Abstract

Introduction: This article sets out to be a review regarding agents that affect contraction and relaxation of the ureter in order to establish a basis for current and future treatments for upper urinary tract obstruction. Material and Methods: A complete review of the English literature using MEDLINE was performed between 1960 and 2007 on ureter physiology and pharmacology with special emphasis on signal transduction mechanisms involved in the contractile regulation of the human ureter. Results: Activation of muscarinic and adrenergic receptors increases the amplitude of ureteral contractions. The sympathetic nerves modulate the contractions by α-adrenoceptors and relaxation by β-adrenoceptors. The purinergic system is important in sensory/motor functions and ATP is an important non-adrenergic non-cholinergic (NANC) agent causing contraction. Nitric oxide (NO) is a major inhibitory NANC neurotransmitter causing relaxation. Serotonin causes contraction. Prostaglandin F2α contracts whereas prostaglandin E1/E2 relaxes the ureter. Phosphodiesterases (PDE) and the Rho-kinase pathway have recently been identified in the human ureter. PDE-IV inhibitors, K⁺ channel openers, calcium antagonists, α1-adrenoceptor antagonists and NO donors seem to be promising drugs in relieving obstruction and facilitating stone passage. Conclusions: Further understanding of the ureteral function and pharmacology may lead to the discovery of promising new drugs that could be useful in relieving ureteral colic, facilitating spontaneous stone passage, preparing the ureter for ureteroscopy as well as acting adjunctive to extracorporeal shock-wave lithotripsy.

Introduction

Urolithiasis is a common disease worldwide and its incidence in Western countries is growing [1]. Urinary stones are frequently located in the ureter and most ureteral stones are reported to be located distally [2]. Stones <3 mm in diameter have a better chance to pass spontaneously in the majority of cases, whereas stones >6 mm in the ureter are unlikely to pass in most situations [3]. Therefore, active watchful waiting forms one of the treatment options in some clinical scenarios. Minimal invasive treatment strategies such as extracorporeal shock-wave lithotripsy and ureteroscopy are frequently applied procedures in ureteral stone disease. However, indications for watchful waiting might be extended by addition of so-called 'expulsive medical therapy'.

One of the most important functions of the pyeloureteral complex is to ensure the unidirectional transport of urine from the kidney to the urinary bladder. Ureteral peristalsis is initiated by spontaneous activity of renal
pelvis pacemaker cells; thereafter electrical and mechanical activities are conducted to inactive distal regions [4, 5]. Although ureteral peristalsis is essentially regulated by the myogenic mechanisms [6–8], neurogenic factors also play an important role in this process [5]. Electrical activity is propagated distally from cell to cell causing a contraction wave propelling urine distally in boluses [9]. Extra- and intracellular microelectrode recordings have identified two populations of smooth muscle cells as well as a population of renal interstitial cells that all display spontaneous electrical activity [10]. Several mechanisms are proposed in the physiological control of ureteral peristalsis and smooth muscle tone. Of note, an increase of cytoplasmic free calcium concentration is regarded to be the principal mechanism in smooth muscle contraction. The ureter has an efferent and an afferent innervation including cholinergic, adrenergic and non-adrenergic non-cholinergic (NANC) components [5]. Innervation of the lower ureter is shown to be denser than the upper ureter in humans [11]. The cellular mechanisms underlying neurogenic and myogenic contractions are not exactly elucidated and need further research.

Many factors are involved in the interaction between the ureter and stones, therefore it is prudent to understand mechanisms involved in the contraction and relaxation of the ureter. These mechanisms would possibly lead to discovery of new drugs that might facilitate stone passage, relieve symptoms and act as an adjunctive treatment to existing conventional modalities. The present review focuses on signal transduction mechanisms involved in the contractile regulation of the human ureter (table 1). We provide an overview of neurotransmitter pathways and discuss mechanosensory signal transduction mechanisms and their clinical relevance in the upper urinary tract obstruction.

