Symposium

Pharmacology of the lower urinary tract

Martin Hennenberg, Christian G. Stief, Christian Gratzke

Department of Urology, Ludwig-Maximilans University, Munich, Germany

ABSTRACT

Pharmacology of the lower urinary tract provides the basis for medical treatment of lower urinary tract symptoms (LUTS). Therapy of LUTS addresses obstructive symptoms (frequently explained by increased prostate smooth muscle tone and prostate enlargement) in patients with benign prostate hyperplasia (BPH) and storage symptoms in patients with overactive bladder (OAB). Targets for medical treatment include G protein-coupled receptors (α_1-adrenoceptors, muscarinic acetylcholine receptors, β3-adrenoceptors) or intracellular enzymes (5α-reductase; phosphodiesterase-5, PDE5). Established therapies of obstructive symptoms aim to induce prostate smooth muscle relaxation by α_1-blockers or PDE5 inhibitors, or to reduce prostate growth and volume with 5α-reductase inhibitors. Available options for treatment of OAB comprise anitmuscarinics, β_3-adrenoceptor agonists, and botulinum toxin A, which improve storage symptoms by inhibition of bladder smooth muscle contraction. With the recent approval of β_3-antagonists, PDE inhibitors, and silodosin for therapy of LUTS, progress from basic research of lower urinary tract pharmacology was translated into new clinical applications. Further targets are in preclinical stages of examination, including modulators of the endocannabinoid system and transient receptor potential (TRP) channels.

Key words: Alpha1 adrenoreceptor, arginine vasopressors, endocannabinoids, 5 alpha reductase, muscarinic receptors, phosphodiesterase, vitamin D

INTRODUCTION

α_1-adrenoceptors, muscarinic acetylcholine receptors, 5α-reductase, and phosphodiesterases are established targets for pharmacologic therapies of lower urinary tract symptoms (LUTS). Further strategies are in preclinical stages of examination, or are awaiting approval following clinical studies. Therapy of LUTS includes voiding symptoms ("obstructive") in patients with benign prostatic obstruction (BPO), and storage symptoms ("irritative") in patients with an overactive bladder (OAB).

The aim of any pharmacological therapy is an amelioration of symptoms by relaxation of prostate smooth muscle, reduction of prostate volume, or relaxation of bladder smooth muscle. What these strategies have in common is that their mechanisms are closely related to pathophysiology of LUTS. Understanding the principles of pathophysiology and pharmacology in the lower urinary tract provides the basis for current and future therapies. Here, we briefly summarize the pharmacological basis of available therapies and targets showing promising results either in preclinical studies or in clinical stages of examination.

For correspondence: Dr. Christian Gratzke,
Urologische Klinik, Marchioninistr 15, 81377 München, Germany.
E-mail: Christian.Gratzke@med.uni-muenchen.de

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Pathophysiology of LUTS

Urethral obstruction in patients with BPO is frequently explained by exaggerated α_1-adrenergic prostate smooth muscle contraction and by prostate growth [Figure 1].[1,2] Both may cause bladder outlet obstruction (BOO), resulting in obstructive storage symptoms.[1,2] Accordingly, α_1-adrenoceptors and prostate growth are important targets for therapy of LUTS in patients with BPO.[3] In patients with OAB, irritative symptoms are caused by spontaneous, uncontrolled phasic contractions of bladder smooth muscle (detrusor overactivity, DO) [Figure 1].[4] Therefore, prevention of detrusor contraction and decreasing smooth muscle tone in the bladder is an important strategy for medical treatment of these symptoms.[4] It is now well known that relationships between LUTS, their etiology, and organ-specific context are highly variable.[5] It has been proposed that the causal relationship between BOO,

