed characteristic effects on the cystometric parameters in anesthetized guinea pigs as compared with other drugs for pollakiuria or incontinence. TAK-637 increased the volume threshold without any substantial effect on voiding pressure. Voiding pressure itself is not necessarily equivalent to bladder muscle contractility under the present experimental conditions, because it depends on the balance of urethral pressure and bladder muscle contractility. However, TAK-637 seems to have no effect on the bladder muscle contractions, because it did not change the female guinea pig urethral pressure in the present study. As it was technically difficult to introduce the catheter into the bladder in male guinea pigs, female guinea pigs were used. Although the urethra of male and female guinea pigs might have pharmacologically or physiologically different characteristics, we have no information as to whether the pysiological functions of tachykinin NK_1 receptors are different in the two sexes. It seems reasonable to assume that TAK-637 has no effect on the urethral pressure of male guinea pigs either. Therefore, TAK-637 is considered to have no effect on the bladder muscle itself as was reported for high-dose capsaicin treatment in rats (Santicioli et al., 1985; Maggi et al., 1986). The structurally unique tachykinin NK_1 receptor antagonist, (±)-CP-99,994, also increased the volume threshold. Based on these results, the effect of TAK-637 is thought to be mediated via its tachykinin NK_1 receptor antagonistic effect. However, unlike TAK-637, (±)-CP-99,994 significantly decreased voiding pressure. This effect of (±)-CP-99,994 on voiding pressure can be explained by its affinity for the calcium channel (McLean et al., 1993).

Even if tachykinin receptors in the bladder are involved in the contraction of the bladder, they are probably tachykinin NK_2 receptors and not tachykinin NK_1 receptors (Giuliani et al., 1993; Bushfield et al., 1995; Zeng et al., 1995). It seems to be reasonable to assume that tachykinin NK_1 receptors in the bladder are not involved in the distension-induced bladder contractions. Tachykinin NK_1 receptors in the bladder are thought to be involved in inflammatory events such as plasma extravasation (Eglezos et al., 1991).

The present results support the idea that TAK-637 raised the volume threshold by acting on the sensory component of the micturition reflex; it blocked the sensory processing in the spinal cord in which substance P has been suggested to be involved (Lecci et al., 1993).

The anti-pollakiuria agents used in these experiments also increased the volume threshold, but they all decreased the voiding pressure at the same time, though the effect of propiverine was statistically non-significant. Therefore, it is safe to say that the mechanism by which TAK-637 increased the bladder capacity is quite different. This implies that TAK-637 could be a pharmacologically unique anti-pollakiuria agent.

In conscious animals, TAK-637 as well as the other drugs increased the volume threshold in a dose-dependent manner. A ceiling effect was observed in the dose–response curve of TAK-637. There are several possible explanations for this. For one, TAK-637 could have caused an increase in the residual urine volume by excessive inhibition of the micturition reflex at higher doses, resulting in an apparent decrease in volume threshold. However, this may not be the case, because there was no experimental evidence suggesting a decrease in voiding efficiency: TAK-637 did not decrease voiding pressure or increase urethral pressure. It is more likely that neurotransmitters or modulators other than substance P may also be involved in the sensory transmission from the primary afferents to the secondary neurons in the spinal dorsal horn (Birder and De Groat, 1992; Kakizaki et al., 1996) and substance P may play only a partial role in the sensory system. Indeed, intravenous administration of TAK-637 did not completely inhibit the micturition reflex at any dose tested.

The effective dose (0.01 mg/kg, p.o.) of TAK 637 was unexpectedly low in comparison with the one which could be estimated from the results in urethane-anesthetized animals, although the dose was quite comparable to the in vivo tachykinin NK_1 receptor-antagonistic-effective dose (ID_{50} = 33 μg/kg, p.o.) in guinea pigs (Natsugari et al.,

1999). The reason for this is not clear at the present time. However, animals with chronically implanted intravesical catherters can be regarded as a model of clinical detrusor hyperreflexia (Yaksh et al., 1986; Morikawa et al., 1989). In the present study, the mean voiding volumes in the conscious animals were on average about one half those for the animals in which chronic intravesical catheters had not been implanted, suggesting that something like detrusor overactivity was caused. It is highly conceivable that the bladder functions of the animals were not physiologically normal and that some inflammation-related pathological conditions might have been caused by the implanting of the chronic intravesical catheter. Increases in the density of tachykinin NK_1 receptors in the urinary bladder have been reported with interstitial cystitis in both animals (Buffington and Wofe, 1998) and humans (Marchand et al., 1998). In preliminary experiments, indomethacin, an analgesic, clearly increased the bladder capacity in conscious animals, but did not show an effect in urethane-anesthetized animals. Therefore, we might have to consider possibilities other than NK_1 receptor upregulation, that is, sensory activity from the bladder is so enhanced that sensory modulators such as analgesics and substance P antagonists are highly effective for amelioration. Therefore, the possibility that the animals had become highly sensitive to tachykinin NK_1 receptor antagonists should be taken into account. If this was the case, TAK-637 would be extremely useful for treating some types of detrusor overactivity caused by bladder irritability induced by inflammatory events like cystitis.

The etiologic factors of overactive bladder are not yet clearly understood. However, in part, increased afferent activity could possibly induce detrusor hyperreflexia (Moore et al., 1992). Intravesical capsaicin as well as resiniferatoxin are known to improve detrusor hyperreflexia in humans (Fowler et al., 1994; De Ridder et al., 1997; Lazzeri et al., 1997). If its mechanisms of action can be fully explained by desensitization of substance P-containing sensory unmyelinated C fibers from the bladder, TAK-637 would be an alternative for intravesical capsaicin treatment.

Taken together, the results of previous studies and the present study indicate that further study on TAK-637 is worthwhile in order to develop a new medicine which is effective for frequency and urge micturition and does not create voiding difficulties.

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