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CHAPTER 9

PHARMACOLOGICAL MODULATION OF URETERIC PERISTALSIS IN A CHRONICALLY INSTRUMENTED CONSCIOUS PIG MODEL. II: EFFECT OF ADRENERGIC STIMULATION AND INHIBITION

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ABSTRACT

OBJECTIVES: The hypothesis that stimulation and inhibition of the $\alpha$- and $\beta$-adrenoceptors lead to an increase and a decrease, respectively, of ureteric contractile function in vivo in a chronically instrumented large animal study, was tested.

METHODS: Twelve female pigs (72 ± 4 kg) were studied. A measuring catheter was introduced and positioned in the right ureter. Nephrostomy, arterial, venous and cystostomy catheters were left in situ. Ureteric peristalsis was studied before and after administration of propranolol, isoprenaline, doxazosine, urapidil and phenylephrine.

RESULTS: Systemic effects of the agents demonstrated that functionally effective doses were used. Administration of $\alpha$-adrenergic receptor agonists led to a higher contraction force and frequency. $\alpha$ inhibitors caused a decrease in contraction force, but the frequency of ureteric peristalsis was not changed. $\beta$-adrenergic stimulation led to a dramatic decrease in contraction amplitude and frequency, whereas administration of $\beta$-inhibitor increased contractile force but did not change the frequency of peristalsis.

CONCLUSION: Stimulation of $\alpha$ and $\beta$-adrenoceptors leads to modulation of peristaltic frequency and force of ureter contractions as formulated in our hypothesis. Inhibitors of $\alpha$- or $\beta$-adrenoceptors have an effect on contraction force, but do not have an effect on peristaltic frequency.
INTRODUCTION

Ureteric peristalsis is myogenic in origin, but is modulated by a complex regulatory circuit that depends on the functional properties of the smooth muscle cells and the innervation from the autonomic nervous system. If one considers the ureter as a pumping unit, the volume of urine transported can only be altered by increasing the peristaltic frequency and/or the bolus volume. The pressure generated by ureteric peristalsis should be sufficient to propel the urinary bolus forward and prevent simultaneously a backward leak. Pharmacological modulation of ureteric peristalsis may offer new insight for the treatment of (partial) obstructive uropathy and/or wide ureters. Histologically, noradrenergic nerves have been found in several species in the adventitia, the smooth muscle and the submucosal layer of the entire ureter. Stimulation of α- and β-adrenoceptors stimulates and inhibits upper urinary tract (UUT) contractility in vitro and in vivo.

Controversy exists about the physiologic basis for applying medication, which interferes with the adrenergic system. β-adrenergic inhibitors are widely used for a variety of indications, such as hypertension, cardiac arrhythmia or failure, angina pectoris or infarction, migraine prophylaxis, pheochromocytoma and tremor simplex. α1-inhibitors are also prescribed increasingly in recent years for the treatment of lower urinary tract symptoms associated with prostatic enlargement. A controlled, chronically instrumented animal model study of the pharmacological (side) effects of these agents on the ureter is unavailable. We report in this article our results obtained during a 6-week long experiment with chronically instrumented pigs. In this model, we tested the hypothesis that α1- and β-adrenergic stimulation leads to stimulation and inhibition of ureteric peristaltic force and frequency, respectively, and that inhibition of these receptors has the reverse effect.
MATERIALS AND METHODS

The experimental design and procedures followed in our study have been reported in detail {submitted J Urol}. Permission of the local ethical committee for laboratory animals was obtained after a statistical estimate revealed that nine animal would be sufficient.

Twelve female pigs were instrumented as follows: A special electronic measuring catheter to register peristaltic wave activity was implanted in the right ureter in an antegrade fashion. Tunneled nephrostomy, venous, arterial and vesicostomy catheters were also implanted. A blanc registration of ureteric peristaltic activity (REF) was undertaken during perfusion of the renal pelvis with 0.25 ml/min saline at body temperature. The effects of administration of agonist and antagonist to α1- and β-adrenoceptors was subsequently recorded using a rotatory schedule of drug administration at intervals of 3 days to minimize interactions between the respective agents. Ureteric peristalsis was visualized using a perfusion of the renal pelvis with 0.25 ml/min iodine contrast and x-ray fluoroscopic control in the sedated animal at the end of the study. Any systemic effects were registered, using blood pressure, ECG and clinical monitoring of side effects as parameters. The results were statistically analyzed and are reported as mean ± SEM.

