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# How Sacral Nerve Stimulation Neuromodulation Works

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The refractory overactive bladder represents one of the most challenging problems in urology. Current treatments for patients who have refractory overactive bladder or patients who cannot tolerate antimuscarinic pharmacotherapy are limited. For example, augmentation enterocystoplasty traditionally has been offered as a last resort in such situations. Intestinal augmentation using bowel, however, is a major operation with significant potential short-term and long-term complications. Even without complications, most patients are dismayed by the need for lifelong intermittent bladder catheterization after such reconstructive bladder surgery. Many patients refuse such therapies because the treatment may prove more troublesome than the disease [1].

Functional electrical stimulation is a nonsurgical modality that has proved effective for the condition of urge incontinence. Stimulation techniques have used surface electrodes, anal and vaginal plug electrodes [2–4], and dorsal penile nerve electrodes [5,6]. The theory underlying the mechanism of action of sacral nerve stimulation (SNS) is similar. Sacral neuromodulation, however, seems to offer the advantage of more durable, consistent control of lower urinary tract dysfunction. As a minimally invasive urologic procedure, it also has demonstrated long-term efficacy and safety. Furthermore, in addition to the treatment of refractory urge incontinence, sacral neuromodulation has been used to treat voiding dysfunction and idiopathic urinary retention.

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This article discusses how SNS can treat the seemingly disparate spectrum of lower urinary tract dysfunctions—urinary urge incontinence, dysfunctional voiding, and idiopathic urinary retention [7–10]. The implantable system (Medtronic, Minneapolis, Minnesota) is comprised of a neurostimulator, an extension cable, and a lead with quadripolar electrodes. The electrode is implanted in one of the sacral foramen, most commonly the S3 foramen. The pulse generator later is implanted permanently in a subcutaneous pocket of the superior buttock. Subsequent adjustments of the stimulator impulse settings can be accomplished easily and noninvasively with an electronic programming device [11–14].

This article first discusses the pertinent neuroanatomy and neurophysiology relating to SNS. Understanding the fundamental blueprint of the central nervous system controls of micturition are essential to appreciating how SNS can treat a wide range of lower urinary tract dysfunctions.

## Micturition reflexes

Normal micturition depends on neural pathways in the central nervous system. These pathways perform three major functions: amplification, coordination, and timing [16]. The nervous system control of the lower urinary tract must be able to amplify weak smooth muscle activity to provide sustained increases of intravesical pressures sufficient to empty the bladder. The bladder and urethral sphincter function must be coordinated to allow the sphincter to open during micturition but to remain closed at all other times. Timing reflects the volitional control of voiding that occurs with toilet training in human

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development. It also affords us the ability to initiate voiding over a wide range of bladder volumes (Fig. 1). In this regard, the bladder is a unique visceral organ that exhibits predominately voluntary rather than involuntary (autonomic) neural regulation. Several important reflex mechanisms contribute to the storage and elimination of urine and modulate the voluntary control of micturition [17].

The bladder is also an unusual organ because it is functionally "turned off" most of the time, and then turned on in an "all-or-none" manner to eliminate urine. Thus, it behaves differently than other visceral organs such as the heart, blood vessels, and gastrointestinal tract, which receive a tonic autonomic regulation. The ability to "turn on" micturition is facilitated by positive feedback loops in the micturition reflex pathway. In this manner, amplification of bladder afferent activity can activate sufficient efferent excitatory input to the bladder, which in turn initiates a bladder contraction. This positive feedback, mediated in part by supraspinal parasympathetic pathways to the pontine micturition center, is an effective mechanism for promoting efficient bladder emptying and minimizing residual urine.

This positive feedback mechanism, however, also can pose a potentially significant liability. In the presence of neuropathology, this system design can contribute to the emergence of bladder hyperactivity and random urge incontinence. Because of the positive feedback design, loss of central inhibitory controls or sensitization of bladder afferent signaling can lead to the unmasking of involuntary voiding. To balance this design, nature has provided other mechanisms for inhibitory modulation of the micturition reflex. These more primitive mechanisms reside in the spinal cord, and can be awakened by various somatic and visceral afferent nerve stimulations [22–24]. The spinal organization of these inhibitory mechanisms has been elucidated by electrophysiologic studies in animals [25,26]. The authors hypothesize that these modulatory mechanisms can be activated by SNS in the treatment of overactive bladders.

