Sex Differences in the Physiology and Pharmacology of the Lower Urinary Tract

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Key Words

Sex difference • Overactive bladder • Micturition • Physiology • Pharmacology • Lower urinary tract

Abstract

Sexual dimorphism is not only noticed in the prevalence of many diseases, but also in multiple physiological functions in the body. This review has summarized findings from published literature on the sex differences of the pathophysiology and pharmacology of the lower urinary tract (LUT) of humans and animals. Sex differences have been found in several key areas of the LUT, such as overactive bladder, expression and function of neurotransmitter receptors in the bladder and urethra, and micturition patterns in humans and animals. It is anticipated that this review will not only evoke renewed interest for further research on the mechanism of sex differences in the pathophysiology of the LUT (especially for overactive bladder), but might also open up the possibilities for gender-based drug development by pharmaceutical industries in order to find separate cures for men and women with diseases of the LUT.

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Introduction

Sex is a key biological variable that should be considered in all basic physiological and biological research

since sexual dimorphism is observed in many physiological processes in humans and animals [1], emphasizing the importance of sex difference in biomedical research, which must be acknowledged and addressed [2, 3]. To improve health for both women and men, we must understand specifically how sex modifies disease risk, presentation, and treatment since females and males differ not only in their physiology, but also in the incidence and progression of their diseases [4, 5]. In humans, there is a sex difference in the physiology and prevalence of many diseases. Only some of them are mentioned here since a detailed citation is beyond the scope of this review. For example, sex difference is observed in cardiovascular physiology and disease [6, 7], cerebrovascular disease [8], Parkinson's disease [9], Alzheimer's disease [10], autoimmune diseases [11], multiple sclerosis [12], lung disease [13], depression [14] and pain sensation [15]. Based on the above facts, the present review was formulated from published literature on the findings of sex differences in the physiology and pharmacology of the lower urinary tract (LUT) of animals and humans.

Sex Differences in Overactive Bladder and Urinary Incontinence

The most prominent prevalence of lower urinary tract symptoms (LUTS) in women and men is in the emergence of overactive bladder (OAB) that leads to urinary incontinence (UI), which is the complaint of any invol-

untary urinary leakage. OAB was defined by the International Continence Society as “urgency, with or without urge incontinence, usually with frequency and nocturia” [16]. However, OAB may be more accurately defined as a hypersensitivity disorder rather than a syndrome characterized by urgency [17]. OAB wet refers to when urinary urge incontinence (UUI) is present, while OAB dry refers to when incontinence is absent [18].

Detrusor overactivity (DO) is the urodynamic hallmark of OAB, characterized by involuntary bladder conditions [18]. The prevalence of DO increases with age, which might have neurogenic and/or myogenic etiology [19, 20]. Moreover, DO might be due to increased urethral sensations as well [21]. In addition to DO, other age-related changes in LUTS, such as detrusor underactivity (DU) (which commonly affects micturition function in the elderly population), is also recognized. DU might be due to impairment in the structural and functional changes of the bladder, and its true prevalence among the elderly population remains largely unknown [22, 23].

There are many factors that attribute to the pathophysiology of OAB. The function of the LUT is determined by a complex neural hierarchy of the central and peripheral nervous system. While patients may appear to have similar symptoms, in reality, the underlying mechanisms may be diverse [24]. OAB, DO, and DU are all pathological conditions of the LUT that can have major impacts on quality of life and social functioning [25, 26].

Several epidemiological studies on OAB have been conducted in different world populations considering gender as an important factor. Although the overall prevalence of OAB was similar in both men and women, a sex-specific prevalence of OAB symptoms differed substantially [27, 28]. It has been observed that OAB symptoms are significantly higher and more frequently observed in women than in men [29–31], especially OAB wet [31, 32], UUI, stress urinary incontinence [33–36], and nocturia [37]. However, one study reported that the prevalence of UUI is lower in women than men [38]. It has been suggested that elderly women with LUTS have lower functional bladder capacities than elderly men [32, 39].

