Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction

Floor van der Pal[a], John P.F.A. Heesakkers[a] and Bart L.H. Bemelmans[b]

Purpose of review

Neuromodulation is a successful treatment for patients with refractory lower urinary tract dysfunction. In the recent years, more applications of various types and ways have been developed and put into clinical practice. It is important, therefore, for urologists to know the existing theories on the working mechanisms that explain the effect. Although much research has been devoted to this subject for the past 35 years, the working mechanism is still unknown. This review presents an overview of the different theories and research into the physiological background of neuromodulation during the past 3 decades with emphasis on recent developments.

Recent findings

Specific receptors in the spinal cord have been identified, which are involved in the working mechanism of neuromodulation. The maximal effect of neuromodulation is not directly reached, indicating that neuromodulation induces learning changes (i.e. neural plasticity). The carry-over effect could be caused by negative modulation of excitatory synapses in the central micturition reflex pathway.

Summary

Neuromodulation in the treatment of stress incontinence probably induces physiological changes in the sphincter muscles and pelvic floor. In the treatment of overactive bladder syndrome, nonobstructive voiding dysfunction and chronic pelvic pain, the mechanism of action seems to be more complicated. Most likely, it is a combination of the different suggested modes of action, involving the neuroaxis at different levels.

Keywords

lower urinary tract dysfunction, mechanism of action, neuromodulation, review

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[a]Department of Urology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands and [b]Department of Urology, Free University Medical Centre, Amsterdam, The Netherlands

Correspondence to John P.F.A. Heesakkers MD, PhD, Department of Urology (659), Radboud University Nijmegen Medical Centre, P.O. Box 9101, NL-6500 HB Nijmegen, The Netherlands
Tel: +31 24 3616712; fax: +31 24 3541031; e-mail: j.heesakkers@uro.umcn.nl

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Abbreviations

PET	photon emission tomography
PTNS	percutaneous tibial nerve stimulation
SNS	sacral nerve stimulation
TENS	transcutaneous electrical nerve stimulation

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Introduction

Patients with lower urinary tract dysfunction can have complaints varying from voiding disorders (impaired micturition or nonobstructive urinary retention) to storing disorders (overactive bladder wet and dry) and chronic pelvic pain. Lower urinary tract dysfunction in neurogenic patients is caused by the injury of the peripheral or central nervous system, and in nonneurogenic patients, it is usually unknown.

Neuromodulation offers an alternative treatment for patients who are refractory to conservative treatment (behavioural techniques, physiotherapy, clean intermittent catheterization or pharmacotherapy) and not ready for irreversible surgery. Neuromodulation is defined as the physiological process in which the influence of the activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction [1]. Different therapies, like intravesical stimulation, pudendal nerve stimulation, sacral nerve stimulation (SNS) and lower limb stimulation, have been developed with varying success rates [2,3]. In the recent years, more applications of various types and ways have been developed and put into medical practice [4•,5,6,7•,8–12]. It is important for urologists to know the existing theories on the working mechanisms that explain the effect. Although much research has been done, the working mechanisms of neuromodulation are still unknown. This review presents an overview of the different theories and research into the physiological background of neuromodulation in the past 3 decades, with emphasis on recent developments.

Chronic pelvic pain

In the treatment of pain, the working mechanism is believed to be a gate-control mechanism [13]. The gate-control theory states that pain perception does not depend on pain receptors sending information to the brain, but on the pattern of peripheral nervous input [14]. It is believed that a gate-control mechanism is

present at the spinal segmental level, which can prevent the sensation of pain and the reaction to it. Interneurons of the substantia gelatinosa of the spinal cord dorsal horn create gating components. Presynaptic inhibition or facilitation of afferent fibres (Fig. 1) modulates the input to the spinal transmission neurons. Activity in A-fibres excites substantia gelatinosa neurons that, in turn, inhibit synaptic transmission and close the gate, which results in hypoalgesia. Hyperalgesia is caused by C-fibre activity resulting in increased presynaptic transmission. Furthermore, it is supposed that the impulses from the dorsal horn are controlled by a descending system containing fibres from the brainstem, thalamus and limbic lobes.

