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Effects of ketanserin and DOI on spontaneous and 5-HT-evoked peristalsis of the pig ureter *in vivo*

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1 The influence of 5-hydroxytryptamine (5-HT) receptor agonists and antagonists on the ureter motility was investigated *in vivo* on intact ureters of anaesthetized pigs. Drugs were administered intravenously or topically.

2 5-HT induced a dose-dependent increase in the frequency of ureter contractions in anaesthetized pigs when given intravenously (0.0001–1 mg kg^{-1}; ED_{50} 0.066 mg kg^{-1}) or topically (0.001–1 mg ml^{-1}; EC_{50} 0.043 mg ml^{-1}). Significant increases in heart rate and blood pressure were observed when the drug was given intravenously but not topically.

3 The 5-HT_{2A} agonist, DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane) increased the frequency of ureteral contractions in a dose-dependent manner (1–300 μg kg^{-1} i.v.). Calculation of ED_{50} indicated this compound to be about 1.5 times more potent with an efficacy of 23% compared to 5-HT.

4 The 5-$HT_{2A/2C}$ antagonist, ketanserin (0.5 mg kg^{-1}) and the 5-HT_{2C} antagonist, methysergide (1 mg kg^{-1}) antagonized the 5-HT-induced ureter peristalsis when given intravenously. Contraction amplitude, blood pressure and heart rate were not affected by the antagonists.

5 Intravenous (0.0001–1 mg kg^{-1}) and topical (0.0001–1 μg ml^{-1}) ketanserin significantly decreased the frequency of spontaneous ureteral contractions to about 30% of controls, which could be partly reversed by 5-HT (0.3 mg kg^{-1} i.v.). The contraction amplitude, contractions of the contralateral, saline perfused ureter, heart rate and mean arterial blood pressure were not affected.

6 Thus, contractility of porcine ureter is mediated by 5-HT_2 receptors. Their antagonists ketanserin and methysergide seem to be promising drugs for treatment of acute ureteric colic or in preparing the ureter for ureteroscopy.

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Abbreviations: DAU 6285, *endo*-8-methyl-8-azabicyclo [3.2.1] oct-3-yl-2,3-dihydro-6-methoxy-2-oxo-1H-benzimidazole-1-carboxylate HCl; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; EC, effective concentration; ECG, electrocardiogram; ED, effective dose; 5-HT, 5-hydroxytryptamine

Introduction

So far a wide variety of 5-hydroxytryptamine (5-HT) receptors and their subtypes have been characterized in different tissues and the nomenclature for 5-HT receptors has undergone a considerable evolution during the past ten years, principally in response to a rapidly expanding database of information concerning structure and function at the molecular level. According to the current opinion there are seven main classes of 5-HT receptors and some of these groups comprise multiple receptor subtypes: 5-HT_1 (1A, 1B, 1D, 1e, 1f), 5-HT_2 (2A, 2B, 2C), 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, 5-HT_7 (Martin, 1998). It should be noted that receptors previously labelled 5-HT_1-like are a heterogeneous population of 5-HT_{1B}, 5-HT_{1D} and 5-HT_7 receptors (Saxena *et al*., 1998).

5-HT is well known to induce ureteral contractions in isolated ureter preparations from different species (Hertle & Nawrath, 1986; Dodel *et al*., 1996; Kuwahara, 1983; Long & Nergardh, 1978; Gidener *et al*., 1995; 1999; Benzi *et al*., 1970; Iselin *et al*., 1997) and *in vivo* (Abrahams & Pickford, 1956; Catacutan-Labay *et al*., 1966; Boatman *et al*., 1967). Nevertheless it is still unclear which 5-HT receptor subtype is responsible for the stimulating effect and whether 5-HT is physiologically involved in ureter motility. Long & Nergardh (1978) demonstrated that 5-HT evoked a concentration-dependent increase of contractions in isolated human ureter strips which could be blocked by methysergide, a mixed 5-$HT_{1/2A/2C}$ receptor antagonist. In accordance with these results other authors reported an inhibition of 5-HT-evoked contractions on human ureter *in vitro* by methysergide and the 5-$HT_{2A/2C}$ receptor antagonist ketanserin that also interacts with α-adrenergic and histaminergic receptors (Gidener *et al*., 1995; Leysen *et al*., 1981). However, the effect of 5-HT was unaltered after blocking 5-HT_3 and 5-HT_4 receptors and cholinergic muscarinic receptors (Gidener *et al*., 1995). In a more recent work of Gidener *et al*. (1999), 5-HT-evoked contractions on

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human ureter strips could be antagonized by ketanserin. In addition, combined administration of the 5-HT$_4$ receptor antagonist DAU 6285 and the 5-HT$_3$ receptor antagonist ondansetron caused a rightward shift of the cumulative concentration-response curve of 5-HT. Given individually, the 5-HT receptor antagonists methiothepin with higher affinity to 5-HT$_7$ than to 5-HT$_{1A}$, ondansetron and DAU 6285 were unable to antagonise the contractions evoked by 5-HT. In a recently published work 8-hydroxy-2-(n-dipropyl-amino)tetralin HBr (8-OH-DPAT; 5-HT$_{1A/7}$ receptor agonists), sumatriptan (5-HT$_{1B/1D}$ receptor agonist), 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI; 5-HT$_{2A/2C}$ receptor agonist), 2-methyl 5-HT (5-HT$_3$ receptor agonist) and renzapride (5-HT$_4$ receptor agonist) all failed to induce a contractile response, whereas 5-carboxyaminotryptamine maleate (5-CT; 5-HT$_{1A/1B}$ receptor agonist) evoked contractions on isolated human ureter specimens (Gidener *et al*., 1999).