In addition to OAB and UI, there is a sex variation in the incidence of DO and DU. It has been reported that DO is significantly higher in males than females [32, 40], suggesting in contrast to male OAB, that DO might not be a major underlying cause of female OAB [32]. Similarly, a greater prevalence of DU has been observed in elderly men compared to elderly women [22, 41]. However, under certain pathological conditions such as cere-

brovascular accident, female patients may suffer from a greater decrease in bladder emptying (i.e. DU) than male patients [42].

In addition to the presence of a sex difference in OAB in adults, interestingly there is a sex difference in nocturnal bladder control in boys and girls. Nocturnal enuresis, which is the most common UI in children, was twice more common in boys than girls [43–45]. In this correlation, it has been suggested that UI in children and adults might have different causes and should be treated differently [46]. However, there might be a strong link in the emergence of UI between these two different ages of life as well [47].

Apart from these findings, sex also has profound influences in developing UI under certain pathophysiological conditions. It has been observed that obesity’s adverse risk for UI was significant only in elderly females when compared to males in general [48]. Besides, women with diabetes mellitus have a significantly greater risk of developing UI than men [49–53]. UI due to interstitial cystitis (IC), a painful bladder disease, is also more prevalent in women, affecting as many as 1 in 4 to 5 women compared to only 1 in 20 men [54], suggesting a role of female sex hormones in IC [55]. Moreover, bladder cancer (BC), which can obstruct the normal flow of urine and cause UI, is more prevalent in men than in women. There is a 4:1 male:female predominance of BC [56–58]. However, it should be noted that sex-specific hormone receptors (androgen and estrogen receptor- β) cannot alone be responsible for gender differences in BC rates because they were expressed in similar rates in both sexes [59].

Sex Differences in the Pharmacology of LUT

Experiments have been conducted to determine the influence of gender and the estrous cycle on the contractility of rat bladder in response to cholinergic stimulation. Bladder strips from female rats in all stages of the estrous cycle were more sensitive to carbachol than those from the males [60]. Significant differences have also been reported in the magnitude of field stimulated relaxation between the bladder neck and urethra of both male and female rabbits, where maximal response was significantly greater in the male than in the female [61]. However, it has been reported that although gender does not influence the contractility of human detrusor, any gender variability of bladder functions must reside elsewhere [62].

From a pharmacological standpoint, prominent sex differences have been reported in the neurotransmitter

receptors of the LUT of humans and animals. Expression of muscarinic receptor subtypes (M1 and M3) was lower in the trigone of females. On the contrary, a higher expression of M2 and M5 was observed in the trigone of males [63]. However, with respect to the urothelium, more M2 was expressed in adult men than women. This was reversed in old age, i.e. more M2 was expressed in elder women than men [64].

Regarding the distribution of the adrenergic receptor (AR) in the human bladder, a significantly higher amount of α_1 -AR was present in the trigone of women compared to men [65]. In animal studies, it has been reported that α_2 -AR density was considerably higher in the female urethra than in the male urethra of rabbit [66–68]. In addition to α -AR, the expression of β -AR was greater in the detrusor and trigone of the female rabbit bladder than the male rabbit bladder [69].

Apart from adrenergic neurotransmission, a sex difference in the cholinergic and purinergic components of neurotransmission in the bladder has been observed in guinea-pig (GP) and mice. It has been observed that the cholinergic component was predominant in the male bladder than the female bladder [70, 71]. On the contrary, the purinergic component was predominant in the female bladder than the male bladder [70]. This finding was meaningful in context to a human study where it has been shown that urinary purine ratios, especially the ATP/creatinine ratio, was 4 times higher in female controls than male controls, and this ratio was also about 2 times higher in female OAB patients than male benign prostatic hyperplasia patients. Therefore, females may have some essential factor that increases ATP release from the bladder epithelium, and this putative factor may be one of the causes of OAB in females [72].

However, some contradictory reports have indicated that muscarinic receptors did not differ between male and female rat bladders [73], and that moreover, there is a greater proportion of purinergic neurotransmission in the male rat [74], contradictory to the findings of Patra et al. [70]. Possible discrepancies between these two works might be due to differences in species, and as well as in the in vitro preparation of detrusor strips when studying neurotransmission. Patra et al. [70] used GP detrusor strips with intact urothelium, whereas Creed et al. [74] used rat detrusor strips without urothelium. Because of the well established fact that the urothelium plays a significant role in bladder function in both rats [75, 76] and humans [77], the findings of Patra et al. [70] seem to be more meaningful since natural integrity of the detrusor was maintained with intact urothelium. Therefore, it

should be emphasized that selection of animal species is an important factor for bladder research in order to extrapolate the results of animal studies to similar effects in human.

