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Current and emerging pharmacological targets for medical expulsive therapy

Running title: Targets for medical expulsive therapy

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Abstract:

The primary goals of medical expulsive therapy are to increase the rate of stone expulsion along the ureter to avoid ureteral obstruction and reduce ureteral colic, and thus avoid the need for surgical and more invasive interventions. This review focuses on the findings from *in vivo* and *in vitro* animal and human studies that have investigated the pharmacological mechanisms controlling ureteral motility and their translation to current and potentially new clinically used drugs for increasing rate of stone expulsion along the ureter. The complicated contractility profile of the ureter, which alters with age, tissue segment region, orientation, and species, contributes to the difficulty of interpreting studies on ureteral pharmacology, which translates to the complexity of discovering ideal drug targets for medical expulsive therapy. Nevertheless, the current drug classes clinically used for patients with stone lodgement include α_1-adrenoceptor antagonists, calcium channel blockers and NSAIDS, while there are promising targets for drug development that require further clinical investigations including the phosphodiesterase type 5 enzyme, β-adrenoceptors and 5-HT receptors.

Background

Urolithiasis, also known as urinary stones or calculi, is a common condition affecting approximately 1 in 10 individuals with increasing incidence and prevalence worldwide. It is associated with a substantial economic impact and in the United States alone, it is estimated that US $2.1 billion was spent on management of the disease in the year 2000 and the expenditure is projected to reach US $4.1 billion by 2030 [1].

Calculi form in the kidney where they are typically asymptomatic. However, if they move along the ureter, this can cause an excruciating colicky pain known as renal or ureteric colic.. Choosing treatment and management modalities for urolithiasis is dependent on stone size, location, composition, and the exhibiting symptoms. Patients often present to the emergency department with severe pain requiring analgesia. Patients with obstructed infected kidneys require urgent decompression with either nephrostomy or stent while those who are afebrile, with normal contralateral kidney and normal renal function would often be managed conservatively[2]. The likelihood of spontaneous calculus passage varies greatly between patients, and has been shown to be dependent on stone size; stones that are less than 4mm in diameter have a high chance of passing spontaneously, while stones greater than 5mm generally do not [3]. In cases of asymptomatic and smaller stones, 'watchful waiting' can be recommended, with or without the addition of medical expulsive therapy [2].

The primary goals of medical expulsive therapy are to increase the rate of stone expulsion along the ureter to avoid ureteral obstruction and reduce ureteral colic, and ultimately, avoid the need for surgical and more invasive interventions which are associated with complications. Effective medical expulsive therapy can benefit patients by reducing the need for hospitalization and invasive surgical procedures to manage the condition. Additionally, this pharmacological

therapy can also be beneficial for patients who have undergone shockwave lithotripsy, a non-invasive procedure where shock waves are administered to fragment stones, to assist the passage of fragmented stones. This review summarises *in vitro* and *in vivo* studies of both animal and human tissues that have investigated the pharmacological mechanisms controlling ureteral motility, and their translation to current clinically used drug classes for medical expulsive therapy. We also outline emerging pharmacological targets that are believed to have the potential to be the future of effective medical expulsive therapy but require more clinical studies to demonstrate their efficacy.

Anatomy and physiology of the ureter

The adult human ureter is a muscular tube consisting mainly of smooth muscle cells lined by a multilayered transitional epithelium, the urothelium, and can be anatomically divided into three parts: the proximal, middle and distal ureter. There are two distinct layers of smooth muscle cells: an inner longitudinal layer, responsible for ureteral shortening and the movement of urine, and the outer circular layer that coats the ureteral walls and contracts to generate intraluminal pressure [4]. Ureteral peristalsis is the propagation of waves of smooth muscle contraction and relaxation down the muscular tube to propel urine from the kidneys to the bladder, which is the primary function of this organ [4]. This process is regulated by the renal pacemaker cells which are the interstitial cells of Cajal (ICC)-like cells, found in the renal pelvis and proximal regions of the human ureter [5]. The absence of the ICC-like cells in the distal regions of the ureter suggests that ureteral peristalsis is initiated at the renal pelvis and the proximal region of the ureter then conducted myogenically down the ureteral tube [5]. The most common location for lodgement of ureteral calculi is the distal ureter approaching the ureterovesical junction (also termed the intravesical ureter), where it enters the bladder [3].