In vivo studies on the ureteral effects of 5-HT were reported about 40 years ago, and information is available from *in vitro* studies, including human tissues using subtype specific 5-HT receptor agonists and antagonists. However, the later results were not yet confirmed *in vivo*. The purpose of this study was to investigate the effects of 5-HT and the 5-HT$_{2A/2C}$ receptor agonist DOI and the 5-HT$_2$ antagonists ketanserin and methysergide on porcine ureter motility *in vivo*, a model in which the regulation of motility by adrenoceptors has been investigated extensively (Danuser *et al*., 2001).

Methods

Experimental design: in vivo

Thirty-two male and female pigs (18 – 30.5 kg) were anaesthetized with thiopental (8 mg kg^{-1} i.v.) after premedication with ketamine (10 mg kg^{-1} body weight i.m.), xylazine (2 mg kg^{-1} i.m.) and atropine (0.05 mg kg^{-1} i.v.). Endotracheal intubation was then performed and anaesthesia was maintained with halothane ($0.5 \pm 0.05\%$, end tidal concentrations) in nitrous oxide-oxygen (ratio 2 : 1). As previously described (Danuser *et al*., 2001), one catheter was inserted into the carotid artery to measure arterial blood pressure, and another catheter was placed into the jugular vein to administer infusions and drugs. A double lumen 6-french catheter was inserted through the animal's lateral abdominal wall into each renal pelvis. One lumen was placed in the renal pelvis allowing perfusion of the upper urinary tract, the other lumen was placed in the mid-portion of the ureter to measure intraluminal pressure. Contractions in both ureters, arterial blood pressure and heart rate (ECG) were recorded using a Hellige recording system (SMU 611, Freiburg, Germany).

Perfusion with saline 0.5 ml min^{-1} of each ureteropelvic unit was performed for 30 min to assess base line frequency and amplitude of ureteral contractions. These served as controls in experiments with topical drug application. In experiments with intravenous drug administration an intravenous bolus of the solvent was administered to determine control values. Then successively higher doses of drug solution were administered every 5 min. In experiments with topical drug application the ureters were perfused with a rate of 0.5 ml min^{-1}. One ureter was perfused with increasing concentrations of drug solutions every 10 min and the contralateral ureter was perfused with saline. Frequency and amplitude of ureteral contractions were analysed during the first 5 min after the intravenous injection of the drug and in experiments with topical drug application from minute 5 to 10 after beginning of the perfusion.

Data analysis

A repeated measures analysis of variance (ANOVA) was used for an overall analysis of the data (expressed as percentage inhibition or stimulation of control (NaCl) or 5-HT-evoked response). Subsequently, a one-way ANOVA was run at each time point to compare treatments. Paired contrasts were adjusted for multiple comparisons using the Dunnett procedure (Dunnett, 1955).

Concentration-response curves were calculated from the log concentration-effect curves using a Hill equation and estimation *via* least squares method (MatLab Simulation Software, Release 12, The MathWorks, Inc., Cambridge, MA, U.S.A., 2000). The underlying equation for Hill function is: $\text{Response} = V_m \cdot C^{nH} \cdot (C^{nH} + K^{nH})^{-1}$ where V_m is the maximal attainable response, K is the half-effective concentration (EC_{50}, i.e. the concentration yielding half of the maximum effect), and the exponent n_H describes the shape of the function (Hill coefficient). When n_H is below 1, the response curve rises rapidly from the origin showing no apparent threshold response; when n_H is greater than 1, the response curve has a flat area with little additional response near the origin.

Statistical significance of any comparisons made on the basis of this model (e.g. testing to see if the Hill coefficient equals 1) were made using the Wald Statistic. Confidence bounds presented for parameters in the Hill model are also based upon the Wald Statistic (Portier *et al*., 1993).

Drugs

5-Hydroxytryptamine hydrochloride was purchased from Alexis, Läufelfingen, Switzerland; ketanserin tartrate and methysergide (Fluka, Buchs, Switzerland) were dissolved in physiological saline. DOI (1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane was purchased from Fluka, Buchs, Switzerland.

