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Anatomical, physiological and pathophysiological features of the lower urinary tract in gender and age aspects

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In the review article, based on the results of modern clinical and experimental studies, gender and age-related features of the anatomy, physiology and pathophysiology of the lower urinary tract are considered. The features of the structure and functioning of the urothelium, myothelium, neurothelium and endothelium of the lower urinary tract in men and women are described in detail. A separate section of the review is devoted to the peculiarities of hormonal regulation of the lower urinary tract, depending on gender and age.

Keywords: sexual dimorphism; lower urinary tract; detrusor; urethra; pelvic floor; urothelium; endothelium; myothelium; neurothelium; sex steroid hormones.

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Анатомо-физиологические и патофизиологические особенности нижних мочевых путей в гендерном и возрастном аспектах

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В обзорной статье на основе результатов современных клинико-экспериментальных исследований рассматриваются гендерные и возрастные особенности анатомии, физиологии и патофизиологии нижних мочевых путей. Подробно описаны особенности строения и функционирования уротелия, миотелия, нейротелия и эндотелия нижних мочевых путей у мужчин и женщин. Отдельный раздел обзора посвящен особенностям гормональной регуляции нижних мочевых путей в зависимости от половой принадлежности и возраста.

Ключевые слова: половой диморфизм; нижние мочевые пути; детрузор; уретра; тазовое дно; уротелий; эндотелий; миотелий; нейротелий; половые стероидные гормоны.

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ЭКО•ВЕКТОР

INTRODUCTION

Sexual identity is a fundamental aspect of human physiology, which equally divides the entire living population into two, but this significant biological variable is rarely considered when developing basic physiological research, when transferring results from basic science into clinical research, or when developing personalized medical strategies [1]. Sexual differentiation is one of the most important biological characteristics of all living organisms, including humans, and it has a significant and sometimes key influence on the formation, development, and functioning of many organs and organ systems [2, 3].

The lower urinary tract (LUT) is one of the classic examples of sexual structural and functional dimorphism, which is actively studied to optimize modern diagnostics and pharmacotherapy of LUT diseases in relation to the gender identity of the patients [4–6]. Sexual dimorphism is characteristic of nearly all anatomical structures that form the LUT. However, there is a new hypothetical endocrine–autocrine–paracrine model of interactions between the urothelium, afferent and efferent nerve terminals (neurothelium), vessels (endothelium), muscle cells (myothelium), and myofibroblasts of all LUT structures. According to this model, all these structures constitute a single anatomical and functional system, and its elements are in constant interaction and interinfluence with each other (Fig. 1) [7–11].

Sexual aspects of the LUT urothelium

The urothelium is a specialized epithelium that is located in its connective tissue plate (lamina propria) and lines the LUT inside in the form of 5–7 rows of cells represented by three layers. These layers appeared apical (one layer of umbrella cells, which are in direct contact with urine and serve as a physiological barrier between it and underlying tissues), intermediate (2–3 layers of intermediate cells), and basal (2–3 layers of basal cells) [12]. When the bladder is full, the umbrella cells stretch and flatten, and when the bladder is empty, the cells are cuboidal [13]. The umbrella cells of the superficial urothelium got their name because, in 70%–90% of the cases, peculiar outgrowths (plaques) are found on their