Although investigating pharmacological agents that suppress ureteral contractility might appear to be a simple and straightforward undertaking, a number of factors add complexity to this task. It is well established that isolated tissues from other parts of the urinary tract, like the bladder and urethra, exhibits tonic contraction upon stimulation with exogenous agonists [6]. However, isolated ureteral tissues develop bursts of phasic activity that varies in frequency and amplitude depending on the receptor system stimulated, which adds complexity to measuring these contractile responses [7]. The complicated contractility profile exhibited by the ureter in response to activation of various receptors using exogenous agonists is illustrated in Figure 1.

Additionally, changes in receptor expression and functionality along the length of the ureter [8] and differences in pharmacology between circular and longitudinal smooth muscle [4] have also been demonstrated. Significant differences between species are also observed. Although ureters from most species including humans, pigs and guinea pigs are predominantly under the control of the adrenergic system, the rat ureter appears to respond mainly to muscarinic receptor stimulation [9], suggesting that the choice of species is important in pre-clinical studies. Porcine tissues are commonly utilised as a reliable model for the pharmacological study of this tissue since they portray similar contractile activities and responses to those in human. Age is also a factor shown to alter the contractility exhibited by this tissue [7] and therefore increases considerably the difficulty of investigating ureteral pharmacology, which translates to the complexity of discovering ideal drug targets for medical expulsive therapy. In spite of this, several drug classes are currently used clinically in patients with ureteric stones to improve the passage of stones and mostly, act to induce ureteral smooth muscle relaxation.

Current Medical Expulsive Therapy

α-adrenoceptor antagonists

The earliest ureteral studies suggest that both α-adrenoceptors and β-adrenoceptors are involved in regulating rat ureteral contractility [10]. Subsequently, *in vitro* functional studies of isolated porcine and human ureters suggest that the predominant response to noradrenaline is contraction, implying the functional dominance of α_1-adrenoceptors over β-adrenoceptors [11, 12]. There are three main subtypes of α_1-adrenoceptors, α_{1A}, α_{1B}, and α_{1D}, while the α_{1L} is a phenotype of α_{1A}-adrenoceptor showing atypical low-affinity for prazosin. The 4 subtypes of α_1-adrenoceptors are predominantly coupled by G-proteins of the $G_{q/11}$ family to activate the phospholipase C mechanism, which stimulates smooth muscle contraction. In the human ureter, mRNA expression for the three main subtypes of the α_1-adrenoceptors have been observed [13]. Immunohistochemical staining and radio-ligand binding later demonstrated the prevalence of the α_{1D} and α_{1A}-adrenoceptor subtypes over the α_{1B}-adrenoceptor subtype in the human ureter [8]. Although the expression of α_{1D}-adrenoceptors was observed to be the greatest, a functional pharmacological study performed on the isolated human ureter suggested that the α_{1A}-adrenoceptor plays the major functional role in mediating contractile responses [14]. Similar observations were found in the isolated porcine ureter, cementing its similarity and reliability as a model for pharmacological studies on this tissue [11].

Despite these initial findings, the use of α_1-adrenoceptor antagonists as an agent for medical expulsive therapy was not investigated in the clinical setting until the 21st century. Clinical trials on kidney stone management prior to this focused on stone removal techniques like rigid ureteroscopy or shock wave lithotripsy. Clinical studies on the pharmacological treatment of ureteral stone were solely focused on pain relief [15, 16]. The first clinical studies reporting on the efficacy of the α_{1A}/α_{1D}-adrenoceptor antagonist tamsulosin demonstrated that this agent, was

