Dynamics and modulation of ureteric peristalsis
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Citation for published version (APA):
Roshani, H. (2003). Dynamics and modulation of ureteric peristalsis

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CHAPTER 1

THE FUNCTIONAL PROPERTIES OF THE UPPER URINARY TRACT

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INTRODUCTION

When the rate of diuresis is normal, the upper urinary tract evacuates urine from the kidney into the bladder using peristaltic activity. Ureteric peristalsis is initiated by the activity of smooth muscle cells with pacemaker properties in the renal pelvis and calyces. The impulse itself is transmitted from cell to cell through gap-junctions. To understand different aspects of ureteric peristalsis, myogenic and neurogenic theories have been proposed. The myogenic theory explains how and why peristalsis is observed in an isolated ureteric segment in vitro and in vivo and why it persists in a denervated ureter, after kidney transplantation, or even after reverse ureteric auto-transplantation. The neurogenic theory now emphasizes the role of neuronal activity in fine-tuning ureteric peristalsis, arguing that both activities are, in a sense, complimentary.

Controversy continues to exist about the exact localization of pacemaker cells in the upper urinary tract. The calyces and proximal renal pelvis are believed to be the site of this activity, but species-related differences in the anatomical organization of the renal pelvis and calyces are reported. Nevertheless, pacemaker properties have been assigned to specialized smooth muscle cells with pale cytoplasm and fibroblast-like cells.

Using EMG studies, it has been reported that the whole renal pelvis works as a pacemaker unit. This is called the "multiple coupled oscillators" model with several pacemaker subunits. It is suggested that these pacemaker signals have to be synchronized and summed to be able to trigger a peristaltic wave in the ureter. Pyelic distention due to diuresis modulates the peristaltic frequency by changing the degree of synchronization between the subunits. A hierarchic gradient of auto-rhythmicity exists from proximal to distal in upper urinary tract. When the proximal portion of the upper
urinary tract fails to function for any reason, control of ureteric peristaltic activity is assumed by more distal regions.\textsuperscript{20}

**SCOPE OF THESIS**

An extensive review of the available literature on form and function of the ureter with special attention to the myogenic and neurogenic regulatory factors governing ureteric motility and unidirectional urine transport was undertaken. Using the Medline database, a series of 321 publications on the subject of ureteric peristalsis was found. Of these, 141 articles were summarized. Based on the reported findings and controversies, we postulated a hypothesis and undertook stepwise investigations to test the validity of the hypothesis that ureteric peristalsis is intrinsically a myogenic activity, with neurogenic activity regulating ureteric motility in such a way that unidirectional urine transport is ensured.

We first studied the functional anatomy and the endoluminal ultrasonographic (ELUS) features of distal ureter in man and pig (Chapters 2 and 3).\textsuperscript{28,29} The organization of the ureteric smooth muscle fibers at the level of the ureterovesical junction (UVJ) is different from that in the rest of the ureter. The peripheral circular layer changes its pitch and merges with the longitudinal inner layer, permitting only shortening of the intramural segment of the ureter. The ureteric wall is thus able to pull self back over the urinary bolus and open the ureteric orifice – a phenomenon commonly visualized by the urologist at endoscopy. The bolus is thus evacuated into the bladder cavity while the juxtavesical ureteric segment remains constricted due to the long lasting constriction of the circular layer. This is an important functional anatomical characteristic, which inhibits reflux during this crucial moment when the ureteric orifice is wide open. The distal propagation of this excitation and contraction zone along the trigonal smooth muscle fibers pulls back the ureteric orifice to its normal position and closes it. Using this biomechanical model, we postulated that for different rates of diuresis the ureteric peristalsis is modulated by the autonomic nerves in the ureter.

