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Characterization of histamine receptors in the ureter of the dog

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Abstract

We investigated the effects of histamine on the motility of isolated segments from canine ureters and characterized pharmacologically the histamine receptors involved. We also evaluated the effects of various autacoids (5-HT, carbachol, noradrenaline, thromboxane, prostaglandin $F_{2\alpha}$) on the motility of canine ureters. Histamine as well as the H_1 receptor agonist 2-(2-pyridyl)ethylamine elicited a concentration-dependent contraction. This contractile response was antagonized by dimethindene, causing a rightward shift (pA_2 8.30) and a reduction of the slope and the maximal effect (pD'_2 6.01) of the concentration-response curve. The histamine H_2 receptor antagonist cimetidine in a concentration of 10^{-5} mol/l was ineffective concerning the concentration-response curve for histamine. After precontraction of the ureter segments (5-HT, carbachol, prostaglandin $F_{2\alpha}$), a concentration-dependent relaxant effect was evaluated in the presence of histamine or the histamine H_2 receptor agonist impromidine. The histamine H_2 receptor antagonist cimetidine attenuated the relaxant response, causing a rightward shift of the concentration-response curve. All autacoids except thromboxane were capable of increasing contractility in canine ureters. Comparing the absolute contractile force in the presence of prostaglandin $F_{2\alpha}$, 5-HT, carbachol, noradrenaline and potassium, we found that histamine exhibits the most marked effect on this parameter in the canine ureter. It is concluded that there are two types of histamine receptors modulating contractile activity in the canine ureter: histamine H_1 receptors, which mediate contraction, and histamine H_2 receptors, which mediate relaxation (in the precontracted tissue).

Keywords: Ureter; Histamine receptor; Histamine H_1 receptor; Histamine H_2 receptor; 5-HT (5-hydroxytryptamine, serotonin); Prostaglandin; Noradrenaline

1. Introduction

Histamine receptors are widely distributed in animal organs and tissues (Hill, 1990; Schwartz and Haas, 1992). By means of their pharmacological sensitivity, three distinct subtypes of receptors (1 through 3) have been identified, for which specific agonists and antagonists as tools for their classification are available (Arrang et al., 1987; Casy, 1991; Van der Goot and Bast, 1991). Only recently the molecular structure of the histamine H_1 receptor as well as of the histamine H_2 receptor has been elucidated (Ruat et al., 1991; Yamashita et al., 1991). Both histamine receptors are G-protein coupled (Ruat et al., 1994); the H_3 receptor is probably linked to a GTP regulatory protein as well (Endou et al., 1994; Schlicker et al., 1994).

The effects mediated by histamine H_1 receptors comprise a large variety of actions affecting the cardiovascular system (Borchard and Hafner, 1986; Levi et al., 1991), extravascular smooth muscle and the nervous system (Schwartz and Arrang, 1991). Histamine H_2 receptors are present in the cardiovascular system (Endou and Levi, 1995), in the gastrointestinal tract, in the lung (Barnes, 1989; Foreman, 1991) and in the nervous system (Pollard and Schwartz, 1987). The actions mediated by the histamine H_3 receptor are closely related to nervous tissue as it is described as a presynaptic receptor on histaminergic and non-histaminergic neurons of the central and autonomic nervous system (Arrang et al., 1992; Schlicker et al., 1994). Activation of the receptor regulates histamine release, formation and turnover in nerve cells, but also inhibits the release of several other neurotransmitters (noradrenaline, acetylcholine, 5-HT, dopamine, etc.). Apart from their role in the central nervous system, there is evidence for the involvement of histamine H_3 receptors in the functions of the heart (Göthert et al., 1995), lung (Cardell and Edvinsson, 1994), the vascular system (Ea-Kim and Oudart, 1988; Trzeciakowski, 1987) and the digestive system (Bertaccini and Coruzzi, 1995; Ishikawa and Sperelakis, 1987).