**Table 1.** Receptors and agents involved in contraction and relaxation of the ureter

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tors leads to ureteral contraction via activation of phospholipase C (PLC), which in turn leads to formation of second messengers (inositol trisphosphate (IP₃) and diacetylglycerol (DAG)) [17] (fig. 1). IP₃ is involved in the mobilization of calcium from sarcoplasmic reticulum [18], whereas DAG increases calcium influx across the cell membrane via the activation of protein kinase C [19]. However, stimulation of muscarinic receptors (M₃) leading to contraction of the urinary bladder was shown to cause Ca²⁺ entry via nifedipine-sensitive channels and Rho kinase activation as well as phospholipase D and store-operated Ca²⁺ channels, albeit to a lesser extent [20, 21]. Therefore, the role of the aforementioned mechanisms in the bladder needs further attention in the ureter. On the other hand, activation of Gᵢ proteins, consequently inhibiting adenylate cyclase activity by formation of cAMP, also plays a role in contractile mechanisms via inhibiting relaxation (fig. 1) [22]. Acetylcholine is a cholinergic agonist and functions both as a neurotransmitter at preganglionic parasympathetic neuroeffector junctions (nicotinic sites) and postganglionic parasympathetic neuroeffector junctions (muscarinic sites). The presence of muscarinic M₂ receptors in the porcine intravesical ureter and M₁, M₃ and/or M₄ subtypes seems to be responsible for the cholinergic innervation of the ureter in the porcine model [22]. Stimulation of muscarinic receptors by carbachol causes contraction of the pig isolated intravesical ureter [23]. However, Roshani et al. [24] demonstrated that smooth muscle motor activity in the mid and the distal ureter was not modulated by muscarinic receptors in the porcine model. In another study, cholinergic receptor stimulation by muscarinic agonist carbachol in anesthetized dogs had a suppressive effect on ureteral pressure and peristalsis in obstructed ureters [25]. Tomiyama et al. [26] suggested that carbachol-induced contraction in the isolated canine ureter was mediated through the M₃-receptor.

**Adrenergic Pathways**

α- and β-adrenoceptors were first detected in the human ureter in the 1970s and α-adrenoceptors were shown to predominate in number [27].

α₁- and α₂-Adrenoceptors

α₁-Adrenoceptors have been detected both in animal and human ureters [28, 29]. Similar to muscarinic receptors, activation of α₁-adrenoceptors can activate the PLC/IP₃/DAG pathway and may cause contraction (fig. 1). The density of α₁-adrenoceptors (α₁A and α₁D) in the ureteral smooth muscle has been shown to be greater than other adrenoceptors [30]. Blockage of these receptors inhibits basal tone, peristaltic frequency and ureteral contractions [31]. Noradrenaline, an α-adrenergic agonist, increases ureteric peristaltic activity and muscle tone upon stimulation. Although α₁D-adrenoceptor subtype has been shown to predominate in the human ureter at the mRNA level [32], this does not mean that these receptors, expressed at the protein level, play the functional role as shown by other studies [33]. Tamsulosin, selective α₁A- and α₁D-antagonist, is commonly used in the management of benign prostatic hyperplasia [34]. However, due to its selective anti-adrenergic effects, it has also successfully been used in patients with distal ureteric stones and was found to increase stone expulsion rate, decrease expulsion time and reduce the need for hospitalization and endoscopic procedures [35, 36]. Apart from tamsulosin, other α-re-

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**Fig. 1.** Second messenger systems in the ureter. Ach = Acetylcholine; ATP = adenosine triphosphate; NE = noradrenaline; PLC = phospholipase C; IP₃/DAG = inositol trisphosphate/diacetylglycerol; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A; AC = adenylate cyclase; MLC = myosin light chain; MLCP = myosin light chain phosphatase; MLC p’tase = myosin light chain phosphatase, M₂-, M₃- and β₂-receptors are coupled to G proteins, + = activation, – = inhibition.
ception-blocking agents in combination with glucocorticoids and Ca\(^{2+}\) entry blockers have also successfully been used in the management of ureteric stones. Michel and de la Rosette [37] have recently published an excellent review summarizing α-blocker treatment for urolithiasis.