We then proceeded to investigate, in the acute pig model, the electromyographic (EMG) activity (Chapter 4), the wall movements (Chapter 5) and the pressure generation (Chapter 6) in the ureteric
wall of the middle and distal ureter during the passage of a peristaltic wave at normal rates of diuresis $^{30-32}$. This was the first essential step to confirm the myogenic origin of the peristaltic wave. We could confirm that EMG activity of the ureter precedes movement of ureteric wall and generates a high pressure zone along the ureter which is both long lasting and strong enough to propel the urinary bolus unidirectionally from the proximal to distal end and to prevent backward leakage. Our studies in the acute pig model convinced us of the need for a chronic animal model to confirm that autonomic neurogenic modulation of ureteric peristalsis exists and can be proven. We subsequently developed a single catheter to simultaneously register EMG activity, wall movements (as a function of impedance fluctuation) and pressure generation inside the ureter of chronically instrumented pigs (Chapter 7). As part of this study, we also monitored the recovery of ureteric peristalsis after operative procedures on the pyelocalyceal system and analyzed the modulatory effects of cholinergic, adrenergic and nitrergic agents \textit{in vivo}.

We have demonstrated that ureteric peristalsis persists in the initial hours after an operation on the pyelocalyceal system but disappears during the first postoperative day. Normal function is only re-established a week from the date of manipulation. Recovery follows in a gradual and hierarchic pattern from proximal to distal. At low rates of diuresis, peristaltic frequency is directly related to the pyelocalyceal urine load. Ureteric contraction force is increased in the mid-ureter when the rate of diuresis is increased, but contraction force fails to increase in the distal and juxtavesical ureter. In our chronically instrumented animal model, ureteric smooth muscle motor activity at the mid- and distal ureter level is not modulated by muscarinic receptors (Chapter 8), indicating that the postulated spasmolytic effect of anti-cholinergic therapy for renal colic in humans has to be questioned.

$\beta$-adrenergic stimulation and inhibition were demonstrated to lead to relaxation and activation of the ureteric contractility, respectively (Chapter 9). $\alpha_1$-adrenergic agonists stimulate phasic and tonic contraction of upper urinary tract. Administration of antagonists for $\alpha_1$ or $\beta$-receptors does not affect ureteric peristaltic frequency. $\beta$-adrenergic blockade led to higher intraluminal ureteric
resistance due to a more powerful ureteric contraction and, hence, will probably support the prevention of reflux of urine back into the ureter. $\alpha$-adrenergic receptor blockade decreases the intraluminal ureteric resistance and could therefore theoretically be a trigger for vesico-ureteral reflux.

The biological effect of NO on the regulation of ureteric motility is regional and corresponds with the distribution of NOS (Chapter 10). Systemic inhibition of NO synthesis results in a significant rise in tonic and phasic contractions of the distal ureter, whereas an extra supply of substrate (L-arginine) does not affect phasic or tonic contractility of the ureter. These findings indicate that activity of the distal ureter is probably inhibited upon activation of local NOS+ nerves. From our animal model studies, the fundamental role of NO metabolism in modulating distal ureter motility is established.

**BIOMECHANICAL CONDITIONS GOVERNING URINARY TRANSPORT IN THE UPPER URINARY TRACT**

*The ureter as collapsed tube with peristalsis*

At physiological rates of diuresis, urine is transported as separate urinary boluses by peristaltic waves. The peristaltic activity and the separate boluses within the ureteric lumen actively isolate the kidney and the upper urinary tract from the content of the bladder and its shifts in pressure. As ureteric peristalsis is not strictly periodic, the peristaltic frequency indicates only an approximate number of contractions per unit of time. At low rates of diuresis, extraperistaltic flow is the flow leaking between peristaltic waves during relaxation of the ureteric muscle. The intrinsic peristaltic carrying capacity is defined as the upper limit of steady peristalsis and is approx. two ml/min in the pig $^{33,34}$. Beyond this limit, consecutive boluses merge and form an open tube $^{33}$. Total ureteric carrying capacity is defined as the maximal volume of urine passing through the ureter per unit of time when the ureter is acting as an open tube above its intrinsic peristaltic carrying capacity. In most cases, even at higher rates of diuresis, the flow remains laminar $^{33-35}$. Increasing urine flow will result in higher peristaltic frequencies up to intrinsic peristaltic carrying capacity. The higher the peristaltic frequency, the
better the upper urinary tract is isolated from the contents of the bladder lumen \(^{19-21,36}\).