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In the genito-urinary tract, histamine is one among several autacoids that possess potent physiological properties (Adaikan and Karim, 1991; Anderson, 1993). Immunological reactions can stimulate histamine release from mast cells and basophils, causing abnormalities ranging from ureter dilatation and diminished peristalsis to vesicoureteric reflux or obstruction. In respect to histamine, H_1 as well as histamine H_2 receptors have been described in vertebrates (Fredericks, 1975; Imaizumi et al., 1989; Kondo et al., 1985; Naik et al., 1979; Poli et al., 1987; Reimann et al., 1984; Rubinstein et al., 1987; Taniyama et al., 1984). Contractile effects are attributed to an activation of histamine H_1 receptors in the ureter, the bladder, the urethra and the vas deferens of different species, whereas relaxant effects may involve the actions of histamine H_2 receptors alone or together with histamine H_1 receptors. Data on the presence and functions of the histamine H_3 receptor subtype on (autonomic) nerve terminals of the genito-urinary tract are thus far preliminary (Poli et al., 1994; Vassilev et al., 1991).

The present investigation was designed to study the effects of histamine on motility and to obtain evidence for the presence of histamine H_1 and H_2 receptors in the canine ureter. Furthermore we characterized the effects of several autacoids (5-HT, noradrenaline, carbachol, prostaglandin $F_{2\alpha}$, thromboxane) in comparison to histamine in the ureter of the dog.

2. Material and methods

The experiments were performed on isolated preparations of the ureter from adult dogs. After killing of the animal, both ureters were immediately removed, cleaned of adhering tissue and six ureteral strips measuring approximately 20×3 mm were prepared. Each of them was mounted vertically on a tissue holder and suspended in a 10 ml bath filled with 'Krebs-Henseleit' solution, consisting of (mmol/l): NaCl 118.5, KCl 4.7, $CaCl_2$ 1.8, $MgSO_4$ 1.2, $NaHCO_3$ 25.0, NaH_2PO_4 1.2, glucose 10.1, sodium pyruvate 2.0. The pH and the temperature of the bath solution were maintained at 7.40 and 35°C respectively and the bath solution was continuously oxygenated with a gas mixture of 95% O_2 and 5% CO_2. The organ preparations were connected by twine to a force-displacement transducer (Statham UCII, Gould Advance, USA) and isometric force development was recorded after amplification on an ink-writing recorder (Hellige, Germany). All strips were initially stretched to 10 mN and allowed to accommodate to this length and to the bath milieu for at least 60 min before experiments were begun. Some of the ureteral preparations developed spontaneous contractions whereas others were devoid of spontaneous activity (Yamaguchi, 1991). The present study was carried out using ureteral preparations with no spontaneous activity.

Phentolamine (10^{-7} mol/l) and pindolol (3×10^{-7} mol/l) were added to the bath solution before experiments in the presence of histamine were started to exclude indirect effects of transmitters on α- and β-adrenoceptors released by histamine from presynaptic stores. The agonists were added by cumulative administration in 0.5 log units. The concentrations are given as final molar concentrations in the bath solution.

2.1. Characterization of contractile responses to histamine

Cumulative concentration-response curves for histamine were obtained in the absence and in the presence of the specific histamine H_2 receptor antagonist cimetidine (3×10^{-5} mol/l; incubation time: 30 min) to exclude a histamine H_2 receptor-dependent influence on the contractile response.

Cumulative concentration-response curves for histamine in the absence and in the presence of the specific histamine H_1 receptor antagonist dimethindene (3×10^{-9}–3×10^{-5} mol/l; incubation time: 30 min) were registered. In order to attribute the contractile activity to a specific histamine receptor subtype, we investigated the effect of the specific histamine H_1 receptor agonist 2-(2-pyridyl)ethylamine.

Because tachyphylaxis developed while a second cumulative response curve was being made, preparations from the same animal were compared in each individual experiment, with at least two segments serving as control.