Results

Stimulant systemic effects of 5-HT are inhibited by ketanserin and methysergide

5-HT given intravenously (0.1 – 300 μg kg^{-1} i.v.; $n = 12$) significantly increased the frequency of ureteral contractions from 0.2 to 10.6 contractions min^{-1} in a dose dependent manner ($P \leqslant 0.0001$) as shown in Figures 1A and 2A. A significant increase in frequency started at a dose of 1 μg kg^{-1} ($P = 0.0052$). A maximal effect was seen at a dose of 300 μg kg^{-1} ($P < 0.0001$) with an ED_{50} of 66.0 μg kg^{-1} (confidence interval (95%) = 12.8 – 340 μg kg^{-1}) and an estimated maximal effect of 14.38 contractions min^{-1} (95% confidence interval = 9.03 – 22.9 contractions min^{-1}). The stimulating effect on frequency disappeared after a 20 min break, but could be reproduced by another maximal dose of 5-HT (300 μg kg^{-1} i.v.). The amplitude of ureteral contrac-

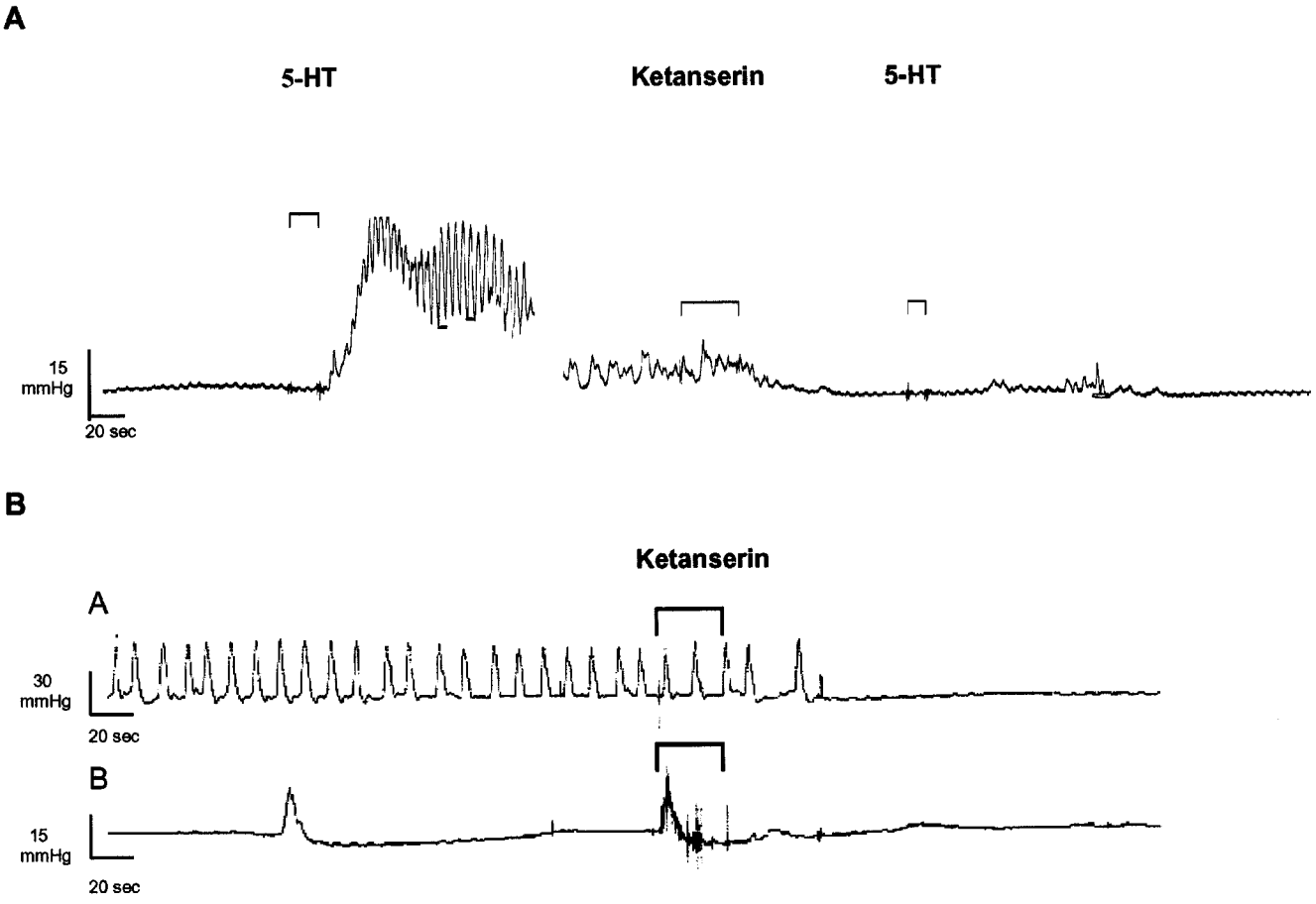

Figure 1 (A) Effect of 5-HT (0.3 mg kg^{-1} i.v.) on spontaneous ureteral contractions in a pig under anaesthesia. Ketanserin (0.5 mg kg^{-1} i.v.) antagonized the 5-HT induced contractions and prevented any effect on ureter peristalsis of another maximal dose of 5-HT (0.3 mg kg^{-1} i.v.). Original recording. (B) Upper trace A: Stimulant effects of 5-HT induced topically by continuous perfusion (1 mg ml^{-1}) of the ureter throughout the experiment as blocked by ketaserin 0.5 mg kg^{-1} in an anaesthetised pig. Lower trace B: Simultaneous pressure registration in the contralateral NaCl perfused ureter from the same animal as in trace A. Original recordings.

