Overview of Recent Progress in Neuropharmacology of Lower Urinary Tract Function

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The functions of the lower urinary tract, to store and periodically release urine, are dependent on the activity of smooth and striated muscles in the urinary bladder, urethra, and external urethral sphincter. This activity is unusual in its pattern and organized by neural control mechanisms in the brain, spinal cord, and peripheral ganglia. Many of the neural circuits have switch-like or phasic patterns of activity, unlike the tonic patterns characteristic of other autonomic pathways such as those to cardiovascular organs. In addition, micturition is under voluntary control and depends on learned behavior that develops during maturation of the nervous system, whereas many other visceral functions are regulated involuntarily.

Various neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate, nitric oxide, and neuropeptides, both in the periphery including bladder urothelium and in the central nervous system have been implicated in the neural regulation of the lower urinary tract. Due to these complex controlling mechanisms of micturition, injuries or diseases of the nervous system, as well as drugs and disorders of the peripheral organs, can produce voiding dysfunctions such as urinary frequency, urgency, pain and incontinence or inefficient voiding and urinary retention.

For the treatment of overactive bladder (OAB) targeting the peripheral nervous system, muscarinic receptor antagonists have classically been used; however, β 3-adrenergic receptor agonists have recently been developed and proven effective for OAB. For the treatment of lower urinary tract symptoms (LUTS) with benign prostatic hyperplasia (BPH), which includes both storage and voiding symptoms, α 1-adrenergic receptor antagonists and, more recently, phosphodiesterase inhibitors have been prescribed. Although they are still in preclinical stages, pharmacological modulation of urothelial-afferent interactions targeting purinergic, muscarinic/nicotinic cholinergic and neurokinin receptors has been investigated. Also, pharmacological targets for LUTS treatments have been found in the central nervous system (spinal cord and brain) including those in serotonergic, noradrenergic, dopaminergic/adenosinergic and GABA/glycinergic systems. Thus, in the first portion of this symposium, I will overview and discuss the recent advancements of neuropharmacology of lower urinary tract function and dysfunction.