2.2. Characterization of relaxant responses to histamine and impromidine

In order to establish a contribution to the relaxant response of stimulation of the histamine H_2 receptor, it was necessary to precontract the tissue (Tayo and Bevan, 1986). A fixed dose of several agonists was used to induce contraction of the isolated strips of the ureter of the dog: KCl (3×10^{-2}, 4×10^{-2} mol/l, 8×10^{-2} mol/l), 5-HT (10^{-4} mol/l), prostaglandin $F_{2\alpha}$ (10^{-6} mol/l), carbachol (2.5×10^{-4} mol/l), and noradrenaline (10^{-4} mol/l). Due to a short-lived contraction burst, no relaxation curve for impromidine could be evaluated after application of potassium (Jennings et al., 1995) in the concentrations described above. This short-lived contraction is in contrast with previous publications (Sakanashi et al., 1985). The contractile response to the other substances was stable for the duration necessary to perform the experiments as demonstrated in separate control experiments.

2.3. Effect of 5-HT, prostaglandins and other substances

Cumulative concentration-response curves were obtained in the presence of 5-HT (3×10^{-8}–3×10^{-4} mol/l), thromboxane (10^{-10}–10^{-7} mol/l), prostaglandin $F_{2\alpha}$ (10^{-9}–3×10^{-4} mol/l), carbachol (data not shown) and noradrenaline (data not shown) in order to quantify the effect on the canine ureter.

2.4. Data analysis

In the presence of the histamine H_1 receptor antagonist dimethindene a shift of the cumulative concentration-response curve was observed, indicating competitive antagonism. In order to quantify the amount of competitive antagonism and thereby to analyze the affinity for histamine H_1 receptors we used the pA_2 values. According to Van den Brink (1977) these were calculated as:

$$pA_2 = -\log[B] + \log\left(\frac{[A_2]}{[A_1]} - 1\right)$$

where [B] is the concentration of the antagonist, $[A_1]$ EC_{50} of the agonist in the absence of the antagonist and $[A_2]$ EC_{50} of the agonist in the presence of the antagonist.

The pA_2 value is defined as the negative logarithm of the concentration of an antagonist which causes a shift of the cumulative concentration-response curve to the right by a factor of 2.

However, not only competitive antagonism in the presence of dimethindene was observed. In addition dimethindene (Reinhardt and Borchard, 1982) reduced the slope and the maximum response of histamine concentration-response curves, depending on the concentration used. This indicates an additional non-competitive antagonism. To quantify this non-competitive antagonism we calculated the pD'_2 values according to Van den Brink (1977):

$$pD'_2 = -\log[B] - \log\left(\frac{E_{A_{max}}}{E_{A_{max}} - E_{A_{max\,B}}} - 1\right)$$

where [B] is the concentration of the antagonist, $E_{A_{max}}$ the maximal effect of the agonist in the absence of the antagonist and $E_{A_{max\,B}}$ the maximal effect of the agonist in the presence of the antagonist.

The pD'_2 value is equal to the negative logarithm of the concentration of an antagonist which causes a reduction of the maximum response by a factor of 2. EC_{50} values were calculated from the concentration-response curves by use of the logit analysis procedure (Ashton, 1972; Hafner et al., 1977; Kenakin, 1987). Results in the text are expressed as mean values ± S.D.. Significance levels for the difference between two groups were analyzed by the use of Student's t test. A P value of 0.05 or less was considered statistically significant.

2.5. Drugs

The following drugs were used: histamine dihydrochloride (Merck, Germany), 2-(2-pyridyl)ethylamine (SK&F, UK), dimethindene (Zyma, Germany), impromidine (SK&F), cimetidine (Sigma, Germany), prostaglandin $F_{2\alpha}$ (Serva, Germany), thromboxane (U46619; Upjohn, USA), carbamoylcholine hydrochloride (carbachol, Merck), KCl (Merck), phentolamine (Ciba Geigy, Germany), pindolol (Sandoz, Germany), L-noradrenaline Arterenol (Hoechst, Germany).

All drugs except dimethindene were dissolved in distilled water before being added to the bath solution. Dimethindene was dissolved in ethanol. The vehicle did not affect the results, as demonstrated in separate control experiments.