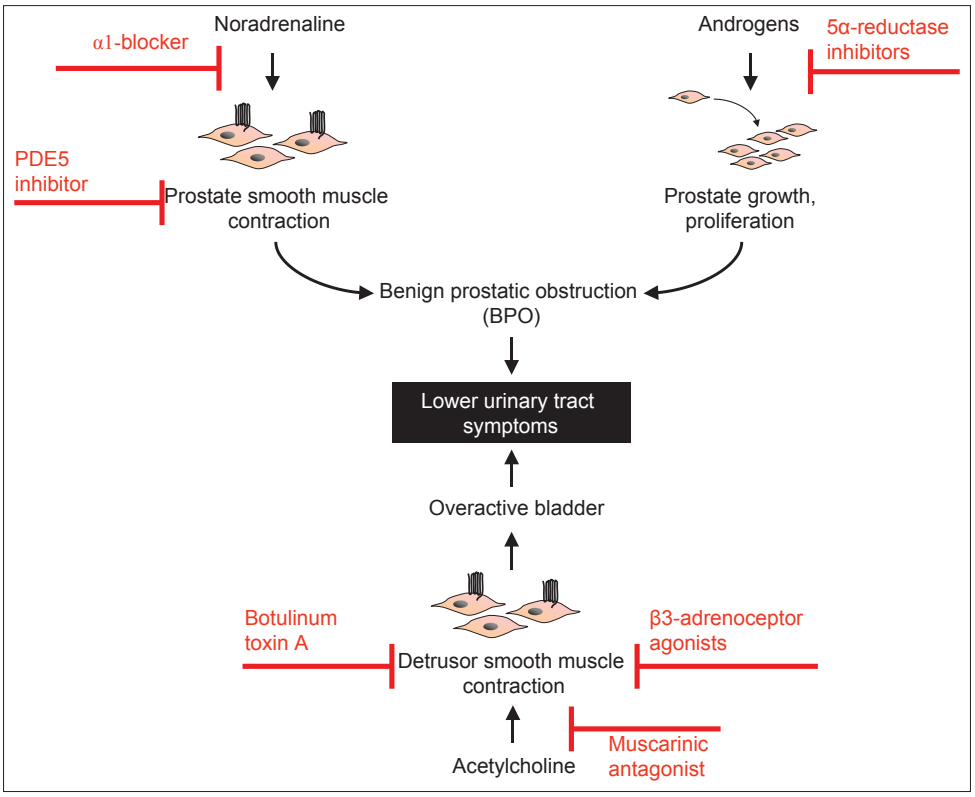

Figure 1: Pathophysiology and medical therapy of LUTS. Obstructive symptoms are frequently explained by benign prostatic obstruction, due to enhanced prostate smooth muscle tone and prostate enlargement. Both may contribute to urethral obstruction. Application of α_1-blockers or PDE5 inhibitors cause improvement of obstructive symptoms by relaxation of prostate smooth muscle, while beneficial effects of 5α-reductase inhibitors occur by reduction of prostate growth and volume. Storage symptoms ("irritative") are often caused by an overactive bladder, due to overactivity of detrusor smooth muscle contraction. Consequently, available options for treatment of storage symptoms are based on relaxation and quiescing of bladder smooth muscle tone, by application of muscarinic receptor antagonists, β3-adrenoceptors agonists, or botulinum toxin A

maximum flow rate (Qmax), and symptom scores may be lower as previously assumed.[6]

α_1-adrenoceptors

Three subtypes of α_1-adrenoceptors are known from the lower urinary tract, designated as α_{1A}, α_{1B}, and α_{1D}.[7,8] In the human prostate, the α_{1A} subtype covers around 70% of the total α1-adrenoceptors population and is responsible for smooth muscle contraction.[7,8] Prostatic expression of α_{1B}-adrenoceptors is most likely confined to the glandular epithelium, while α_{1D} is expressed by intraprostatic blood vessels.[9] α_1-adrenoceptors in the prostate and elsewhere may occur in two phenotypes, designated as α_{1A} and α_{1L}, both belonging to the α_{1A} subtype.[10,11] Although both are products of the same gene (*Adra1A*), factors deciding whether *Adra1A* mRNA is translated as α_{1A} or α_{1L} are still unknown.[11] It has been proposed that interaction with the binding partner CRELD1α (cysteine-rich epidermal growth factor-like domain 1α) may confer the unique pharmacological profile of α_{1L} to α_{1A}-adrenoceptors.[11] Both phenotypes show distinct pharmacological properties. A key difference is their affinity to the non-selective α_1-adrenoceptor antagonist prazosin, which is high for α_{1A}, but low for α_{1L}.[11] α_{1A}-adrenoceptors may also occur in the bladder, where they mediate smooth muscle contraction in the human trigonum and bladder base.[7,10] In animal models, the subtype distribution of α_1-adrenoceptors in the lower urinary tract may differ.[7]