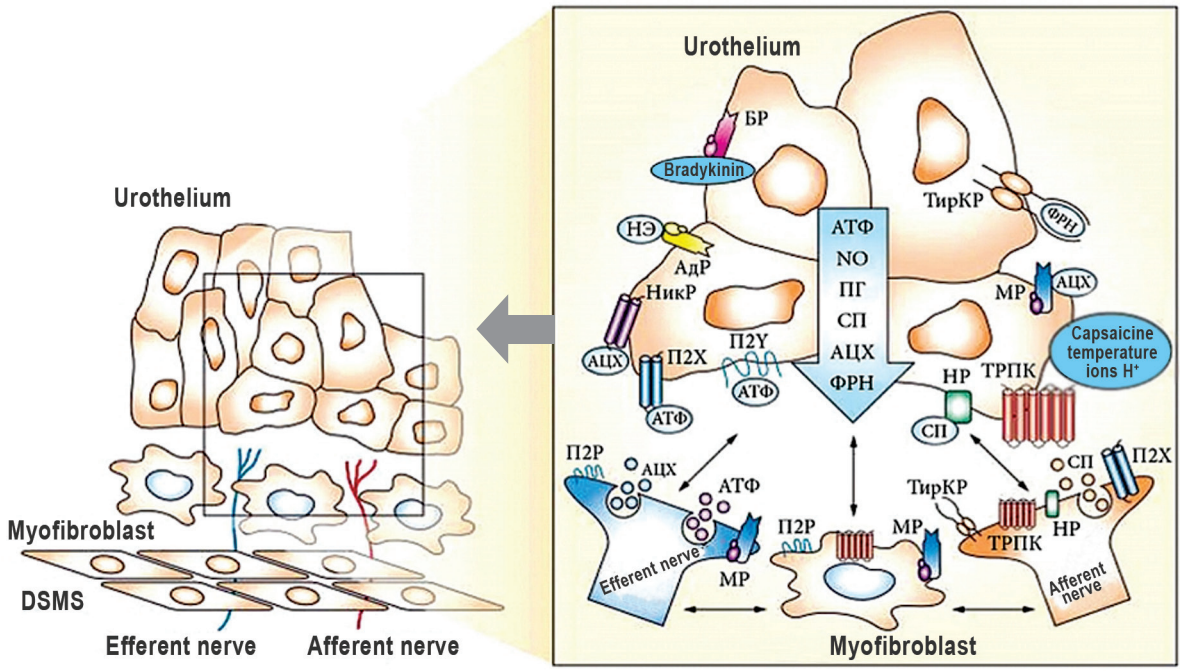

Fig. 1. A hypothetical model of interactions between urothelial cells (urothelium), afferent and efferent nerve endings (neurothelium), vessels (endothelium), smooth muscle cells and myofibroblasts of the lower urinary tract [10, 11]. NO – nitrogen oxide; АдР – adrenergic receptor; АТФ – adenosine triphosphate; АЦХ – acetylcholine; Бр – bradykinin receptor; ГКД – detrusor smooth muscle cell; МР – muscarinic receptor; НикР – nicotinic receptor; НР – neurokinin receptor; НЭ – norepinephrine; П2Р – purinergic receptor subtype 2; П2Х and П2Y – purinergic receptors of the X and Y subtypes; ПГ – prostaglandins; СП – substance R; ТирКР – tyrosine kinase receptor with high affinity for nerve growth factor; ТРПК – transit receptor of potential channels; ФРН – nerve growth factor

Рис. 1. Гипотетическая модель взаимодействий между уротелиальными клетками (уротелием), афферентными и эфферентными нервными окончаниями (нейротелием), сосудами (эндотелием), гладкомышечными клетками и миофибробластами нижних мочевых путей [10, 11]. NO — оксид азота; АдР — адренергический рецептор; АТФ — аденозинтрифосфат; АЦХ — ацетилхолин; БР — брадикининовый рецептор; ГКД — гладкомышечная клетка детрузора; МР — мускариновый рецептор; НикР — никотиновый рецептор; НР — нейрокининовый рецептор; НЭ — норэпинефрин; П2Р — пуринергический рецептор подтипа 2; П2Х и П2У — пуринергические рецепторы подтипов Х и Y; ПГ — простагландины; СП — субстанция Р; ТирКР — тирозинкиназный рецептор с высокой аффинностью к фактору роста нервов; ТРПК — транзитный рецептор потенциальных каналов; ФРН — фактор роста нервов

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membrane facing the lumen of the urinary tract, giving the cells a "toothed" appearance and consisting of uroplakins that form macromolecular structures (hexagonal shape), providing, along with tight junction proteins, the barrier function of the urothelium [14].