3. Results

3.1. Characterization of contractile responses to histamine

Histamine in the range of 10^{-7} mol/l–3×10^{-3} mol/l induced a concentration dependent contraction of the ureteral segments (Fig. 1), the response being maximal at 3×10^{-3} mol/l (EC_{50}: $4.97 \times 10^{-5} \pm 1.03 \times 10^{-5}$ mol/l). The histamine H_2 receptor antagonist cimetidine in a concentration of 3×10^{-5} mol/l was ineffective against the amine (Fig. 1). However, the contractile response of the tissue to histamine was significantly antagonized in the presence of increasing concentrations of dimethindene (3×10^{-9}–3×10^{-5} mol/l) as indicated by a rightward shift of the concentration-response curve. The rightward displacement of the concentration-response curve was used in a Schild analysis (Van den Brink, 1977). The concentration ratios for dimethindene yielded a line with a slope of 0.89 with a corresponding (pA_2) value of 8.30. In addition dimethindene reduced the slope and the maximum response of the concentration-response curve for histamine (pD'_2 value: 6.01; Fig. 2).

Pyridylethylamine, a relatively selective agonist for the histamine H_1 receptor subtype, induced a concentration-dependent contraction similar to histamine but was about six times less potent by comparing EC_{50} values (EC_{50}: $2.95 \times 10^{-4} \pm 0.54 \times 10^{-4}$ mol/l; Fig. 3) and achieved only 73% of the maximal effect of histamine (Fig. 6).

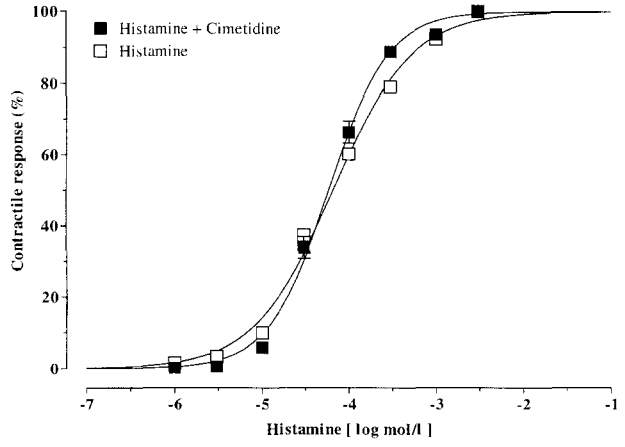

Fig. 1. Concentration-response curves for histamine (10^{-7}–10^{-3} mol/l) on the canine ureter in the absence (□, $n = 30$) and in the presence (■, $n = 11$) of 3×10^{-5} mol/l of cimetidine. The concentration-response curves were individually normalized to 100%.

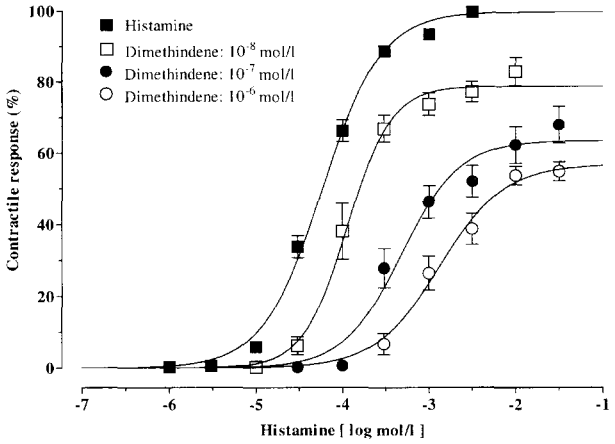

Fig. 2. Suppression of the maximal effect of the concentration-response curve for histamine in the absence (■, $n = 11$) and in the presence of the histamine H_1 receptor antagonist dimethindene (10^{-8} mol/l (□, $n = 8$), 10^{-7} mol/l (●, $n = 8$), 10^{-6} mol/l (○, $n = 6$)) on the canine ureter. Dimethindene induced a reduction of the slope and a suppression of the maximum response. The concentration-response curves were plotted as percentage of the maximal effect of control.

