ABSTRACT

In most cases of stress urinary incontinence, the rhabdosphincter retains some capacity to compress the urethra and prevent urine loss. Thus, clinicians have hypothesized that increased neural activation of the rhabdosphincter may improve symptoms of stress incontinence. Sphincter motor neurons, which innervate the rhabdosphincter, differ significantly compared with other spinal motor neurons. Sphincter motor neurons have uniform size, distinctive transverse and longitudinal dendritic bundles, and remarkably high concentrations of various neurotransmitters, making them an attractive target for the development of drugs to treat stress urinary incontinence. An investigational drug, duloxetine, shows promise for improving symptoms of incontinence because of its ability to increase sphincter motor neuron activity during urine storage without interfering with bladder-sphincter synergy.


Increasing neural activity to the striated urethral sphincter, or rhabdosphincter, may improve stress urinary incontinence symptoms. The rhabdosphincter is innervated by axons originating from Onuf's nucleus, a longitudinally oriented group of small somatic motor neurons in the sacral spinal cord (Figure 1).

With their uniform size and distinctive transverse and longitudinal dendritic bundles that likely serve as conduits for somatic and visceral inputs, sphincter motor neurons are unique compared with other spinal motor neurons. These neurons also exhibit remarkably high concentrations of various neurotransmitters and receptors. This chemical neuroanatomy is associated with distinctive neuropharmacologic responses that have implications for bladder and urethral function and for urinary incontinence.

The unique characteristics of urethral sphincter motor neurons make these neurons an attractive target for the development of drugs that selectively increase sphincter activity during fecal storage without producing increases in residual fecal volume. Duloxetine, an inhibitor of both norepinephrine and serotonin, is a candidate pharmacologic agent that has promise for treatment of urinary incontinence.

BASIC NEUROUROLOGY

The urethra is composed of an inner layer of longitudinal smooth muscle, a middle layer of circular smooth muscle, and an outer layer of striated muscle. Extrinsic efferent innervation of the urethra includes sympathetic, parasympathetic, and somatic nerves. Sympathetic input originates in the upper lumbar spinal cord. Preganglionic and postganglionic fibers travel through the hypogastric nerve and innervate both longitudinal and circular urethral smooth mus-
Parasympathetic innervation emanates from the sacral parasympathetic nucleus. Axons from preganglionic parasympathetic neurons traverse the pelvic nerve; parasympathetic postganglionic fibers also innervate both longitudinal and circular smooth muscle. Somatic innervation originates in sphincter motor neurons in Onuf's nucleus in the sacral spinal cord. Axons from these motor fibers traverse the pudendal nerve and innervate the striated muscle (Figure 2).

Coordination of the innervation activity occurs through central nervous system reflex pathways. Storage reflexes are initiated when the bladder is distended, activating myelinated afferent fibers that traverse the pelvic nerve and make synaptic connections with interneurons in the sacral spinal cord. These interneurons in turn activate sympathetic preganglionic neurons, which stimulate the release of norepinephrine from postganglionic sympathetic nerve terminals.

Norepinephrine release initiates several prominent actions related to urinary function. Norepinephrine can stimulate beta adrenergic receptors in detrusor smooth muscle to induce relaxation. Release of norepinephrine from terminals along the urethra activates alpha-1 adrenergic receptors to induce contraction of the circular and longitudinal smooth muscle.

In addition to this slow, tonic, sympathetic storage reflex associated with the activation of smooth muscle, a more rapid, phasic, somatic storage reflex is associated with striated muscle activation. This rapid activation provides a quick response to a sudden increase in bladder pressure, as might be initiated by coughing, laughing, or sneezing. The rapid somatic storage reflex is sometimes called the guarding reflex or continence reflex and is also activated by myelinated bladder afferent fibers, which traverse the pelvic nerve and stimulate sacral sphincter motor neurons via interneurons of a segmental sacral spinal reflex.

During micturition, distention of the bladder activates myelinated afferent fibers that traverse the pelvic nerve, project to the sacral spinal cord, and ascend to the periaqueductal gray matter and pontine micturition center, which integrate inputs from higher brain centers (e.g., cortex and hypothalamus) to determine whether the social and environmental context is appropriate for micturition. If micturition is appropriate, descending axons from the pontine micturition center activate parasympathetic neurons to stimulate the release of acetylcholine from postganglionic parasympathetic neurons to produce a bladder con-
traction through stimulation of muscarinic (M2 or M3) cholinergic receptors. When this micturition reflex is initiated, the central nervous system simultaneously coordinates urethral relaxation by inhibiting both the sympathetic and somatic storage reflexes.