Isoprenaline (0.04 mg/kg) and propranolol (0.07 mg/kg) were administered intravenously to stimulate and to inhibit, respectively, the β-adrenergic receptors. Phenylephrine (0.02 mg/kg) is administered as an α-adrenergic receptor agonist. Doxazosine (0.7 mg total dose) and Urapidil (20 mg total dose) were used as α1-adrenergic receptor antagonists in separate sessions.

Care and follow-up of animals

Daily each animal was systematically examined. In all animals, urinary leak from the nephrostomy ceased within 24 hours. Urinary sediment and culture samples were collected and were always negative. Daily physical examination revealed no evidence of pyelonephritis. Ultrasound studies (B&K 3535) of the kidneys were undertaken before every data registration session. Only one animal revealed dilatation of the pyelocalyceal system and was excluded from the study. Nursing care of the animals was also regularly undertaken by the investigator to
cultivate and develop a social bond and to reduce animal stress to minimum during the study.

RESULTS

Qualitative description of the registered peristalsis

The criteria used to distinguish a peristaltic wave were as described previously. Registration was possible in every experimental session. In two pigs, only a single channel registration was possible, because of technical failure. One pig destroyed the measuring catheter. The animal was re-operated to place a new catheter.

X-ray imaging studies revealed the presence of normal peristalsis at 6 weeks post-operatively but the catheter was displaced proximally by ca 2 cm relative to its localization on the first day.

Quantitative description of the registered peristalsis

The variation of $P_{\text{max}}$ (maximal amplitude of peristaltic phasic contraction) and frequency of ureteric peristalsis in REF and after administration of propranolol, isoprenaline, urapidil, doxazosine and phenylephrine group separately is illustrated in Figures 1 and 2, and Tables 1 and 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Values of $P_{\text{max}}$ in cm H$_2$O in all experimental conditions</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Propranolol</td>
</tr>
<tr>
<td></td>
<td>mid-ureter</td>
</tr>
<tr>
<td>REF</td>
<td>45.0 ± 1.4</td>
</tr>
<tr>
<td>Drug</td>
<td>56.7 ± 1.5</td>
</tr>
</tbody>
</table>

Table 1: Numeric data of $P_{\text{max}}$ in cm H$_2$O in the experimental conditions shown in Fig. 1
Table 2: Numeric data of peristaltic frequency in min⁻¹ in the experimental conditions shown in Fig. 2

\( P_{\text{max}} \) is affected by both \( \beta \)- and \( \alpha_1 \)-adrenergic receptor stimulation and inhibition \((P < 0.05)\). Propranolol and phenylephrine administration resulted in a significant increase of the \( P_{\text{max}} \) in both the mid and distal ureter. The administration of isoprenaline and doxazosine resulted, on the contrary, in a significant decrease in \( P_{\text{max}} \). Urapidil resulted in a decrease of \( P_{\text{max}} \) only in mid ureter, whereas the distal ureter was not affected. Isoprenaline decreased the ureteric peristaltic frequency, whereas phenylephrine strongly increased peristaltic frequency. The other drugs used (propranolol, doxazosine and urapidil) did not change the frequency of ureteric peristalsis significantly.
Figure 1: Response of the middle and distal ureter segments to α- and β-adrenergic stimulation and inhibition. Propranolol and phenylephrine significantly increased the contraction force relative to the effect of saline perfusion alone (REF). Isoprenaline, doxazosin and urapidil resulted in a significant decreased $P_{\text{max}}$, which for urapidil was confined to the mid-ureter. Error bars represent SEM. Numeric data are presented in Table 1.

Hydrostatic pressure in the renal pelvis fluctuated rhythmically in a fashion that was not synchronous with respiration. Hydrostatic pressure of renal pelvis was elevated between 12-15 cm H$_2$O in the phenylephrine group, which is significantly higher than control (0-6.5 cm H$_2$O) and propranolol group (3.5-7.5 cm H$_2$O). The rhythmic variation of hydrostatic pressure in renal pelvis was not altered by the other drugs. Intra-vesical pressure was not affected significantly by any of the administrated drugs.
Figure 2: Effect of stimulation and inhibition of adrenoceptors on ureteric peristalsis. Only isoprenaline and phenylephrine caused a decrease (0.3 ± 0.04 min⁻¹ in isoprenaline group compared with 2.1 ± 0.04 min⁻¹ in REF) and an increase (3.3 ± 0.4 min⁻¹ in phenylephrine group compared with 1.8 ± 0.2 min⁻¹ in REF) in peristaltic frequency, respectively (P < 0.05). Error bars represent the SEM. Numeric data are presented in Table 2.

