Mintage Journal of Pharmaceutical & Medical Sciences
REVIEW ARTICLE
ISSN 2320 –3315

URODYNAMIC PHYSIOLOGY:A PERSPECTIVE

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Received -19-08-16; Reviewed and accepted -05-09-16

ABSTRACT

Filling and emptying of the urinary bladder is finely regulated through rich innervation of urinary tract. The multilevel neural control of micturition involves autonomic neurotransmitters and specialized urothelial physiology. Keen understanding of urodynamic physiology is essential to understand and properly manage the functional urinary tract disorders. The primacy of the role of afferent C fibers, as well as TRPV1 receptors in effecting storage and voiding of urine, is suggested in contemporary research,both in healthy individuals and patients . The article attempts a brief review of the neurophysiology of lower urinary tract function with an emphasis on the role of C fibers and TRPV1 receptors.

Keywords: Urodynamics, afferent C fibers, Vanilloid receptor. Urinary bladder.

INTRODUCTION

Urine continuously moves from kidney toe bladder through ureteric peristaltic activity. Voiding is a periodic voluntary event. The processes of storage and voiding have an orderly organization. This involves the coordinated function of detrusor muscle, urethral smooth muscle and sphincter (striated muscle), as well as voluntary muscles of the pelvic floor. Timely coordination among muscular elements participating in micturition is a complex process. This involves multiple structures of central nervous system, i.e. ascending and descending somatic and autonomic pathways (1). The informed or conscious control is exerted by cerebral cortex while lower centres in pons and lumbosacral spinal cord exert intrinsic control on lower urinary tract function.

Urine Voiding and storage

During physiological urine storage, the external and internal urethral sphincters and the levator ani muscle are under constant contraction. The detrusor muscle of bladder is relaxedallowing gradual filling and increase of bladder capacity, avoiding sensory inputs that may raise pressure, within. This is termed bladder accommodation. Filling of the bladder generates afferent sensation for voiding. Voiding is effected on finding suitable conditions, when co-ordinated detrusor muscle contractions ensue with a relaxation of sphincter complex of bladder and urethra. Where circumstances don't suit voiding, the micturition centre in pons is kept suppressed by cortical centres.Storage and voiding are organized for proper operation through the connections of neuromuscular elements

The Bladder Nerves

Bladder function is controlled by four major nervous reflex arcs. Volitional control of cerebral cortex on storage and voiding is exerted through a defined loop I. This loop traverses the pons and dorsomedial aspect of frontal cortex. Basal ganglia, limbic system and cerebellum, render inhibitory inputs in to this loop. Stimulation is rendered from anterior pontine and posterior hypothalamic loci.

Regulation of contraction time of detrusor muscle for complete emptying of bladder depends on proper function of loop II.The volume/pressure sensory afferents arising from bladder, relay on to centres in pontine reticular formation. Efferent reticulo-spinal fibers emerge from intermediolateral gray matter horn of sacral segment of spinal cord, and innervate detrusor muscle.

Appropriate co-ordination among detrusor and sphincter contraction/relaxation activities is affected through loop III. The afferents from detrusor reach to the spinal nuclei of pudendal nerve. The efferent alpha-motor neurons innervate the external urethral sphincter. Loop IV is additional regulator, employing innervations of external urethral sphincter by supraspinal and segmental neurons.

Reflex activity of any of the loops is modulated by non-adrenergic non-cholinergic autonomic transmitters. The modulators of post synaptic responses include substance P, CGRP(calcitonin gene related peptide),VIP (vasoactive intestinal peptide),nitric oxide, Neuropeptide Y, serotonin, adenylate cyclase activating peptides of pituitory,galanin, ATP etc(2,3).