In addition to these reports on the sex differences of adrenergic, cholinergic and purinergic neurotransmission in the bladder, several reports have shown a prominent sex difference on other aspects of LUT function. A sex difference has been observed in acid-sensitive ion channels (ASIC) and transient receptor potential vanilloid type 1 (TRPV1) channels. Both are key channels for extracellular protons that might underlie the acid-evoked pain perception in the mouse bladder. In the urothelium, the *ASIC1* gene was highly expressed in males than in females, whereas the expression level of *ASIC2* in the detrusor was higher in female mice than in male mice. The expression of *TRPV1* in the bladder also showed a sex difference (male < female) [78].

A prominent sex difference in the proportion of collagen and muscle in the body and neck of the bladder and urethra was reported between male and female dogs. Females had a higher proportion of collagen and a lower proportion of muscle tissues than males [79]. Further studies by the same authors have reported a sex difference in the expression of cyclooxygenase-2 (COX-2) in the LUT of dogs. Females expressed more COX-2 mRNA than males [80]. Reports are also available on the sex difference in the expression of nerve growth factor (NGF) mRNA in the bladder of male and female rats following bladder outlet obstruction (BOO). A 2-fold increase in bladder NGF mRNA following BOO was only observed in females [81]. A sex difference of peroxisome proliferators-activated receptors (PPAR) mRNA was also present in the bladder smooth muscle of pig. PPAR- δ may play a role in the effects of the metabolic syndrome on bladder smooth muscle. PPAR- δ mRNA was 2-fold higher in males than in females [82]. Furthermore, recently, it has been demonstrated that there is a sex difference in phosphodiesterase type 5 (PDE5) expression and biological activity in male and female bladder of rat. PDE5 activity is more pronounced in males when compared to female, suggesting that the male bladder is a more suitable target for PDE5 inhibitors in treating LUT symptoms than the female counterpart [83].

It has also been reported that perfusion of the canine bladder urothelium differed by sex. There was significantly greater perfusion of the bladder urothelium in males than in females, but not in the detrusor muscle [84]. Similarly, there was a sex difference in anoxia-glucosepenia and reperfusion (A-G/R) damage in the bladder of

rats [85] and GPs [86]. The urinary bladder of male rats was more susceptible to A-G/R damage than females, suggesting that estrogen might be a neuroprotective hormone in females [85]. However, the higher resistance of the female urinary bladder to A-G damage might also be partly due to the higher glycogen content in the female bladder [86].

Furthermore, a sex difference in the production of nitric oxide reaction products (NO₂/NO₃-) was also present in the rat model of cyclophosphamide induced cystitis. Female rats treated with cyclophosphamide had significantly higher levels of NO₂/NO₃- in urine when compared to male rats, suggesting the role of nitric oxide in the manifestation of IC predominantly found in females [87]. It has also been reported that there was a sex difference in the expression of progesterone receptor (PR) in the mouse urethra. Expression of PR in the female urethra was estrogen-inducible, whereas in males, no evidence was obtained for the estrogen receptor-linked control of the PR expression [88]. Finally, sex and age related changes in connexin 43 expression have been reported in normal rat bladder. Connexin 43 is a key structural protein of gap junctions in bladder smooth muscle. It was observed that the expression of connexin 43 mRNA in normal detrusor muscle cells showed age-related changes, especially in male rats [89].

Sex Differences in Micturition Pattern

It has been reported that both detrusor pressure at maximum flow and maximum detrusor pressure during voiding were found to be significantly higher in men than in women [90]. In rats, the external urethral sphincter (EUS) activity causes high frequency oscillations, and this motor activity is necessary for efficient urine expulsion during micturition. It has been observed that the amplitude of the pressure oscillations in the EUS is greater in males than in females [91]. Sex differences also exist regarding voiding pattern in male and female rats. During voiding, maximum flow rate was lower and micturition time was shorter in female rats as compared to the male rats [92]. Further studies have shown that the functional difference in these dimorphic micturition patterns in rats might be due to the dimorphic nature of the perineal muscles in the EUS. In females, the EUS is poorly developed, whereas in males, it is extensive and thick [93].