Systemic side effects of investigated drugs
β-adrenergic group: Propranolol and isoprenaline caused a significant decrease (60 ± 3 min⁻¹) and increase (186 ± 3 min⁻¹), respectively, in heart rate (control: 83 ± 4 min⁻¹, P < 0.05). Blood pressure dropped to 90/20 ± 2/5 mmHg with isoprenaline and to 120/75 ± 7/5 mmHg with propranolol in comparison to 150/85 ± 6/7 mmHg in the control phase (P < 0.05). The average diuresis of pigs in the propranolol, isoprenaline and control groups was 69 ± 1 ml/hour, 32 ± 1 ml/hour and 66 ± 0 ml/hour respectively (P < 0.05 in isoprenaline). Isoprenaline also caused intense reddening of the skin due to extensive peripheral vasodilatation. Some pigs vomited and one pig died 92 min after administration of isoprenaline.
**α1-adrenergic group:** Heart rate was affected by doxazosine (120 ± 4 min⁻¹), urapidil (89 ± 1 min⁻¹) and phenylephrine (150 ± 6 min⁻¹) in comparison to the controls (83 ± 4 min⁻¹, P<0.05). Doxazosine (120/70 ± 8/6 mmHg) and urapidil (110/60 ± 4/4 mmHg) had an antihypertensive effect while phenylephrine (200/112 ± 12/9 mmHg) increased the blood pressure (control: 150/85 ± 6/7 mmHg, P<0.05). The average rate of diuresis in the doxazosine, urapidil, phenylephrine compared to the control group was 67 ± 1 ml/hour, 63 ± 0 ml/hour 67 ± 0 ml/hour and 66 ± 0 ml/hour, respectively (P>0.05).

**DISCUSSION**

Many studies have been published on the pharmacological aspects of ureteric peristalsis, but we could not find data on the effects of noradrenergic pharmacological modulation in a chronically instrumented, awake animal model. Such a model is susceptible to secondary infection and inflammation resulting from the implanted foreign bodies for measurement purposes. Highest priority was therefore given to prevention of infection and prophylactic antibiotics were administered. In addition, maximal sterility during the operative procedure was employed and all precautions were undertaken to detect and prevent hydro-uretero-nephrosis during the study period.

*Validity of the experimental model and the control studies*

The adrenergic receptor agonists and antagonists alter blood pressure. Urine production may drop dramatically as a result of an acute pre-renal kidney failure. To compensate for such a sudden drop in the fluid load of the renal pelvis, we perfused the renal pelvis throughout the nephrostomy with a minimal amount of saline pre-warmed to body temperature and administered it at a constant flow of 0.25 ml/min which is equivalent to 15 ml/hour diuresis per kidney. This preload is associated with an increase in $P_{\text{max}}$ in the mid-ureter (REF), but did not change $P_{\text{max}}$ in the distal ureter (article submitted J. Urology and not shown here). This regional effect on the $P_{\text{max}}$ may be explained by the decreased ability of the distal ureter to exert a powerful contraction, because the architecture of the smooth muscle bundles at this level differs from that seen in the mid ureter.
The results registered by us after drug administration confirm recorded data in the literature about the influence of β-adrenergic manipulation on ureter peristalsis. The cardiovascular side effects of isoprenaline, a non-selective β agonist, were dramatic and led to death of one pig after the completion of the experiment. Lower doses of isoprenaline used in this study also revealed the total absence of the ureter peristalsis for approximately 600 sec after the administration of this drug. Peristalsis in the ureter is gradually restored, but remains at a lower frequency and contraction force for many minutes. After restoration, the ureteric peristalsis was initially irregular in amplitude and rhythmicity, suggesting continued inhibition of the β-adrenergic receptor. Contrary to available literature, administration of isoprenaline (1gr/L saline at body temperature) through the nephrostomy did not reduce ureteric contractility in our model (not shown).

Propranolol, a non-selective β antagonist causes a significant increase in $P_{\text{max}}$, but fails to increase ureteric peristaltic frequency. The side effects of propranolol were measurable, but did not lead to significant cardiovascular symptoms. After propranolol treatment, ureteric peristaltic activity continued to be regular and predictable in time. The dose of propranolol needed to achieve a ureteric response is relatively low. This makes the β blockade a potential therapeutic option for the treatment of a partially obstructed upper urinary tract if adequate ureteric muscle function is still present. The β-receptors are homogeneously expressed in the ureter. This fact, together with the inhibitory effect of the β-adrenergic stimulation on the ureteric peristalsis, gives these receptors an important therapeutic potential for ureteric relaxation.