tions was increased from 9.8 to 17.2 mmHg but this effect was not significant. A significant increase in heart rate was seen at a dose of 0.1 and 0.3 mg kg^{-1} ($P<0.01$) while the mean arterial blood pressure slightly decreased only at the lower doses used in these experiments (1–3 μg/kg) ($P<0.05$) but not at higher doses used as shown in Figure 2A.

The 5-HT$_{2A/2C}$ antagonists ketanserin (0.5 mg kg^{-1} i.v.; $n=6$) or methysergide (1 mg kg^{-1} i.v.; $n=6$) given after the highest dose of 5-HT respectively, both significantly decreased the frequency (ketanserin: $P<0.005$; methysergide: $P<0.0005$) whereas the decrease in the amplitude of ureter contractions was not statistically significant. These effects were not abolished by a repeated administration of intravenous 5-HT at the maximal dose. The 5-HT-induced effect on arterial blood pressure could be antagonized by ketanserin ($P<0.05$), but not by methysergide (Figure 2A).

Stimulant topical effects of 5-HT are inhibited by ketanserin

Topical application of 5-HT (0.3–1000 μg ml^{-1}; $n=8$) significantly increased the frequency of ureteral contractions from 0.6 to 6.8 contractions per minute in a concentration-dependent manner as illustrated in Figure 2B and C. The lowest exposure showing a significant increase in frequency starting at a concentration of 30 μg kg^{-1} ($P<0.01$) with a calculated EC_{50} being 42.5 μg ml^{-1} (95% confidence interval = 4.5–403 μg ml^{-1}) and V_m estimated to be 10.3 contractions min^{-1} (95% confidence interval = 6.52–16.19 contractions min^{-1}). The maximal effect was seen at a concentration of 0.3 mg ml^{-1} 5-HT and no further increase was observed at the highest concentration (1 mg ml^{-1}) used in this experiment.

The amplitude of ureteral contractions increased from 11.5 to 23.6 mmHg as shown in Figure 2C but this effect was calculated to be significant ($P<0.05$) only at the highest concentration used (1 mg ml^{-1}). After the drug was washed out by perfusing the ureter with saline, the effect of 5-HT on contraction frequency, but not on the amplitude, could be reversed. A second perfusion of the ureter with 5-HT solution at the maximal concentration (1 mg ml^{-1}) resulted in an increase of the contraction frequency from 2.1 to 13.1 contractions per minute, which could be reversed by intravenous administration of ketanserin 500 μg kg^{-1} ($P\leqslant 0.0001$). These findings are illustrated in Figure 2B and C.