## Afferent and efferent pathways

Efferent outflow to the lower urinary tract can be activated by spinal afferent pathways as well as input from the brain. Afferent input from the pelvic visceral organs and somatic afferent pathways from the perineal muscle and skin are important. Somatic afferent pathways in the pudendal nerves that transmit noxious and non-noxious information from the genital organs, urethra, prostate, vagina, anal canal, and skin can modulate voiding function [15–17].

Bladder afferent nerves are critical for sending signals of bladder fullness and discomfort to the brain to initiate the micturition reflex. The bladder afferent pathways are composed of two types of axons: small myelinated A-delta fibers and unmyelinated C-fibers. A-delta fibers transmit signals mainly from mechanoreceptors that detect bladder fullness or wall tension. The C-fibers, on the other hand, mainly detect noxious signals and initiate painful sensations. The bladder C-fiber

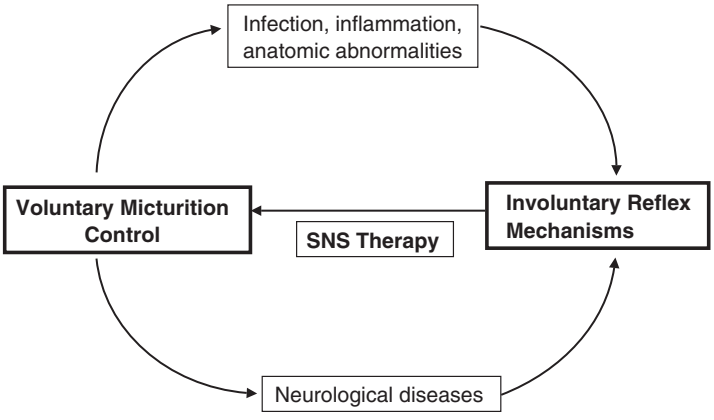


Fig. 1. The concept of SNS is to modulate the abnormal involuntary reflexes of the lower urinary tract and restore voluntary control.

nociceptors perform a similar function and signal the central nervous system when we have an infection or irritative condition in the bladder. C-fiber bladder afferents also have reflex functions to facilitate or trigger voiding [18–20]. This can be viewed as a defense mechanism to eliminate irritants or bacteria. The C-fiber bladder afferents have been implicated in the triggering of reflex bladder hyperactivity associated with neurologic disorders such as spinal cord injury and multiple sclerosis. Capsaicin and its ultrapotent analog, resiniferatoxin, are specific C-fiber afferent neurotoxins undergoing clinical trials for the treatment of lower urinary tract dysfunction relating to C-fiber alterations [15].

Bladder hyperactivity and urinary incontinence are believed to be mediated by the loss of voluntary control of voiding and the appearance of primitive voiding reflex circuitry. This lower urinary tract storage disorder can result from the re-emergence of neonatal reflex patterns that were suppressed during postnatal development or from the formation of new reflex circuits mediated by C-fiber afferents [21]. Under normal conditions, the latter are believed to be mechano-insensitive and unresponsive to bladder distension (hence the term *silent C-fibers*). As a consequence of neurologic or inflammatory diseases or possibly the aging process, however, the silent C-fibers may become sensitized to bladder distension and thus trigger micturition reflexes [18–20]. This type of bladder hyperactivity theoretically could be suppressed by blocking C-fiber afferent activity or by interrupting reflex pathways in the spinal cord by SNS.

### Guarding reflexes

An important bladder-to-urethral reflex is mediated by sympathetic efferent pathways to the urethra. This excitatory reflex promotes urethral smooth muscle contraction during the bladder storage phase, and is called the *guarding reflex* [27,28]. This positive reflex is not activated during micturition, but instead when bladder pressure is increased momentarily during events such as a cough or exercise. A second guarding reflex is triggered and amplified by bladder afferent signaling, which synapses with sacral interneurons that in turn activate urethral external sphincter efferent neurons through the pudendal nerve [8]. The activation of pudendal urethral efferents pathways contracts the external urinary sphincter and prevents stress urinary incontinence (Fig. 2).