Apart from the anatomical differences contributing to sex difference in the micturition pattern of rats, there is diurnal variation in the frequency of micturition in male

and female rats. Micturition frequency was increased in male rats in the early morning hours [94]. Recently, cystometric study was used to monitor sex difference in micturition patterns in conscious male and female Sprague-Dawley, spontaneously hypertensive (SHR), and Wistar-Kyoto (WYK) rats. Interestingly, the micturition interval in the male rats, regardless of strain, was shorter compared to the female rats of the respective strains, suggesting that under physiological conditions, frequency of micturition of the males was higher than female Sprague-Dawley, WKY and SHR [95].

In addition to these studies focused on micturition in rats, there were considerable sex differences in different aspects of the micturition pattern in mice. When tested in circular open fields, striking sex differences in the pattern of deposition were shown in terms of both the number and distribution of the urine spots. Male mice produced a large number of spots that were regularly dispersed, while females produced relatively fewer spots with a more clumped distribution, thus suggesting a sex difference in mouse micturition pattern [96].

From the functional stand point, prominent urinary retention was noticed only in male mutant mice lacking M2 and M3 muscarinic receptors, suggesting the importance of cholinergic neurotransmission in males in order to induce detrusor contractility. In contrast to this apparent urinary retention phenotype in the male mice, the bladder distension in the female mice was mild, suggesting that cholinergic neurotransmission might be less important to induce micturition in females [71, 97].

Urothelial defects due to uroplakin deficiency were associated with significant alterations in gender specific bladder function in mice. Uroplakins are protein subunits present in the apical cells of the urothelium. In particular, the increased bladder capacity, micturition pressure, and demonstrable non-voiding contractions were observed in the male uroplakin II knockout mice (UPII KO-M). On the contrary, a mild reduction was noticed in the sensitivity of the detrusor from female UPII KO-M to carbachol induced contractions [98].

In serotonin reuptake transporter knockout mice, females exhibited bladder dysfunction, characterized by a significant increase in the frequency of spontaneous non-voiding bladder contractions and a decrease in void volume compared to control female mice. These differences were not observed in male serotonin reuptake transporter knockout mice [99]. Moreover, female BALB/C mice exhibited a significantly larger number of non-voiding contractions and urine drippings (increased number of small urine spots) compared to male mice [100].

Sex Difference in LUT Function: Chemicals and Drugs

There was a sex difference in the responsiveness to intravesical infusion of diluted acetic acid (A/A) in mice. The extent of the decrease in the micturition interval due to A/A infusion was much less in males than in females, suggesting that the female bladder was more sensitive to the acid irritation than the male bladder. Identification of the mechanisms underlying this sex-specific characteristic might be helpful in elucidating pathogenesis of IC in females [101]. Further studies conducted by the same researchers in order to elucidate the mechanism of A/A irritation in mice have suggested that TRPV1 channels were involved in the sex difference in the LUT response to A/A irritation, and that this irritation occurred via 'cross-talk' between the bladder and urethra [102].

Apart from the noxious stimulus, the effect of tolterodine, a non-specific antimuscarinic drug, was studied on micturition in rats. The effect of tolterodine was gender specific, suppressing water consumption and urine production only in females, not in males [103]. Moreover, darifenacin, a selective M3 muscarinic receptor antagonist, showed a greater potency in inhibiting the frequency of OAB induced by intra-arterial acetylcholine administration in female rabbits than in the male rabbits [104].

A smaller sex difference has also been observed with a new drug candidate for UI and bladder hyperactivity in rat. Bioavailability of this drug was higher in females than in males [105]. Recently, the effectiveness of two COX inhibitors, ketoprofen and meloxicam, was studied in the micturition pattern of male and female SHR and WKY rats. Results of this study have shown that these two COX inhibitors increased micturition intervals, i.e. decreased micturition frequency. More interestingly, these effects were significantly greater in male WKY and SHR than in female WKY and SHR, suggesting that the effectiveness of COX inhibitors in bladder function is gender related [106]. Moreover, previously, it has been reported that potentiation of the purinergic component of the neurogenic response by histamine was higher in female GP bladders than in male GP bladders [70].