Currently, several types of uroplakins have been identified in the urothelium, namely, UP-Ia (molecular weight, 27 kDa), UP-Ib (molecular weight, 28 kDa), UP-II (molecular weight, 15 kDa), and UP-III (molecular weight, 47 kDa) [15–17]. Hu et al. [18] examined male and female rats and found that the identification of UP-II in these animals was associated with defective glycosylation, smaller urothelial plaques of umbrella cells, and increased their water permeability. Aboushwareb et al. [19] revealed specific sex differences in UP-II- and UP-III-knockout mice. Thus, male mouse knockout of UP-II showed signs of functional bladder decompensation, presenting as a decrease in effective pressure and an increase in residual urine. In female rats with the same knockout, no changes were detected. A study of the excitability of detrusor myocytes in uroplakin-knockout mice revealed sex differences, where female rats showed decreased excitability, while male ones showed no changes in myocyte excitability [19]. These data confirmed that uroplakin deficiency in the urothelium can induce bladder dysfunction.

In addition to its barrier function, the urothelium performs the most important sensory function, as it contains numerous ion channels and regulatory proteins of various receptors (i.e., adenosinergic, purinergic, adrenergic, bradykinin, neurokinin, muscarinic, and cholinergic), which ensure the interaction of urothelial cells with each other and unites them into a single functional system [20, 21]. The urothelium releases various small molecules and neurotransmitters in response to a mechanical or chemical stimulus. In addition, because the urothelium contains specialized acid-sensitive ion channels, it maintains a constant pH level and controls bladder sensitivity. The expressions of ASIC1 are more pronounced in male rats, while that of ASIC2 is more pronounced in female ones [22]. Although the impaired expression of ASIC1 channels in the intestine decreases its mechanical sensitivity, the functional consequences of this difference in the expression of these channels in the urinary bladder remain unknown [23].

The urothelium of the urinary bladder also plays an important role in the innate immune response when uropathogens are detected, and the higher incidence of LUT infections in women suggests a significant regulatory role of estrogen in this process. Studies on female mice and urothelial tissues of women have shown that estrogens mediate the defense mechanisms of the urothelium against *Escherichia coli* by regulating the activity of type β (ER-β) estrogen receptors identified in the urothelium; therefore, ER-β plays an important role in the pathogenesis of inflammatory diseases of the bladder in women [24–26].

Recent studies have revealed that high-conductivity potassium channels (BK channels) in the umbrella cells of the surface urothelial layer are regulated by calcium and lipopolysaccharides [27, 28]. A study suggested a relationship between the activity of urothelial BK channels and the expression of estrogen receptors, i.e., ER-β type, in the implementation of the urothelial innate immune response in LUT infections in women, whereas estradiol increases the expression of BK channels, and the blockade of its effects led to the opposite effect in an experimental mouse model of oophorectomy [29].

Myothelial sexual dimorphism of the LUT

Detrusor. The normal bladder is a reliable reservoir controlled by the nervous system for storing urine and its periodical emptying. It represents a complex of smooth muscle elements combined into a single functional syncytium [30, 31]. The detrusor muscle is thicker in men than in women because more pressure is required to empty the bladder through the longer male urethra [32]. The ratio between the smooth muscles and connective tissues in the detrusor is not different in women and men of any age, and studies have shown that the contractile ability of the human detrusor is independent of sex [12, 33].

The human bladder can be detected as early as week 10 of intrauterine development. Although the trigone is believed to be of mesodermal origin, the rest of the bladder originates from the endoderm; some studies have shown that the trigone also has an endodermal origin [34]. Favorito et al. [35] evaluated morphological differences in the detrusor smooth muscle of women and men and did not find differences in the volumetric density of fetal nerves, smooth muscle cells, or collagen at weeks 13–20 after conception [35].