It is widely accepted that beneficial effects of α-blockers in patients with obstructive LUTS are explained by smooth muscle relaxation in the prostate.[1,2,7,8] In addition, it is now clear that mechanisms besides prostate smooth muscle relaxation are involved in therapeutic effects of α_1-blockers.[12] These may include actions on the bladder microcirculation, and α_1-adrenoceptors in the urothelium, in afferent nerves, or in bladder smooth muscle.[12] In fact, α_1-blockers may improve symptoms in women, in men without BPO, or in animal models, where a prostate-dependent contribution can be excluded.[8,13-15]

While α_1-adrenoceptors in the lower urinary tract were intensively studied at expression level, their intracellular signaling or posttranslational regulation attracted less attention.[7] Following receptor stimulation, activation of intracellular signaling cascades via receptor-associated heterotrimeric G proteins leads to contraction of prostate smooth muscle [Figure 2].[1] Activation of phospholipase C (PLC) causes formation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG), leading to activation of myosin light chain (MLC) kinase by calcium-dependent

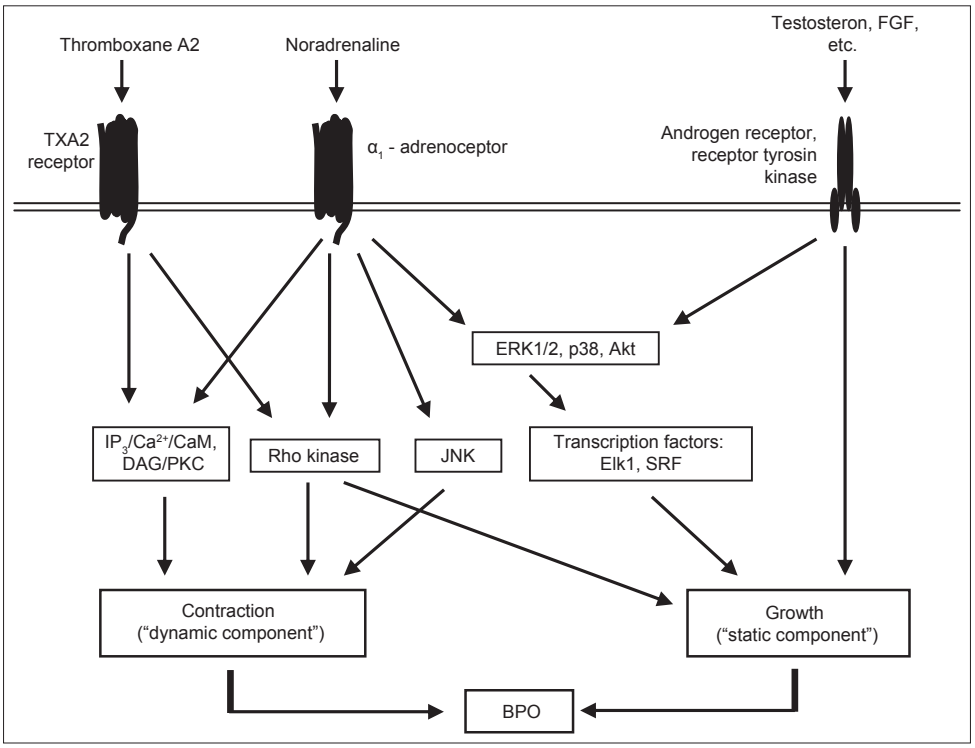

Figure 2: Mechanisms of prostate smooth muscle contraction and assumed connections to the regulation of prostate growth. In contrast to earlier concepts, α_1-adrenoceptors in the prostate are no longer regarded as isolated receptors mediating exclusively contraction. In fact, α_1-adrenoceptors in the prostate are part of a signaling network, where different receptors and non-adrenergic mediators cooperatively regulate prostate smooth muscle tone and growth, leading to benign prostate obstruction. Prostate α_1-adrenoceptors lead to contraction by activation of the IP_3/Ca^{2+}/calmodulin pathway, of DAG/protein kinase C, of the RhoA/Rho kinase pathway, and by a JNK-dependent mechanism. At least the Ca^{2+}- and Rho kinase-dependent mechanisms are shared by TXA2 receptors, which cause prostate smooth muscle contraction in parallel to α_1-adrenoceptors. In addition, α_1-adrenoceptors share intracellular effectors with hormone receptors and growth factors (e. g. fibroblast growth factor): Stimulation of prostate α_1-adrenoceptors leads to activation of ERK1/2, Akt and transcription factors, which are well known to mediate growth and differentiation

mechanisms, and to deactivation of MLC phosphatase via protein kinase C (PKC) [Figure 2].[1] Result is an increased MLC phosphorylation, being the prerequisite for smooth muscle contraction.[1] In parallel to PLC, the monomeric GTPase RhoA is activated by G proteins.[16] RhoA activates Rho kinase, which subsequently leads to contraction by MLC phosphatase inhibition [Figure 2].[16]