Our data shows that during peristalsis in vivo an approximate length of 10 cm ureter muscle remains excited for approximately 4 seconds and generates approx. 35 cm water pressure at mid-ureteric level \(^{31,37}\). The generated pressure decreases to approx. 20 cm of water at the juxtavesical level and to 7 cm of water at the submucosal level \(^{37}\). As the propagation velocity of peristalsis is relatively fast (2 cm/sec), the bolus is evacuated from the ureteric orifice when some portion of the ureter is still constricted (Chapters 4, 5 and 6) \(^{31}\).

*The ureter as an open tube without peristalsis*

Advantages of the open-tube transport of urine are a higher transport capacity at a lower level of energy consumption, especially in the upright position of the individual. However, the upper urinary tract is then exposed to the potentially harmful effects of high bladder pressures and reflux. The maximum particle velocity of intra-ureteric urine is in the central portion of the urinary column, while at the periphery particles are practically stationary. This results in parabolic laminar flow vectors \(^{34}\). The ureter itself behaves as a non-uniform passively distensible tube with elastic properties with two anatomically defined obstructions \(^{38-42}\). The mid-ureter, The first obstruction is the mid-ureter, where the main pelvic vessels cross and control the flow rate at relatively low detrusor pressure (during the beginning of the bladder-filling phase). The ureterovesical junction (UVJ) acquires an obstructive character during high detrusor pressure in a full bladder and at micturation. These two resistance-determining moments are especially important during the extra- or non-peristaltic flow at relatively low flow rates.
For laminar flow through an inert (rigid) tube of finite length, the law of Hagen-Poiseuille states that

\[ F = \pi. \left( \frac{R^4}{8} \right). \eta. \left( \frac{P}{L} \right) \]

with \( F \): flow; \( R \): tube radius; \( \eta \): liquid viscosity; \( P \): pressure; and \( L \): tube length. This equation only applies at relatively high rates of diuresis when the ureter acts as an open tube, but the flow inside is still without turbulence because of its low Reynolds number (see below). \( P \) is a summation of gravity and pressure difference between the renal pelvis and the distal ureter. Flow is directly proportional to the fourth power of the tube radius. A simple dilatation of the ureter by 20% will more than double the flow through it, if other factors remain unchanged. A low Reynolds number (\( Re < 100 \)) implies a laminar, inertia-free flow. In the case of the ureter, the Reynolds number can be calculated from the formula:

\[ Re = \frac{V. R^2}{\eta. \lambda} \]

with \( V \): wave velocity; \( R \): radial length; \( \eta \): liquid viscosity; \( \lambda \): wave length. Assuming \( V \): 3 cm/sec; \( R \): 1.5 mm; \( \eta \): 0.007 cm²/sec; and \( \lambda \): 15 cm \(^4\), \( Re \) varies between 0.65 and 1.5, thus supporting a laminar flow in the ureter.

To conclude therefore, flow from the upper urinary tract is dominated by an alteration of peristaltic and extra-peristaltic discharge (leakage) at lower rates of diuresis i.e. below the intrinsic peristaltic carrying capacity. An open tube scenario as described above is used to transport urine at higher volume of diuresis using simple laws of physics.

**MOTOR ACTIVITY OF THE UPPER URINARY TRACT**

_Pacemaker activity and conduction of the impulse_

Excitation waves spread from the renal pelvis to the ureter through gap junctions and cause a phasic contraction, which in turn brings about transport of the urinary bolus. A first-degree conduction block, which is blockage of some action potentials at the level of pyelocalyceal system, corresponds with a slow, inhomogeneous conduction of signal at the site of pacemaker cells in the renal pelvis.
It is related to the refractory period of excited cells and the poor coupling between them. A second-degree conduction block is blockage of action potentials at the level of uretero-pelvic junction when these signals are not synchronized. Thus, not every pacemaker excitation of the renal pelvis propagates itself to the ureter during normal diuresis. Accumulation of urine in the pyelum increases the readiness of the uretero-pelvic junction to allow passage of an incoming “pacemaker” wave.

The maximal peristaltic frequency cannot exceed the pacemaker frequency. By increasing diuresis, bolus volume increases until the ureter acts as an open tube. Latent ureteric pacemakers give rise to ureteric dysrhythmia. Dysrhythmia can be initiated by neurokinin A, noradrenaline, histamine, serotonin, bradykinin, endothelin-1 and bacterial products. The refractory period of the ureteric muscle is several seconds. This protects the ureter against the development of anti-peristaltic activity of an ectopic pacemaker.

