Pharmacologic Targets on the Female Urethra

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Abstract

Introduction: This article reviews the mechanisms affecting contraction and relaxation of the urethra in order to establish a basis for current and future treatments for urinary incontinence in women. Material and Methods: A review of the English literature using MEDLINE was performed between 1970 and 2008 on female urethra pharmacology, urinary incontinence, and mechanisms involved in contraction and relaxation of the female human urethra. Results: -Adrenoceptors (ARs) cause contraction and β-ARs cause relaxation. Use of selective α-agonist and β-AR blocker agents might have potential for the treatment of stress urinary incontinence. Tolerable doses of cholinergic agonists did not have significant effects on intraurethral pressure. Nitric oxide seems to be the major nonadrenergic-noncholinergic inhibitory transmitter causing relaxation. c-kit-positive interstitial cells seem to regulate urethral tone. The roles of adenosine triphosphate and carbon monoxide have not been fully investigated in humans. Neuropeptides function similarly to the urinary bladder. Prostanoids cause urethral contraction and relaxation depending on their subtypes. Serotonin enhances the strength of urethral sphincteric contractions. The Rho-kinase pathway also appears to be modulating smooth muscle contraction in the urethra. Conclusions: Understanding of the urethral function and pharmacology may lead to the development of promising new agents which might be useful in the management of urinary incontinence in women.

Urinary incontinence is a common medical condition affecting many women worldwide. Approximately one-third of elderly individuals suffer from urinary incontinence [1] and almost 40% of younger women aged 20–45 years suffer from urinary incontinence symptoms that significantly affect their quality of life [2]. The prevalence of stress, urge, and mixed urinary incontinence has been reported to be 40, 25, and 29%, respectively, in Turkey [3]. Stress urinary incontinence (SUI) is defined as involuntary leakage of urine by effort, exertion, sneezing or coughing. As such, pelvic floor muscle training, behavioral therapies and surgery are the main treatment options.

The lower urinary tract (LUT) consists of the urinary bladder and urethra. Two principal functions of the urinary bladder are urine storage and emptying. The urethra maintains urinary continence by relaxing during the voiding phase and contracting during the urine storage phase [4].

Several transmitters and receptors are reported to be involved in LUT physiology. In order to fully understand the clinical implications of LUT function, it is important...
to transform the scientific basis of LUT physiological and pharmacological mechanisms to clinical practice. In our previous review, we summarized the physiology and pharmacology of the human urinary bladder [5]. In order to complement our previous work, the aim of the present review is to outline the pathways involved in the contraction and relaxation of the human female urethra and discuss their significance related to current and future pharmacological therapy for urinary incontinence in women.

**Pelvic Floor Problems/Dysfunction and SUI**

Although intrinsic urethral dysfunction is an etiological factor for the onset of urinary incontinence in women, pelvic floor problems and dysfunction are more important for the development of female urinary incontinence.

The levator ani muscles, endopelvic fascia, muscular structures of the sphincter and the pelvic floor musculature comprise a single system maintaining urinary continence in women. The physiological organization of Onuf’s nuclei and of levator ani motorneurons together with reflex control of the tonic activity is important for the formation of maintained force in slow-twitch muscle fibers which is an essential part of the normal urinary continence function [6].

Pregnancy and vaginal delivery are the main etiological factors responsible for the formation of genuine SUI and pelvic floor damage leading to pelvic floor dysfunction and problems in women. Most of the pelvic floor damage occurs during the first delivery. Therefore, childbirth is one of the most important causes of SUI in women, particularly following long second stages of labor, traumatic deliveries, large babies and in multigravidae [7]. Pudendal nerve damage mostly occurs after forceps delivery, increased duration of second stage of labor, third-degree perineal tear and high birth weight [8]. Reduced collagen content of the pelvic floor tissue causing pelvic floor dysfunction in patients with pelvic organ prolapse and/or SUI has been demonstrated before [9]. Similarly, defects in the support of the anterior pelvic compartment result in a number of anatomic and physiologic problems such as SUI in women [10]. Although less frequently seen in women, pelvic fracture is a risk factor for pelvic floor dysfunction [11].