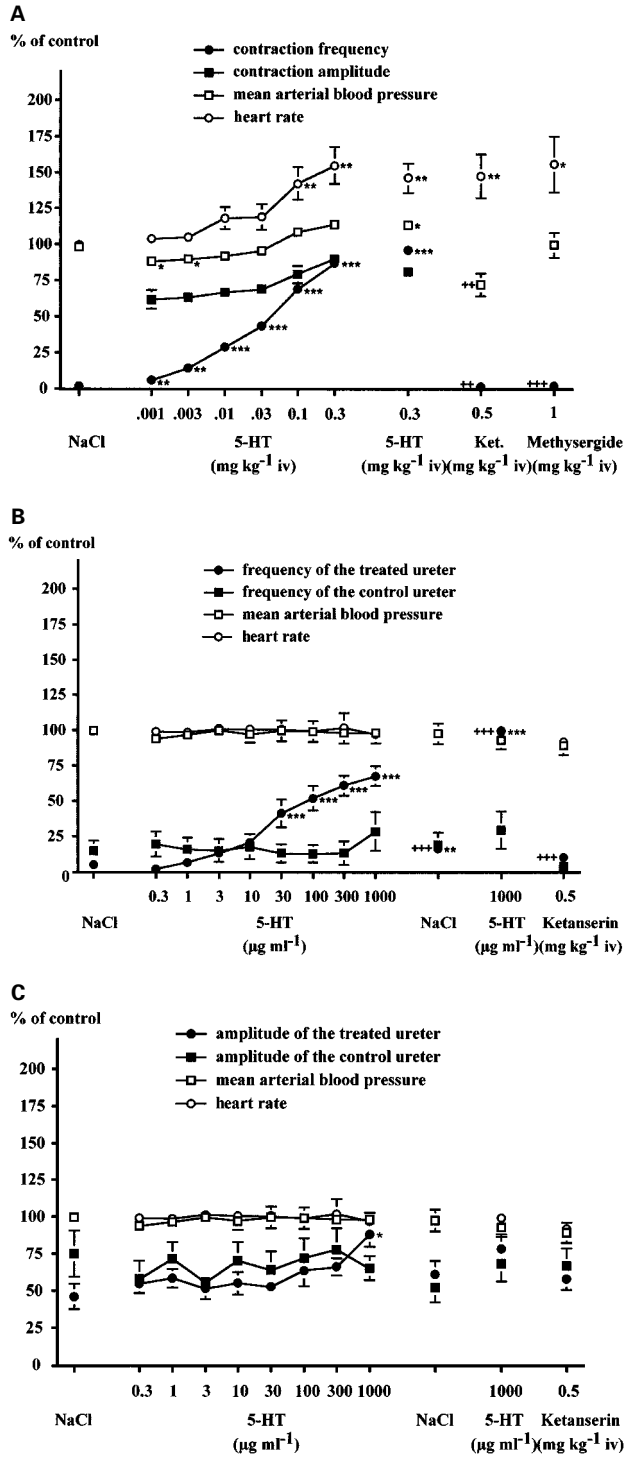

Figure 2 Effect of intravenous (A) successively increasing doses of 5-HT on contraction frequency, amplitude, mean arterial blood pressure and heart rate in pigs ($n=10$). The effect of 5-HT was antagonised by ketanserin ($n=5$) or methysergide ($n=5$). Effect of topical 5-HT on the frequency (B) and amplitude (C) of ureteral contractions during perfusion of one ureter with increasing concentrations of 5-HT (treated ureter) and perfusion of the contralateral ureter with saline (control ureter), as well as effects on mean arterial blood pressure and heart rate in pigs ($n=8$). Symbols represent mean values and vertical lines show s.e.mean. */**/*** Statistically significant different from controls at a significance level of $P<0.05/0.01/0.001$. $^{+/++/+++}$ Statistically significant different from the last 5-HT effect at a significance level of $P<0.05/0.01/0.001$.

The contraction frequency of the contralateral, saline perfused ureter, was slightly increased from 0.5 to 1.0 contractions per minute ($P>0.05$), while the contraction amplitude, the heart rate and the mean arterial blood pressure remained stable (Figure 2B and C).

Stimulant effects of DOI are inhibited by ketanserin

The 5-HT$_{2A/2C}$ receptor agonist DOI, when administered intravenously (1–300 μg kg^{-1}), increased the frequency of ureteral contractions. This effect appeared to be dose-dependent with the effect being significant ($P<0.01$) at a dose of 30 μg kg^{-1} reaching the most pronounced effect ($P<0.0001$) at the highest dose of 300 μg kg^{-1} i.v. used in these experiments as shown in Figure 3. The calculated ED$_{50}$ value is 43.6 μg kg^{-1} with a lower and upper 95% confidence interval of 1.54 μg kg^{-1} and 122.8 μg kg^{-1}, respectively, and a maximal effect of 3.26 contractions min^{-1} (95% confidence interval: 2.25–4.74 contractions min^{-1}). No effects on mean arterial blood pressure and heart rate were seen.

Ketanserin (1 mg kg^{-1}) given after the highest dose of DOI, resulted in a significant decrease in frequency of contractions ($P<0.05$). Heart rate and the mean arterial blood pressure were not affected. 5-HT administered intravenously was 4.85 times less potent than DOI but the maximal effect was 4.4 times higher when compared to the effects obtained by intravenously administered DOI. These findings are illustrated in Figure 4.

Spontaneous ureteral contractions are inhibited by ketanserin

Ketanserin given intravenously (0.3–1000 μg kg^{-1}; $n=6$) significantly decreased, in a dose-dependent manner, the frequency of ureter contractions from 2.9 to 0.7 contractions per minute with the reduction being significant starting at a dose of 0.3 mg kg^{-1} ($P<0.05$) attaining a maximal effect at

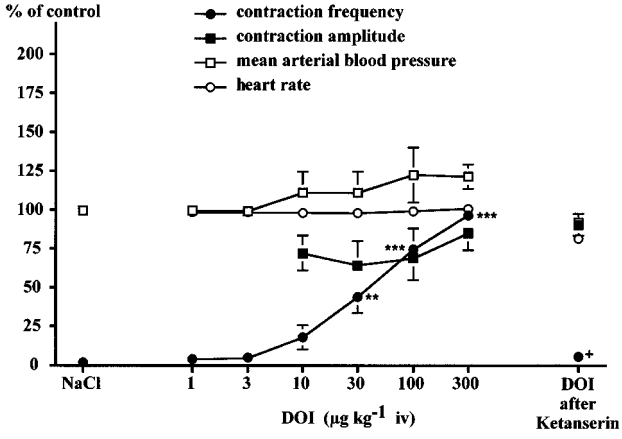

Figure 3 Effect of intravenous successively increasing doses of DOI on contraction frequency, amplitude, mean arterial blood pressure and on heart rate in pigs ($n=4$). The effect of DOI 300 μg kg^{-1} i.v. was antagonised after injection of ketanserin mg kg^{-1} i.v. ($n=4$). Symbols represent mean values and vertical lines show s.e.mean. */**/***Statistically significant different from controls at a significance level of $P<0.05/0.01/0.001$. $^{+}$ Statistically significant different from the last drug effect at a significance level of $P<0.05$.