**Different cells in the renal pelvis and their membrane characteristics**

Based on electrophysiological properties, three different types of pyelic cells have been identified. Pacemaker cells, which account for ca 10% of pyelic cells, have a relatively high resting potential (-42 mV compared to -56 mV of other renal pelvis smooth muscle cells). A slowly rising onset, followed by a fast phase of depolarization characterizes their action potential. A second, more ureteric type of smooth muscle cell has a slower depolarization phase and a long-lasting plateau phase. Finally, an intermediate type of smooth muscle cell exists. The action potential of the ureter is long lasting, with a plateau of approx. 1 second.

Two types of ion channels are responsible for the depolarization of the ureteric smooth muscle: a “fast” Ca\(^{2+}\) channel, and a “slow” Ca\(^{2+}/Na^+\) channel, which are involved in the initial spike and in the plateau phase of the action potential, respectively. K\(^+\) channels are responsible for the repolarization of the ureteric smooth muscle (Fig. 1).
Figure 1: Schematic presentation of the ionic current transport involved in the ureteric action potentials in humans. Rapid depolarization occurs when the resting potential reaches the threshold of -50 to -40 mV. A fast inward extra-cellular Ca\(^{2+}\) wave depolarizes the membrane potential to an overshoot of +30 mV. A slow inward current of sodium and calcium maintains the plateau phase of approx. 1 second. Repolarization to reestablish the resting potential is initiated by an outward, in part calcium-dependent potassium current.

The calcium current is the main inward current detectable in the smooth muscle cells of the ureter\(^{60-64}\) and may explain the sustained tonic contractions of the ureter. Potassium (mostly via Ca\(^{2+}\) dependent channels) is by far the most important current for determining repolarization and variation in the duration of the action potential. Ca\(^{2+}\) dependent K\(^+\) channels seem to be the major target for the excitatory action of noradrenaline and histamine in the ureter\(^{65}\). Noradrenaline prolongs the duration of the action potential by suppressing the activity of the K\(^+\) channel. A reduction of extra-cellular Na\(^+\) decreases the plateau phase of the action potential of the ureter. Na\(^+\) replacement with Li\(^+\) does not lead to recovery of this phenomenon and results in decay of intracellular Ca\(^{2+}\). Ca\(^{2+}\) channels also are required for the propagation of ureteral contractions and for electromechanical coupling in the ureter smooth muscle. Intracellular Ca\(^{2+}\) stores are apparently not essential for excitation-contraction coupling but contribute to a setting of the resting membrane potential, probably through the activation of Ca\(^{2+}\)-dependent K\(^+\) channels.

*Variable parameter of modulation of motor activity.*
Frequency and contraction force of ureteric peristalsis are two parameters, which can be modulated in different scenarios of urine transport. Distal propagation of the ureteric peristalsis can never take place in a higher frequency rate than that, which is imposed from the pyelocalyceal system. In other words, the ureteric peristaltic frequency can only be down regulated from proximal to distal. Contraction force of peristaltic activity depends to amount of smooth muscle contributing the circular layer of the ureter and its modulation status (Chapters 8-10).

**Modulation of ureteric frequency**

Ureteric peristaltic frequency is initiated by the pacemaker activity of pyelocalyceal system. Pacemaker activity may become more frequent or better synchronized in the renal pelvis. These parameters are determined by a) degree of filling of the renal pelvis that is monitored by fast mechano-receptor U1 units (see later) and/or b) chemical composition of the urine, e.g. different concentrations of K+, prostaglandin or H+, which is monitored by chemo-receptors R2 units (see later). This type of modulation affects the peristaltic frequency using pyelo-ureteral reflexes including an afferent, spinal cord segment and efferent branch. α-Adrenergic nerves potentiated by NPY+ nerves are probably the main efferent branches of these reflexes that increase the ureteric peristalsis.