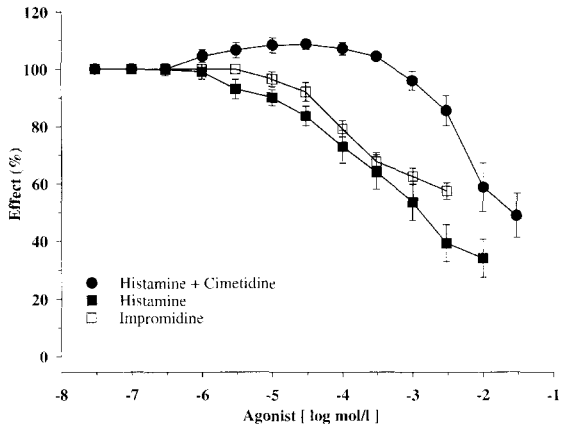

Fig. 4. Relaxation of ureteral segments precontracted with 5-HT (10^{-4} mol/l) in the presence of impromidine (3×10^{-6}–3×10^{-2} mol/l; □, $n = 5$), histamine (3×10^{-7}–10^{-2} mol/l; ■, $n = 9$) and histamine plus cimetidine (3×10^{-7}–3×10^{-2} mol/l; ●, $n = 6$). Cimetidine was added in a concentration of 3×10^{-5} mol/l. Responses are expressed as a percentage of 5-HT-induced contractions. In all experiments dimethindene (10^{-5} mol/l) was present.

3.2. Characterization of relaxant responses to histamine and impromidine

Histamine may cause a concentration-dependent relaxation of precontracted tissue preparations. The relaxant effects of histamine were studied after precontraction with a single dose of either 5-HT (10^{-4} mol/l) or carbachol (2.5×10^{-4} mol/l) or prostaglandin $F_{2\alpha}$ (10^{-6} mol/l).

Histamine as well as the histamine H_2 receptor agonist impromidine (Buschauer, 1988; Durant and Duncan, 1983) induced a concentration-dependent relaxation of the precontracted tissue. In 5-HT precontracted ureteral segments, histamine (10^{-7}–10^{-2} mol/l) and impromidine (10^{-7} mol/l–3×10^{-4} mol/l) elicited a reduction to 38.40 ± 2.60% and 57.50 ± 1.90% of the maximal contractile response, respectively (Fig. 4).

When the histamine H_2 receptor antagonist cimetidine (10^{-5} mol/l) was added to the bath solution a biphasic effect could be observed: low concentrations of histamine induced a small contractile response, followed by a relaxant effect at higher concentrations. The relaxation following stimulation with histamine was significantly attenuated in the presence of cimetidine (Fig. 4).

The dilator response to impromidine in prostaglandin $F_{2\alpha}$- and carbachol-precontracted tissue was less pronounced than that for 5-HT. In carbachol-precontracted tissue impromidine (10^{-7}–3×10^{-4} mol/l) reduced the maximal contractile response to 60.30 ± 5.30%. In the presence of prostaglandin $F_{2\alpha}$ a reduction to 72.90 ± 0.80% took place following the application of impromidine (10^{-7}–3×10^{-4} mol/l).

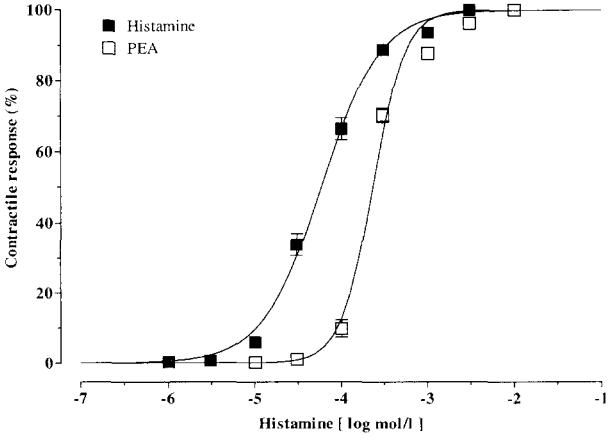

Fig. 3. Concentration-response curve of histamine (10^{-7}–10^{-3} mol/l; ■, $n = 11$) and of the histamine H_1 receptor agonist pyridylethylamine (PEA) (10^{-6}–10^{-2} mol/l; □, $n = 11$) on the ureter of the dog. The concentration-response curves were individually normalized to 100%.