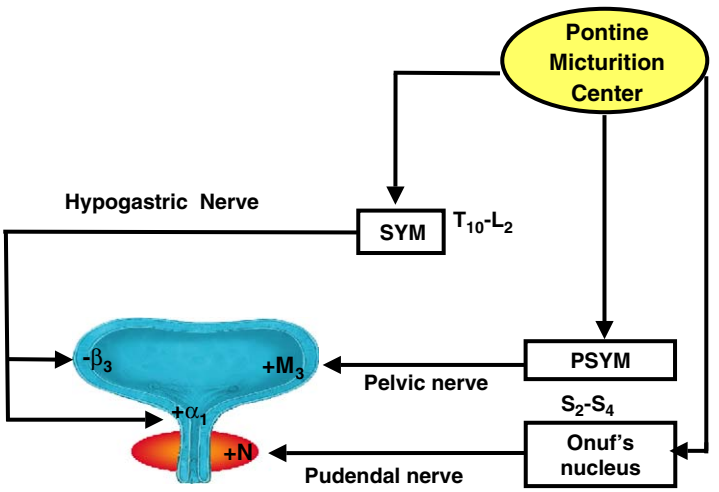


Fig. 2. The key nerves and neurotransmitters of the sympathetic (SYM), parasympathetic (PSYM), and somatic nervous systems involved in bladder control. The parasympathetic nucleus in the sacral cord ($S_2$–$S_4$) facilitates bladder emptying by contracting the bladder through the pelvic nerve acting on a muscarinic receptor ($+M_3$) in the detrusor smooth muscle. Hypogastric and pudendal nerves are switched off during micturition. During bladder storage, activation of the somatic pudendal nerve arises from the Onuf's nucleus in $S_2$–$S_4$ level that contracts the rhabdosphincter activated by nicotinic receptor (+N). In addition, hypogastric nerve activation in the thoracic 10-lumbar-2 ($T_{10}$-$L_2$) spinal cord level contracts the internal smooth muscle sphincter by α-1 adrenergic receptor activity, and relaxes the bladder through β-3 adrenergic receptors.

The brain inhibits the guarding reflexes during micturition.

### Reflexes that promote micturition

The bladder afferent (A-delta or C-fiber) nerves connect with interneurons in the sacral spinal cord. Interneurons synapse with bladder preganglionic (efferent) parasympathetic neurons to form the bladder-bladder reflex [27–30]. Interneurons activated by bladder afferents also synapse with urethral parasympathetic efferents neurons to form a bladder-urethral reflex. The bladder-bladder reflex is an excitatory reflex that becomes activated with the sensing of the full bladder. Once this reflex is turned "on" it remains on to empty the bladder completely. The bladder-urethral parasympathetic reflex is an inhibitory reflex that induces the smooth muscle of the proximal urethra to relax and the urethral outlet to open reflexively immediately before the onset of a bladder contraction (Fig. 3).

### Sacral afferent input can modify micturition reflexes

The guarding and voiding reflexes are activated at different times under different clinical scenarios. Anatomically, however, the sets of neuronal wiring are located closely to each other in the S2–S4 levels of the human spinal cord. Furthermore, both sets of spinal reflex pathways are modulated by several centers in the brain. In this respect, these reflexes can be altered by various neurologic diseases, some of which can unmask involuntary bladder activity mediated by C-fibers (Fig. 4). SNS modulates these reflexes by altering the afferent signaling and, it is hoped, leading to restoration of voluntary micturition.

