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The Basic Neurophysiologic Concept of Lower Urinary Tract Function – the Role of Vanilloid TRPV1 Receptors of Urinary Bladder Afferent Nerve Endings

Neurofizjologiczne aspekty funkcjonowania dolnych dróg moczowych – udział receptorów waniloidowych TRPV1 aferentnych zakończeń nerwowych pęcherza moczowego

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Abstract
The pathophysiology of functional disorders of the urinary bladder is still relatively poorly understood, although the mechanisms controlling the lower urinary tract function have been quite accurately described. The rich innervation of afferent and efferent urinary tract, multi-level neural control of micturition process, the diversity of the autonomic nervous system neurotransmitters, as well as “neuronal activity” of the urotelium determines the correct filling and emptying of the bladder. Functional diseases (OAB – such as overactive bladder) include sensory and/or motor dysfunction of the urinary bladder, leading to sleep disturbances, psychosomatic disorders, lower quality of life, etc. It is known that sensory afferent C fibers and vanilloid TRPV1 receptors are important in the pathogenesis of OAB. Modulation of the activity of these fibers and/or TRPV1 receptors by a number of substances (such as capsaicin, lidocaine, etc.) reduces the symptoms of OAB. Detailed knowledge of the neurophysiology of the lower urinary tract is a prerequisite for proper treatment of functional disorders of the urinary tract. The paper discusses the neurophysiologic basis, the importance of afferent C fibers and vanilloid TRPV1 receptors in lower urinary tract (Adv Clin Exp Med 2012, 21, 4, 417–421).

Key words: neurophysiology, urinary bladder, afferent C-fibers, vanilloid receptor.

Streszczenie

Słowa klucze: neurofizjologia, pęcherz moczowy, afferentne włókna C, receptor waniloidowy.

Urine is produced by the kidneys and is continuously moved into the urinary bladder through the ureters which present regular peristaltic activity. Rather voiding is a physiological process that occurs periodically. Proper function of the lower urinary tract requires the proper organization
of two major phases: the filling (storage) phase, as well as the voiding phase. In these processes detrusor muscle, urethral smooth muscle and sphincter (striated muscle), as well as pelvic floor muscles are involved [1]. Proper time coordination of these muscle structures is complex, which is regulated by multilevel structures of the central nervous system, ascending and descending pathways of somatic and autonomic nervous system [2]. These structures exercise informed (via the cerebral cortex) and instinctive (via the centers in pons and lumbar-sacral section of spinal cord) control over the proper function of lower urinary tract [3]. Physiologically, in the storage phase the external and internal sphincter of urethra, as well as the levator ani muscles are in constant tension (contracted), while the detrusor muscle is relaxed, allowing the gradual increment of bladder capacity with little increase in intravesical pressure with normal sensory inputs. Such a phenomenon is described as accommodation. In normal conditions detrusor muscle should not present a spontaneous contractile activity during storage phase. If circumstances do not allow to urinate, the inhibitory effect of supratontine centers on micturition center in the pontine-mesencephalic gray matter automatically prevents the start of micturition when the bladder filling, and in a consequence bladder afferent outputs generates the first sensation to void. In a healthy person, this leads to the relaxation of bladder detrusor muscle and parallelly to the contraction of urethral sphincter and pelvic floor muscles, allowing urine to be maintained for some time, and inhibit voiding induction. Only in favorable conditions does voiding occur through a coordinated bladder detrusor muscle contraction and relaxation of the sphincter complex of the urinary bladder and urethra. This close relationship of consecutive events to ensure the correct organization of storage and voiding phase realizes the importance of neurological and muscular connections that determines the proper function of the lower urinary tract.

**Innervation and Neural Control of Urinary Bladder**

Structure and the nerves pathways controlling the urinary bladder function can be divided into four major reflex arcs (loops) [4]. The loop I runs between the reticularis nuclei in pons, and the dorsal-medial surface of the frontal lobe. It remains under the inhibitory influence of basal ganglia, the cerebellum, as well as the limbic system. While the anterior area of the pons and the posterior part of the hypothalamus stimulates its activity. This loop is responsible for informed control of storage and voiding phase. Properly-functioning loop II determines the correct duration of the detrusor muscle reflex until complete bladder emptying. The loop II consists of afferent (propriocceptive, spinal – bulbar) nerve pathways extending from the urinary bladder to the pons reticular complex, as well as of efferent (reticular – spinal) routes to intermedialateral nuclei of sacral spinal cord and to detrusor muscle. Loop III forms of detrusor afferent nerve route to the pudendal nerves nuclei in spinal cord and alpha – motor neurons innervating external urethral sphincter. This loop is responsible for proper coordination of detrusor and sphincter activity (contraction and relaxation). Additionally, the supraspinal and segmental innervation of the external urethral sphincter creates a loop IV. Each loop reflex activity may be altered due to the release of several neuromodulators of non-adrenergic, non-cholinergic (NANC) autonomic nervous system (ANS) changing the postsynaptic response, especially sensory branch of the nervous system. These include substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), nitric oxide (NO), neuropeptide Y (NY), serotonin, pituitary adenylate cyclase-activating peptides (PACAPs), galanin, adenosine triphosphate (ATP) [5–8].