Urethra. The muscle layer of the urethra contains oblique and longitudinal muscle fibers surrounded by circular fibers in both women and men. The muscular layer provides basic resistance to urine flow, which is further enhanced by the rich vascularization of the urethra [36]. In addition, α1 and α2 adrenergic receptors, consisting of several subtypes and regulating the contractility of smooth myocytes, contribute to the functions of the urethra in both sexes. Male rabbits have the same number of α1 and α2 adrenergic receptors, but female rabbits have a much higher density of α2 adrenergic receptors [37]. Alexandre et al. [38] examined the effect of various agonists and antagonists on urethral smooth muscles and revealed that phenylephrine, norepinephrine, potassium chloride, and stimulation with an electric field caused stronger muscle contractions in men. However, no sex differences were noted in response to the administration of N-nitro-L-arginine, atropine,

or a P2X1-purine receptor antagonist. The expressions of the RNAs of α1A-adrenergic receptor and tyrosine hydroxylase in the urethra were significantly higher in men than in women. Therefore, α1-adrenergic receptors may not be very important for the contraction and functionality of the urethra in women [38].

Oswald et al. [39] studied the intrauterine development of the internal urethral sphincter in 37 human fetuses and found that the volume of the internal sphincter is significantly greater in male fetuses than in female fetuses, which is partially caused by muscular hypertrophy and leads to a decrease in the urethral lumen [39]. This may be due to transient urethral obstruction distal to the bladder neck during the hormone-dependent growth stimulation, particularly by testosterone, in men. Jin et al. [40] showed that the differentiation of smooth muscle cells in the bladder and urethra is crucial in the development of mesonephric duct prolapse during intrauterine fetal development [40].

The striated musculature provides pelvic floor support and coordinates urinary initiation and bladder emptying. The architecture of the striated muscles in the detrusor and urethra coincides with the arrangement of muscle fibers and connective tissues [41, 42]. Striated muscle fibers have two types, namely, slow contraction (type I) and fast contraction (type II) muscle fibers [43]. Type I fibers have more acid-resistant ATPases, more mitochondria, thicker Z-disks, higher amounts of oxidative enzymes, and a contraction time of approximately 100 ms. Type II fibers have a higher concentration of alkali-resistant ATPases, fewer mitochondria, and a contraction time of approximately 30 ms [43, 44]. The fiber type of striated muscles affects their susceptibility to damage and repair and varies by sex. In rats, the female and male urethras differ macro- and microscopically. In contrast to typical skeletal muscles, the myofibrils of the female urethral sphincter are 3–5 times smaller in diameter than the striated pelvic floor muscles because these cells lack peripheral nuclear localization [45]. Instead, the nuclei of myocytes are located in the center, with sizes similar to the diameter of the fibril. Unlike other skeletal muscles, these cells have no attachment points and are in direct contact with the adjacent connective tissue [46]. Similar to skeletal muscles, the striated musculature of the rat urethra expresses desmin and dystrophin; desmin runs orthogonally to Z-shaped lines, outlining sarcomeres, while dystrophin is localized in the sarcolemma of myocytes in female rats [45]. In male rats, two longitudinal bands of connective tissue segment the sphincter into two lateral bundles, and myofibrils do not form myotendinous connections with adjacent connective tissue. The striated elements of the sphincter form a longitudinal thick layer visible in male rats, while the sphincter is thin and more rounded in female rats [46]. Bierinx et al. [47] found two types of myofibrils in the urethra of male rats, which were characterized predominantly by type II "fast" fibers, similar to female rats; however, individual fibers taken near the urethral lumen contained slow contraction myofibrils (type I). In addition to the bladder neck, striated muscles are located in the middle part of the urethra, and recent studies using immunohistochemical methods have shown that rapid-contraction muscle fibers predominate among the fibers [48]. Chen et al. [49] identified fast contraction fibers in the proximal urethra in male rats.