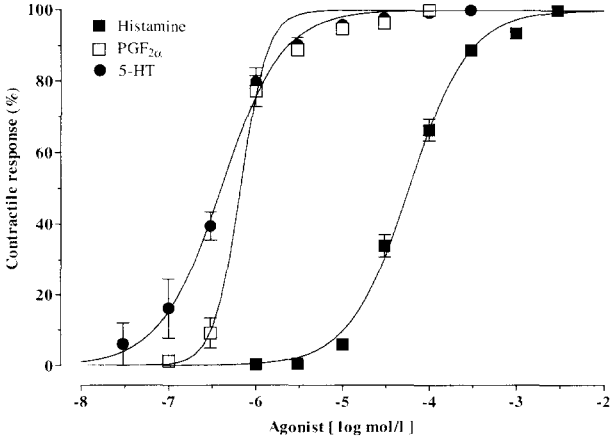

Fig. 5. Concentration-response curve of 5-hydroxytryptamine (3×10^{-8}–3×10^{-4} mol/l; ●, $n = 5$), prostaglandin $F_{2\alpha}$ (10^{-9}–3×10^{-4} mol/l; □, $n = 6$) and histamine (10^{-7}–10^{-3} mol/l; ■, $n = 11$) on the canine ureter. The concentration-response curves were individually normalized to 100%.

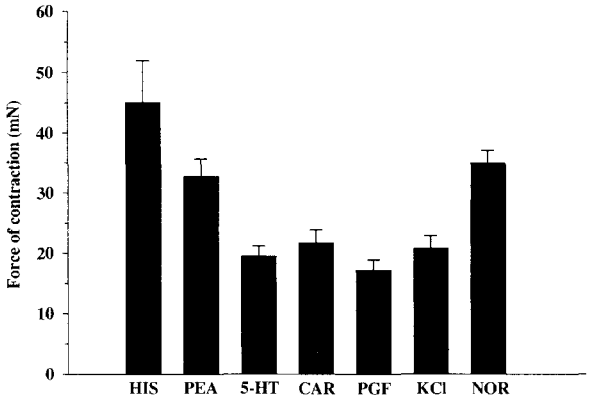

Fig. 6. Comparison of the absolute contractile response of the canine ureter in the presence of different agonists. The contractile response in mN. Histamine (HIS; 3×10^{-3} mol/l, $n = 11$): 45.1 ± 6.9 mN; pyridylethylamine (PEA; 10^{-2} mol/l, $n = 11$): 32.8 ± 2.9 mN; 5-HT (5-HT; 10^{-4} mol/l, $n = 5$): 19.5 mN ± 1.7 mN; carbachol (CAR; 2.5×10^{-4} mol/l, $n = 6$): 21.7 ± 2.2 mN; prostaglandin $F_{2\alpha}$ (PGF; 10^{-6} mol/l, $n = 6$): 17.2 ± 1.7 mN; KCl (KCl; 8×10^{-2} mol/l, $n = 6$): 20.8 ± 2.1 mN; L-noradrenaline (NOR; 10^{-4} mol/l, $n = 6$): 35.0 ± 2.1 mN.

3.3. Effect of 5-HT, prostaglandins and other substances

5-HT, known as a potent agonist of the smooth muscle of the gastrointestinal tract, elicited concentration-dependent contractions of the smooth muscles of the ureter (Fig. 5), which were found maximal at a concentration of 10^{-4} mol/l (EC_{50} value: $4.90 \times 10^{-7} \pm 0.39 \times 10^{-7}$ mol/l).