Noninvasive treatment options for female SUI include pelvic floor muscle training, lifestyle interventions, bladder retraining and pharmacotherapy, whereas more invasive options include anti-incontinence devices, periurethral bulking agent injectables and surgery [12]. Postpartum pelvic floor exercises seem to be an effective conservative treatment modality in decreasing postpartum urinary incontinence, suggesting the importance of pelvic floor problems in the formation of SUI in women [13].

**Structure and Innervation of the Female Urethra**

The female urethra is surrounded by 3 layers of muscle tissue: (1) thick inner (central) longitudinal smooth muscle layer, (2) thin, middle, circular smooth muscle layer, and (3) outer striated muscle layer (rhabdosphincter) (fig. 1). The rhabdosphincter surrounds the longitudinal mid-point of the urethra and is thickest anteriorly and thinnest posteriorly. Circular and longitudinal smooth muscles and rhabdosphincter are tonically active during the storage of urine. The rhabdosphincter becomes active when abdominal pressure rises. However, during voiding all urethral muscles relax. In the elderly and particularly after menopause, rhabdosphincter atrophies at the level of the bladder neck and dorsal urethral wall are strongly associated with developing SUI [14].

The female urethra is innervated by the parasympathetic, sympathetic and somatic nervous system, and all include sensory afferent fibers (fig. 1) [15, 16].

**Pelvic Nerve**

Preganglionic parasympathetic neurons are located in the sacral spinal cord and their axons make synapsis with postganglionic neurons located in the pelvic plexus. These pathways are mainly cholinergic but they also include purinergic, peptidergic and nitrergic pathways innervating the urethral smooth muscles [17, 18]. Sensory fibers originate from the dorsal root ganglia (DRG) of the sacral spinal cord and are composed of myelinated (Aδ) and unmyelinated (C) fibers. Urinary tract infection, bladder outlet obstruction and spinal cord injuries may affect these fibers, leading to overactive bladder and urinary incontinence.

**Hypogastric Nerve**

Efferent fibers from the inferior mesenteric ganglion and fibers in the upper lumbar spinal cord form the hypogastric nerve. The main transmitter involved in the sympathetic postganglionic fibers is noradrenaline (NA), but purinergic and peptidergic transmitters also take part in the neurotransmission process. Hypogastric nerve
Pudendal Nerve

The pudendal nerve mainly contains motor fibers originating from Onufrowicz’s nucleus (Onuf’s nucleus) located in the ventral horn of the sacral spinal cord innervating the urethral rhabdosphincter, external anal sphincter, compressor urethrae and urethrovaginal sphincter muscles. The pudendal nerve has also sensory fibers originating from the sacral DRG innervating the urethra, rectum, clitoris and perineal skin [20]. However, sympathetic fibers compose a minor component innervating the vasculature of the pelvic organs.

Pathways Involved in Contraction and Relaxation of the Female Urethra

Complex interactions between bladder neck and urethra maintain urinary continence in women. However, these mechanisms are not fully elucidated. Mucosal seal effect of the urethra, a competent bladder neck and a functional urethral sphincter are the principal mechanisms maintaining urethral closure and continence in women [21]. Urethral striated muscle, which is called the rhabdosphincter or external urethral sphincter, plays an important role in urethral continence. Animal studies demonstrated that duloxetine increases the concentrations of both serotonin and NA in the sacral spinal cord region, leading to the stimulation of the rhabdosphincter activity, thus preventing urine leakage [22]. Recently, significant improvement of urinary incontinence was demonstrated in patients who were treated with myoblasts and autologous stem cells injected into the rhabdosphincter in the female urethra, demonstrating its crucial role in urinary continence [23]. The control of the adrenergic (sympathetic), cholinergic (parasympathetic) and nonadrenergic-noncholinergic (NANC) mechanisms on urethral smooth muscle tone (intraurethral pressure) is critical for the maintenance of urinary continence [24].