Experimental data from animals indicate that somatic afferent input to the sacral spinal cord can modulate the guarding and bladder-bladder reflexes. de Groat [29] has shown that sacral preganglionic outflow to the urinary bladder receives inhibitory inputs from various somatic and visceral afferents, as well as a recurrent inhibitory pathway [22–24]. The experiments also have provided information about the organization of these inhibitory mechanisms [25,26]. Electrical stimulation of somatic afferent in the pudendal nerve elicits inhibitory mechanisms [21]. This is supported by the finding that interneurons in the sacral autonomic nucleus exhibit firing correlated with bladder activity and demonstrate inhibition by activation of somatic afferent pathways. This electrical stimulation of somatic afferent nerves in the sacral spinal roots could inhibit reflex bladder hyperactivity mediated by spinal or supraspinal pathways. In neonatal kittens and rats, micturition as well as defecation are elicited when the mother cat licks the perineal region [21]. In those species, this reflex seems to be the primary stimulus for micturition in the newborn. If the young kitten or rat is separated from its mother, urinary retention occurs.

To induce micturition in humans, the perineal afferents must activate the parasympathetic excitatory input to the bladder but also suppress the urethral sympathetic and sphincter somatic guarding reflexes. Successful suppression of the

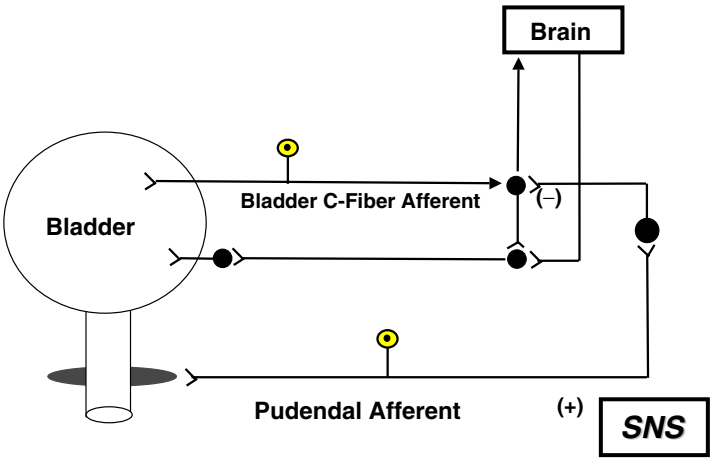


Fig. 3. Pudendal afferent nerve stimulation can inhibit the micturition reflex.

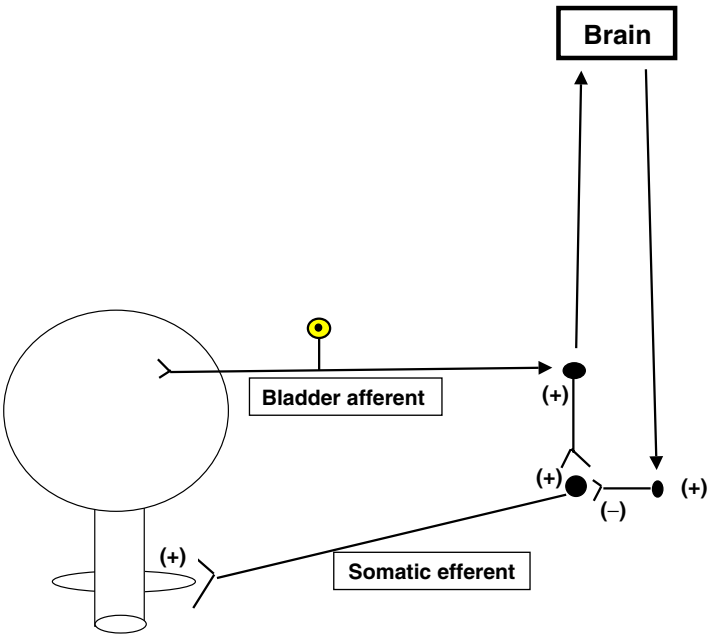


Fig. 4. The guarding reflex prevents urinary incontinence. When there is a sudden increase in intravesical pressure, such as during a cough, the spinal guarding reflex contracts the urinary sphincter to prevent urinary incontinence. The brain turns off the spinal guarding reflex to urinate.

guarding reflexes by SNS enables the enhancement of voiding in the subset of patients who have so-called "idiopathic urinary retention."

The perineal-to-bladder reflex is prominent during the first 4 postnatal weeks. As the kitten approaches the weaning age of 7 to 8 weeks, this perineal-to-bladder reflex dissipates and eventually disappears. In adult animals and humans, perineal stimulation or mechanical stimulation of the sex organs (vagina or penis) have the opposite effect of inhibiting the micturition reflex [17,23,27,28].