Besides contraction, α_1-adrenergic Rho kinase activation in the prostate has been linked to proliferation of prostate cells and therefore to prostate growth [Figure 2].[17] In fact, an involvement of α_1-adrenoceptors in prostate growth and hyperplasia has been repeatedly suggested.[18-20] However, α_1-blockers do not reduce prostate volume.[21,22] Recent evidence from experimental studies unequivocally proved the existence of signal transduction by prostate α_1-adrenoceptors, which is not involved in contraction. This may be termed as "non-motoric" signaling, and comprises a panel of pathways including mitogen-activated protein kinases, Akt, and transcription factors, which are all activated by α_1-adrenoceptors in the human prostate [Figure 2].[23-26]

Different α_1-adrenoceptor antagonists ("α-blocker") are routinely applied for treatment of obstructive symptoms.[27] Although their subtype selectivity may differ, their efficacy is similar in appropriate doses.[10,27] Application of α_1-blockers still represents a gold standard for medical therapy of BPO.[27] The recent approval of silodosin in the USA and Europe reflects a high interest for α_1-blockers with improved subtype selectivity and efficacy.[10,28,29] Before the introduction of silodosin, tamsulosin had the highest α_{1A}-selectivity and was the most prescribed of all available α_1-blockers.[10,30] Naftopidil, which is available for therapy of obstructive symptoms in India, blocks α_{1D}-adrenoceptors in addition to α_{1A} and has a comparable efficacy to tamsulosin.[31,32]

α_1-blockers cause rapid amelioration of mild to moderate symptoms, which frequently persists for several years.[3,21,22,27] However, they do not prevent the progression of benign prostate hyperplasia (BPH), as the rate of acute urinary retention, the need for invasive therapy, or serum PSA levels are not reduced by α_1-blockers.[21,22,27] Together, this leads to application of combination therapies (α_1-blockers with 5α-reductase inhibitors) or non-medical, ablative therapies in many patients, if effects from α_1-blockers are insufficient.[27] Despite the marked improvement of symptoms by α_1-blockers, their efficacy is in fact limited. Symptom scores may be reduced 30-50% by α_1-blockers, while placebos may cause an improvement of 10-34%.[3,27,33] Similarly, α_1-blockers enhance maximum flow

rate (Qmax) by 15-40%, while increases up to 27% were observed by treatment with placebos.[3,27,33] This points to non-adrenergic mediators of contraction, contributing to prostate smooth muscle tone in parallel to α_1-adrenoceptors. Indeed, thromboxane A2 (TXA2) induces smooth muscle contraction in the human prostate, by activation of TXA2 receptors [Figure 2].[34] Finally, the contribution of further mediators cannot be excluded.

5α-reductase

Prostate growth in BPH depends on testosterone.[35,36] Testosterone is metabolized to dihydrotestosterone (DHT) by 5α-reductases (5-AR).[35,36] In the prostate, 5-AR-2 is the prevailing isoform, being located to stromal and basal cells.[35,36] DHT has a 4-5 fold higher affinity for androgen receptors as testosterone.[35,36] Consequently, inhibition of 5-AR by 5-AR inhibitors (5-ARI) abolishes prostate growth and reduces prostate size.[3,27] Therapy with 5-ARIs is applied to prevent the progression of BPH.[3,27] While finasteride selectively inhibits 5-AR-2, dutasteride inhibits both isoforms (5-AR-1, -2).[37] Beneficial effects of 5-ARIs become apparent 3-6 month after continuous application. Finasteride and dutasteride may reduce LUTS by 30% and prostate volume by 25%.[3,27,37]

In rats, reduction of prostate volume can be obtained by treatment with the luteinizing hormone-releasing hormone antagonist, cetrorelix.[38] Cetrorelix is available for anti-cancer treatment. However, approval for therapy of LUTS and BPH (as a benign disease) appears unlikely, due to the inappropriate balance of benefits and side effects.