Adrenergic Pathways

α-Adrenoceptors

Closure of the bladder neck and urethra depends on the adrenergic system to some extent [25]. Urodynamical studies demonstrated that α-adrenoceptors (ARs) maintain almost 50% of the intraurethral pressure in humans [26, 27]. The α1-AR subtype is the predominating postjunctional α-AR in the human urethral smooth muscle (fig. 3) [28]. NA (both α1- and α2-AR agonist), not clonidine (α2-AR agonist), produced concentration-de-
pendent contractions in all urethral levels in the females. These contractions were most intense in mid to proximal urethra. Sympathetic nerves acting via $\alpha_1$-ARs seem to be the principal mechanism maintaining resting urethral tonus (fig. 2, 3) [29]. Three $\alpha_1$-AR subtypes ($\alpha_{1A}/\alpha_{1B}/\alpha_{1D}$) have been detected and $\alpha_{1A}$ is found to be the pre-

dominating receptor in the human lower urinary tract [30, 31]. The role for $\alpha_{1L}$-Ars, a distinct conformational state of the $\alpha_{1A}$-ARs, has also been proposed [32]. Discovery of a selective urethral $\alpha_1$-AR subtype agonist has important clinical significance, because this agent might be used in the treatment of urinary incontinence in women. Although low levels of $\alpha_{1D}$-AR mRNA was detected in the female urethra, $\alpha_{1B}$-AR mRNA was not identified [33]. $\alpha_2$-ARs regulate the release of NA from adrenergic nerves in the urethra (fig. 3) [25]. Notably, clonidine was demonstrated to decrease intraurethral pressure in humans. This effect might be due to effects on adrenergic nerve terminals or central nervous system leading to a decrease in peripheral sympathetic nervous activity [34]. In the guinea pig urethra, the prejunctional $\alpha_{2A}$-subtype was suggested to be responsible for the secretion of NA. However, the release of other currently unknown mediator(s) might also act through $\alpha_2$-ARs and warrants further research [35]. A recent study showed that $\alpha_{1L}$-ARs mediate smooth muscle contraction of the female pig urethra. This mechanism seems to be responsible for contraction of the longitudinal and circular urethral muscle, thus maintaining the sympathetic control of intraurethral pressure and continence [36].

**$\beta$-Adrenoceptors**

Bladder response to norepinephrine (NE) presents with two distinct characteristics: relaxation via $\beta$-ARs in
the body of the bladder (fig. 2) [37, 38], and contraction mediated via \(\alpha\)-ARs in the bladder base and urethra (fig. 2, 3) [24, 30, 39–41]. Although \(\beta_2\)-ARs were detected in the human bladder neck [42], \(\beta_3\)-ARs predominated in the human bladder [43]. Administration of \(\beta_2\)-AR agonists reduced intraurethral pressure in humans, but \(\beta\)-AR antagonists did not have similar acute effects [44]. However, blockage of \(\beta\)-ARs might increase urethral tone by enhancing the effects of NA on \(\alpha\)-ARs. This effect might prove a role for SUI treatment [45]. On the other hand, clenbuterol (a selective \(\beta_2\)-AR agonist) was shown to increase maximal urethral pressure [46]. Clinical improvement in patients with stress incontinence by clenbuterol was suggested to occur due to its action on urethral striated and/or pelvic floor muscles [37, 47].

\(\beta\)-ARs were suggested to cause cyclic adenosine monophosphate (cAMP)-mediated smooth muscle relaxation and muscarinic receptor stimulation (\(M_2\)) by indirectly inhibiting cAMP formation [48]. In dogs, \(\beta_2\) stimulants were demonstrated to increase the contraction of fatigued urethral sphincter [49]. \(\beta\)-ARs mediate relaxation through \(\beta_1\), \(\beta_2\), or \(\beta_3\) receptors and they have been shown in the bladder and urethra in several species including humans [39, 50]. In the pig urethra, \(\beta_2\)- and \(\beta_3\)-ARs were demonstrated to mediate relaxation in response to isoproterenol (\(\beta\)-AR agonist) [51]. In the human urethra, radioligand-binding studies demonstrated the presence of \(\beta_2\)- and \(\beta_3\)-AR subtypes. Therefore, agents acting via these receptors might have a promising role in the management of urinary incontinence in women [27].