effective in accelerating the passage of small or moderately sized stones from the distal ureter and also reduced episodes of colic [17-19]. Following on from this, tamsulosin was also demonstrated to be effective as adjunctive medical therapy, facilitating the passage of stone fragments after shock wave lithotripsy [19]. While these studies indicate the efficacy of tamsulosin, later clinical investigations have suggested that tamsulosin does not increase the rate of stone expulsion above that of placebo [20, 21]. Common adverse effects of tamsulosin reported in these trials include dizziness, hypotension, headache, and retrograde ejaculation [18, 21]. The use of selective the α_{1A}-adrenoceptor antagonist silodosin, as a substitute for tamsulosin has also recently received increasing attention and been reported to significantly increase stone expulsion rate [22]. Interestingly, naftopidil has also been shown to significantly increase stone expulsion rate, despite its lower affinity for the α_{1A} subtype [23] (see Table 1[24]). Both silodosin and naftopidil have similar adverse effects profile to tamsulosin [22] and therefore, are not necessarily better treatment options. Consequently, the current recommendations for medical expulsive therapy by the European (EAU) and American (AUA) Urological Associations recommend the use of α-blockers as the most viable option for stones between 5mm – 10mm lodged in the distal ureter [2, 25].

Calcium channel blockers

It is well established that in most tissues, smooth muscle contraction classically occurs via an increase in intracellular calcium, and calcium channel blockers are commonly used to suppress smooth muscle contractions in disorders including hypertension, angina and arrythmias. Therefore, it is not unexpected that calcium channel blockers, including nifedipine, verapamil and dialtiazem, suppress spontaneous rhythmic activity and also inhibit ureteral contractile activity induced by electrical stimulation, potassium and phenylephrine in isolated ureteral tissues from human [12] and pig [26]. Studies comparing the effects of calcium channel blockers on

proximal and distal ureter showed that they reduce contractile tone to a greater extent in the latter region, where stones are known to be most commonly located [27]. These findings suggest its potential efficacy in promoting relaxation of the ureteral tube.

While there is a relatively early study in the literature on nifedipine administration to kidney stone patients, this investigation only evaluated pain relief in patients, where nifedipine did not significantly provide pain relief [15]. Subsequent clinical studies demonstrated that nifedipine is effective in augmenting stone passage when used in combination with corticosteroids [16]. While the majority of later clinical trials that investigated the value of nifedipine alone as a treatment demonstrated that it is effective in increasing expulsion rate, most studies have shown that it has significantly lower efficacy in comparison to tamsulosin [18, 20]. In addition, nifedipine was associated with a higher number of adverse events including nausea and vomiting, headache and drowsiness [18] when compared to placebo or tamsulosin-treated patients. Hence, despite some promising results with calcium channel blockers in basic research, the focus of medical expulsive therapy in the clinical context has remained on α_1-adrenoceptor antagonists.

Non-steroidal anti-inflammatory drugs

It is well known that the formation of prostaglandins (PG) requires cyclooxygenase (COX) enzymes, which convert arachidonic acid to an intermediate PGH_2, which is then metabolised to PGD_2, PGE_2, $PGF_{2\alpha}$ and PGI_2. There are two isoforms of the COX enzyme: COX-1, a constitutive form expressed in many tissue, and COX-2, an inducible form induced by various stimuli including stretching of muscle, mucosal injuries and inflammatory mediators, and nerve stimulation [28].

An early *in vitro* study on the isolated human ureter demonstrated that $PGF_{2\alpha}$ significantly increased contractile response whilst PGE_2 inhibited contractions [29]. In later pre-clinical

studies, the non-selective COX inhibitor indomethacin and the selective COX-2 inhibitor NS-398 were shown to dose-dependently inhibit spontaneous rhythmic activity in the human and pig, whilst exogenously applied prostaglandins stimulated contractile responses [30, 31]. However, the COX inhibitors do not appear to have any effect on agonist-induced (phenylephrine, 5-HT) or electrically-induced ureteral contractions in the human and porcine ureter [7, 32]. Due to discrepancies in findings from these studies, it is unclear whether the COX/PG system would be a suitable pharmacological target to promote stone expulsion. Nevertheless, increases in COX-2 expression and production of inflammatory prostaglandin was demonstrated with acute ureteral obstruction in the human ureter which suggests the enzyme is likely to be involved or altered during stone lodgement [33].