Muscarinic receptors

In the lower urinary tract, muscarinic receptors are of outstanding importance for smooth muscle contraction in the bladder detrusor, while their relevance for smooth muscle tone in the prostate or urethra is minor.[39] Prevailing subtypes in the human detrusor are M2 and M3, which account for 70% and 20% of the total muscarinic receptor population.[39] Contraction of detrusor smooth muscle is primarily mediated by M3 receptors.[4,39] Muscarinic receptors are activated by acetylcholine, released from parasympathetic nerves.[4,39] In addition to smooth muscle cells, muscarinic receptors in the bladder are found in the urothelium and in presynaptic nerve terminals, the latter being involved in the regulation of neurotransmitter release.[4,39] Interestingly, the intracellular mechanisms leading to smooth muscle contraction by muscarinic receptors in the detrusor strongly resemble those used by α_1-adrenoceptors in the prostate, as they involve IP_3/Ca^{2+}, DAG/PKC, and Rho kinase.[4]

Muscarinic antagonists are routinely applied for the treatment of storage symptoms in patients with OAB.[4,39] Several antagonists are available, despite different affinities and subtype selectivities. Nevertheless, side effects and efficacy are similar between all substances. Although application of antimuscarinics represents the gold standard of medical OAB therapy, the efficacy may not be fully satisfactory.[4] In fact, patients adherence to the therapy is quite low: Up to 45% or more patients discontinue the therapy, due to the perception that the medication is not working.[40]

Combinations with muscarinic antagonists may be effective in patients, where monotherapy with 5-AR or α_1-blockers is insufficient. Despite initial concerns that such combinations may induce urinary retention, the combination of tolterodine with dutasteride may be effective and safe in patients with OAB and symptoms secondary to BPH.[41] Similarly, combinations of antimuscarinics with α_1-blockers have been recently addressed by clinical studies.[27]

Phosphodiesterases

Phosphodiesterases hydrolyze the cyclic nucleotides, cGMP and cAMP, which both mediate smooth muscle relaxation in the lower urinary tract and other organs.[42] In the prostate, cGMP is synthesized by guanylyl cyclases, which are activated by nitric oxide (NO) released by neuronal NO synthase (nNOS) as a neurotransmitter, or by inducible NOS (iNOS) from macrophages.[43] Inhibitors for the cGMP-specific PDE5 were introduced in the 90's, for the treatment of erectile dysfunction (ED). PDE5 inhibition causes accumulation of cGMP in smooth muscle cells, promoting cGMP-mediated relaxation.[42] While PDE5 inhibitors are now available for treatment of LUTS in patients with BPH, cAMP-specific PDE4 is currently under preclinical investigation.[44]

The PDE5 inhibitor tadalafil has been approved very recently for treatment of obstructive symptoms in patients with BPH in the USA and Europe.[27,45] The advantage of tadalafil to other PDE5 inhibitors may be its extended half-life, allowing a once-daily application for treatment of LUTS.[45] The efficacy of tadalafil is comparable to that of α_1-blockers.[46] In contrast to most other medical options for LUTS treatment, high attention has to be paid to possible contraindications, excluding the application of PDE5 inhibitors.[27] Patients receiving nitrates, potassium channel openers, nicroandil, or the α_1-blockers doxazosin or terazosin cannot be treated with PDE5 inhibitors, due to high risks of dangerous interactions.[27] Further contraindications are unstable angina pectoris, recent myocardial infarction (<3 mo) or stroke (<6 mo), myocardial insufficiency, hypotension, poorly controlled blood pressure, hepatic or renal insufficiency, and anterior ischemic optic neuropathy with sudden loss of vision after previous use of PDE5 inhibitors.[27]

Arginine vasopressin

The antidiuretic hormone, arginine vasopressin (AVP), is a key regulator of body water homeostasis and in the control of urine production.[47] AVP promotes water reabsorption and

decreases water as well as total urine volume.[47] It is released to compensate dehydrated conditions, resulting in water reasorption and formation of a concentrated, low volume urine.[47] In parallel, AVP induces moderate vasoconstriction and elevation of blood pressure by activation of AVP receptor 1 (V1), to counteract hypovolemic states.[47]

The vasopressin receptor 2 (V2)-selective agonist, desmopressin, is available for the treatment of nocturia secondary to nocturnal polyuria in adult patients.[27] Desmopressin reduces the overall number of nocturnal voids and prolongs the periods of undisturbed sleep.[27] Nevertheless, it is rarely used for treatment of nocturia in adults. According to the role of AVP for urine homeostasis, desmopressin has been considered for the treatment of OAB.[47] Urodynamic actions were addressed by two clinical studies, with promising results.[47] Nevertheless, this did not proceed to clinical application.