**β-Adrenoceptors**

When norepinephrine is released from adrenergic nerves, stimulation of β-adrenoceptors activates adenylate cyclase to increase cAMP. Then, cAMP activates protein kinase A which in turn causes relaxation (fig. 1) [38]. The relaxant action of cAMP is partially related to its effect to cause an uptake of calcium in the sarcoplasmic reticulum which in turn decreases the free intracellular calcium concentration. Although cAMP is a second messenger for β-adrenoceptors, recent experimental studies carried out in rat urinary bladders suggest that, in addition to the cAMP-dependent pathway, Ca\(^{2+}\)-activated K\(^+\) channels are also involved in the β-adrenoceptor agonist-induced relaxation in pre-contracted detrusor muscle [39–41]. It has been shown that both β\(_2\) and β\(_3\)-adrenoceptor subtypes are detected in the human ureteral smooth muscle and they mediate induced adrenergic stimulation by causing ureteral relaxation [42]. On the other hand, β\(_1\)-adrenoceptors have little relaxing effects compared to β\(_2\)- and β\(_3\)-receptors [42]. In an experimental study in rabbits, it was demonstrated that ureteral smooth muscle relaxation by β-adrenergic stimulation reduced ureteral wall tension [43]. Similarly, the selective β\(_3\)-adrenoceptor agonist (CL-316243) appears to be useful in reducing ureteral pressure above the obstructed ureteral site, in promoting ureteral relaxation and in increasing urine flow particularly around the point of obstruction in dogs [44]. In an experimental study on mice ureters, a mixture of β\(_3\)- and putative β\(_4\)-adrenoceptor agonists was shown to consistently reduce pacemaker activity via mediation of putative β\(_4\)-adrenoceptors [45]. Similarly, KUL-7211, a β-receptor agonist, has been demonstrated to selectively stimulate β\(_2\)- and β\(_3\)- ureteral adrenoceptors leading to relaxation in rat ureters. The authors concluded that this agent might prove useful to relieve ureteral colic and promote stone passage in human subjects [46].

**NANC Pathways**

**Purinergic System and ATP**

Purinergic mechanosensory transduction has been suggested to play a role in causing visceral pain [47]. It has been shown that guinea pig ureter epithelium releases adenosine 5'-triphosphate (ATP) both tonically (at rest) and phasically (on distension) stimulating afferent nerve terminals via purinergic receptors [48]. The purinergic system plays an important role in sensory and motor functions in the ureter and ATP is an excitatory transmitter that causes contraction upon release by neuronal and non-neuronal sources (fig. 2) [49]. ATP is released with mechanical stretch and electrical field stimulation and contribution of ATP release from neuronal sources is much lower compared to non-neuronal sources [50]. ATP, present on subepithelial sensory nerve fibers, acts on purinoceptors (P2X and P2Y) in humans and in pigs and sends information to the pain centers located in the brain and initiates local reflexes [47, 49, 50]. Therefore, ATP was suggested to be an important NANC component [50]. Of note, ATP activates P2X purinoceptors (ligand-gated cation channels) that promote influx of extracellular Ca\(^{2+}\) into muscle cells (fig. 1). Activation of P2Y\(_3\) or P2Y\(_4\) purinoceptors induces smooth muscle contractions via a PLC/IP\(_3\) signaling pathway and causes release of intracellular Ca\(^{2+}\) [51]. It has been demonstrated that distension of the guinea pig ureter releases ATP from the epithelium in a pressure-dependent manner and this process activates P2X\(_3\) purinoceptors on the subepithelial sensory nerves causing pain and contraction [52]. Therefore, drugs targeting purinergic receptors might act as analgesics in the treatment of ureteral colicky pain. An additional advantage would be facilitating spontaneous ureteral stone passage that warrants further research.
Nitric Oxide (NO)

L-Arginine-derived NO is the major inhibitory NANC neurotransmitter in the lower urinary tract [49]. Neuronal NO synthase (NOS)-positive neuronal axons and nerve-ending-like structures have been detected in muscular layers of the human ureter suggesting that ureteral relaxation may involve the NO pathway [53]. NOS-reactive nerves have also been demonstrated immunohistochemically in the human intravesical ureter. A recent study suggested that the L-arginine/NO/cyclic GMP pathway may play a role in the regulation of the valve function of the ureterovesical junction [54]. NO has been shown to have a smooth muscle-relaxing effect in various animal species and in humans. Mastrangelo et al. [55] showed that urothelium-produced NO inhibits contractile responses in the proximal ureter in rats. NOS was also demonstrated in the nerve fibers of porcine intravesical ureter and was suggested to mediate the inhibitory neurotransmission [56]. Neuronal NOS-positive nerves have also been shown in the human ureter, particularly in the distal part which seems to have an important function regarding peristalsis and ureterovesical junction motility [57]. Therefore, this pathway may also be a new target for new drugs producing relaxation of the human ureter.