The earlier clinical trials investigating the effects of non-steroidal anti-inflammatory drugs (NSAIDs) solely focused on their ability to alleviate colic, and not their efficacy in increasing stone clearance. Due to the apparent role of prostaglandins in increasing pain sensitivity, it is not surprising that these studies reported that NSAIDs are capable of relieving colic in urolithiasis patients [34] . Therefore, although the primary goal of medical expulsive therapy is to promote stone passage, NSAIDs are occasionally prescribed with α_1-antagonists to patients presenting with accompanying colic and for relief of pain and to reduce inflammation. Diclofenac and celecoxib are the most commonly used NSAIDs for ureteral colic. In later studies where stone passage rate was considered, these pharmacological agents were shown to be effective in reducing pain and elicit very few side effects. However, they fail to alter stone expulsion rate on their own [23, 35]. Additionally, most studies have only involved a short-term prescription of NSAIDs to avoid many of the adverse effects associated with prolonged treatment. Although many clinical trials have shown that NSAIDs in combination with either α_1-adrenoceptor antagonists or calcium channel blockers are an effective treatment [23, 35],

beneficial effects of this drug class appear to be solely pain relief with no effect on calculus expulsion time.

Future Directions for Medical Expulsive Therapy

Although literature on ureteral studies is limited, there are a number of physiological processes that have been associated with the control of ureteral functions which could contribute to the optimisation of medical expulsive therapy. The emerging drug targets which are believed to have the most therapeutic potential are phosphodiesterase type 5 enzymes (PDE_5), β-adrenoceptor agonists and 5-HT receptors.

Phopshodiesterase (PDE) inhibitors: These drugs attenuate the function of PDE enzymes that normally depress intracellular cAMP or cGMP levels, by catalysing the hydrolysis of these second messengers. In smooth muscle cells, these inhibitors generally enhance cAMP/cGMP levels by preventing their breakdown by PDE, thus enhancing the actions of nitric oxide (NO) and promoting relaxation of smooth muscle. Of the 11 gene families of the PDE superfamily, PDE_5 is targeted clinically by inhibitors including sildenafil and tadalafil, mainly for managing conditions like erectile dysfunction, pulmonary hypertension and benign prostatic hyperplasia. In the human ureter, PDE enzymes are found to be functionally present, particularly PDE_1, PDE_2 and PDE_5, with inhibition of the latter producing the largest relaxing effect[36]. The PDE_5 inhibitor rolipram is capable of relaxing the rabbit ureter *in vivo* without any significant circulatory side effects[37]. Furthermore, the PDE_5 inhibitors sildenafil, tadalafil and vardenafil reduce KCl-induced tonic contractions in the human isolated ureteral smooth muscle *in vitro*[38]. Whilst there is pre-clinical evidence to support the clinical use of these agents, the value of this class of drug for treatment of calculus, is still in its infancy. In particular, the benefit of using these PDE drugs in combination with tamsulosin is controversial where it was reported that

there is no significant difference in calculus expulsion rate between patients administered with tamsulosin alone and patients treated with combined tamsulosin and tadalafil [39]. However, other studies suggest that combination therapy is more effective, and stone expulsion time and colic episodes are reduced in patients who receive tamsulosin and tadalafil compared to those who received tamsulosin alone[40]. Further clinical investigations are required to assess the potential efficacy of PDE_5 inhibitors alone and in combination with other drugs or treatments like shockwave lithotripsy.

β-adrenoceptor agonists: In the lower urinary tract, β2- and β3- adrenoceptors have both been observed to induce relaxation in the detrusor muscle of the urinary bladder[6]. The lack of alternatives to antimuscarinics for overactive bladder symptoms and the potential of this pharmacological target sparked the development of mirabegron, the first β_3-adrenoceptor agonist which has been shown to be effective in reducing symptoms clinically[6]. Since then, mirabegron has been a popular alternative treatment as it has a lower adverse reaction rate compared to antimuscarinics which is the primary overactive bladder pharmacotherapy option. Although there is generally a functional dominance of α_1-adrenoceptors in the ureter, β-adrenoceptors, particularly β_2-adrenoceptors, have been clearly demonstrated in the human ureter by receptor-binding assay[41]. Isoprenaline-induced relaxations were antagonized by the β_2-selective antagonist ICI-118,551 and the β_3-selective antagonist SR 58894A, but not the β_1-adrenoceptor antagonist CGP20712A in the porcine ureter *in vitro*[42] and *in vivo*[43]. KUL-7211, a β_2/β_3-adrenoceptor agonist also potently and selectively relaxed isolated human ureteric tissues[44]. These results suggest that the receptor subtypes mediating relaxation in human and pig ureter include β2- and β3-adrenoceptors. Although to our knowledge, there are no clinical trials reported on the use of β_2/β_3-adrenoceptor agonists for stone expulsion, given the success of this drug class in reducing lower urinary tract symptoms by inducing relaxation of smooth

muscle, we believe there may be potential for use of β_2/β_3-adrenoceptor agonists to promote expulsion of stones lodged in the ureter.