Sensory and motor innervations in urinary bladder are complex and integrated. Variety of sensory receptors express in mucosa, submucosa and detrusor muscle.Both somatic and autonomic innervations of lower urinary tract carry afferent fibres.Afferents mainly route through hypogastric nerves and to a smaller extent,the pelvic and pudendal nerves. These carry information on degree of bladder filling (4).Stretch of bladder wall stimulates mechanoreceptors linked to parasympathetic afferents. Stimulation of nociceptors causes input both in sympathetic and parasympathetic afferents. Pudendal nerves conduct afferent inputs of bladder stretch, urinary flow sense, pain and temperature from urethra and urethral sphincter.

The Unmyelinated Afferent C Fibers

Sensory signals are carried via A-delta fibers, which are myelinated and via the C fibers, which are unmyelinated. The C fibers are normally dormant. Micturition reflex is primarily induced by A-delta fiber signals(5).C fibers carry irritative signals, sensation of filling (mechanoreception), as well as stimuli potentially injurious to mucosal barrier(nociception) (6).C fibers mediate an "alternative" mechanism for activating micturition reflexat spinal level. This has major implication also in causing functional disorders, e.g. detrusor over activity. Micturition centre of spinal cord injury patients is delinked with the cerebral cortex. The C fibers become "primary" route of initiating voiding in such instance (7).

The urothelium is active sensory part of bladder, pivotal in regulating bladder activity. Urothelium of bladder neck and trigon has high receptor density and afferent spots(8). Urothelium modulates the afferent and efferent function of nerve fibers and smooth muscle response via release of inflammatory mediators(neurokinins, prostaglandins), growth factors(nerve growth factor) and neuropeptides, consequent to mechanical and nociceptive stimuli(9).

Sensory purinergic fibers transact physiologic function of the purinergic receptor subtypes present in bladder and urethra. Increasingly these are implicated in functional disorders of bladder. Physiological role is being defined for nerve fibers expressing vanilloid receptors TRPV1 (transient potential cation channel subfamily V, member 1), the C fibers bearing receptors

for tachykinins, prostanoids and even TRPA1 receptors (transient receptor potential ion channel of the Ankyrin type A1), as also their involvement in pathology of lower urinary tract function (10-13).

The afferent C fibers express receptors for inflammatory mediators and growth factors. Upon stimulation such receptors cause sensitization in the C fibers, whereupon they may overreact to urothelium derived stimuli. The local over reactivity may lead to "neurogenic inflammation".

The Vanillod Receptors on Afferent C Fibers

The TRPV1 receptors on afferent C fibers sense potentially damaging stimuli eg.,H+ ions,lipoxygenase products,temperatures above 43C,undue change in urine composition(eg.pH below 4.5 in ketoacidosis or hyperosmolarity due to glycosuria) etc. These TRPV1 membrane integral receptors occur on nonselective ion channels with high Ca2+ permeability. Activation of TRPV1 receptors results in increased Ca2+ influx, mast cell activation, activation of protein kinase C, NADH-oxidoreductase and a nuclear transcription factor (14).

Pain mediators, such as ATP, bradykinin, prostaglandin E2 etc, cause over expression of TRPV1 receptors on the afferent C fibers.This is implicated in development of visceral hypersensitivity and functional disorders of bladder and lower urinary tract. Inflammatory mediators, especially nerve growth factor activate TRPV1 receptors, resulting in sensitization of C fibers. Additionally, the TRPV1 receptors may suffer post-translational modification. This would result in lowered excitation threshold (15-17).

Proper modulation of afferent activity of the C fibers, which regulate the lower urinary tract is therefore, crucial in maintaining normal bladder function. Conservative approaches to managing overactive bladder and associated incontinence, emphasize lifestyle modification; proper diet and fluid intake; patient education on normal and abnormal voiding; timed voiding; pelvic muscle training and urge inhibition. Pelvic muscle strengthening in neural insufficiency is supplemented by electrical and magnetic stimulation therapies with uncertain benefits(18-19).Aging and diabetes associated neuropathic changes cause detrusor underactivity.A cholinergic pharmacotherapy is also marred with adverse effects and uncertain in benefit(20).All the recent understanding added on regulatory neurophysiological mechanisms, is relevant to conceiving effective pharmacotherapy, treading the thin line between detrusor over activity and under activity.

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