Histamine

It was demonstrated that two types of histamine receptors modulate the contractile activity of the human ureter, whereby histamine H1-receptors cause contraction and histamine H2-receptors cause slight relaxation [58]. H1-receptors have been shown to be predominant over H2-receptors with regard to efficacy of coupling in the human ureteral muscle. However, administration of both H1- and H2-receptor antagonists was not able to modify the basal tone and motility of ureteral strips [59]. Similar to humans, histamine had a spasmogenic effect in the canine ureter [60], causing contraction via H1-receptors in the sheep ureterovesical junction [61] and inducing relaxation via H2-receptors in the buffer ureter [62].

Serotonin (5-Hydroxytryptamine, 5-HT)

5-HT was shown to increase the tone of the pig intravesical ureter via 5-HT2A receptors [63]. 5-HT2 receptor antagonists (ketanserin and methysergide) antagonized the 5-HT-induced ureter peristalsis and decreased the frequency of spontaneous ureteral contractions in the pig and were suggested as being promising drugs for the management of ureteral colic [64].

5-HT has been hypothesized to act as a potential neurotransmitter-mediating contraction in the human ureteral smooth muscle [65]. However, the receptor responsible for the contractile response of the 5-HT in the human ureter could not be clearly detected [66]. Ondansetron, a selective 5-HT3 receptor antagonist, was found to have acceptable pain-relieving properties in patients with acute ureteral colic, suggesting that 5-HT3 receptors might also play an important role in the human ureteral function [67].

Prostanoids

Prostanoids (prostaglandins and thromboxanes) are synthesized by cyclooxygenase (COX) enzymes which are found in two isoforms: COX-1 (a constitutive form) and COX-2 (an inducible form) [49, 68]. The isoform COX-1 is normally expressed in many tissues and organs, and plays an important role in maintaining physiologic functions. COX-2 is another isoform which can be induced by various stimuli, including stretching of the muscle, mucosal injuries, nerve stimulation, and inflammatory mediators involving the ureter [49]. Prostanoids (prostaglandins (PGs), thromboxanes, prostacyclins) seem to play an important role in ureteral contractility. It has been demonstrated that PGE2 increases contractility in obstructed ureters and relaxing normal and non-obstructed ureters in pigs. Thus it has been suggested as an important target in ureteral obstruction [69]. Although published results vary, ureteral smooth muscle seems to be contracted by PGF2α and relaxed by PGE1 and PGE2 in animals and humans [70].

It has been demonstrated that COX-2 mRNA and protein levels are up-regulated in obstructed human ureters [68]. Norregaard et al. [71] showed that COX-2 is increased in obstructed rat and human ureters. Induction of COX enzymes increases prostanoid synthesis which is associated with ureteral obstruction. 15-Hydroxyprostaglandin dehydrogenase (PGDH) is the enzyme responsible for PG degradation. PGDH enzyme activity is demonstrated to be suppressed in the human ureter during obstruction. Therefore, increased prostanoid concentrations in ureteral obstruction seem to be due to both increased synthesis and decreased degradation [72].

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the management of renal colic because of their spasmytic properties. Diclofenac (a non-selective COX inhibitor) and NS-398 (a selective COX-2 inhibitor) were demonstrated to inhibit ureteric contractions [73]. Similarly, celecoxib (a selective COX-2 inhibitor) and indomethacin (non-selective COX inhibitor) both inhibit PG release in the ureter even in the presence of COX-2 induction [74]. As a result, selective COX-2 in-
Inhibitors may be useful with fewer side effects in the management of patients with renal/ureteral colic.