Serotonergic drugs: The receptors for 5-HT are typically classified according to their primary signalling mechanism into four subtypes: the 5-HT_2 (A, B, C) receptors acting via phospholipase C activation, 5-HT_4, 5-HT_6, and 5-HT_7 receptors via activation of adenylyl cyclase, 5-HT_1 (A, B, D, E, F) and 5-HT_5 (A, B) via adenylyl cyclase inhibition and 5-HT_3, a ligand-gated ion channel. In the lower urinary tract, there are reports suggesting the role of ketanserin-sensitive smooth muscle 5-HT_2 receptors in 5-HT-evoked contractile response of the human bladder[45]. The presence of pre-junctional modulation by 5-HT in the lower urinary tract has also been demonstrated in the human[46] bladder via 5-HT_4 receptors. Activation of these receptors potentiates cholinergic contractile responses by enhancing acetylcholine release from cholinergic nerves. In isolated strips of human ureter, 5-HT induced concentration-dependent contractions[47]. In the pig intravesical and distal ureter, these responses are mediated via the 5-HT_{2A} receptor subtype[47, 48]. Similar pharmacological profiles between human and the porcine ureter thus far suggest there is a potential that this receptor subtype can be targeted. Identifying the source of 5-HT in the ureter is essential but proving to be a difficult task, as to our knowledge, the existence of 5-HT containing or 5-HT producing neurons has yet been reported. It is suggested that mast cells might be the source of 5-HT in this tissue, as 5-HT-containing enterochromaffin cells, which are present in the gastrointestinal tract, have not been identified in the ureter[49]. Mast cells have been observed in all layers of the porcine ureteral wall under normal conditions[49, 50]. Mast cells present in the ureter are potentially involved in maintaining local homeostasis and also play a role in the regulation of ureteral motility via the release of mediators including histamine and 5-HT during inflammation[50]. Since previous findings have reported that histamine fails to exert any significant response from the ureter[7], it

is possible that mast cell regulatory mechanisms occur via 5-HT in this tissue. Although it is difficult to directly translate these pre-clinical findings without clinical trials on serotonergic drugs, this receptor mechanism might have clinical potential to be a target for medical expulsive therapy, especially in inflammatory circumstances.

In addition to these emerging drug targets, there is a recent published study that have proposed the possibility of administering drugs locally to the ureter, to induce relaxation. While the study was performed in a porcine model and requires translation to humans, their findings suggest a significant advantage of local therapy with relaxants over oral tamsulosin in inducing ureteral relaxation [51]. Since local therapy can be applied in much greater doses in comparison to the threshold tolerance of oral medications, this novel delivery method widens the opportunity for exploration of more targets to promote stone passage along the ureter.

Conclusion

The efficacy of most currently used pharmacological agents, namely tamsulosin, nifedipine and NSAIDs, in increasing stone expulsion rate, is still questionable. While their adverse effects are considered mild, there are still significant factors to be considered in the choice of treatment as they can affect patients' quality of life. Despite the promising targets emerging from recent pre-clinical reports in the literature, research on the ureter is sparse, compared to the vast amounts of studies on other parts of the urinary tract. The development of more effective medical expulsive therapy agents, that can both increase stone expulsion rate and relieve colic will be advantageous for patients with ureteral stones to avoid the need for more invasive procedures. In order to achieve this aim, a greater understanding of the physiological and pharmacological mechanisms involved in the contractility of the ureter will be required.

Conflict of Interest Statement

None to report or disclose.

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Tables

Table 1. pK_D values of the α_1-adrenoceptor medical expulsive therapy drugs at the α_1-adrenoceptor subtypes[24]

Drug	α_{1A}	α_{1B}	α_{1D}	Selectivity
Tamsulosin	9.67	8.12	9.18	α_{1A}/ α_{1D}
Silodosin	9.61	6.50	6.94	α_{1A}
Naftopidil	7.97	6.82	7.06	α_{1A}