**Cholinergic Pathways**

**Muscarinic Receptors**

Urethral smooth muscle receives a rich cholinergic innervation [52, 53]. Muscarinic receptors (\(M_2\) and \(M_3\)) seem to be acting for the increase of the bladder base and urethra (fig. 2) [24, 30, 54]. Although the \(M_2\) subtype is predominating in number in the urinary bladder [55, 56], \(M_3\) receptors are mainly responsible for contraction [57, 58]. Four subtypes of muscarinic receptors (\(M_1\), \(M_2\), \(M_3\) and \(M_4\)) have been demonstrated in the rat bladder [59] and \(M_1\), \(M_2\) and \(M_3\) receptors were shown to cause contraction in the rabbit urethra [60, 61]. On the other hand, pig urethra appears to have predominantly \(M_2\) receptors. Contraction of the pig urethra was demonstrated to be predominantly mediated by \(M_2\) and \(M_3\) receptors in the circular muscle and only by \(M_3\) receptors in the longitudinal muscle [48]. Stimulation of the muscarinic receptors on the urethral smooth muscle was demonstrated to cause contraction in humans mainly in the longitudinal layer [25]. In an experimental study using female human urethral tissues, acetylcholine contracted only proximal urethra and bladder neck [29]. Tolerable doses of cholinergic agonist administration did not have any significant effect on intraurethral pressure in humans [62]. Carbachol (cholinergic agonist) inhibits release of NE from adrenergic nerve and Ach from cholinergic nerve terminals by acting upon prejunctional muscarinic receptors, hence decreasing urethral tone and intraurethral pressure (fig. 4) [63]. \(M_2\) receptors are involved in the contraction of the smooth muscle via the following mechanisms: (1) inhibition of cyclic adenosine monophosphate (cAMP) mediated smooth muscle relaxation by \(\beta\)-adrenoceptors (fig. 2) [55], (2) opening of non-specific cation channels, thereby leading to cellular depolarization and calcium influx into the cell [64, 65], and (3) under pathologic conditions such as denervation or neuromogenic dysfunction [66, 67]. The muscarinic receptor subtypes in the human urethra that cause contraction are not currently well established. This area warrants further research in order to explore the role for use of selective muscarinic agents in the treatment of female urinary incontinence.

**Nonadrenergic, Noncholinergic (NANC) Pathways**

During voiding, urethral relaxation and detrusor contraction occurs simultaneously [68]. Factors contributing to urethral relaxation can be summarized as follows: (1) presynaptic muscarinic receptor stimulation (inhibition of NE release causes decreased proximal urethral tone) (fig. 4), (2) longitudinal urethral smooth muscle contraction due to muscarinic stimulation (resultant urethral shortening and widening decreases intraurethral pressure) (fig. 2), and (3) NANC mechanisms (explained below).

**Nitric Oxide (NO)**

L-Arginine-derived NO was shown to be present in the urothelium and afferent nerves [69] which appeared to be the major NANC inhibitory transmitter in the LUT [70, 71]. Its main effect was proximal urethral relaxation [72–76]. Nitric oxide synthase (NOS) is responsible for NO synthesis and has calcium-dependent and calcium-independent isoforms. The calcium-dependent form has 2 isoforms: endothelial and neuronal NOS [77]. Neuronal NOS (nNOS) was demonstrated in the urethral muscle
and lamina propria, whereas endothelial NOS (eNOS) was detected in the urothelium and endothelium of submucosal blood vessels [78, 79]. NO activates guanylate cyclase producing cyclic guanosine monophosphate (cGMP) and this leads to smooth muscle relaxation [80]. Mechanisms involved in smooth muscle relaxation based on cGMP production are summarized in figure 5 [81–85]. cGMP has been detected in the urothelium and submucosa of the urethra [79, 86] and NOS and soluble guanylate cyclase activities have been demonstrated in the urethral mucosa and smooth muscle [87]. The presence of phosphodiesterase type 5 (PDE-5) and cGMP has been
shown in the female urethra. Inhibition of PDE-5 with drugs like sildenafil, vardenafil and tadalafil caused NO/cGMP-mediated relaxation [88].