However, despite these evidences of sex difference on the effects of drugs in bladder function, some studies have reported that the efficacy or tolerability of tolterodine and beta-AR agonist is unlikely to be affected to a major extent by gender [107–109]. Therefore, it is needless to say that further research in basic and clinical areas need to be done, with a major focus on sex difference in muscarinic receptor antagonist and beta-AR agonist action on LUT functions.

Possible Mechanism of Sex Difference in LUT Function

The mechanisms governing these sex differences in LUT functions, particularly OAB and micturition patterns, are yet to be explored. However, there might be several possible mechanisms that should be taken into consideration.

Firstly, OAB and micturition patterns might be due to the differences in the anatomical structure and function of the bladder outlet in men and women [27, 110–112]. Anatomically, a better distribution of the branches of the hypogastric nerve to the trigone has been reported in women, compared to a poor supply in men [113]. Furthermore, structurally, EUS in male rats is extensive and thick compared to females [92, 93]. It was also reported that longitudinal smooth muscle of male canine urethra play a predominant role during micturition, as compared to a minor role of the urethral smooth muscle in females [114]. Moreover, from a functional point, electrical stimulation of the hypogastric nerve produced significant reduction in urethral pressure in females compared to males [115]. Thus, it should be emphasized that the urethra plays a major role in sex difference in LUT function.

Secondly, as far as central regulation of micturition is concerned, important structural and neurochemical differences have been observed between male and female brains [116–119]. It has been observed that the pontine micturition center and periaqueductal grey could be identified in both sexes as far as regulating micturition. However, pelvic floor muscle control seems to induce different activation intensities in men and women [120]. With subsequent studies using functional magnetic resonance imaging techniques, it has been observed that the responses of the right thalamus and several other right-hemispherical regions during intentional modulation of bladder sensation were stronger in women than men [121].

Finally, sex hormones should be considered as a key factor in regulating the sex differences in LUT functions in humans and animals, especially the effects of estrogen and progesterone in females [122–126] and androgen in males [127–129]. Estrogen and progesterone play a crucial role in maintaining the integrity of the structure and function of the LUT via their central and peripheral effects. Nevertheless, the role of central and peripheral cholinergic and purinergic receptors in regulating micturition cannot be ruled out either [70, 71, 130].