The discussed gate-control mechanism is believed to be the working mechanism for neuromodulation in the treatment of chronic pelvic pain [15–17]. Neuromodulation is supposed to restore the control at the spinal segmental 'gate' as well as at supraspinal sites such as the brainstem and limbic system nuclei. Studies [18,19] using transcutaneous electrical nerve stimulation (TENS) support the existence of descending inhibition, as is supposed in the gate-control theory of Melzack and Wall [14]. The rostral ventral medulla seems to be involved in this and serotonin and opioids are probably used to reduce pain. Finally, it has been suggested that the analgesic effects could be mediated by the modulation of autonomic activity [20] and that adenosine plays a role in the mechanism of action [21,22].

Overactive bladder syndrome

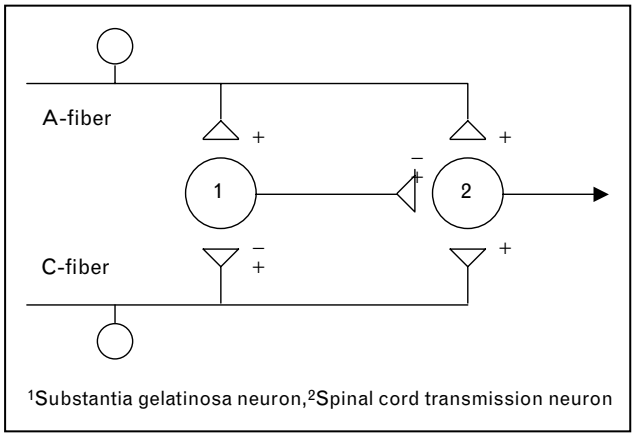
Several theories on the working mechanism of the bladder have been proposed. It has been suggested that SNS induces pelvic floor muscle hypertrophy and changes the histochemical properties of the muscle, resulting in improved pelvic floor efficiency [23]. This is supported by animal studies [24] in dogs that showed hypertrophy of striated external sphincter muscle fibres and increased urethral closure pressure during chronic SNS. Afterwards, it was stated that this theory is more applicable to the treatment of stress urinary incontinence [25]. Direct motor pathway stimulation and retrograde spinal motor neuron stimulation in Onuf's nucleus, or central inhibitory pathway activation via afferent pudendal nerve stimulation could, however, suppress instable bladder contractions. The latter seems to be more logical as neuromodulation is usually applied below the threshold for the motor response. Up until now data supporting this assumption have not been presented.

Another theory is activation of sensory nerves [26]. This is supported by research studying the latency of the motor response (i.e. the anal wink) to SNS demonstrating that the latency was approximately 10 times longer than would be expected if the response was mediated by direct motor-nerve stimulation [27]. Moreover, the latency of cortical responses is shortened during chronic SNS, indicating the activation of somatosensory afferent fibres [28].

Activation of the sensory nerves supports the gate-control theory that has been used as the working mechanism of neuromodulation in the treatment of chronic pain. This finding is supported by animal studies [29] demonstrating that spino-bulbo-spinal pathways are involved in the normal micturition reflex. A-delta bladder afferents project to pontine nuclei in the brainstem, which in turn give rise to inhibitory and excitatory input to lumbo-sacral reflexes controlling bladder and sphincter function. Sensory input from the pelvic floor via large myelinated pudendal fibres may control erroneous bladder input conveyed by A-type or C-type bladder afferents 'at the gate' via sacral segmental interneurons and supraspinally by way of the spino-bulbo-spinal reflex system. When a gate-control system is attributed to the inhibitory influences of interneurons from the somatic pudendal nuclei on parasympathetic pelvic nuclei within the spinal cord and brainstem, the cause of overactive bladder syndrome could be a deficiency of the inhibitory control systems involving the pudendal afferent nerves [30]. Therefore, it has been suggested that neuromodulation treats overactive bladder syndrome by restoring the balance between the inhibitory and excitatory control systems. The latter could be done at various sites in both peripheral and central nervous systems [31]. This is shown in Fig. 2.