New targets

Preclinical studies revealed several targets, which were related to promising results in experimental models. Some of them were recently transferred into clinical stages of examination and may await approval for clinical application in LUTS therapy.

β3-adrenoceptor agonists

In the human lower urinary tract, β_2- and β_3-adrenoceptors induce smooth muscle relaxtion, while the function and expression of β_1-adrenoceptors are of minor importance.[7,48] In addition to smooth muscle cells, β-adrenoceptos in the lower urinary tract may be present in the urothelium and in afferent nerves.[7,48] In the bladder, β-adrenoceptors enhance urine storage, while their function in the prostate or urethra is less understood.[7,48] β_3-adrenoceptors cover > 95% of the total β-adrenoceptor mRNA pool in the human bladder and induce detrusor relaxation.[48] In the human prostate, β_2 is the prevailing subtype at protein level; in fact, β-adrenergic activation inhibits α1-adrenergic prostate smooth muscle contraction via β_2-adrenoceptors.[48]

With regard to clinical application, β_3-adrenoceptors in the bladder attracted large attention. Following randomized clinical studies, mirabegron, a β_3-adrenergic agonist, has now been approved for the treatment of OAB in Europe, Japan, and the USA.[49-52] Nevertheless, long-term experiences with mirabegron during clinical application are still missing.[53] Although proof-of-concept studies with two other agonists, solabegron and ritobegron, yielded promising results, these agonists did not proceed to clinical application to date.[53]

Endocannabinoids and TRP channels

The endocannabinoid system and transient receptor potential (TRP) channels have been recognized as important regulators of smooth muscle tone in the lower urinary tract.[54,55] Cannabinoid receptors, TRPA, and TRPV cooperatively mediate smooth muscle relaxation in the prostate, urethra, and bladder.[54,55] In this process, mechano-afferent signals cause activation of the cannabinoid receptor 2 (CB2) and TRP channels on sensory neurons, leading to the release of NO and cyclooxygenase activation by neurons, which finally results in postsynaptic smooth muscle relaxation [Figure 3].[55] In contrast to animal models, where CB1 strongly inhibits bladder smooth muscle contraction, endocannabinoid effects in the human lower urinary tract are prevailingly mediated by CB2.[54,56]

While cannabinoid receptors and TRP channels have been intensively studied *in vitro* and in animal models, evidence for urodynamic effects in patients is still rare.[56-60] Accumulation of endocannabinoids by inhibition of their degradation has been proposed as a new strategy for improvement of LUTS.[61] Endocannabinoid degradation is promoted by fatty acid amide hydrolase (FAAH).[61] In rats, FAAH inhibition by oleoyl ethyl amide (OetA) caused urodynamic alterations, which may improve symptoms in OAB.[61] In proof of concept studies, intravesical application of the vanilloid TRPV agonist capsaicin or resiniferatoxin increased bladder capacity and decreased urge incontinence in patients with neurogenic and non-neurogenic DO.[62] Clinical studies focused on the application of cannabinoids for the treatment of bladder dysfunction in multiple sclerosis (MS).[54] However, results were divergent and are not easy to discriminate from placebo effects in MS.[54]

Botulinum toxin

Type A botulinum toxins (BTX-A), in particular onabotulinumtoxin A (BoNT-ONA, "botox"), has been investigated for use in the lower urinary tract. While intraprostatic injection is still controversially discussed and effects on obstructive symptoms may be limited,[63,64] its application in the bladder is now an established therapy