Besides the strong evidence from animal research that identified somatic afferent modulation of bladder and urethral reflexes, there are also data from clinical physiologic studies. Such research reinforces the view that stimulation of sacral afferent circuits can modify bladder and urethral sphincter reflexes. For example, functional electrical stimulation offers a favorable nonsurgical treatment for many patients who have detrusor instability. Stimulation techniques typically use surface electrodes, anal and vaginal plug electrodes [2–4], and dorsal penile nerve electrodes [5,6].

The success of pelvic floor electrical stimulation relies on convergence of common visceral and somatic sensory innervation pathways in the central nervous system [31]. By stimulating somatic afferents pathways, it is possible to block the processing of visceral afferent signals being delivered to the same region of the spinal cord. One example is the technique of posterior tibial nerve stimulation. With electrical stimulation of this nerve or its dermatome, it is possible to block sensory afferent inputs from the bladder [32,33]. Olhsson and colleagues [4] report success using electrical somatic nerve stimulation with transvaginal probes in women and transrectal probes in men. Despite a documented average 45% increase in bladder capacity, however, only half of their patients reported a 30% decrease in the frequency of micturition. Fall [2] also reported favorable long-term results of vaginal electrical stimulation in the treatment of refractory detrusor instability and stress urinary incontinence. Seventy-three percent of women who had detrusor instability became asymptomatic during treatment, whereas 45% remained free of symptoms after discontinuation of therapy. Many patients, however, required up to 6 months of therapy before benefit was apparent.

## How sacral nerve stimulation works

The authors hypothesize that the effects of SNS depend on electrical stimulation of somatic afferent axons in the spinal roots, which in turn modulate

voiding and continence reflex pathways in the central nervous system. The afferent system is the most likely target because beneficial effects can be elicited at intensities of stimulation that do not activate movements of striated muscles [34–36].

Urinary retention and dysfunctional voiding can be resolved by inhibition of the guarding reflexes. Detrusor hyperreflexia can be suppressed by two mechanisms: (1) direct inhibition of bladder preganglionic neurons and (2) inhibition of interneuronal transmission in the afferent limb of the micturition reflex.

How do sacral somatic afferents alter lower urinary tract reflexes to promote voiding? In adults, brain pathways are necessary to turn off sphincter and urethral guarding reflexes to allow efficient bladder emptying. Thus spinal cord injury produces bladder sphincter dyssynergia and inefficient bladder emptying by eliminating the brain mechanisms (Fig. 5). This also may occur after more subtle neurologic lesions in patients who have idiopathic urinary retention, such as after a bout of prostatitis or urinary tract infection.

As discussed previously, tactile stimulation of the perineum in the newborn cat also inhibits the bladder-sympathetic reflex component of the guarding reflex mechanism. Before the development of brain control, the pudendal nerve can initiate efficient voiding by activating bladder efferent pathways and turning off the excitatory pathways to the urethral outlet [15,16,18]. The authors hypothesize that SNS can elicit similar responses in patients who have urinary retention, turning off excitatory outflow to the urethral outlet and promoting bladder emptying. Because sphincter activity can generate afferent input to the spinal cord that can inhibit reflex bladder activity, an indirect benefit of suppressing sphincter reflexes would be a facilitation of bladder emptying function. This also may be useful in this patient population.

Conversely, how do sacral afferents also play a role in the inhibition of the overactive bladder? Several reflex mechanisms may be involved in the SNS suppression of bladder hyperactivity. Afferent pathways projecting to the sacral cord can inhibit bladder reflexes in animals and humans through two means: (1) by inhibiting the sacral interneuronal transmission and (2) by direct inhibition of bladder preganglionic neurons of the efferent limb of the micturition reflex circuit. The source of afferent input may be somatic, visceral, or both: namely, sphincter muscles, distal colon, rectum, anal canal, vagina, uterine cervix, and cutaneous innervation from the perineum.