Peripheral innervation of the urinary bladder consists of an integrated complex of sensory and motor nerves. The mucosa, submucosa and detrusor muscle have been found to contain a wide range of sensory receptors via the information is transmitted by myelinated Aδ-fibres, as well as unmyelinated C-fibres. However, unmyelinated C-fibres (so-called ‘silent fibres’) do not exhibit electrical activity in normal conditions. They are characterized by slow afferent signals conduction (about 2 m/s), which is related to the lack of myelin sheaths and their small diameter (about 0.2 µm) [9]. Efferent impulses are conducted by highly myelinated fibres (alfa-motor nerves). The presence of afferent nerve fibers has been described in somatic and autonomic nerves innervating the lower urinary tract. Peripheral sensory innervation of the urinary bladder and urethra runs mainly through the afferent pathways via hypogastric nerves and, to a lesser extent, by the pelvic and pudendal nerves. Afferent pathways are responsible for receiving and transmitting information concerning the degree of bladder filling [1, 3]. In terms of sensory innervation, there is some degree of specialization in the field of incoming stimuli. Urinary bladder stretching increases the flow of information from mechanoreceptors in parasympathetic nerves, such a pelvic nerves, and to a lesser extent in hypogastric nerves. Activation of nociceptors increases the inputs in sympathetic and parasympathetic nerves. However, the afferent inputs of bladder stretching,
urine flow sensations, temperature and pain from the urethral sphincter and the urethra are conducted via pudendal nerves.

The Role of Afferent Unmyelinated C-Fibres in Lower Urinary Tract Function

Previous observations have shown that the micturition reflex is induced by signals from the Aδ-fibers, because the majority of afferent C-fibers normally shows no electrical activity [10]. C-fibers are responsible for sensations associated with the bladder filling (mechanoception), as well as with the irritative signals, such as irritation, chemical, thermal (cold), potentially damaging stimuli mucosal barrier (nociception) [11, 12]. Their stimulation leads to the activation of micturition. This "alternative" conductive system mediated by afferent C-fibres, closed at the level of the spinal cord, is one of the leading mechanisms of pathogenesis of functional disorders of the urinary tract, including overactive bladder (OAB) and/or detrusor overactivity (DO). As well as constitutes the "primary route" activating voiding in patients after spinal cord injury, to whom the micturition center is outside the course-modulating effects of central nervous system [13–16]. In humans and animals afferent fibers have been identified within submucosa and detrusor muscle. The submucosal fibers form neural spots lying between layers of the urothelium. Additionally, some of them are even located on the basal layer of the bladder’s urothelium. The greatest concentration of afferent fibres spots are found in the neck and triangle of the bladder [17–20]. A few years ago urothelium and submucosa membranes were considered a passive barrier to urine and blood. Currently, the urothelium is considered an active sensory structure of the urinary bladder, which plays a pivotal role in urinary bladder activity regulation. Many substances in urine run through the urothelium to the muscles of the bladder due to the presence on its surface a number of receptors and ion channels [2, 21]. The urothelium modulates the afferent and efferent functions of nerve fibers and smooth muscle via the release of inflammatory mediators (neurokinins, prostaglandins), growth factors (NGF – Nerve Growth Factor) and neuropeptides in response to mechanical and nociceptive stimuli. These factors make the urothelium modulate the activity (and possibly “chemical coding”) of peripheral nerve fibers [22, 23]. Currently, an increasingly important role in the pathogenesis of functional disorders of the urinary bladder is attributed to sensory purinergic fibers whose main transmitter is ATP, which affects a number of subtypes of purinergic receptors (class PX and PY) of the bladder and urethra. Also, a crucial role in the lower urinary tract play the nerve fibers expressing polymodal vanilloid receptors TRPV1 (Transient Receptor Potential Channel subfamily V, member 1) [6, 24, 25]. In addition, it appears that tachykinin receptors (NK-1 and NK-2) and prostacyclin receptors identified at nerve endings of group C play an important role in urinary tract activity [26, 27]. Discovered recently by Du et al. [28] TRPA1 receptors (Transient Receptor Potential channel of the Ankyrin type A1) located on the afferent fibers of group C innervating the bladder are also probably involved in mechano- and/or nociception. It was shown that the supply of TRPA1 agonists leads to the development of detrusor overactivity through a C-fiber-mediated neural arch. In addition, observations of Strøeg et al. confirmed their probable participation in the transduction of afferent impulsion [29]. Nevertheless, the role of these receptors in the pathogenesis of overactive bladder remains unclear. It seems that the sensitivity of C-fibers depends on the expression of receptors for inflammatory mediators and growth factors. The pathogenesis of the OAB development and in the intensification of symptom severity in the course of OAB play an important role two phenomena: 1) the process of sensitization and 2) the local effector function of afferent C-fibers. In case of sensitization, the increase of the sensitivity of these fibers to a series of stimuli acting on urothelium occurs. Contrary, increased activation of C-fibers, and hence severe local effector function of these fibers leads to the development of so-called “neurogenic inflammation”. It is known that hypersensitivity of afferents nerves in the course of OAB revealed an excessive response to the agonists, which may intensify the symptoms reported by patients with OAB. Yokoyama et al. [30] showed an increased response to the action of muscarinic agonists. Also, Harrison et al. [31] observed the occurrence of hypersensitivity reactions following administration of cholinergic agonists and substances that open potassium channels in the detrusor muscle.