Table 1. Summary of the major sex differences of the pathophysiology of LUT

Female	Male
Studies in human ↑ OAB wet, UI, SUI and nocturia ↑ UI in obesity, diabetes and interstitial cystitis ↓ Expression of M1, M3 in the adult trigone ↑ Expression of M2 in the bladder in old age ↑ Expression of α -AR in the trigone ↑ ATP in the urine of normal and OAB patients ↓ Bladder capacity in elderly women Better distribution of HGN in the trigone Studies in animals ↑ Purinergic NT in GP bladder ↑ Potentiation of PuNT by HIST in GP bladder ↑ Expression of α and β -AR in rabbit bladder ↓ Expression of ASIC1-mucosa, mouse bladder ↑ Expression of ASIC2-detrusor, mouse bladder ↑ Expression of TRPV1 in mouse bladder ↑ Collagen and ↓ muscle content in dog LUT ↑ Expression of NGF in rat bladder after BOO ↓ Expression of PPAR- δ in pig detrusor ↓ Expression of PDE5 in rat bladder ↓ Perfusion in the canine urothelium ↓ Susceptibility to A-G/R damage in rat bladder ↑ NO ₂ /NO ₃ in rat urine after CPY treatment ↓ Pressure oscillations – rat EUS during voiding ↓ Flow rate and shorter voiding time in rat EUS is poorly developed in rat ↓ Micturition frequency in conscious rat Mild urinary retention in mice lacking M2, M3 ↓ sensitivity to CARB – detrusor of UPII KO-M ↑ Sensitivity to A/A infusion in mouse bladder Tolterodine lowers urine production in rat ↓ Effects of KETO and MELO in rat voiding ↑ Inhibition of OAB by Darifenacin in rabbit Urethral smooth muscle – minor role in voiding ↓ Relaxation of urethra of rabbit following EFS Connexin43 expression – not regulated by aging	Studies in human ↑ detrusor overactivity and detrusor underactivity ↑ nocturnal enuresis in boys and ↑ BC in men ↑ expression of M2, M5 in the adult bladder ↓ expression of M2 in the bladder in old age ↓ expression of α -AR in the trigone ↓ ATP in the urine of normal and BPH patients ↑ detrusor pressure during normal voiding poor supply of the branches of HGN in the trigone Studies in animals ↑ cholinergic NT in GP and mouse bladder ↓ potentiation of PuNT by HIST in GP bladder ↓ expression of α and β -AR in rabbit bladder ↑ expression of ASIC1- mucosa, mouse bladder ↓ expression of ASIC2-detrusor, mouse bladder ↓ expression of TRPV1 in mouse bladder ↓ collagen and ↑ muscle content in dog LUT ↓ expression of NGF in rat bladder after BOO ↑ expression of PPAR- δ in pig detrusor ↑ expression of PDE5 in rat bladder ↑ perfusion in the canine urothelium ↑ susceptibility to A-G/R damage in rat bladder ↓ NO ₂ /NO ₃ in rat urine after CPY treatment ↑ pressure oscillations – rat EUS during voiding ↑ flow rate and longer voiding time in rat EUS is extensive and thick in rat ↑ micturition frequency in conscious rat ↑ urinary retention in mice lacking M2, M3 ↑ bladder capacity in UPII KO-M ↓ sensitivity to A/A infusion in mouse bladder no effects of Tolterodine on urine production in rat ↑ magnitude of effects of KETO, MELO-rat voiding ↓ inhibition of OAB by Darifenacin in rabbit urethral smooth muscle – major role in voiding ↑ relaxation of urethra of rabbit following EFS connexin43 expression-aging regulates-rat bladder

↑ = Higher; ↓ = Lower; SUI = stress urinary incontinence; BPH = benign prostatic hyperplasia; HGN = hypogastric nerve; NT = neurotransmission; HIST = histamine; CPY = cyclophosphamide; CARB = carbachol; KETO = ketoprofen; MELO = meloxicam; EFS = electrical field stimulation.

Conclusion

Studies cited in this review have suggested evidence of significant sex differences in several aspects of LUT functions under pathophysiological conditions in both humans and animals (table 1). It is being increasingly realized that neither do identical processes occur in men

and women, nor that identical therapeutics will apply [116] since significant differences exist between men and women with respect to their response to hormone and drug treatment for a broad range of diseases [131–137]. Considering the facts that the pathophysiology of male LUTS might be different from female LUTS, diagnosis and treatment of OAB and LUT function amongst men

and women should be conducted separately, which will bring a new approach to health care in this area [32, 40, 138, 139].

In fact, this idea of separate treatment options might be meaningful in context to a previous report, which has shown that female IC patients were non-responsive to anti-cholinergic medication in alleviating their painful bladder problems, despite the fact that anti-cholinergic medication is the standard treatment option for OAB in both men and women [140]. Possible reasons of this resistance to anti-cholinergic drugs might be due to an up-regulation of purinergic neurotransmission (PuNT) [141] and augmented release of ATP in the bladder of female IC patients [142]. Eventually, this upregulation of PuNT might further interact with the increased release of inflammatory mediators present in the IC bladder in order to augment the painful bladder symptoms of female IC

patients. Such possibilities might occur as observed from the finding that PuNT of the bladder was potentiated by histamine, bradykinin, and substance-P [143, 144]. Thus it has been suggested that purine receptor antagonists might be an option for treatment of IC and other diseases of the LUT where PuNT is upregulated [145, 146].

In fact, gender specific medicine training has been successfully integrated into an existing Dutch GP training curriculum with an impact on gender awareness [147]. However, it is needless to say that further research is required to resolve some of the discrepancies, especially in understanding the molecular aspects of the sex differences in the physiology and pharmacology of LUT functions. Eventually, this new approach might encourage pharmaceutical industries to initiate efforts of gender-based drug development in order to combat diseases of the LUT, which might eventually lead to separate therapeutic options for men and women.

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