Recently, c-kit (CD117)-positive interstitial cells have been demonstrated in the urinary tract (i.e. urethra). These cells formed a network immunoreactive for GMP and have been suggested to function as a pacemaker in the regulation of urethral tone [89, 90]. We also demonstrated these cells in the human bladder and urethra (see fig. 6) and are currently investigating their role in lower urinary tract symptoms in women [unpubl. data].

**Adenosine Triphosphate (ATP)**

Adenosine, adenosine diphosphate (ADP) and ATP are extracellular purines which are involved in cellular signaling via cell-surface receptors (fig. 7) [91–96]. It has been shown that ATP is released with electric field stimulation and mechanical stretch of the bladder. However, the contribution of ATP release from neuronal sources is much lower compared to nonneuronal sources (urothelium) [97]. ATP is believed to cause smooth muscle relaxation via G-protein-coupled P2Y receptors [98] and activation of cAMP-dependent protein kinase A [99]. ATP was demonstrated to cause urethral smooth muscle relaxation in various species such as pigs [100, 101], guinea pigs [102], rabbits [103] and hamsters [104]. The pharmacologic effects of ATP and other purines on the human female urethra are not very clear and need further scientific attention.

**Carbon Monoxide (CO)**

Heme oxygenase-1 (HO-1) and HO-2 (present in the nerve fibers located in the LUT and urethra of the pigs) are the two enzymes responsible for CO production [100]. CO was shown to cause relaxation of the urethra via cGMP in pigs (see fig. 5 for actions of cGMP in the urethral smooth muscle) [100]. Furthermore, immunoreactivity for HO-2 was demonstrated in neuronal structures innervating the male and female urethral sphincters [105]. Clearly, functional impact of CO on the urethra is another area for exploration.

**Neuropeptides**

Vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), tachykinins and endothelins are neuropeptides that are shown to be involved in urethral contraction and relaxation mechanisms similar to the urinary bladder [5].

**VIP**

VIP-positive nerves have been demonstrated in the human urethra and various other species [25]. Although
its effect on the human female urethra is unclear, VIP was shown to relax the isolated rabbit and guinea pig urethral strips [106, 107].

**NPY**

In the isolated female rabbit and rat urethra, NPY was demonstrated to have inhibitory effects [108, 109]. However, the effect of NPY on human female urethra needs to be clarified by functional studies.

**Tachykinins**

Substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are tachykinins that are present in the afferent nerves of the lower urinary tract and act on NK1, NK2, and NK3 receptors [5]. Tachykinins were shown to cause urethral contraction in various species including humans [110–113], but their role in female urethral physiology remains elusive. The amount of peptide-containing (NPY, VIP and SP) nerve supply to the perineal muscles in patients with genitourinary prolapse with concomitant urinary incontinence was compared to that of healthy controls [114]. The density of these nerves was found to be significantly less in the latter group compared to the incontinent group, suggesting a possible role for tachykinins in female urinary continence mechanisms. Functional importance of tachykinins in the etiology of urethral instability has to be validated with future research.

**Endothelins**

Endothelin (ET) receptors were shown in the urethral smooth muscle and urothelium in various animals [115–117]. ET-1 subtype was demonstrated to cause urethral smooth muscle contractions via ET-A receptors in the rabbit [118, 119]. However, human studies regarding endothelins and urethral function are lacking.

**Prostanoids**

Prostanoids [prostaglandins (PG) and thromboxanes (TX)] are synthesized by cyclooxygenase (COX) enzymes [5]. In the human female urethra, PGF$\text{2}_{\alpha}$ leads to contraction [120], whereas PGE$_1$ and PGE$_2$ cause relaxation [25] leading to a decrease in the maximum urethral pressure and reduction in the urethral closure pressure. In addition, intravesical PGE$_2$ administration was shown to decrease the urethral closure pressure in healthy women [121].