Stimulation with prostaglandin $F_{2\alpha}$ (10^{-9}–3×10^{-4} mol/l) caused also a concentration-dependent contraction of the ureter, resulting in an EC_{50} value of $6.82 \times 10^{-7} \pm 0.28 \times 10^{-7}$ mol/l (Fig. 5). In our study the thromboxane analogue U46619 (Hernández et al., 1995) showed no effect on the canine ureter in the concentrations investigated (10^{-10}–10^{-7} mol/l).

Comparing EC_{50} values obtained in the presence of histamine, we found 5-HT (prostaglandin $F_{2\alpha}$) to be about 100 (70) times more effective than histamine itself. Nevertheless, the maximal absolute contractile response to 5-HT and prostaglandin $F_{2\alpha}$ and the other investigated substances was less marked than that to histamine. Fig. 6 compares the results concerning the absolute contractile force of the different spasmodic agents used in this study. We found histamine (100%) to be the agonist with the highest intrinsic activity, whereas 5-HT (43%; $n = 5$), carbachol (48%; $n = 6$), KCl (46%; $n = 6$) produced only a half-maximal contractile effect compared with that observed in the presence of histamine. L-Noradrenaline (Muraki et al., 1994) exhibited 78% of the response to histamine.

4. Discussion

The present results confirm previous data (Bertaccini et al., 1983; Chen et al., 1957; Khanna et al., 1977) showing that histamine may play an important role in physiological and pathophysiological conditions in the genito-urinary tract (Lennon et al., 1993). We found that histamine mediates a dual effect in the ureter of the dog, which can be attributed to the two histamine receptor subtypes. The histamine-mediated contraction seems to be related with excitation of the histamine H_1 receptor subtype. This is supported by the dimethindene-induced rightward shift of the concentration-response curve. The slope of 0.89 is yet in accordance with competitive antagonism at one receptor site and the dissociation constant value (pA_2) of 8.30 corresponds with those found in histamine receptor subtype characterization carried out previously (Reinhardt and Borchard, 1982). Additionally, the histamine H_1 receptor agonist pyridylethylamine induced a concentration-dependent contraction of the ureteral tissue. Pyridylethylamine is known as a selective agonist of the histamine H_1 receptor subtype but its affinity for the receptor is smaller than that of histamine. The activity of pyridylethylamine has been reported to be about 6% of that of histamine (Ganellin, 1982; Zingel et al., 1995). In our study pyridylethylamine was about 6 times less effective than histamine when comparing EC_{50} values. The finding that pyridylethylamine mimics the histaminergic effect supports the notion of H_1 receptors in the canine ureter. Histamine H_1 receptor-mediated contractions have been detected in certain parts of the genitourinary tract as well as in other tissues (Cardell and Edvinsson, 1994; Jennings et al., 1995).

In several different tissue preparations it has been reported that a precontraction of smooth muscles may disclose a histamine relaxant effect, which implies mainly histamine H_2 receptors (Dachman et al., 1993; Jennings et al., 1995; Muller et al., 1993; Tayo and Bevan, 1986). Depending on the species and the tissue investigated, a co-activation involving the histamine H_1 receptor subtype may also be found, especially, if an endothelium-dependent relaxation occurs (Beyak and Vanner, 1995; Satoh and Inui, 1984; Webber et al., 1988).

In the ureter, histamine induced a concentration-dependent relaxation of the precontracted tissue. This effect was mimicked by the histamine H_2 receptor agonist impromidine, but not in the presence of the histamine H_1 receptor agonist pyridylethylamine (data not shown). However, histamine was not able to completely abolish the contractile effect seen in the presence of 5-HT, prostaglandin $F_{2\alpha}$ or carbachol: a maximal relaxant response of 62% was found in the canine ureter, which is in accordance with effects found in other tissue preparations (Poli et al., 1994).