Doxazosine and urapidil are α1-adrenergic receptor antagonists. They were used because most α-receptors in the ureter seem to be α1-receptors. Urapidil has a central 5-HT$_{1A}$-agonist mechanism, which inhibits development of reflex tachycardia. Both medications have a similar effect on $P_{\text{max}}$. Why the distal ureter is not affected by urapidil, is not understood at present.

α1 blockade is an established therapy for lower urinary tract symptoms (LUTS) caused by a benign prostatic enlargement (BPE). Our results demonstrate that such blockade affects ureteric peristalsis.
negatively. This negative effect would be especially important if infravesical obstruction also leads to increased bladder pressure, which in turn is detrimental to drainage from the UUT. The ureteric peristaltic frequency is not affected by \( \alpha_1 \) blockade. The cardiovascular side effects were also negligible.

Phenylephrine is a nonselective \( \alpha \) adrenergic receptor agonist. Its inotropic and chronotropic effects are well demonstrated \textit{in vivo} in our animal model study. Tachycardia and hypertensive side effects were considerable. Since the expression of the \( \alpha_1 \)-adrenoceptors seems to be homogeneously spread throughout the entire ureter \cite{18,27-29} its stimulation is directly correlated to ureteric contractility. The \( \alpha_1 \) receptor was the most important receptor stimulating ureteric peristalsis.

Administration of \( \alpha_1 \)-adrenergic stimulants (phenylephrine) leads to higher hydrostatic pressure in the renal pelvis, which is not encountered with the other drugs used. This observation supports the concept that \( \alpha_1 \)-adrenergic stimulation increases tonic contraction of ureteric muscle. Inhibition of the \( \alpha_1 \)-adrenergic stimulation receptor may reduce tonic activity in the ureter. We were unfortunately unable to measure such an effect because our measuring set-up was not adapted for this goal and the hydrostatic pressure in our control group varied between 0-6.5 cm H\(_2\)O, which is already relatively low, making it difficult to record a further decrease.

\textit{Design of an ideal pharmacologically active agent}

Indications for the use of a spasmolytic agent are generally propagated in clinical medicine for the treatment of colic contractions due to small ureteric stones or intra-ureteric operative manipulation \cite{10}. The choice of an appropriate drug depends on the duration of action required.

Most receptor agonists, including those for the various adrenoceptors, have a short half-life. They mimic the effects of the neurotransmitters, which are normally active for a quite short time only to effectuate the synaptic signal transmission. If a long lasting receptor agonist activity is desired, the neurotransmitter or the mimetic is commonly administered via a continuous parenteral infusion. Such an administration is feasible during operative procedures. However, over-stimulation of the receptor can lead to desensitization or even a total
loss of signal transduction. Side effects are common since autonomic receptors are widely spread in the organism and the selectivity of the available agonists towards receptor subtypes, like e.g. α1A, α1B, is still meager.

Antagonists, on the other hand, are commonly long lasting agents. Since they merely suppress the more or less pronounced activity of the natural neurotransmitters, they are better tolerated and the side effects are generally less problematic. These two reasons make antagonists much more suitable to be administered orally and in outpatient clinics.

Suppressing the inhibitory activity of β adrenoceptor activity by means of an antagonist leads to stronger contractions. However, the contraction frequency is not influenced by β adrenoceptor blockade. It subsequently will increase the ureteric resistance to flow and thus protect the UUT from the backwards-urinary leak. At higher rates of diuresis, dilatation of the renal pelvis can take place since the ureteric resistance is increased. Inhibition of the stimulatory activity of the α1-adrenoceptors leads to decreased $P_{\text{max}}$. The frequency is insensitive to α1-adrenoceptor blockade as well. Under these conditions, the ureter is very susceptible to urinary reflux. Interestingly, none of the adrenoceptor antagonists was able to influence the peristaltic frequency in the present study.

CONCLUSION

β-adrenergic stimulation and inhibition were demonstrated to lead to relaxation and activation of the ureteric contractility, respectively. α-adrenergic agonists stimulate phasic and tonic contraction of UUT. Administration of antagonists for α1 or β-receptors does not affect ureteric peristaltic frequency.

β-adrenergic blockade led to higher intraluminal ureteric resistance due to more powerful ureteric contractions and thus a better prevention of reflux of urine back into the ureter. α1-adrenergic receptor blockade decreases the intraluminal ureteric resistance and can thus trigger vesico-ureteral reflux. This finding may be of some significance in clinical urology for the use of these drugs in the treatment of lower urinary tract symptoms associated with benign prostatic enlargement.
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