Editorial Focus: Spinal Interneurons and Micturition Reflexes: Focus on “Characterization of a Spinal-Urine Storage Reflex- Inhibitory Center (SUSRIC) and its Regulation by Serotonin 5-HT$_{1A}$ Receptors in Female Cats”

Margaret A. Vizzard

Department of Neurology and Department of Anatomy and Neurobiology, University of Vermont College of Medicine, Burlington, 05405, USA

Correspondence to: Margaret A. Vizzard, Ph.D.
University of Vermont College of Medicine
Department of Neurology
D415A Given Research Building
Burlington, VT 05405
Phone: 802-656-3209
Fax: 802-656-8704
Email: Margaret.Vizzard@uvm.edu
Generations of effort have been devoted to understanding how the human body stores and periodically releases urine. Micturition is regulated by neural circuits in the brain and spinal cord that coordinate the activity of the smooth and striated muscles of the lower urinary tract (LUT) (7, 9, 10, 12). These circuits act as on-off switches to shift the urinary tract between two modes of operation: storage and elimination. Storage and periodic elimination of urine requires a complex neural control system that coordinates activities of a variety of effector organs including bladder smooth muscle and smooth and striated muscle of the urethral sphincters and multiple levels of nervous system integration (15, 16). Three neural pathways regulate the LUT: 1) sacral parasympathetic (pelvic) nerves provide excitatory input to the bladder; 2) thoracolumbar sympathetic nerves provide inhibitory input to the bladder and excitatory input to the bladder neck and urethra; and 3) sacral somatic (pudendal) nerves that innervate the striated muscles of the sphincters and pelvic floor (15, 16). Each of these sets of nerves contains afferent (sensory) as well as efferent (motor) axons. Lower urinary tract reflex mechanisms organized at the level of the lumbosacral spinal cord are modulated predominantly by supraspinal control (7, 9, 12, 16).

Dysfunction of neural control of LUT functions presents a major problem in clinical management of patients suffering from a large number of neurological injuries (e.g., upper motor neuron disease after spinal cord injury, stroke) or disorders (e.g., multiple sclerosis, Parkinson’s disease) (1, 2). Deficits on the afferent and efferent limbs of the micturition reflex are associated with a wide range of clinical urinary tract problems. Deficits on the afferent side will affect reflex function and sensation and may contribute to bladder pain syndrome (BPS)/interstitial cystitis (IC) along with urothelial dysfunction and mast cell involvement (18). Deficits on the efferent side of the reflex can affect the detrusor smooth muscle and urethral
outlet. Stress urinary incontinence (SUI), a prevalent condition in women, is characterized by a reduction in outlet resistance during urine storage due to weakness in the urethral sphincter/rhabdosphincter mechanism due to target tissue weakness and/or peripheral nerve dysfunction (4). Information related to normal organization of the micturition reflex and its alteration have tremendous potential to increase our understanding of bladder disorders and develop new therapeutic approaches.

**Micturition Reflex**

*Voiding reflex*

Elimination of urine involves coordinated contraction of detrusor and relaxation and dilation of the urethral outlet. This involves inhibition of sympathetic output to the bladder and urethral outlet and activation of the parasympathetic pathway. Relaxation of urethral smooth muscle is achieved by reduction of adrenergic and cholinergic excitatory inputs and release of nitric oxide to elicit smooth muscle relaxation (12). Contraction of detrusor smooth muscle is activated by parasympathetic cholinergic efferent input to this muscle.