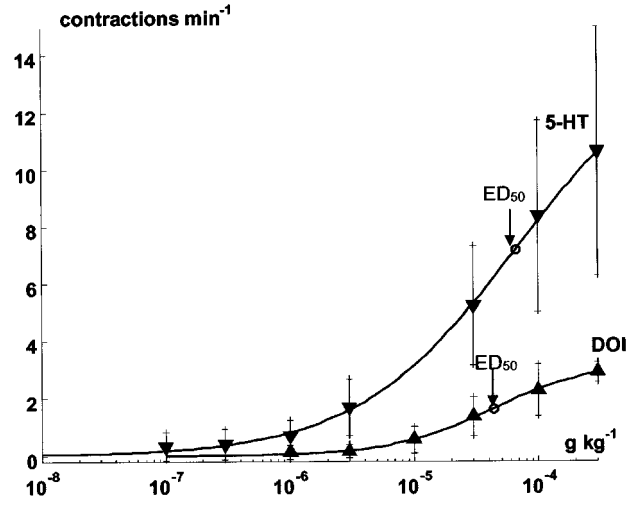

Figure 4 Dose response curves of the frequency of contractions (peaks min^{-1}) in porcine ureter of anaesthetized animals were calculated for 5-HT and DOI. Symbols represent mean and s.d. are shown by vertical bars.

the highest dose used (1 mg kg^{-1}) ($P<0.005$) as shown in Figure 5A. The calculated ED_{50} for reduction is 18.6 μg kg^{-1} (95% confidence interval = 1.17 – 294 μg kg^{-1}) and V_m being a 57% reduction in the frequency seen prior to drug administration.

No effect was observed in the amplitude of contraction, heart rate and mean arterial blood pressure (Figure 5A). 5-HT (300 μg kg^{-1} i.v.), given after a second administration of the maximal dose of ketanserin (1 mg kg^{-1} i.v.) resulted in an increase in the contraction frequency ($P>0.05$). No effect on mean blood pressure and amplitude of contractions was observed. But again, 5-HT resulted in an increase in heart rate ($P<0.05$).

Ketanserin given topically (0.01 – 1.0 mg ml^{-1}, $n=6$) significantly decreased the contraction frequency from 2.0 to 0.8 contractions min^{-1} or to 37% of controls only at the highest concentration (1 mg ml^{-1}) used in this study ($P\leqslant0.05$) as illustrated in Figure 5B. This effect could not be reversed by a washout with saline. No effect of ketanserin was seen regarding the amplitude of contractions as shown in Figure 5C.

The frequency and the amplitude of ureteral contractions of the contralateral, saline perfused ureter, were not affected (Figure 5B and C).

Intravenous 5-HT (300 μg kg^{-1} i.v.) given during a second perfusion of the ureter with ketanserin at the maximal concentration used in these experiments (1 mg ml^{-1}), increased the contraction frequency from 0.8 to 5.5 contractions per minute ($P\leqslant0.005$), whereas the amplitude was not affected. This effect was also observed in the contralateral, saline perfused ureter. 5-HT resulted in an increase in the frequency of contractions ($P\leqslant0.001$) and the amplitude of contractions increased from 12.2 to 16.8 mmHg ($P\leqslant0.05$). 5-HT evoked an increase in blood pressure (84 to 98 mmHg), which was not statistically significant but 5-HT induced a significant acceleration of the heart rate from 116 to 170 beats min^{-1} ($P\leqslant0.05$) as illustrated in Figure 5B and C.

Discussion

In the present study, we demonstrated that 5-HT receptors are involved in pig ureter motility. To our knowledge this is the first report showing the effect of 5-HT on the smooth muscle of the porcine ureter *in vivo*.

5-HT significantly increased contraction frequency of ureter peristalsis in anaesthetized pigs after intravenous administration in a dose-dependent manner (Figure 2A). In accordance with our work on the ureteral smooth muscle, stimulating effects of 5-HT in several *in vitro* studies on specimens from dogs (Dodel *et al*., 1996), man (Dodel *et al*., 1996; Kuwahara, 1983; Long & Nergardh, 1978; Gidener *et al*., 1995; 1999; Iselin *et al*., 1997) and guinea-pigs (Benzi *et al*., 1970) have been shown, and *in vivo* studies in dog ureters (Abrahams & Pickford, 1956; Catacutan-Labay *et al*., 1966; Boatman *et al*., 1967) also support our findings. The contractile response has been shown to be biphasic in dogs (Mazzella & Schroeder, 1960) but this was not observed in the present experiments in pigs, as can be seen in Figure 1.