**5-Hydroxytryptamine (5-HT, Serotonin)**

Onuf’s nucleus is located in the sacral spinal cord. Motor neurons present in Onuf’s nucleus have dense populations of noradrenergic and serotonergic terminals that control urethral function. Animal studies have shown that $\alpha_1$-adrenoceptors and serotonin receptors in Onuf’s nucleus facilitate sphincter contraction [122]. 5-HT and NA were suggested to function as modulatory neurotransmitters in the excitation of motor neurons controlling rhabdosphincter activity in the presence of glutamate [22].

Duloxetine hydrochloride is a balanced serotonin and NE reuptake inhibitor and functions acting on Onuf’s nucleus. Serotonin and NE activate the pudendal motor neurons in Onuf’s nucleus and enhance the strength of urethral sphincter contractions [123–127]. In phase III [128, 129] clinical trials, duloxetine was found to be efficient and tolerable in the treatment of SUI in women. However, nausea was the most common side effect. Duloxetine 80 mg/day (40 mg twice daily) was suggested to be the optimum dose in women with SUI [127]. Moreover, duloxetine was shown to have a significant effect on the excitability of pudendal motor neurons and urethral sphincter contractility in a urodynamic study conducted in healthy women [130].

Although duloxetine has been approved for treatment of SUI in Europe, pharmaceutical companies withdrew their applications to Food and Drug Administration (FDA) in 2005 because of manufacturers’ failure to demonstrate the drug’s positive risk-benefit ratio.

**Rho-Kinase**

Circular smooth muscle in the urethra exhibits spontaneous tone that maintains urinary continence and its relaxation during micturition is necessary for voiding [131]. Rho-kinase modulates the smooth muscle contraction via phosphorylation of myosin light chain [132]. Activation of Rho-kinase inhibits smooth muscle myosin phosphatase, leading to Ca$^{2+}$ sensitization of the smooth muscle, thus causing contraction of the muscle [133] (fig. 8). It has recently been demonstrated that female pig urethral tone is dependent on Rho-guanosine triphosphatase and Rho-associated kinase [134]. The significance of Rho-kinase pathway in the contraction and relaxation of human female urethra needs to be investigated.

**Effects of Hormones on Urethral Function**

Estrogen receptors are mainly detected in the squamous epithelium of bladder trigone and proximal and distal urethra rather than urothelium of the female lower urinary tract. In contrast, progesterone receptor expression was shown to vary in the female urinary tract [135]. Squamous epithelium of the female LUT was shown to express greater levels of cell proliferation in estrogen-re-
Female Urethral Pharmacology

Several beneficial effects of estrogen on female LUT were reported. Mainly, increased urothelium thickness, increased number of adrenergic receptors and increased sensitivity in urethral smooth muscle increase urethral sphincter tone [137, 138]. In addition, sympathetic neurons were demonstrated to express estrogen- and progesterone in the female rat proximal urethra [139]. A recent report suggested that 3-month oral and vaginal estrogen therapy significantly decreased the incidence of urinary frequency and nocturia in hysterectomized postmenopausal women with almost 73% subjective improvement of stress incontinence in the oral group and 60% in the topical group [140]. On the other hand, conjugated equine estrogen (CEE) alone and CEE in combination with medroxyprogesterone acetate (MPA) were suggested to increase the risk of urinary incontinence among continent women [141]. Although the use of estrogen and progesterone supplementation for more than 3 months in postmenopausal women suffering from SUI has been accepted as a common clinical practice before proceeding with more invasive treatment modalities, a meta-analysis reviewing 23 trials on estrogen treatment in postmenopausal women failed to show promising evidence of clinical improvement in female patients suffering from SUI [142].

Androgen receptors were also demonstrated in the urethral and bladder epithelium of rabbits [143]. In the human embryos, epithelium of the urethral groove and mesenchyme of the urethral folds showed positive staining for androgen receptors [144]. However, the impact of androgens on female urethra is still under investigation.

Urinary incontinence is not a rare condition during pregnancy. Obviously, continence dysfunction is a result of anatomical and functional alterations in the bladder and urethra [145]. Although the anatomical changes regarding the urethra are established during pregnancy [146], alterations at the receptor and cellular levels need to be clarified.