**Neuropeptides**

The ureter contains capsaicin-sensitive sensory nerves [75]. Neuropeptides such as vasoactive intestinal polypeptide (VIP), endothelins, tachykinins and angiotensins are synthesized in the lower urinary tract and their roles in ureteral function is not clear. Release of tachykinins, substance P (SP), neurokinin (NK) A and neuropeptide K (NPK) from sensory nerves cause excitation. In contrast, release of calcitonin gene-related peptide (CGRP) causes inhibition of ureteral peristalsis [76].

**Tachykinins**

NKA, NKB and SP are tachykinins that are present in primary afferent nerves which mainly have afferent functions [77]. It was demonstrated that tachykinins cause a direct contraction of the pig intravesical ureter via NK-2 receptors. SP and NKA were shown to enhance the NANC excitatory neurotransmission of the pig intravesical ureter [78]. Peptide-containing nerves VIP, NPY, CGRP and SP were all demonstrated particularly in the lower human ureter [11]. NK-2 receptor is the main receptor leading to tachykinin-induced contraction of the human ureter. SR-48,968, NK-2 receptor antagonist, reduced spontaneous ureteral contraction rate by 97% [79].

**Vasoactive Intestinal Polypeptide (VIP)**

VIP and adenylyl cyclase-activating polypeptide were demonstrated to relax the pig ureter via smooth muscle receptors [80] and also VIP receptors and SP-containing nerves were demonstrated in the human ureter [11].

**Calcitonin Gene-Related Peptide (CGRP)**

CGRP inhibits electrically-evoked myogenic contractions of the guinea pig ureter leading to relaxation [82]. In the human ureter, CGRP-positive nerve density was detected to be lower than other species and these nerves were mainly found around the blood vessels and in the submucosa rather than the smooth muscle [11, 83, 84].

**Neuropeptide Y (NPY)**

It was shown that equine intravesical ureter has rich NPY innervations suggesting the potential contractile motor activity of this peptide. NPY potentiates phasic contractions and tone created by noradrenaline via Y2-receptors [85]. NPY-containing nerves were also demonstrated in the human ureter [11]. A dense innervation of the pyeloureteral junction with intrinsic obstruction type concerning NPY- and VIP-containing nerves were shown in humans [83]. Further research is needed in order to explore the functional relevance of neuropeptides in ureteral physiology and pharmacology.

**Rho-Kinase Pathway**

The increase in cytoplasmic free Ca$^{2+}$ concentration ([Ca$^{2+}$]$_i$) is regarded to be the principal mechanism in smooth muscle contraction. Secondary mechanisms that can modulate smooth muscle contractility independently of [Ca$^{2+}$]$_i$, level have recently been identified. The Rho-kinase pathway has been suggested to play an important role in ureteric smooth muscle contractility independent of intracellular Ca$^{2+}$ level [86]. It has been shown that Rho-kinase is expressed in the sheep ureter and it mediates agonist- and EFS-induced contractions as well as spontaneous contractile activity [87]. Activation of Rho-kinase inhibits smooth muscle myosin phosphatase by phosphorylating its regulatory subunit, which in turn prevents the dephosphorylation of myosin light chain, leading to Ca$^{2+}$ sensitization of the smooth muscle [88]. Therefore, inhibition of Rho-kinase may result in smooth muscle relaxation. Y-27632, a specific Rho-kinase inhibitor, has recently been demonstrated to relax smooth muscle preparations in the human ureteral smooth muscle [88]. Other studies also demonstrated the presence of a Rho-kinase pathway in ureters of different animal species and its inhibition led to ureteral relaxation [87, 89]. We have recently demonstrated that Rho kinase activity has been significantly increased in obstructed rabbit ureters compared to non-obstructed ureters suggesting that Rho kinase inhibitors may serve as new therapeutic targets in the treatment of ureteral colic/stones [unpubl. data]. There is a strong belief among scientists that the Rho-kinase pathway plays an important role in the complex mechanism of human ureteral contractility and tone.

**Miscellaneous**

**Adenosine**

Adenosine was demonstrated to relax the pig intravesical ureter via activation of A2B receptors, located in the smooth muscle, independent from prostanoids or NO [90].