**Neurourology of Stress Incontinence**

Stress incontinence occurs when bladder pressure exceeds the urethra’s ability to prevent urine flow. In a healthy person, coughing, laughing, or sneezing creates bladder pressure that is dispersed more or less uniformly across the entire length of the urethra, causing compression of the urethra and preventing urine flow. In a patient with stress urinary incontinence, anatomical descent of the bladder may occur, causing less of the urethra to be compressed and possible urine leakage. Nerve damage or myopathy also reduces the rhabdosphincter’s ability to compress the urethra, which may result in urine leakage.

In most cases of stress urinary incontinence, the rhabdosphincter retains some capacity to compress the urethra and prevent urine loss. Based on this knowledge, clinicians have hypothesized that increased neural activation of the rhabdosphincter will improve symptoms of stress incontinence. Neuropharmacology may offer a solution.

Efforts to increase neural activation of the rhabdosphincter require a rational approach to the identification of neurotransmitters or neural receptors that activate sphincter motor neurons in Onuf’s nucleus. Preclinical studies found that the uniqueness of Onuf’s nucleus compared with other somatic motor nuclei in the spinal cord provides a good prospective target for a drug designed to treat stress incontinence. Sphincter motor neurons are densely packed in Onuf’s nucleus, and the cells have a fairly uniform size (smaller than alpha motor neurons but larger than gamma motor neurons). The neurons exhibit dense dendritic bundling in both the longitudinal and transverse planes, reflecting extensive segmental and rostrocaudal interconnections that may be important in synchronous activation or inhibition of the neurons as a group.

Remarkably, these dendritic bundles have high concentrations of growth factor receptor p75, indicating that some aspect of Onuf’s nucleus is highly dependent on nerve growth factor. Compared with surrounding areas, Onuf’s nucleus also has high concentrations of the opioid peptides leucine-enkephalin and met-enkephalin, suggesting an ability to target sphincter motor neurons without affecting other motor neurons using opioid drugs.

Sphincter motor neurons in Onuf’s nucleus are surrounded by dense accumulations of noradrenergic and serotonergic terminals. In concordance, Onuf’s nucleus also exhibits dense accumulation of serotonin-2 (5-HT2) receptors. Stimulation of the receptors with a 5-HT2 agonist results in a marked increase in the guarding reflex that prevents urine leakage.

Alpha adrenergic receptors are important in the control of Onuf’s nucleus. Inhibition of the alpha-1 adrenergic receptors with prazosin diminishes the sphincter reflex, indicating that endogenous norepinephrine stimulates the motor neurons to produce a large-amplitude reflex, which is facilitated through the alpha-1 receptors.

The findings relative to norepinephrine and serotonin and their respective receptors suggest an opportunity for pharmacologic intervention to treat incontinence. An investigational drug, duloxetine, inhibits reuptake of both norepinephrine and serotonin, resulting in enhanced stimulation of the neurotransmitters’ receptors that significantly increases bladder capacity and external urethral sphincter activity. Preclinical and clinical studies show that duloxetine can allow a large-amplitude bladder contraction, while simultaneously inhibiting the sphincter (ie, maintaining bladder-sphincter synergy) and should not promote urinary retention. Bladder-sphincter synergy appears to be maintained by the selective facilitatory effects of serotonin and norepinephrine on glutamate-induced activation of the sphincter motor neurons. Norepinephrine and serotonin alone have no effect on sphincter motor neurons; these neurotransmitters can produce facilitatory effects on the sphincter activity only in the presence of glutamate. If glutamate is not trying to activate the sphincter motor neurons, increasing serotonin and norepinephrine has no effect.

As an analogy, norepinephrine and serotonin facilitate the effects of glutamate in much the same manner as a volume control affects a stereo system’s sound. When the stereo is turned off (ie, no glutamate activation), the volume controls (ie, serotonin and norepi-
nephrine) do nothing. Similarly, when the stereo is turned on (i.e., glutamate activation), increasing the volume (i.e., enhancing the effects with serotonin and norepinephrine) causes the sound to be louder (i.e., the sphincter motor neurons are more active).

**Summary**

Motor neurons found in Onuf’s nucleus have unique properties that distinguish them from those neurons that control skeletal muscles in other parts of the body. Neurons in Onuf’s nucleus are small and have bundled dendrites, do not exhibit any of the monosynaptic reflexes seen in most other motor neurons, have strong visceral control of their excitatory and inhibitory activities, and receive direct hypothalamic inputs—traits that are not characteristic of other motor neurons.

The neurons involved in bladder and urethral function have unique neurotransmitter and receptor profiles for norepinephrine, serotonin, enkephalins, nerve growth factor receptor, and neurotrophic receptors. The alpha-1 adrenoreceptor and 5-HT2 receptors facilitate the sphincter reflex, but the effect is modulatory in nature. Glutamate is required to activate the neurons.

The unique anatomy, physiology, cell biology, and pharmacology of motor neurons in Onuf’s nucleus make them a promising target for new therapies to treat stress urinary incontinence. The activity of the neurons can be increased pharmacologically during urine storage without interfering with bladder-sphincter synergy.

**REFERENCES**


