# New Frontiers of Basic Science Research in Neurogenic Lower Urinary Tract Dysfunction

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**KEYWORDS**

• Lower urinary tract • Afferents • Animal model • Central nervous system

**KEY POINTS**

- Due to the complexity of the neural mechanisms regulating the lower urinary tract, micturition is sensitive to a wide variety of injuries and diseases, resulting in neurogenic lower urinary tract dysfunction.
- In animal models of cerebral infarction (CI) produced by occlusion of middle cerebral artery, the balance between excitatory glutamatergic neurons and inhibitory glycinergic or GABAergic in the brain might be disrupted, leading to neurogenic lower urinary tract dysfunction.
- In animal models of parkinson disease (PD) produced by disruption of nigrostriatal dopaminergic pathways, bladder overactivity is primarily induced by disruption of D1-like dopamine receptor-mediated inhibition of the micturition reflex.
- In animal models of multiple sclerosis (MS) induced by experimental encephalomyelitis, neurogenic lower urinary tract dysfunction associated with detrusor overactivity is developed as seen in patients with MS.
- In animal models of spinal cord injury (SCI), hyperexcitability of C-fiber bladder afferents is a major pathophysiological basis of neurogenic lower urinary tract dysfunction, and various neural plasticities in peripheral and central nervous systems are identified.

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## INTRODUCTION

The functions of the lower urinary tract to store and periodically eliminate urine depend on neural reflexes located in the brain, spinal cord, and peripheral ganglia.[1] Coordination between the bladder and urethra maintain storage phase and work reciprocally. Thus, urine storage and elimination depend greatly on the central nervous system. This dependence on the central nervous system distinguishes the lower urinary tract from many other visceral structures, such as the gastrointestinal tract and cardiovascular system that maintain a certain level of function because of the local pace-making mechanism inside the organ, even after elimination of extrinsic neural input. In addition, voiding is under voluntary control and depends on learned behavior that develops during maturation of the central nervous system, whereas many other visceral organs are regulated involuntary.[2,3]

Due to the complexity of the neural control of lower urinary tract, micturition is sensitive to numerous injuries, medical diseases, and drugs that affect the nervous system. Neurologic mechanisms are an important consideration in the diagnosis and treatment of voiding disorders. Thus, this article focuses on neurophysiologic mechanisms in the control of lower urinary tract function and their alterations that contribute to the pathologic conditions involved in the central nervous system, such as cerebral infarction (CI), Parkinson disease (PD), multiple sclerosis (MS), spinal cord injury (SCI), and spina bifida.

## NEUROPHYSIOLOGY OF THE LOWER URINARY TRACT

### *Bladder and Urethra*

The lower urinary tract is composed of the bladder and the urethra, the 2 functional units for storage (the bladder body, or reservoir) and elimination (the bladder neck and urethra, or outlet) of urine. The bladder and urethra function reciprocally. As the bladder fills during the urine storage phase, the detrusor remains quiescent, with a little change in intravesical pressure, adapting to the increasing volume by increasing the length of its muscle cells. Furthermore, neural pathways that stimulate the bladder for micturition are quiescent during this phase, and inhibitory pathways are active.[4,5]

In normal rats, external urethral sphincter (EUS)–electromyogram (EMG) recordings, which are widely used for evaluating the urethral function, exhibit tonic activity before onset of voiding and bursting activity during voiding (Fig. 1). This EUS bursting during voiding is characterized by clusters of high-frequency spikes separated by low tonic activity, and produces rhythmic contractions and a relaxation of EUS that present a pumping action of EUS.[6–12] The EUS bursting activity and pressure oscillations in cystometrograms are abolished by bungarotoxin, a neuromuscular

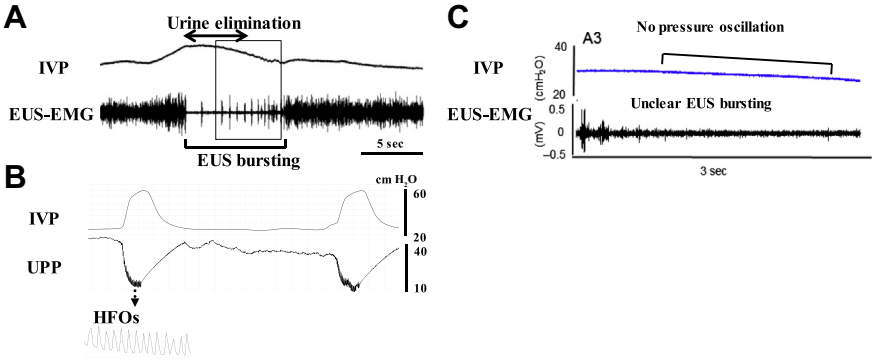


**Fig. 1.** Representative recordings of simultaneous measurement of intravesical pressure (IVP) and EUS-EMG activity or urethral perfusion pressure (UPP) in a rat (*A* and *B*) or a mouse (*C*). The EUS-EMG exhibits tonic activity before the onset of voiding and bursting activity during voiding (*A*). The bursting produces rhythmic contractions and relaxation of the EUS and is thought to generate a urethral pumping action during voiding, which is seen as high-frequency oscillations (HFOs) on UPP (*B*). In contrast, most mice exhibited reduced EUS activity without bursting and no obvious pressure oscillation on the cystometrogram during voiding. ([*A*, *C*] *Adapted from* Kadekawa K, Yoshimura N, Majima T, et al. Characterization of bladder and external urethral activity in mice with or without SCI–a comparison study with rats. Am J Physiol Regul Integr Comp Physiol 2016;310:R752–8; and [*B*] *From* Miyazato M, Sasatomi K, Hiragata S, et al. Suppression of detrusor-sphincter dysynergia by GABA-receptor activation in the lumbosacral spinal cord in spinal cord-injured rats. Am J Physiol Regul Integr Comp Physiol 2008;295:R336–42.)