In humans, the structure of the muscular apparatus of the urethra is significantly different between men and women. When using histochemical methods and electron microscopic analysis of samples obtained using cystourethrectomy, Gosling et al. [44] identified type I muscle fibers of 15–20 μm in diameter (slow contraction fibers) in the urethra of both men and women and muscle fibers of both types in *m. levator ani* 3. Other authors revealed that striated muscles of the female urethra consist mainly of type I fibers [50–52], while the striated muscles extend from the male urethra through the prostate and consist of both slow and fast fibers of various diameters; however, its functional significance remains unknown [53, 54]. In humans, the identification of nitrergic nerve fibers in rhabdosphincter suggests that nitric oxide (NO) plays an important role in the control of striated muscles in the urethra, regulating their relaxation and contractility [55–57]. Ho et al. [53] showed the presence of NO synthases (NOS) in 86% of fast muscle fibers and in 29% of slow muscle fibers in the sarcolemma of myocytes of the male urethra [53].

Urogenital pelvic diaphragm. The pelvic floor musculature supports the abdominal and pelvic organs and regulates the mechanisms of the retention of feces and urine [58]. The muscular components of the pelvic floor include the levator muscles and coccygeal muscle [59]. *M. levator ani* contains a heterogeneous population of type I and II muscle fibers, but histological studies have shown a predominance of type I fibers, which clinically correlates with the static nature of the pelvic floor and its role in maintaining the internal organs of the abdominal cavity and pelvis [44]. A smaller population of type II fibers supports the pelvic floor during periods of increased abdominal pressure, and the number and diameter of these fibers decrease with age. However, their proportions are not different between men and women [60, 61]. Tobin et al. [62] found that the *m. levator ani* of a rat embryo exhibits sexual dimorphism; during antenatal development, male embryos contain significantly fewer motor units (153 versus 350), and each unit has a relatively smaller cross-sectional area (89.2 μm^2 versus 120.8 μm^2) compared with that in female fetuses. With the postnatal development of rats, the cross-sectional area of the motor units decreased slightly in both sexes, but the number of motor units in male rats increased

rapidly to 2726 by day 6 after birth, which is caused by the influence of testosterone [62]. In their experimental studies, Niel et al. [63] showed that satellite cells (a population of myogenic stem cells) located on the periphery of the pelvic floor muscle fibers are influenced by androgens and can play a role in sexual dimorphism. Thus, the number of satellite cells in *m. levator ani* of newborn male rats was higher than that in newborn females. With prenatal exposure to testosterone, the number and size of satellite muscle cells in female rats increased; therefore, sex differences in muscle tissue found in developing rats are due to sexual dimorphism in satellite cells sensitive to androgens [63]. These animal studies are consistent with a study that analyzed sex differences in human fetuses and showed that, during development, *m. levator ani* forms as a thick muscle layer in boys, while it is a thin muscle in girls, and its bundles are integrated with connective tissue [64].

Sex characteristics of the regulation of endothelial function and blood supply to the LUT in terms of age

The endothelium mainly helps in maintaining vascular homeostasis by synthesizing and secreting substances involved in the expansion (vasodilators) and narrowing (vasoconstrictors) of the vessels. Progressive endothelial dysfunction, as one of the aspects of vascular aging, has been identified as a key initiating stage in the pathogenesis of atherosclerosis [65]. Endothelial function is controlled by several factors that differ in men and women, and it is associated with the expression of sex hormone receptors in the endothelium, which have a major effect on endothelial metabolism and consequently on the tone of the vascular wall and regional blood flow [65]. Thus, differences in the reaction of blood flow to the infusion of intraperitoneal acetylcholine in men and women have been established. In particular, in normotensive premenopausal women, acetylcholine-mediated vasodilation slightly decreased (by approximately 0.5% annually); however, disorders of endothelium-dependent vasodilation became evident only after menopause, in which the response to acetylcholine decreased faster (2.1% per year). In women, no sex differences in smooth muscle function response to sodium nitroprusside administration were noted, which confirmed the effect of menopause on endothelium-dependent rather than endothelium-independent vasodilation [66]. The well-known consequences of menopause on LUT are united by the term "genitourinary menopausal syndrome," which includes the following conditions: decreased volume and speed of blood circulation in LUT structures, thinning of the mucous membranes and urothelium, decreased bactericidal and barrier function of the urothelium, hypoxia, ischemia, and fibrosis in pelvic organs, which increase significantly the risk of vulvovaginal and cystourethral atrophic changes [67]. In women of reproductive age, due to cyclical changes in sex hormones during the menstrual cycle, the same cyclical changes in the blood flow of the LUT are observed, i.e., from the main pronounced arterial blood flow in phase 1 of the cycle (estrogen effects) to its minor decrease and development of the veno-discirculatory phenomena in the small pelvis in phase 2 (effects of progesterone). Moreover, cyclical changes in estrogen and progesterone levels in women are associated with increased severity of LUT symptoms (LUTS) immediately before menstruation [67]. Moderately obese postmenopausal women may be more susceptible to endothelial dysfunction than men and postmenopausal women without moderate obesity, whether or not they have type 2 diabetes mellitus [68]. In addition, the length of the urethra in women increases in the middle of the menstrual cycle at the peak of the effect of estrogen [69]. By contrast, in men with normal blood pressure levels, acetylcholine-induced vasodilation decreased with age (approximately 1.8% per year), which coincided with the average rate of the decrease in the level of testosterone secretion in men. This may indicate the role of testosterone in the synthesis of NO in the vascular endothelium and its pronounced vasoprotective effect. Numerous clinical and experimental studies have shown a significant relationship among low testosterone levels, pelvic atherosclerosis, ischemia, and fibrosis of the LUT in men [70–72].