The supraspinal involvement in the 'the gate-control' theory is supported by electroencephalogram (EEG) studies during SNS [32]. These studies have demonstrated that both short and long latency cortical potentials can be reproduced with a maximum at the sensory

Figure 1 Schema of the gate-control theory

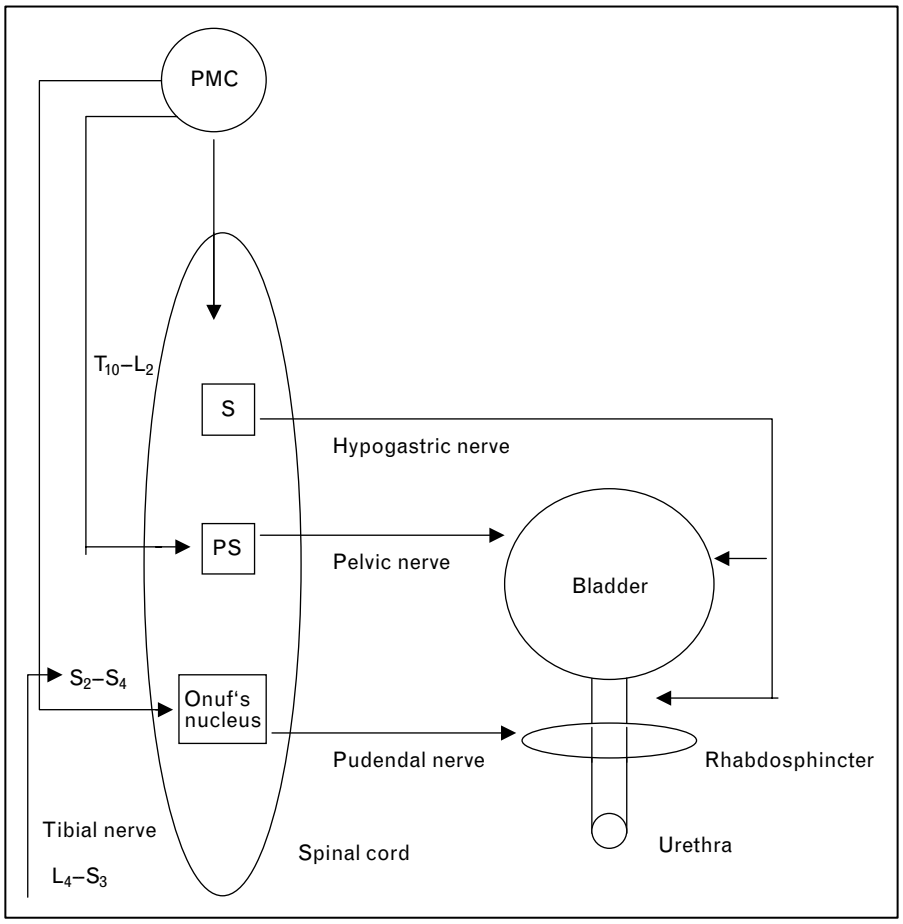


[1]Substantia gelatinosa neuron,[2]Spinal cord transmission neuron

(1) Substantia gelatinosa neuron and (2) spinal cord transmission neuron.

Figure 2 The nervous systems that are involved in controlling the bladder and the working mechanism of neuromodulation

The bladder is controlled by sympathetic (S), parasympathetic (PS) and somatic nervous systems that are regulated by the pontine micturition centre (PMC). Micturition (bladder contraction) is facilitated by activation of the parasympathetic system through the pelvic nerve (S_2–S_4). Continence is facilitated by both sympathetic system through the hypogastric nerve (T_{10}–L_2, bladder relaxation and internal sphincter contraction) and somatic system through the pudendal nerve (S_2–S_4, rhabdosphincter contraction). It is unclear if the tibial nerve (L_4–S_3) modulates the bladder function through the pelvic nerve or pudendal nerve or both.



