Bladder Afferent Signaling: Recent Findings

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Abbreviations And Acronyms

ATP = adenosine triphosphate
DO = detrusor overactivity
DRG = dorsal root ganglia
ICC = interstitial cells of Cajal
LUT = lower urinary tract
OAB = overactive bladder
RTX = resiniferatoxin
TRP = transient receptor potential

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Purpose: Much current research on lower urinary tract physiology focuses on afferent mechanisms. The main goals are to define and control the signaling pathways by which afferent information is generated and conveyed to the central nervous system. We summarize recent research on bladder afferent mechanisms.
Materials and Methods: We systematically reviewed the literature by searching PubMed® up to June 2009 with focus on the last 5 years.
Results: At least 2 signaling pathways can be identified, including the urothelial and the myogenic pathway. The urothelial pathway is a functional unit consisting of the urothelium, interstitial cells and afferent nerves in the lamina propria. Signaling occurs via muscle-mucosal mechanoreceptors, mucosal mechanoreceptors and chemoreceptors. The myogenic pathway is activated via in-series mechanoreceptors responding to distention and via spontaneous contractile activity in units of myocytes generating afferent noise.
Conclusions: To control dysfunctional micturition we must know more about all components involved in normal micturition control, including how afferent information is handled by the central nervous system.

Key Words: urinary bladder, afferent pathways, muscle contraction, urothelium, urination disorders

In the last decade research in the field of LUT physiology/pharmacology has provided much new information and the emergence of several new concepts of central and peripheral nervous control of voiding, and voiding dysfunction etiology.[1] The search for new therapy for voiding disorders has been intensive and new targets for drugs aimed at micturition control have been defined, such as urothelial signaling mechanisms.[2] Although our understanding of bladder function has increased in recent years, the detrusor muscle and its functional regulation still provide considerable challenges for future basic, clinical and translational research. The detrusor muscle has for many years been a target of drug treatment. However, depression of detrusor contractility, resulting in decreased ability to empty the bladder, has not produced any success in treating voiding dysfunction.

Voiding contraction is a result of coordination of the contractile units of the detrusor,[3] made possible by the concerted action of bladder motor nerves and ICC. It is the goal of treatment, eg for DO and OAB symptoms, not to interfere with emptying ability but rather to eliminate involuntary bladder contractions. In this context the difference between whole bladder contraction and the contractile activity of its individual myocytes should be emphasized. The detrusor muscle is not quiet during the filling phase. Myocytes and contractile units show uncoordinated spontaneous activity

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that can produce firing in afferent nerves, contributing to uncontrolled micturition reflex activation and sensations, eg of urgency.

Much current research on LUT physiology focuses on afferent mechanisms. Currently we are learning how to control 2 identified signaling pathways by which afferent information is generated and conveyed to the central nervous system, that is the urothelial and the myogenic pathway. We focus on these pathways with particular reference to their role in the pathophysiology of DO and OAB syndrome, and discuss future directions of research aimed at controlling bladder activity.

AFFERENT PATHWAYS

The pelvic, hypogastric and pudendal nerves carry sensory information in afferent fibers from the LUT to the lumbosacral spinal cord.[4] In humans the somata of the pelvic and pudendal afferent nerves are located in DRG at sacral segments S2-S4 and the somata of the hypogastric nerve in DRG are at thoracolumbar segments T11-L2 (fig. 1). After entering the spinal cord the primary afferent fibers of the pelvic and pudendal nerves travel rostral in Lissauer's tract. Sensory information is transmitted to second order neurons in the spinal cord. Pelvic nerve afferents monitor bladder volume during the storage phase and the amplitude of bladder contractions during voiding. Thus, sensory nerves initiate the micturition reflex and reinforce the drive that maintains bladder contraction.