*Bladder filling, storage and the guarding reflex*

The storage mode involves gradual filling of the urinary bladder, sensed by low-level afferent firing of thinly myelinated Aδ fibers (13). The sympathetic pathway contributes to inhibition of parasympathetic efferent input to the detrusor smooth muscle and inhibition of parasympathetic activity in autonomic ganglia (12). Sympathetic pathways sustain contraction of the urethra and urethral sphincter/rhabdosphincter (12). During bladder filling, the parasympathetic innervation of the detrusor is inhibited and the smooth and striated parts of the
urethral sphincter are activated, preventing the involuntary release of urine (12). This process is referred to as the ‘guarding reflex’ or ‘continence reflex’. Involuntary bladder emptying during urine storage involves somatic nerve activity originating from cells in a circumscribed region of the lateral ventral horn, in a region called Onuf’s nucleus (6). Cholinergic sphincter motoneurons project their axons along the pudendal nerve and excite the urethral striated muscle/rhabdosphincter causing its contraction and creating a highly effective barrier to involuntary release of urine (6, 12). The guarding reflex mediated by sphincter motoneurons can be activated by bladder afferent activity conveyed through pelvic nerves and these reflexes are organized by interneuronal circuitry in the spinal cord (11, 12). The guarding reflex is initiated in response to sudden increases in bladder pressure that occur during a cough, sneeze or laugh and activates the striated urethral muscle/rhabdosphincter. During the storage mode, the guarding reflex is tonically active and during and in anticipation of sudden increases in abdominal pressure, it is dynamically active to contract the rhabdosphincter to ‘guard’ against unwanted release of urine during unexpected and sudden increases in intravesical pressure (19).

Under normal conditions, a spinobulbospinal reflex mediates micturition. Lower urinary tract reflex mechanisms organized at the level of the lumbosacral spinal cord are modulated predominantly by supraspinal control (7, 9, 10). Studies have also shown that there is activation of the periaqueductal gray (PAG) matter during bladder filling in humans, and this in turn influences the pontine micturition center (PMC), a part of the brainstem involved in the switch between storage and elimination (12). The PMC is the main excitatory signal to initiate voiding; however, the PMC also receives inputs from other brain regions related to volitional
control (12, 13) so that micturition is restricted to behaviorally and environmentally appropriate situations. One area that may participate in regulating voluntary voiding control is the preoptic nucleus of the hypothalamus (13). Drugs applied to the PMC can change the bladder volume set point (i.e. threshold) at which bladder voiding is induced (12). The PMC receives bladder afferent projections and in turn sends excitatory projections to bladder motoneurons in the preganglionic parasympathetic nucleus of the spinal cord (13). The PMC also excites GABA-ergic and glycinergic inhibitory interneurons that innervate urethral sphincter motoneurons (13). In addition, there are direct cortical connections to Onuf’s nucleus that enable voluntary contraction of the rhabdosphincter (19). Bladder filling afferent information in humans and cats is most likely relayed first to the PAG that has projections to the PMC (5, 12).

Bladder Afferent Pathways and Spinal Cord Circuitry

Bladder afferent neurons travel in the hypogastric and pelvic nerves, and their cell bodies are located in dorsal root ganglia (DRG) at spinal segments S2-S4 and T11-L2 in humans and L6-S1 and L1-L2 in rats (12). Bladder afferent fibers consist of lightly myelinated Aδ fibers and unmyelinated C-fibers. The sensation of bladder filling is conveyed by Aδ fibers, the most important mechanoreceptors (i.e., stretch receptors) of the bladder. C-fibers are normally “silent”, but they do respond to chemical or noxious stimuli, including extreme bladder pressure (12). There is a growing body of literature examining the “awakening” of C-fibers in the context of urinary bladder inflammation or spinal cord injury. Aδ and C-fibers terminate in the urothelium, suburothelium, and smooth muscle layers of the bladder (4). Most bladder afferent fibers project to lumbosacral spinal cord segments, and this is the most important region of the spinal cord relative to signaling the micturition reflex (13). Most
sensory nerves in the bladder are located in a dense suburothelial nerve plexus just beneath the urothelium (4).

Many bladder afferent fibers project to the SPN, synapsing with preganglionic parasympathetic neurons that project to the periphery as well as interneurons (7, 9, 10, 12, 17). Primary bladder afferents from the pelvic and hypogastric nerves also project to the dorsal commissure and superficial dorsal horn (12). Bladder afferent fibers contain a variety of neuropeptides (8). The lumbosacral dorsal commissure, superficial dorsal horn, and SPN all contain interneurons important to urinary bladder function (9, 12). Some bladder afferents synapse with second-order neurons in the lumbosacral spinal cord that project to neuronal populations in the brain involved in micturition control, including the PAG and PMC (9, 12).