cortical area, indicating a supraspinal-mediated site of modulation, most probably in sensory cortex areas. Moreover, combined photon emission tomography (PET) and magnetic resonance imaging (MRI) studies have demonstrated that SNS has no effect on the brain areas that are important for the micturition itself. The activity of the micturition-dominant right hemisphere is, however, relatively reduced and the activity in brain areas that are important for general arousal, bladder filling sensation and the onset of micturition is decreased [33]. Furthermore, the maximal beneficial effect of SNS is reached after several hours or days, indicating learning changes in the brain (i.e. neural plasticity) [34]. This finding is supported by PET studies demonstrating that only brain areas important for motor behaviour learning (i.e. lower trunk motor cortex and the cerebellum) are activated during the first hours of SNS. After the initial period, the pelvic floor and abdominal motor cortical areas are more easily excited and the effects of SNS are prolonged and pronounced [34]. Finally, these studies showed that SNS activates the mid cingulated gyrus, which could result in a temporarily increased awareness of bladder filling.

Another mechanism of the action of SNS could be the activation of the hypogastric sympathetic nerves, which have an inhibitory effect on the parasympathetic fibres at the pelvic ganglia [35]. Furthermore, recent studies have indicated that non-*N*-methyl-D-aspartate (non-NMDA) receptors [36••] and proton-sensitive and heat-sensitive vanilloid receptors [37] are involved in the working mechanism of SNS.

For pudendal nerve stimulation, it has been demonstrated that spinal pathways connect somatic and autonomic reflex circuits, which have mostly an inhibitory mode of action. Two mechanisms have been identified that have their afferent limb in the pudendal nerve and inhibit the bladder directly. At low bladder pressure, bladder contractions are suppressed via sympathetic hypogastric nerves, whereas at high bladder pressure, parasympathetic pelvic excitatory neurons are activated, resulting in central inhibition [38,39]. Furthermore, pudendal nerve stimulation results in the activation of the sympathetic hypogastric nerves and inhibits the excitatory pelvic efferent outflow to the bladder at the

ganglionic level [40]. This finding could be explained by the presence of a gate-control mechanism at the spinal cord to influence either the hypogastric or pelvic afferents. Data supporting this theory have been presented in patients with a complete spinal cord lesion [41]. The study demonstrated that the latencies of bladder neck responses during pudendal nerve stimulation increase significantly and are sensitive to α-blocking agent phentolamine, suggesting the involvement of sympathetic α-adrenergic fibres. Somatic afferent pudendal nerve fibres project to sympathetic neurons in the thoracolumbar spinal cord and the sympathetic bladder neck outflow travels with the hypogastric nerve maintaining the bladder neck tone via α-adrenergic receptors [42–44].

Another suggested mechanism of action is that the sympathetic system is activated that suppresses bladder activity via the β-adrenergic system or spinal interneurons that release inhibitory neurotransmitters such as enkephalin, glycine, or γ-aminobutyric acid [45].

Pudendal nerve stimulation in healthy volunteers showed specific activation of the somatosensory and somatomotor cortex [46] on functional magnetic resonance imaging (fMRI). The first has been confirmed by several studies [47,48]. Furthermore, it has been suggested that the amygdala and periaqueductal grey are activated during pudendal nerve stimulation [46]. Pudendal nerve stimulation-induced cortical activation is, however, not identical to SNS-induced cortical activation. A larger similarity was expected as S_2 and S_3 roots contribute respectively 60.5 and 35.5%, to the overall pudendal afferent activity [49]. The activity of pudendal nerve stimulation was, however, confined to a single level (S_2) in 18% and even to a single root in 8% of the participants. Direct pudendal nerve stimulation, therefore, could be more effective as more afferents are stimulated than during SNS [6,50], as has been confirmed by Peters *et al.* [51•]. To date, no results have been published of a comparative study on cortical activation during SNS and pudendal nerve stimulation in patients with lower urinary tract dysfunction.