Afferents comprise myelinated Aδ fibers and unmyelinated C fibers. Aδ fibers, located primarily in the detrusor smooth muscle layer, respond to detrusor stretching during bladder filling and convey fullness sensations. Unmyelinated sensory C fibers are more widespread and reside in the detrusor muscle, close to the urothelium in the lamina propria and directly adjacent to urothelial cells.[5] There is also good evidence that C fibers carry information on bladder volume changes. For example, in the rat many C fibers (conduction velocity less than 1.3 m second^{-1}) respond to slow distention with physiological volume but do not respond to bladder contraction.[6] Approximately 23% of Aδ fibers and 64% of C fibers studied during ventral root evoked bladder contraction behaved in this fashion. This finding suggests that volume receptor afferents are mainly C fibers that discharge during normal bladder distention but with higher thresholds than Aδ in-series tension receptors[7] and can be activated by various neurotransmitters and chemical mediators released by the detrusor and the urothelium, as described. C fibers with their peripheral nerve endings in the urothelium may be volume afferents, and perhaps chemosensitive and thermosensitive afferents, given

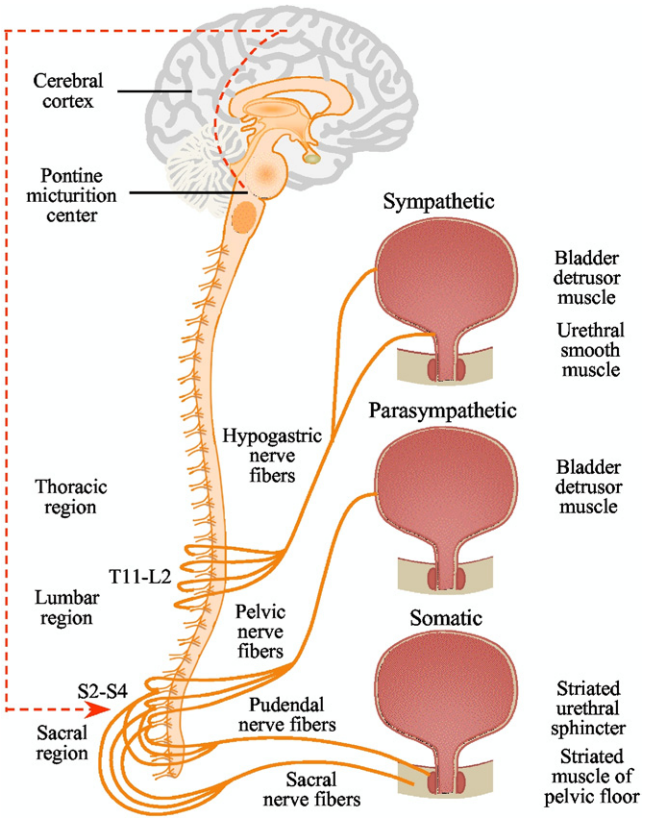

Figure 1. Human LUT innervation. Coordination between bladder and outlet (bladder neck, urethra and urethral sphincters) is mediated by sympathetic (hypogastric), parasympathetic (pelvic) and somatic (pudendal) nerves. Primary cell bodies of Aδ and C-fiber afferents of pelvic and pudendal nerves are contained in lower lumbar and sacral DRG, and afferent innervation in hypogastric nerve arises in rostral lumbar DRG.

their proximity to the intravascular milieu. Approximately 9% of afferents innervating the mouse bladder are found in the urothelium.[8]

AFFERENT NERVE LOCALIZATION IN BLADDER WALL

Sensory neurons have become an attractive target for novel pharmacological treatments for DO/OAB.[9] It is still unclear exactly how many functional classes of distention sensitive afferents innervate the bladder. There are at least 2 types of C-fiber afferents distinguished by central projections and by the presence of neuropeptides. The first type is neuropeptidergic, projects primarily to spinal lamina I and outer lamina II, and is positive for calcitonin gene-related peptide and substance P. The second type is nonpeptidergic, projects to the inner lamina II of the spinal dorsal horn and binds isolectin B4.[10]

Several groups have characterized bladder mechanoreceptors in terms of their adequate mechanical stimuli, chemosensitivity, receptive field site and