Another possible mechanism to increase the peristaltic frequency at the level of renal pelvis is to decrease the inhibition of the activity pacemaker cells. CGRP+ nerves are intensively studied as local inhibitors. They are also present in the renal pelvis, but their density increases distally. These primary afferent nerves are able to inhibit peristaltic frequency, force, and release of mediators from the peripheral endings in a paracrine fashion when triggered. Diminishing this local inhibitory effect, which does not require a reflex arc, will result in a higher peristaltic frequency. The transient and local conduction block produced by CGRP appears to prevent antiperistalsis, especially during low frequency peristalsis of the ureter, when an anti-peristaltic wave would have a greater chance to propel urine back towards the kidney.

According to the _multi-coupled oscillator model_, the ureteropelvic junction is the place that summates and synchronizes the
excitation front from the renal pelvis \(^{19,21,27}\). Contra-phasic (desynchronized) excitation activities will thus extinguish their effect and decrease the ureteric peristaltic frequency subsequently. This mainly inhibitory regulation mechanism is dependent on spatial integration of the incoming excitation front from the renal pelvis \(^{44}\). Another possible regulatory function at the uretero-pelvic junction is the alteration of permissiveness to passage of activation waves, which is probably regulated by inhibitory CGRP+/ SP+ nerves \(^{73,76-79}\). α-Adrenergic nerves may affect the uretero-pelvic junction to increase the ureteric peristaltic activity \(^{80-81}\).

\textit{Modulation of peristaltic force.}

Mechanisms of modulation of peristaltic contraction force and the ureteric tone are concentrated at more distal portion of upper urinary tract. The amount of circular smooth muscle layer of the ureter is the anatomical substrate to generate a contraction.

\textbf{NEUROTRANSMISSION IN THE UPPER URINARY TRACT SUPPORTS A NEUROGENIC MODULATION PREMISE}

Using immuno-histochemistry and radio-immunoassay, a plethora of information has been accumulated concerning the expression of different receptors that presumably play a role in neuromuscular physiology of the ureter.

\textit{Cholinergic Nerves.} The density of AcetylCholinEsterase-positive (AChE+) nerve fibers increases from the renal pelvis downwards to the bladder, with the ureterovesical junction region being most densely innervated \(^{82,83}\). Some of these AChE+ nerves are sensory in origin and co-localize with Calcitonin Gene-Reactive Peptide (CGRP+) nerves \(^{84,85}\).

After nerve stimulation, acetylcholine is released from isolated human, guinea pig and rabbit renal pelvis and ureter \(^{86}\). Acetylcholine increases the tone and phasic contractile activity of different segments of the rat, guinea pig, horse and pig ureter \textit{in vitro} \(^{83,87-89}\). Acetylcholine also increases the peristaltic frequency and decreases the volume of boluses in the dog \textit{in vivo}, whereas the muscarinergic antagonist atropine does not change peristaltic
frequency. Administration of a muscarinic receptor agonist and antagonist in our chronic pig model also revealed that this receptor does not affect the peristaltic frequency or force of contraction in any significant way. Muscarinic receptor activation also does not change tonic activity of the upper urinary tract since the hydrostatic pressure in the renal pelvis was not affected after exposure to either carbachol or atropine.

Noradrenergic nerves. In several species, noradrenergic nerves have been demonstrated in all areas of the ureter and in the blood vessels of the adventitia, the muscle and the submucosal layers of the ureter. α and β adrenoceptors stimulate and inhibit, respectively, the contractility of the upper urinary tract. In dogs, intravenously administrated noradrenaline increases the peristaltic frequency and intra-ureteric pressure but decreases the bolus volume. The result is that the rate of fluid transport decreases. α Inhibition and β stimulation decrease peristaltic frequency and eventually suppresses ureteral peristalsis. In our chronically instrumented pigs, the β-adrenergic receptor was the main inhibitory factor. Administration of isoprenaline not only led to severe systemic β-adrenergic side effects, but also to a complete cessation of ureteric peristaltic activity. Propranolol reversed that inhibitory effect but failed to increase peristaltic frequency. α-Adrenergic stimulation resulted in more powerful and more frequent ureteric peristaltic activity. It also increased the ureteric tonic activity.
Substance P, Neurokinin A and Calcitonin Gene-Related Peptide

Substance P (SP) and neurokinin A (NKA) together are called tachykinine. Together with Calcitonin Gene-Related Peptide (CGRP), they are present as neurotransmitters in afferent nerves of mammalian the upper urinary tract. The SP+/NKA+/CGRP+ fibers run parallel to the long axis of each of the muscle layers. In the ureter, the fibers accumulate in the sub- and intramucothelial areas and in the muscle layer, and decrease in density from the proximal to the distal end of the ureter. In human proximal ureter, 17% of nerves are SP+/CGRP+, this number decreasing to approx. 4% in the distal ureter. These receptors are mostly located around blood vessels and in the submucosa.