Vanilloid Receptors of Afferent Unmyelinated C-Fibres and Urinary Bladder Activity

The polymodal TRPV1 receptors of afferent nerve endings are potentially damaging stimuli sensors such as H⁺ ions, anandamide, lipoxygenase products, the temperature (above 43°C), changes in the composition of urine (pH below 4.5) in the course of diabetic ketoacidosis, high osmolarity:
2000 mOsm/kg as an effect of glycosuria). These integral membrane vanilloid receptors whose natural ligand is 8-methyl-N-vanillyl-6-nonamid (Capsaicin), are located on non-selective ion channels with high permeability for Ca++ ions. Their induction of activation beyond the influx of calcium leads to the activation of mast cells, protein kinase C, NADH-oxidoreductase and a nuclear transcription factor Bkqa-1-acid glycoprotein [32].

TRPV1 receptors are not only sensing the degree of mucosal injury of the urinary bladder. Their increased expression in sensory neurons (called capsaicin-sensitive fibers) caused by pain mediators such as adenosine triphosphate, bradykinin, prostaglandins (PGE 2), leading to sensitization of sensory fibers (the development of visceral hypersensitivity), consequently leads to functional disorders of the lower urinary tract (especially urinary bladder). The mechanisms responsible for sensitization and the activation of capsaicin-sensitive C fibers were not fully explained. Chuang et al. [33] and Vizzard et al. [34] indicate the involvement of inflammatory mediators, mainly nerve growth factor (NGF) in the sensitization of these fibers. These mediators also lead to posttranslational changes in receptor TRPV1, which may result in a lower threshold of excitability of these receptors and lead to sensitization and activation. This fact is confirmed by studies in mice performed by Caterina et al. [35] and Davis et al. [36]. In both cases, the authors assessed the impact of several nociceptive stimuli on the reaction of animals exhibiting hyperalgesia that peripheral tissue inflammation decreases the pain threshold to thermal stimuli, but has no effect in animals lacking TRPV1 receptors. So far, it was thought that unmyelinated sensory C fibers showing positive expression of TRPV1 is not involved in the regulation of the cycle in terms of storage and voiding in normal conditions, because they are insensitive to mechanical stimuli [37]. Surprisingly, Birder et al. [38] in work on mice lacking TRPV1 receptor showed that in such animals there is an increased frequency of urination and increased frequency of low-amplitude contractions that cause no hesitancy. These observations clearly indicate the involvement of TRPV1 receptors in the micturition process, not only in pathological states (e.g., inflammation of the bladder), but also in normal conditions.

In conclusion, the detailed knowledge of the neurophysiology of lower urinary tract and its interactions appears to be of great clinical significance, as well as being a prerequisite for proper treatment of functional disorders of the urinary tract. Proper modulation of afferent activity of C fibers that regulate the lower urinary tract will modulate the urinary bladder dysfunction (e.g. by eliminating detrusor muscle overactivity), while not affecting its contractility. Numerous previous observations indicate the involvement of afferent C fibers, as well as TRPV1 receptors in the regulation of storage and voiding in normal conditions and in the course of urinary bladder disorders (e.g., overactive bladder).

References
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