**Sensory Function**

Sensory innervation of the urethra is conveyed to the spinal cord mainly via the pelvic nerve and dorsal root ganglia and to some extent via the hypogastric nerve [19]. The sensory nerves innervating the rhabdosphincter run through the pudendal nerve to the sacral spinal cord region [19]. Histopathologically, sensory nerves are identified by their sensory neuropeptide contents such as calcitonin gene-related peptide (CGRP), substance P (SP) and tachykinins [19]. Sensory function of the urethra is summarized in figure 9. Purinergic (P2X1–3), vanilloid (VR1), prostanoid (EP, TP) and neurokinin (NK2) receptors have been demonstrated to be located on sensory afferent nerves [5] (fig. 9).

Afferent C-fibers were suggested to be specific sensory fibers specifically related with pain perception (nociception) and they were also shown to initiate a usually inactive, nonvoluntary, spinal micturition reflex [147, 148].

Vanilloid receptors on sensory nerves are activated by thermal and chemical noxious stimuli (temperatures >43°C and pH levels <6) and it has been demonstrated that heat threshold for vanilloid receptor activation could be decreased to physiologic body temperatures by increasing H+ concentration which is seen in inflammation, suggesting the role of vanilloid receptors in chronic inflammatory pain perception [5] (fig. 9).

After capsaicin or RTX binding, VR1 opens, allowing a massive Ca2+ and Na+ inflow into the neuron leading to the arrest of voltage-sensitive Ca2+ conductance, disruption of metabolic pathways and release of neuropeptides [149, 150]. Vanilloids were also shown to reduce nerve growth factor (NGF) in sensory neurons and prolonged NGF deprivation causes neuronal death [151].

It was shown that sensory innervation of the urethral mucosa is involved in inflammatory situations and administration of capsaicin can prevent noninfectious urethral inflammation [152]. Capsaicin (extracted from red...
hot chili peppers) and resiniferatoxin (RTX) (extracted from *Euphorbia resinifera*) are the vanilloid substances that act via binding specific vanilloid receptors on the peripheral terminals of sensory afferents, nociceptive neurons which cause initially excitation then desensitization, and finally neurotoxicity [149].

De Laet et al. [153] determined current perception urethral thresholds (CPTs) by using neuroselective sine-wave currents at 5 Hz (stimulating sensory C-fibers), 250 Hz (stimulating sensory A-delta-fibers), and 2,000 Hz (stimulating sensory A-beta-fibers) in the bladder, posterior, and the distal urethra in young healthy volunteer females. They found that bladder CPTs were significantly higher compared with CPTs in the posterior urethra and in the distal urethra. They did not find any significant difference between the posterior and distal urethra. Kinn et al. [154] also investigated CPTs by using an electrical stimulator connected to a urethral catheter in female patients. They found that CPTs were higher in old than in younger patients and no significant differences in sensitivity between patient groups with stress incontinence, urge, or mixed symptoms were detected. Recently, Kessler et al. [155] investigated the impact of radical pelvic surgery on urethral sensory thresholds in women. They found out that proximal urethral sensory thresholds were increased; however, distal urethral sensory thresholds did not change after radical pelvic surgery. These findings suggest that proximal urethral afferent nerve fibers run through the pelvic plexus in major which are likely to be injured during radical pelvic surgery. On the other hand, afferent innervation of the distal urethra is supplied by the pudendal nerve.

In conclusion, several pathways and receptors are involved in the contraction and relaxation of the human female urethra. Adrenergic system (α- and β-ARs), cholinergic system (muscarinic receptors), NANC pathways and mediators such as NO, ATP, neuropeptides, prostanoids, serotonin and Rho-kinase are believed to play important roles in the physiology of the urethral function. Insufficient urethral closure and function might lead to SUI formation in women. Although the adrenergic system seems to be playing a major role in urethral contraction, management of SUI by α-AR agonist administration has not been successful. Likewise, NO seems to be the major urethral relaxant, but the role of other transmitters in urethral contraction and relaxation needs further research. Understanding these mechanisms at the cellular and receptor level will possibly lead to the discovery of new drugs for use in the treatment of SUI and/or lower urinary tract symptoms in women.
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Female Urethral Pharmacology