A carry-over effect has been shown in animal studies for pudendal nerve stimulation [52] and intravesical stimulation [53], in contrast to SNS in which up untill now no carry-over effect has been described. For intravesical stimulation, the carry-over effect is supposed to be caused by the long-term potentiation of excitatory synapses in the central micturition reflex pathway [53], analogous as has been described for other central excitatory synapses [54]. It has been suggested that the carry-over effect of pudendal nerve stimulation could be caused by the negative modulation of excitatory synapses in the central micturition reflex pathway [52]. This theory is supported by the study of Bear and Malenka [55], which showed that intense activation of inhibitory input to target cells results in a prolonged decrease in synaptic efficacy of excitatory synapses (i.e. long-term depression) in the hippocampus. Long-term depression could be the mechanism of action for the carry-over effect as well as for TENS and percutaneous tibial nerve stimulation (PTNS). Although, a clear carry-over effect has not been described for both therapies in an animal model, it is to be expected as patients are successfully treated with intermittent therapy [56–61]. The modulatory effect of pudendal nerve stimulation could be prolonged by frequent stimulation sessions [52], as the carry-over effect is reversible and patients are treated with frequent stimulation sessions during a certain period before their symptoms improve. This could be the case as well for TENS and PTNS; however, data supporting this assumption have not been presented yet.

Other suggested central modes of action of pudendal nerve stimulation are activation of tonic inhibitory mechanisms and shifts in firing threshold of involved neurons [62].

The mechanism of action for TENS and PTNS in the treatment of overactive bladder syndrome is supposed to be a gate-control mechanism as well [25,30,63]. It has, however, been demonstrated for TENS that different stimulation frequencies have different effects. TENS at 2 Hz is supposed to activate afferent pudendal nerve fibres and 50 Hz stimulation is considered to activate striated paraurethral muscle fibres [30,38]. TENS at 150 Hz is supposed to influence the anterior cutaneous branch of the iliohypogastric nerve or to inhibit the afferents of the pelvic splanchnic nerves that join the inferior hypogastric plexus, resulting in a decreased bladder contractility [56].

Another suggested mode of action for TENS is that it provides relief from pain, resulting in increased bladder filling and postponed micturition [64].

Tibial nerve stimulation, like SNS [65], reduces C-fos protein expression after chemical irritation of the bladder [66], indicating decrement of spinal neural cell activity and therefore, neuromodulative action. C-fos protein is the third messenger that modulates cell activity and is especially expressed in neurons after external stimulation [66] and in the spinal cord after lower urinary tract irritation [67].

The tibial nerve is a mixed nerve containing sensory and motor nerve fibres. PTNS is supposed to treat overactive bladder syndrome by modulating the signals from and towards the bladder via the sacral plexus by retrograde afferent stimulation [61]. This has been confirmed by studies in anaesthetized female cats [68]. The study has

also confirmed the observation that the effect of PTNS is temporary and that maintenance treatment is necessary as PTNS reversibly modulates the micturition reflex in the female cat.

Voiding disorders

Different theories on the mechanism of action have been proposed. Direct afferent pudendal nerve stimulation resulting in a direct change of pelvic floor behaviour [69], as well as a rebound phenomenon [70], suppression of the guarding reflexes [3] and retuning of the L and M regions or 'on–off' switch mechanism in the brainstem [25], has been suggested.

The guarding reflex is a bladder-to-urethral reflex and is mediated by sympathetic afferent pathways to the urethra. The reflex is excitatory and results in contraction of the urethral smooth muscle during the storage phase of the bladder [71]. The guarding reflex is activated during coughing or exercising resulting in momentarily increased bladder pressure, which prevents stress urinary incontinence by contraction of the external urethral sphincter. The reflex is activated as well by signalling of bladder afferents that synapse with sacral interneurons, which in turn activate efferent neurons of the external urethral sphincter [72]. Animal studies have provided data indicating that the guarding reflexes can be modulated by afferent nerve activation and inhibit bladder activity by spinal or supraspinal pathways [73–78].

The retuning of the 'on–off' switch seems to be a more logical mechanism of action for neuromodulation, as nonobstructive bladder retention is supposed to be caused by a malfunction of the 'on–off' switch mechanism due to urethral sphincter and pelvic floor spasticity [79]. Evidence supporting this theory has been provided by PET studies, which showed pontine activation during SNS in patients with urinary retention [80]. Contradicting data have been presented as well. Single photon emission tomography during SNS showed an increase in the regional cerebral blood flow of all brain areas, which are activated during micturition [81]. This study was, however, performed in healthy volunteers and not in patients with nonobstructive voiding dysfunction.