The presence of a histamine H_2 receptor-mediated dilator response is further supported by the effects in response to cimetidine. Cimetidine caused a concentration-dependent rightward shift of the (relaxant) concentration-response curve for histamine. In basal conditions, however, the histamine H_2 antagonist cimetidine did not alter significantly the (contractile) concentration-response curve for

histamine. Thus, histamine H_1 receptor-mediated effects seem to be the result of activation of histamine receptors located on smooth muscle cells.

The response to histamine H_2 receptor stimulation is not as clear. In basal conditions we were not able to detect a histamine H_2 receptor-dependent effect in the canine ureter. Only in precontracted tissue an effect, which involved histamine H_2 receptors, was disclosed. An explanation for this observation may involve affinity or quantity differences for histamine receptors, or activation of ureter neurons which may reduce neuronal discharge or release inhibitory relaxatory compounds, which in turn act on smooth muscles. In recent years a specialized action of histamine, resulting in activation of the enteric nervous system as well as other autonomic ganglia (Frieling et al., 1993; Poli et al., 1994; Wood, 1992), has become evident, which may account for this observation. A concluding comment on this topic is thus far not possible.

The importance of prostanoids in the regulation of the genito-urinary tract has attracted considerable interest in recent years (Al-Ugaily et al., 1986; Cole et al., 1988; Kaygisiz et al., 1995; Thulesius and Angelo-Khattar, 1985; Wooster, 1970). Prostanoids are synthesized locally in the renal pelvis, ureter and bladder and are released by various stimuli. In the ureter, prostaglandins of the E, F, I type as well as thromboxane are synthesized, but to less extent than in other preparations (Zwergel et al., 1991). Several investigators have shown that prostaglandin $F_{2\alpha}$ causes contraction of ureteral preparations, whereas prostaglandins of the E type reduce contractile force (Morita et al., 1994a,b; Thulesius and Ugaily-Thulesius, 1986). These results are in contrast to the findings of Vermue and Den Hertog (1987), who reported that prostaglandins of the F type have no effect on phasic contraction and muscle tone. In our study prostaglandin $F_{2\alpha}$ enhanced markedly contractile force and contractile frequency in canine ureters, while prostaglandin E (data not shown) reduced contractions of the canine ureter. Although thromboxane is synthesized in the genito-urinary tract, we found no effect on the canine ureter, neither under basal nor under precontracted conditions. In the intravesical part of the pig ureter a sustained contraction was reported with the thromboxane analogue U46619 (Hernández et al., 1995).

The physiologic effects of prostanoids in the ureter and the urinary system are not completely understood, but the results so far available suggest a role as modulator of efferent neurotransmission.

5-HT has potent contractile effects in the gastrointestinal system (Woollard et al., 1994) as well as on various parts of the genito-urinary tract, involving 5-HT_1-like receptors, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors (Hoyer et al., 1994). In addition, inhibitory effects due to an interaction with 5-HT_1-like receptors (Corsi et al., 1991) or 5-HT_4 receptors (Waikar et al., 1994) have been found in the bladder of different species. In our experiments 5-HT induced a marked increase of the muscular tone as well as a marked enhancement of the rhythmic contractions of the canine ureter. This is in accordance with previous results (Klarskov and Horby-Petersen, 1986; Saxena et al., 1985). Studies which characterize receptor subtypes involved in the effect of 5-HT on the ureter are scarce (Gidener et al., 1995) as is knowledge of their function in physiological and pathophysiological pathways in the genito-urinary tract. Saxena et al. (1985) suggested that the response to 5-HT may involve direct actions on smooth muscle cells as well as indirect actions on the autonomic innervation.

In conclusion, we have been able to demonstrate that the ureter of the dog possesses two types of histamine receptor. The effect of histamine results in a contractile response mediated via the H_1 receptor, an effect which at high concentrations probably becomes attenuated via the activation of histamine H_2 receptors. The importance of histamine concerning the modulator function on ureteral activity is further supported by its prominent effect on the contractility compared to the effect of other substances as prostaglandins, noradrenaline, carbachol, K^+ and 5-HT. Histamine exhibits the most marked effect on this parameter in the canine ureter.

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