The total area of the pelvic arterial bed in both men and women is significantly lower than the total density of all venous collectors, which determines a high frequency of the formation of venous congestion in this anatomical region with the involvement of the LUT in the process, often simulating urological pathology [73]. Moreover, in men, a relationship is found between the density of the vascular bed of the small pelvis and the blood flow rate in it and the level of testosterone [74]. According to recent reviews and meta-analyses, men with moderate-to-severe LUTS are at increased risk of most cardiovascular complications, and endothelial dysfunction connects them (Fig. 2) [75, 76].

Sex characteristics of pain reception in the LUT

The LUT has extensive innervation, represented by mixed, sensory, and motor autonomic nerve endings (sympathetic and parasympathetic) and motor somatic nerve fibers. Currently, sexual dimorphism in relation to the characteristics of pain reception and perception in men and women is well known, which leads to the conclusion that sex steroid hormones are indirectly involved in their mechanisms. Traditionally, estrogens are believed to be pro-pain hormones, and progesterone and testosterone are anti-pain hormones; therefore, evolutionarily, men are more resistant to acute and chronic pain [77, 78],

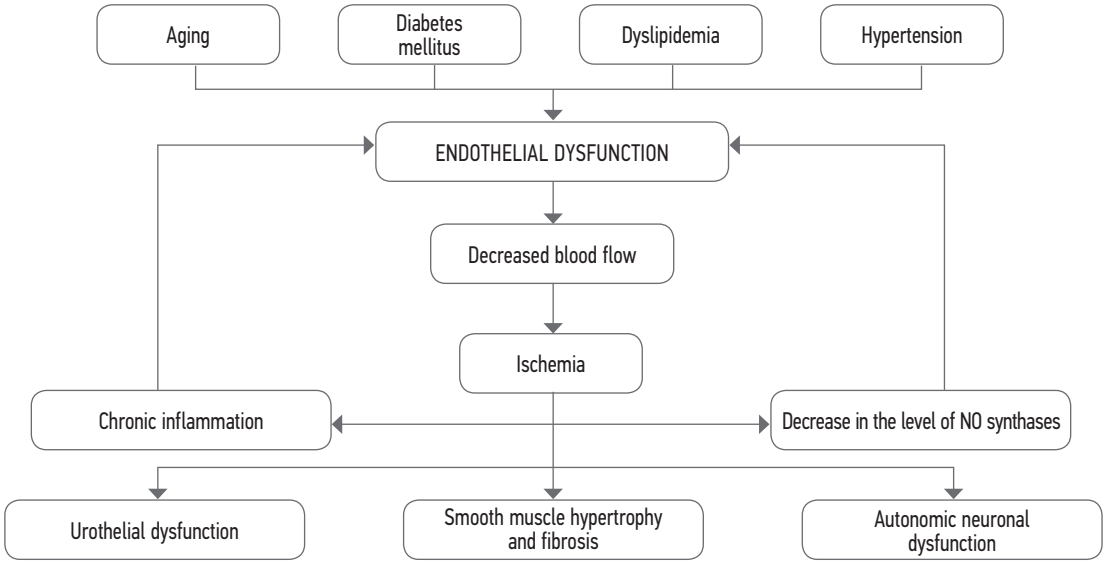

Fig. 2. Scheme of the relationship between endothelial dysfunction and lower urinary tract dysfunction in men [76]
Рис. 2. Схема связи между эндотелиальной дисфункцией и дисфункцией нижних мочевых путей у мужчин [76]

and women often have low pain tolerance [79–81]. A study showed differences between men and women in terms of how they recall the pain experience. Unlike women, men showed increased hypersensitivity to pain under the same painful experiences, and this may be mediated by decreased testosterone levels [82]. Studies analyzing sex differences in people with delayed muscle pain have not reported any significant sex differences [83]. A study of muscle pain induced by saline administration led to an increase in pressure point thresholds in men but not in women [84]. In an endotoxemia model, one of the ways to induce widespread inflammatory pain, a decrease in the initial pain thresholds of pressure in women was detected, but without sex differences after the development of inflammation [85]. The change in pain perception can be caused by various factors, in particular, age. Moreover, no differences in sensitivity to pain were found between older men and women [86], in