In addition, 5-HT has been reported to induce reproducible contractile responses in human ureter tissue which could not be abolished by tetrodotoxin (TTX) and atropine, suggesting that this effect is not mediated by excitation of cholinergic neurons (Gidener *et al*., 1999). Therefore, the small dose of atropin (0.05 mg kg^{-1} i.v.) used in the present experiments during anaesthesia in pigs may not have masked the effects of 5-HT agonists. Other investigators have observed no effect of 5-HT in ureter preparations in various species (Borgstedt *et al*., 1966; Finberg & Peart, 1970). Ancill *et al*. (1972) found that low doses of 5-HT increased peristaltic frequency whereas high doses decreased peristaltic frequency in the rat ureter *in vivo*.

There are different reasons for the contradictions seen in the earlier studies. Species differences concerning the existence of 5-HT receptors and different types or subtypes of 5-HT receptors could contribute to the regulation of ureter motility. In the *in vitro* studies, differences in harvesting, localization, storage, preparation or experimental design could explain the different effects reported. In the *in vivo* studies, small alterations in the renal pelvis can affect peristaltic activity in the ureter and the smooth muscle is particularly susceptible to physical interferences (Ancill *et al*., 1972).

Our results show that intravenous administration of the 5-HT$_{2A/2C}$ receptor agonist, DOI, resulted in a significant and dose-dependent increase in ureteral contractility. Based on calculated ED_{50} values for the frequency of contractions, DOI was about 1.5 times more potent than 5-HT when both drugs were given intravenously. The maximal effect of 5-HT was 4.4 times higher when compared to DOI. These findings suggest that 5-HT$_{2A/2C}$ ligands may be responsible for the increase in the frequency of ureteral contractions. However, because of the lower maximal effect of DOI when compared to 5-HT, 5-HT ligands other than 5-HT$_{2A/2C}$ might be involved in the increase in the frequency of ureteral contractions. In contrast to our results, Gidener *et al*. (1999) reported a lack of agonism by DOI and a weak antagonism by the 5-HT$_{2A}$ receptor antagonist ketanserin on the frequency of contractions in human isolated ureter preparations *in vitro* concluding an absence of 5-HT$_2$ receptors in human ureter. In isolated preparations of the