Of the two mechanisms responsible for somatic and visceral afferent inhibition of bladder reflexes, the suppression of interneuronal transmission in

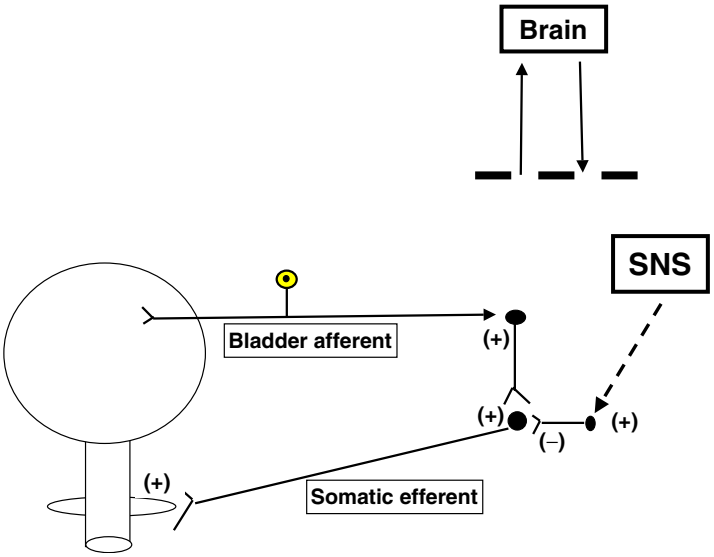


Fig. 5. In cases of neurologic diseases, the brain cannot turn off the spinal guarding reflex to urinate and retention can occur. SNS can restore voluntary micturition in cases of voiding dysfunction and urinary retention by inhibiting the spinal guarding reflex.

the bladder reflex pathway is believed to be involved most commonly in SNS [18,37,38]. It is believed that this inhibition occurs in part on the ascending limb of the micturition reflex and therefore blocks the transfer of signaling input from the bladder to the pontine micturition center. This action would prevent involuntary (reflex) micturition, but not suppress voluntary voiding necessarily. This is the clinical scenario typically observed in SNS therapy of overactive bladder.

The preservation of volitional voiding function suggests that the descending excitatory efferent pathways from the brain to the sacral parasympathetic preganglionic neurons are not inhibited. This latter mechanism would be more effective in turning off micturition reflexes because it would suppress directly firing in the motor outflow from the spinal cord. This can be induced by electrical stimulation of the pudendal nerve or by mechanical stimulation of the anal canal and distal bowel. As discussed, however, it also would be expected to block voluntary and involuntary voiding nonselectively. Therefore, this inhibitory pathway seems to play a lesser role in SNS' mechanism of action. Experience has shown that SNS performed for either voiding dysfunction or overactive bladder syndrome typically allows patients to retain normal voiding mechanisms (Box 1).

**Box 1. Possible mechanisms of sacral nerve stimulation**

- Inhibits postganglionic neurons directly
- May inhibit primary afferents presynaptically
- Inhibits spinal tract neurons involved in the micturition reflex
- Inhibits interneurons involved in spinal segmental reflexes
- May suppress indirectly guarding reflexes by turning off bladder afferent input to internal sphincter sympathetic or external urethral sphincter interneurons
- Postganglionic stimulation can activate postganglionic neurons directly and induce bladder activity (induce voiding), but at the same time can turn off bladder-to-bladder reflex by inhibiting afferent-interneuronal transmission

## Summary

The authors believe that the principles underlying the multiple possible SNS mechanisms of action can be summarized as somatic afferent inhibition of sensory processing in the spinal cord. Regardless of whether the lower urinary tract dysfunction involves storage versus emptying abnormalities, the pudendal afferent signaling serves as a common crossroads in the neurologic wiring of the system. Not only can pudendal afferent input turn on voiding reflexes by suppressing the guarding reflex pathways, pudendal afferent input to the sacral spinal cord also can turn off supraspinally mediated hyperactive voiding by blocking ascending sensory pathway inputs.

For these reasons, SNS can take advantage of the complex neurologic pathways described and offer successful treatment for a seemingly disparate group of lower urinary tract pathologies. SNS is a urologic technique that has proved safe and minimally invasive, and it holds great promise for many patients who have lower urinary tract dysfunction.

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