Neuropeptide Y

Neuropeptide Y-positive (NPY+) nerves have been reported in the human, rat and horse ureter. NPY co-localizes with noradrenaline in sympathetic nerves of noradrenergic motor origin that supply the ureter. In the horse, the density of NPY+ nerves is maximal at the UVJ. Approximately 80% of human intramural nerves in the ureter are NPY+. Approximately 50% of all nerve profiles in the human ureter show co-localization with tyrosine hydroxylase (TH) and NPY, and a further 30% of nerve profiles a co-localization of NPY and vasoactive intestinal polypeptide (VIP), but not TH. Both NPY+/VIP+ and NPY+/TH+ nerves are distributed around blood vessels, localizing to the inner and outer muscle layers, respectively. NPY administration does not affect ureteric muscle tone in vitro, but potentiates the contractile responses to noradrenaline in a concentration-dependent manner. In our chronic animal model we did not study these receptors individually because of their additional role in adrenergic neurotransmission.

Nitrergic nerves

Nitric oxide synthase-positive (NOS+) nerves have been described in human, pig and sheep ureters. NOS+ nerves are distributed to the ureter smooth muscle, around arteries, and in the submucosal layers. These nerves co-localize with both VIP and NPY, and in humans are also found in the ureterovesical ganglia. The relaxing effect of NO on smooth muscle, together with the inhibition
of ureteric relaxation by NO antagonists in the pig model suggest that NO plays a fundamental role in the prevention of vesico-ureteral reflux \(^{111,108}\). Inhibition of NOS resulted in our chronic animal model study in an increase of the phasic contraction force in the distal ureter and in the hydrostatic pressure in the renal pelvis. Exogenous NO donors did not affect ureteric peristalsis.

**SENSORY ACTIVITY IN UPPER URINARY TRACT AND ITS LOCAL MOTORIC EFFECT**

*Afferent chemo-receptor units*
Both mechano- and chemo-receptor afferent units are present in the renal pelvis \(^{112-116}\). Chemo-receptive afferent units have been classified as R1 and R2 units \(^{69,117,118}\). Chemo-receptor R1 units are located around blood vessels and are activated during ischemia. Chemo-receptor R2 units are sensitive to backflow of concentrated urine, bradykinin and the concentration of Na\(^+\) and K\(^+\). R2 chemo-receptors sense the renal medullary interstitial fluid and the final urine produced. The administration of for example SP into the rat renal pelvis increases the afferent discharge of these nerves and induces a contralateral diuretic and natriuretic reflex response that mimics that produced by increasing ureteral pressure \(^{78,115,119}\). This *reno-renal reflex* is abolished by pretreatment with capsaicin, an alkaloid that depletes SP from sensory nerve endings. Both bradykinin and prostaglandin activate the same reflex that is activated by mechanical stimulation of the renal pelvis. Endogenous prostanoids amplify the afferent discharge induced by SP, bradykinin, and increased ureteral pressure \(^{114,120-123}\).

*Afferent mechano-receptor units*
Mechano-receptors in the renal pelvis are sensitive to changes in filling of renal pelvis with urine \(^{124}\). Mechano-receptors of the upper urinary tract have been divided in two main groups: fast U1 units (9% of all mechano-sensitive units) and slow U2 units (91% of all mechano-sensitive units). Fast U1 units have a low threshold to intraluminal distension and respond to contractions of the ureter. U1 units are also presumed to monitor peristalsis \(^{67,68}\). Slow U2 units, on the other hand, show a prolonged response to intraureteric pressure
rise between 5 to 30 mmHg. U2 units are not excited by active contraction \(^{67}\), although they can be excited by compression or distension. U2 units are obvious candidates for transmitting any information producing pain. U2 units were also reported to be chemo-sensitive, being excited by K\(^+\), bradykinin, and capsaicin, much like the poly-modal nociceptors commonly observed in other viscera \(^{67}\). Various chemical stimuli such as urine (> 800 mOsm/liter), bradykinin, or capsaicin are capable of stimulating U2 units \(^{66,16}\).