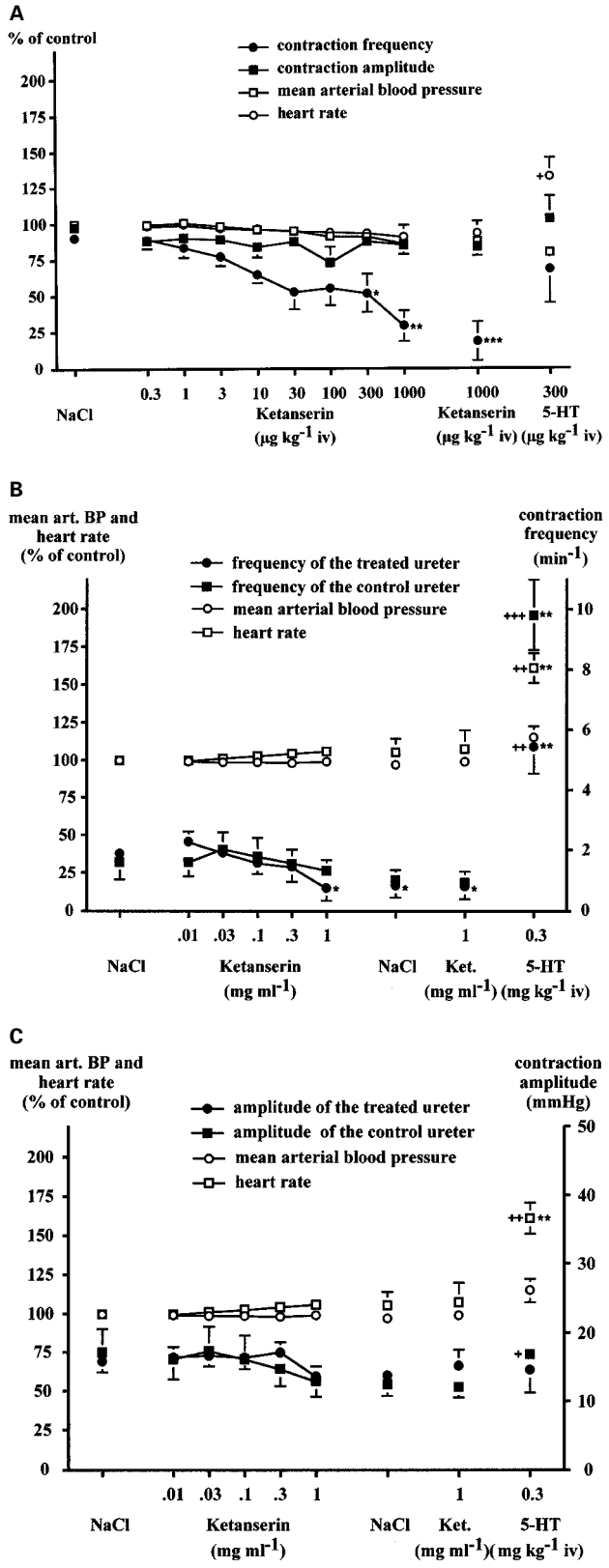

Figure 5 (A) Effect of intravenous ketaserin, given as successively increasing doses, on contraction frequency, amplitude, mean arterial blood pressure (MAP) and on heart rate in pigs ($n=6$). Effect on the frequency (B) and amplitude (C) of ureter contractions during perfusion of one ureter with increasing concentrations of ketanserin solution (treated ureter) and on the other ureter with saline (control ureter), as well as on mean arterial blood pressure and on heart rate in pigs ($n=6$). Symbols represent mean values and vertical lines show s.e.mean. */**/***Statistically significant different from controls at a significance level of $P<0.05/0.01/0.001$. $^{+/++/+++}$ Statistically significant different from the last drug effect at a significance level of $P<0.05/0.01/0.001$.

detrusor muscle from guinea-pigs, DOI was found to result in a stimulation of contractions of this muscle (Messori *et al.*, 1995). In our study, the effect of DOI on the frequency of contractions could be inhibited by ketanserin. Messori *et al.* (1995) also reported a decrease of 5-HT-induced contractile response by ketanserin at a concentration of 0.3 μM. They concluded that the excitatory effect caused by DOI and the inhibitory effect caused by ketanserin give indirect evidence for the presence of 5-HT$_2$ receptors in detrusor muscle of guinea-pigs. Despite the fact that different species were used in both studies, the effects seen with ketanserin and DOI are about the same suggesting a similar effect of 5-HT$_{2A}$-mediated contractions in detrusor muscle from the bladder and in the ureter.

The involvement of 5-HT$_{2A}$ receptors in the ureter contractility is supported by the finding that intravenous administration of ketanserin significantly decreased the frequency of spontaneous contractions in porcine ureter in a dose-dependent manner. Therefore, 5-HT$_{2A}$ receptors are probably involved in spontaneous ureter contractions and moreover they seem to be activated by endogenous 5-HT.

In vascular tissue α_1-adrenoceptor blockade has been suggested as the primary mechanism for the antihypertensive activity of ketanserin in animals (Cohen *et al.*, 1983; 1988; Kalkman *et al.*, 1982; Persson *et al.*, 1982; Fozard, 1982; Humphrey *et al.*, 1982). However, several studies on the ureter demonstrated that α-adrenergic antagonists did not influence peristalsis *in vivo* (Rose & Gillenwater, 1974; Reid *et al.*, 1974; Danuser *et al.*, 2001). Therefore, it is a more likely explanation that the relaxing effect of ketanserin on the ureter is due to antagonism of 5-HT receptors. The pharmacological effects on the ureter caused by a blockade of the 5-HT induced contractions by methysergide and ketanserin suggest an involvement of 5-HT$_{2A/2C}$ receptors. In accordance with our results, 5-HT provoked contractions on human ureters were inhibited by ketanserin and methysergide. However, Gidener *et al.* (1999) reported a weak antagonism by ketanserin on 5-HT-induced contractions in a latter study on human specimens, suggesting no involvement of 5-HT$_{2A}$ receptors (Gidener *et al.*, 1999). Thus the authors could not identify the receptor mediating the contractile response to 5-HT as belonging to the 5-HT$_1$-like (old classification), 5-HT$_2$, 5-HT$_3$ or 5-HT$_4$ classes. Species differences could explain these contradictory results as well as the different experimental designs *in vivo* versus *in vitro*. Even so the participation of different 5-HT receptor subtypes in pig ureter peristalsis cannot be excluded.

Topical application of 5-HT as well as of ketanserin showed a significant effect on the contraction frequency of the drug perfused ureter. 5-HT increased the frequency of contractions, whereas perfusion of ketanserin decreased frequency of ureter peristalsis. Both drugs showed no effect on the contralateral ureter and no systemic effects on heart rate or arterial blood pressure, suggesting a specific local effect and no absorption by the urothelium. This assumption

is supported by the effect of intravenous administration of 5-HT during simultaneous perfusion with ketanserin of the ureter. The ketanserin perfused ureter showed a weaker response to 5-HT than the contralateral, saline perfused ureter.

Further investigation of 5-HT ligands other than 5-HT$_2$ are needed to characterize the 5-HT-evoked peristalsis in porcine ureter. Moreover, a localization of 5-HT subreceptors should be determined in *in vitro* studies.

Conclusions

5-HT facilitates and ketanserin inhibits ureter motility by both intravenous injection and topical drug application. The blocking effects of ketanserin and methysergide suggest the involvement of 5-HT$_{2A/2C}$ receptors in pig ureter peristalsis. These 5-HT receptors seem to be physiologically activated by endogenous 5-HT. Evidence for this hypothesis awaits further testing using more selective 5-HT$_{2A/2C}$ receptor antagonists and agonists. 5-HT antagonists are a promising group of substances, which, topically applied, could be used successfully to prepare ureters for ureteroscopy, while the intravenous administration might be useful in the treatment of acute ureteric stone colic.

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