contrast to the results in young adults [87]. From a mechanistic point of view, variations in pain perception may be associated with differences in brain activation patterns caused by muscle pain, since significant changes in signal intensity in the middle cingulate cortex and dorsolateral prefrontal cortex occur in a sex-dependent dimorphic pattern, which indicates important sex differences in the emotional perception of pain [88]. In diseases or injuries, muscle tissue releases various metabolites, cytokines, and growth factors, which can be accompanied by the infiltration of immune cells. These signals are combined with differential gene expression patterns and receptor interactions in both men and women. In the spinal cord, the increased signals from muscle afferents are possibly modulated by the increased immune reactivity of microglia in men and T cells in women. The perception of pain in the brain may also depend on sex-specific psychological and emotional factors and may be accompanied by pain sensations in men, unlike those in women [89] (Fig. 3).

Sex differences have been found in healthy people and patients with chronic muscle pain; however, more research is required to elucidate the mechanisms underlying these phenomena.

Characteristics of the hormonal regulation of the LUT in sex and age aspects

Estrogen, progesterone, and testosterone receptors are present in the urinary tract of both sexes. The regulatory mechanisms of the expression of sex hormone receptors differ with age [90–94]. In female and male mice, myocytes and fibroblasts of the lamina propria of the urethral wall have a high density of estrogen receptors such as α (ER-α) and β (ER-β), progesterone receptors (PR), and androgen receptors [95]. In men, the striated muscle cells of the rhabdosphincter showed expression of androgen receptors, estrogen receptors of ER-β, and PR; in women, the expressions of ER-α receptors are predominantly associated with PR [95]. Moreover, experimental knockout of ER-α receptors in the LUT of female mice led to a decrease in several PR-positive cells in the urethra, which suggests that ER-α modulate PR expression in the female urethra; however, the expression disorders of neither ER-α nor ER-β changed the PR expression in the male urethra [95]. Cells expressing ER-β and PR receptors are found in the urethral epithelium, while ER-β^+ cells are detected in the epithelium of the urinary bladder and detrusor of both sexes [96]. In humans, the expression of ER-β receptors was only found in the urothelium of the female urinary bladder [97].