Although much is known about the neural control of micturition and the underlying neural substrates, the report by Karicheti et al. (14) in this issue of the American Journal of Physiology, Regulatory, Integrative and Comparative Physiology demonstrates that there is still much to be learned. In contrast to pelvic nerve activation of the guarding reflex, current evidence also suggests an inhibitory component to pelvic nerve stimulation. Karicheti and colleagues (14) have extended our current knowledge of this area with a thorough, elegant and classic electrophysiological study characterizing pelvic afferent-mediated mechanisms involved in inhibition of somatic and sympathetic outflow to the urethra in the cat; mechanisms that are independent of parasympathetic efferent-mediated mechanisms that occur during bladder emptying. Electrical stimulation of pelvic nerves elicited evoked potentials in electromyogram electrodes placed in the urethral sphincter/rhabdosphincter or in hypogastric nerve electrodes in anesthetized cats. Using a conditioning-test paired pulse paradigm, Karicheti and colleagues (14) observed the reflexes evoked by the second stimulus were
inhibited. Importantly, the observed inhibition was still observed after acute spinal cord transection at T10 confirming the spinal cord location of the inhibitory center, which the authors have termed a spinal-urine storage reflex-inhibitory center (SUSRIC). As detailed in the paper (14), additional data from the study suggests two separate SUSRCIs, one being involved in the sympathetic storage reflex and a separate one being involved in the somatic urine storage reflex. Under normal conditions, the authors suggest (14) that a SUSRIC may function as a redundant or additional system to promote urethral relaxation.

Previous studies have demonstrated involvement of serotonergic and noradrenergic neurotransmitter systems in sympathetic and somatic storage reflexes (19). Specifically, 5-HT$_{1A}$ receptor activation is associated with increased urethral sphincter/rhabdosphincter activity. Karicheti and colleagues (14) demonstrate that the 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT, significantly enhances urethral sphincter/rhabdosphincter activity in spinal intact but not spinalized animals. The authors then proceed to determine whether increased urethral sphincter/rhabdosphincter activity is a result of direct facilitation or a reduction in inhibition (disinhibition) using pharmacological approaches with 5-HT$_{1A}$ receptor agonists and antagonists and electrical recording techniques. The authors conclude that 8-OH-DPAT’s effect on urethral sphincter/rhabdosphincter activity results from a reduction in output from the spinal inhibitory center to the rhabdosphincter motoneurons (i.e., disinhibition).

Although our understanding of LUT reflexes continues to expand, most recently with our growing appreciation of the properties of the urothelium (4), the studies by Karicheti and colleagues (14) demonstrate that there is still much to be learned concerning basic neural substrates underlying micturition reflexes. The identification and understanding of the function/regulation of a SUSRIC under normal conditions as described (14) also brings up the
question of the potential role of a SUSRIC in relation to lower urinary tract dysfunction. Karicheti and colleagues (14) speculate that either underactivity or overactivity of SUSRIC may have clinical consequences. For example, it is suggested (14) that underactivity of a SUSRIC may contribute to urinary retention whereas overactivity of a SUSRIC may be involved in the pathobiology of SUI. Such studies are a natural and logical extension to the present study and may demonstrate a potential, novel target of pharmacological intervention to improve micturition dysfunction. Our understanding of the spinal cord interneuronal populations involved in any aspect of the micturition reflex is limited, hampered by difficulties in identifying and subsequently determining function of these interneuronal populations (11). The studies by Karicheti et al. (14) reinforce the need to better understand the contribution of spinal cord interneurons to LUT function, supraspinal modulation, and regulation in health and disease.
Acknowledgments

This work was funded by NIH grants DK051369, DK060481, and DK065989.
References


9. de Groat WC and Kruse MN. Central processing and morphological plasticity in lumbosacral afferent pathways from the lower urinary tract. In: *Basic and Clinical*