**Phosphodiesterases (PDE)**

The PDE enzyme family is responsible for the degradation of cAMP. Thus, PDE inhibitors increase cAMP levels leading to ureteral relaxation. PDE enzymes regu-
late intracellular cyclic nucleotide metabolism leading to contraction and relaxation of the muscle tissue. Cyclic nucleotide PDE influences smooth muscle tone by decreasing the level of cyclic nucleotides. PDE I, II and IV were recently identified in the human ureter and their inhibition were all shown to cause relaxation [91]. A ureter-relaxing effect of particularly PDE IV inhibitors might be useful in ureteric obstruction. Rolipram, a PDE IV inhibitor, and forskolin, an adenylate cyclase activator, were both shown to relax pig ureteral preparations experimentally [80]. Kuhn et al. [92] demonstrated that rolipram and E 4021 (PDE5 inhibitor) relaxed human ureteral strips and concluded that use of selective PDE inhibitors (particularly isoenzymes 4 and 5) might be useful in the management of ureteral stones and ureteral colic.

**K⁺ Channel Openers and NO Donors**

The relaxing properties of the ATP-sensitive K⁺ channel opener and NO donor nicorandil and the new K⁺ channel opener PKF 217-744b were investigated on isolated human ureteral tissue in vitro and in intact ureters of anesthetized pigs in vivo [93]. Both drugs reduced the contraction frequency of the pig ureter after intravenous and topical administration in vivo. Therefore, both PKF 217-744b and nicorandil are seen as promising drugs for clinical application in patients with acute ureteral colic to relieve obstruction and facilitate stone passage or to relax the ureter before ureteroscopy [93]. Cromakalim, a potassium channel modulator, has also been shown to induce a concentration-dependent inhibition of contractions in the isolated human ureteric segments. Cromakalim is also a promising agent with regard to human ureteric contractility [94].

**Calcium Channel Blockers**

Calcium antagonists are known to reduce ureteral contractions [95]. Sahin et al. [96] demonstrated that both endogenous PG synthesis and influx of calcium from the extracellular space is responsible for the spontaneous rhythmic activity of the ureter. Calcium-channel blocking drugs and steroids have been used to reduce ureteral tone and decrease inflammation in patients with ureteral stones [97]. It has been demonstrated that nifedipine (calcium-channel blocker) and 5-methylurapidil (α₁-receptor blocker) produced greater ureteric relaxation in vitro than diclofenac in human ureteral strips causing relaxation mainly in the distal ureter [98]. It has been shown that stone-free rates were significantly greater and time to stone passage was significantly reduced after the use of nifedipine in patients with ureteral stones [97].

<table>
<thead>
<tr>
<th>Table 2: Possible drug groups that cause relaxation of the ureter</th>
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<tr>
<td>Selective α-receptor blockers</td>
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<td>Selective β-receptor agonists</td>
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<td>Drugs targeting nitric oxide pathway (NO donors)</td>
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<td>Selective COX-2 inhibitors</td>
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<td>Phosphodiesterases (PDE IV inhibitors)</td>
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<td>Antimuscarinic agents</td>
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<td>Rho-kinase inhibitors</td>
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**Conclusions and Future Perspectives**

Currently, agents such as selective α-adrenoceptor (α₁A and α₁D) antagonists, β-adrenoceptor (β₂ and β₃) agonists, 5-HT₃ receptor antagonists, PG and COX antagonists, PDE inhibitors, K⁺ channel openers, NO donors, calcium antagonists and Rho-kinase inhibitors seem to be promising agents leading to relaxation of the ureter and thus may be useful for the management of ureteral obstruction (table 2). However, it is not very well known to what extent these mechanisms participate in the ureteral function. Therefore, experimental studies using human ureteral tissues and investigating the percent of contribution of each mechanism to ureteral contractile response might be very helpful to guide current research in relation to ureter pharmacotherapy. A better understanding of mechanisms involved in contraction and relaxation of the human ureter could lead to the discovery of new drugs that might be useful in relieving ureteral colic, facilitating spontaneous stone passage, preparing the ureter for ureteroscopy as well as acting adjunctive to extracorporeal shock-wave lithotripsy.
References