Retuning of the 'on–off' switch could be the mechanism of action as well for PTNS. Up till now, no data, however, have presented this assumption.

According to Vapnek and Schmidt [82], SNS treats nonobstructive retention by eliminating the spasticity of the urethral sphincter and pelvic floor and not by direct activation of the parasympathetic sacral nerves, as the stimulation intensity of SNS is too low for the depolarization of these unmyelinated nerve fibres.

Conclusion

Although many hypotheses have been given and much research has been performed, the exact mechanism of action of neuromodulation in the treatment of lower urinary tract dysfunction is still unclear. In the treatment of stress incontinence, it seems likely that neuromodulation induces physiological changes in the sphincter muscles and pelvic floor. In the treatment of overactive bladder syndrome, nonobstructive voiding dysfunction and chronic pelvic pain, the mechanism of action seems to be more complicated. The mechanism is most likely a combination of the different suggested modes of action, involving the neuroaxis at different levels.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 313).

1 Craggs M, McFarlane J. Neuromodulation of the lower urinary tract. Exp Physiol 1999; 84:149–160.

2 Fandel T, Tanagho EA. Neuromodulation in voiding dysfunction: a historical overview of neurostimulation and its application. Urol Clin North Am 2005; 32:1–10.

3 van Balken MR, Vergunst H, Bemelmans BL. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. J Urol 2004; 172: 846–851.

4 • Bani-Hani AH, Vandersteen DR, Reinberg YE. Neuromodulation in pediatrics. Urol Clin North Am 2005; 32:101–107.

The authors present a new approach to neuromodulation in the treatment of children with voiding dysfunction. An educated team is needed, not to cure the patient, but to reinforce progress and encourage long-term behavioural changes.

5 Baykal K, Senkul T, Sen B, *et al.* Intravesical heparin and peripheral neuromodulation on interstitial cystitis. Urol Int 2005; 74:361–364.

6 Bosch JL. The bion device: a minimally invasive implantable ministimulator for pudendal nerve neuromodulation in patients with detrusor overactivity incontinence. Urol Clin North Am 2005; 32:109–112.

7 • Craggs MD. Objective measurement of bladder sensation: use of a new patient-activated device and response to neuromodulation. BJU Int 2005; 96 (Suppl 1):29–36.

A device was tested for its reliability and accuracy to measure different bladder sensations in patients with overactive bladder, which was demonstrated. Urge sensations were suppressed by neuromodulation; therefore, the device offers the possibility to select patients with overactive bladder for neuromodulative treatment.

8 Groen J, Amiel C, Bosch JL. Chronic pudendal nerve neuromodulation in women with idiopathic refractory detrusor overactivity incontinence: results of a pilot study with a novel minimally invasive implantable mini-stimulator. Neurourol Urodyn 2005; 24:226–230.

9 Karademir K, Baykal K, Sen B, *et al.* A peripheric neuromodulation technique for curing detrusor overactivity: Stoller afferent neurostimulation. Scand J Urol Nephrol 2005; 39:230–233.

10 Spinelli M, Weil E, Ostardo E, *et al.* New tined lead electrode in sacral neuromodulation: experience from a multicentre European study. World J Urol 2005; 23:225–229.

11 Spinelli M, Malaguti S, Giardiello G, *et al.* A new minimally invasive procedure for pudendal nerve stimulation to treat neurogenic bladder: description of the method and preliminary data. Neurourol Urodyn 2005; 24:305–309.

12 van der Pal F, van Balken M, Heesakkers J, *et al.* Tibial nerve stimulation by implant in the treatment of refractory overactive bladder syndrome: 12-month follow up [abstract 257]. In: ICS 2005 Scientific Programme; 2005.

13 Alo KM, Holsheimer J. New trends in neuromodulation for the management of neuropathic pain. Neurosurgery 2002; 50:690–703.

14 Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965; 150:971–979.

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