In female rabbits, injections of progesterone or testosterone decreased the capacity and compliance of the

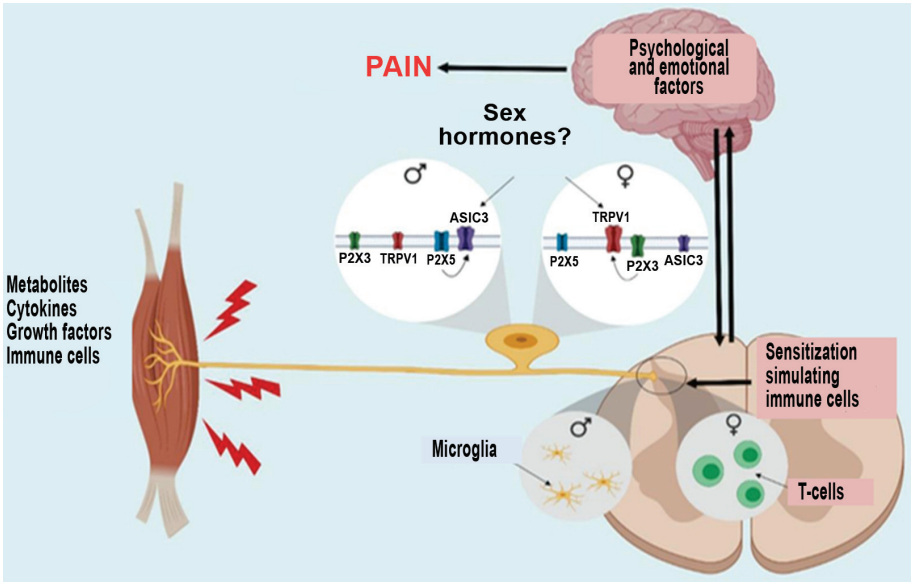

Fig. 3. Gender characteristics of the pathogenesis of muscle pain [89]. TRPV1 – transient receptor potential of vanilloid type 1; P2X3 – type 3 adenosine receptor; P2X5 – type 5 adenosine receptor; ASIC3 – type 3 acid-sensitive ion channel

Рис. 3. Гендерные особенности патогенеза мышечной боли [89]. TRPV1 — транзиторный рецепторный потенциал ваниллоидного типа 1; P2X3 — аденозиновый рецептор типа 3; P2X5 — аденозиновый рецептор типа 5; ASIC3 — кислотно-чувствительный ионный канал типа 3

bladder, whereas estrogen treatment increased them. In male rabbits, testosterone or estrogen injections increase significantly the bladder capacity, but progesterone treatment has no effect [98]. Numerous clinical studies have shown that testosterone therapy in men has significant positive direct and indirect effects on nearly all LUT structures, including the vascular endothelium, neurothelium, muscle structures, and urothelium [99, 100]. The indirect effect of testosterone on the LUT is due to several mechanisms, such as the regulation of neurons of the autonomic nervous system and the activity of cellular enzymes of Rho kinase and phosphodiesterase type 5. In addition, testosterone activates endothelial NOS in the pelvis, which can lead to vasodilation and relief of pelvic ischemia. Bladder blood flow is often reduced in patients with LUTS, and decreased blood flow in the bladder and aging-induced ischemia are associated with the development of anatomical and functional disorders in the detrusor [101–103]. In a laboratory model of testosterone deficiency in male rats, Zhang et al. [104] revealed the rapid development of fibrosis of the bladder wall, which led to a decrease in the volume and contractility of the bladder and an increase in the expression of procollagen I mRNA, which is one of the main markers of age-related fibrosis.

CONCLUSION

Personalized medicine requires considering the sex of the patient to personalize the examination and potentially improve the results of any therapy. For basic science, the first step toward this aim is the provision of more evidence of the mechanistic and regulatory processes, which are both similar and completely different in men and women. Physiology has invariably made a decisive contribution to understanding the regulatory processes that develop in the body under healthy and disease states. In the future, its contribution will continue to form the basis for the development of personalized medicine. With the inclusion of scientific and practical medical problems to achieve scientific excellence in research and medical education, the disparities in healthcare and practical medicine between women and men will be significantly reduced, and the efficiency of treatment in patients of different sexes will improve, and the quality of its implementation will increase.

ADDITIONAL INFORMATION

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