Intense stimulation of afferent ureteric nerves also induces transient changes of cardiovascular function. The ureter is innervated by a large population of U2 mechano-sensitive afferent units with high activation thresholds that do not respond to peristalsis \(^{16,61-68}\). The human pain threshold is reached at a mean ureteral pressure of approximately 30 mmHg. Increases of intraluminal pressure or application of capsaicin to the guinea pig ureter is known to cause a transient increase in systemic blood pressure, heart rate, and changes in respiratory frequency, all indicative of a pain response \(^{16,66}\).

Controversy exists about the fundamental character of ureteric colic. The complete intraluminal obstruction of the ureter provokes restlessness and other behavioral alterations in conscious sheep \(^{125}\). Electrical stimulation of the ureter induces pain and muscular hyperalgesia in rats, but ligature of the ureter on its own does not produce hyperalgesia. This shows that ureteral occlusion as such is not the cause of pain \(^{126-129}\). The combined administration of an antimuscarinic agent and of a cyclo-oxygenase inhibitor eliminates the referred hyperalgesia induced by artificial calculi in rats \(^{126,127}\). Partial obstruction induced by placement of an artificial stone in the ureter produces an increase in the amplitude and a reduction in the frequency of ureteral contractions, as well as a decrease in baseline pressure \(^{130}\). Total obstruction or ligation of the ureter, however, abolishes ureteric motility totally. Intraureteric instillation of capsaicin to produce pain relief in patients suffering from loin pain-hematuria syndrome resulted in a lasting (> 2 months) relief of pain symptoms without evidence of adverse effects on renal function \(^{131}\).

*Sensory nerves and their local effect on ureteric motility*
Afferent nerves involving in upper urinary tract transmit data to the central nervous system to monitor its function and possible noxious agents. They also have a direct local effect on the upper urinary tract motility \(^{4,17,53,97,132-134}\). Capsaicin, electrical stimulation of afferent nerves and bacterial peptides cause a \(\text{Ca}^{2+}\) dependent release of SP, NKA (tachykinins) and CGRP. SP and NKA are powerful positive chronotropic and inotropic agents for ureteric motility. They induce a marked potentiation of phasic and tonic contractility \(^{53,134}\). Locally released sensory neuropeptides cause vasodilatation, an increase in microvascular permeability and mast cell degranulation, as well as recruitment of inflammatory cells to mount a so-called “physiologic neurogenic inflammation”. This neurogenic inflammation may play a key role in urolithiasis and urinary tract infections causing a relative dysfunction of peristalsis \(^{135-138}\).

CGRP inhibits the motility of the isolated renal pelvis and ureter \(^{97-98,139-140}\). The sensitivity to capsaicin-sensitive CGRP+ nerves appears to be present mostly in the distal upper urinary tract. In this way, any anti-peristalsis generated by stimulation of latent pacemakers is suppressed distally \(^{137,141}\). The most important functions of CGRP+ nerves with respect to smooth muscle relaxant activity are stimulation of adenylcyclase and elevation of intracellular cAMP, generation of nitric oxide (NO) and activation of \(\text{K}^+\) channels (hyper-polarization) as described.
Table 1: Survey of neurotransmitter receptors with their topographic distribution and physiological effects in the upper urinary tract

<table>
<thead>
<tr>
<th>Neurotransmitter receptor</th>
<th>Distribution</th>
<th>Highest density</th>
<th>Motor activity</th>
<th>Sensory activity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Proximal</td>
<td>Distal</td>
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<td>Inotopic</td>
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<tr>
<td>Cholinergic</td>
<td>+ ++</td>
<td>Near UVJ</td>
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<td>Submucosally;</td>
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<td>around vessels</td>
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<td>in sub-mucosa</td>
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<td>SP/NKA</td>
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<td>Chemoreceptor</td>
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<td>neurogenic</td>
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<td>: U1, U2, R2</td>
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<td>NPY+</td>
<td>+ ++</td>
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References

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