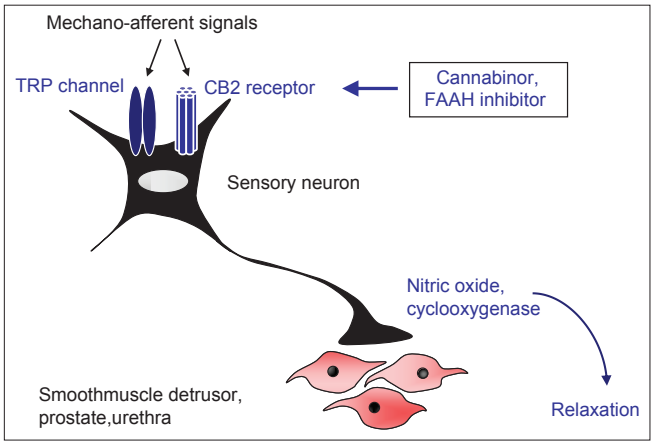

Figure 3: Role of endocannabinoids and TRP channels for regulation of smooth muscle tone in the lower urinary tract. Mechano-afferent signals lead to activation of CB2 receptors and TRP channels (TRPA, TRPV) in sensory neurons. This causes the release of nitric oxide and cyclooxygenase-dependent neurotransmission, finally resulting in smooth muscle relaxation in the detrusor, prostate, and urethra. Consequently, activation of CB2 receptors by Cannabinor or FAAH inhibitors improves LUTS in animal models.

of DO.[65] In the USA and Europe, BoNT-ONA is used for second-line treatment of neurogenic DO, as an alternative for anticholinergic therapy.[65,66] Approval for therapy of idiopathic DO may follow soon, as clinical trials provided encouraging results.[65,67,68]

The botulinum neurotoxins (type A to G) are proteins secreted by strains of *Clostridium botulinum*.[69] They disrupt neurotransmission at neuromuscular junctions by inhibition of presynaptic acetylcholine release.[69] In this process, BTX-A prevents complex formation of synaptic vesicles (containing acetylcholine) with synaptobrevin and syntaxin.[69] Under normal conditions, this is required for the transport of vesicles to the membrane, and subsequent neurotransmitter release.[69] Inhibition of this mechanism accounts for the beneficial effects of BoNT-ONA in DO, as detrusor contraction is explained by equipment of smooth muscle cells with muscarinic receptors, and parasympathetic cholinergic innervation.

Vitamin D

Preclinical studies with the vitamin D receptor agonist, BXL628 (elocalcitol), provided promising results and have been moved into the clinical testing stage. BXL628 prevents proliferation and contraction of smooth muscle cells in the bladder and the prostate, which is thought to be mediated by inhibition of the RhoA/Rho kinase pathway.[70-72] In a placebo-controlled phase II study in 119 patients with BPH (prostate volume >40 ml), application of BXL628 for 12 weeks caused a significant effect on prostate growth.[73] However, this was not paralleled by significant effects on Qmax, which may be related to the short treatment period.[73] The effects on storage symptoms were studied in another trial performed in 257 women with OAB due to idiopathic DO, who received BXL628 for 4 weeks.[74] In this study, treatment with elocalcitol significantly reduced the episodes of incontinence and significantly improved the Patient's Perception of Bladder Condition score (PPBC), while effects on other parameters were lacking.[74] The primary end point, a change in bladder volume at the first involuntary detrusor contraction, was not achieved.[74] Thus, a clinical progress in LUTS treatment by vitamin D-dependent therapies appears unlikely.

Peripheral mechanisms in uropharmacology

For most of the described pharmacologic agents with urodynamic effects *in vivo*, direct effects on smooth muscle cells are well established. These are exerted by receptors on the cell membrane (adrenoceptors, cholinergic receptors) or by intracellular enzymes (PDEs, 5-AR). Numerous studies demonstrated that peripheral mechanisms are of relevance for urodynamic effects as well. Evidence for a contribution of neuronal α_1-adrenoceptors in the central and peripheral nervous system to urodynamic effects of α_1-blockers was provided quite early by several investigators.[8] More recently, it has been demonstrated by intrathecal application that peripheral effects and actions in the spinal cord may contribute to urodynamic effects of muscarinic antagonists, PDE5 inhibitors, and β_3-agonists.[75-77] Less surprising, but noteworthy was the finding that urodynamic alterations induced by FAAH inhibitors can be observed following an intrathecal application.[78]

CONCLUSIONS

Established therapies of obstructive symptoms aim to induce prostate smooth muscle relaxation by α_1-blockers or PDE5 inhibitors, or to reduce prostate growth and volume with 5α-reductase inhibitors. Available options for treatment of OAB comprise antimuscarinics, β_3-adrenoceptor agonists, and botulinum toxin A, which improve storage symptoms by inhibition of bladder smooth muscle contraction. With the recent approval of β_3-adrenoceptor agonists, PDE inhibitors, and silodosin for therapy of LUTS, previous progress in basic research of lower urinary tract pharmacology was translated into new clinical applications. Further targets are in preclinical stages of examination, including modulators of the endocannabinoid system and transient receptor potential channels.

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