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Does Our Limited Knowledge of the Mechanisms of Neural Stimulation Limit Its Benefits for Patients With Overactive Bladder? ICI-RS 2013

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Abstract

Introduction—Neural stimulation has become an established minimally invasive treatment for various lower urinary tract symptoms. The results both short- and long-term are encouraging, however, there is still a lack of knowledge of obvious risk factors, which may affect the outcome of treatment. Although neural stimulation has been embraced by healthcare professionals and patients, the exact mechanism by which neural stimulation works is still unclear.

Discussion—A condense review of knowledge available on this topic is presented. Several research questions are raised. Outlines of research studies, both clinical and basic science, are suggested.

Conclusions—Further studies are necessary to understand mechanism of action of neural stimulation and its implications on treatment outcomes.

Keywords

neural stimulation; overactive bladder

INTRODUCTION

Neural stimulation has become an established minimally invasive treatment for various lower urinary tract symptoms. There are three main neural stimulation methods.

- *Sacral Nerve Stimulation (SNS)* involves applying an electric current produced by the implantable pulse generator, to one of the sacral nerves via an electrode placed through the corresponding sacral foramen.

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- *Pudendal Nerve Stimulation (PNS)* involves applying an electric current produced by the implantable pulse generator, to pudendal nerve via an electrode placed in near proximity to the nerve by the ischial-rectal approach
- *Percutaneous Tibial Nerve Stimulation (PTNS)* involves inserting a tiny needle electrode just above the ankle and stimulating a tibial nerve with electric current.

The results both short- and long-term are encouraging, however, there is still a lack of knowledge of obvious risk factors, which may affect the outcome of treatment. Although neural stimulation has been embraced by healthcare professionals and patients, the exact mechanism by which neural stimulation works is still unclear. There are several hypotheses extrapolated from basic science experiments on bladder reflexes and innervation. Specific and relevant models (clinical and animal) for studying the mechanism of neural stimulation are scarce. Improved knowledge of the mechanism(s) of action of neural stimulation could improve outcomes by more appropriate patient selection and by modifying surgical techniques. We undertook a brief review of our clinical and basic science knowledge with a particular emphasis of outlining the deficiency in our understanding of mechanism of action of neural stimulation. Several research questions are raised. Outlines of research studies, both clinical and basic science, are suggested.

WHAT DO WE KNOW FROM THE CLINICAL STUDIES?

- Sacral Nerve Stimulation (SNS) has been used for refractory overactive bladder “dry” and “wet” for more than a decade. Good outcomes have been reported in 70–80% of patients who received a permanent implant.¹ These results have continued for several years of follow-up, however, reoperation rate is high and in the range of 30–40%.² Although exact mechanism have not yet fully described, several hypotheses have been proposed. Leng & Chancellor suggested that SNS suppresses urgency and alters bladder function through activation of the pudendal afferents and by turning off supra-spinal mediated overactive voiding by blocking ascending sensory pathway input.³ Afferent mediated response to rather direct motor nerve stimulation can explain an anal sphincter contraction observed during peripheral nerve evaluation. Mean latency of response was approximately 10 times longer than would be expected from that resulting from direct motor nerve stimulation.⁴ It is unclear if the same apply to bladder responses as well. It has been postulated however that SNS modulates afferent pathways, altering spinal and supraspinal circuits, restoring balance between inhibitory and excitatory control systems through a Gate-controlled mechanism.⁵ It has also been stated that SNS suppresses detrusor contractions by activation of the bladder-sphincter-bladder reflex. Urine storage reflexes are organized in the spinal cord, whereas voiding reflexes are mediated by a spinobulbospinal pathway passing through a coordination center (the pontine micturition center) located in the brainstem.⁶ Sacral dorsal root neural stimulation reduces c-fos gene expression and bladder hyperreflexia in spinalized rats, through inhibition of afferent c-fiber activity.⁷ This explains some reports of beneficial outcome of SNS on patients with Bladder Pain Syndrome/Interstitial Cystitis.⁸ The beneficial

effect of SNS on urinary retention/voiding dysfunction is much more difficult to explain. It has been suggested that SNS suppresses detrusor inhibitory interneurons and releases the bladder from an augmented sphincter-bladder reflex at the spinal and supraspinal level.⁹

- Clinical outcomes of SNS depend also on specific stimulation parameters because of the different nerve fibers captured with stimulation. This may elicit some therapeutic advantages. The data are however very scarce and with limited clinical significances.^{10,11}
- Pudendal Nerve Stimulation (PNS) has been utilized for overactive bladder (OAB). There are some reports indicating PNS to be superior to SNS. Almost all who failed SNS responded to PNS stimulation (93.2%). Overall, positive PNS response (50% improvement) was achieved in 71% of participants.¹² In another study, after temporary stimulation of pudendal nerve or sacral roots, the majority of the patients chose PNS over SNS (13 vs. 4).¹³
- Percutaneous Tibial Nerve Stimulation (PTNS) has been used for OAB and studied by several investigators.^{14,15} This ambulatory procedure (1× week, 30 min) for 6–8 weeks has positive outcomes in 70–80% and the effect persists for several months with booster treatment. The mechanism of action is believed to be similar to acupuncture, through central nervous system neurotransmitter release. This treatment is reserved for patients who failed other conservative treatments and should be considered as experimental treatment because of scarce literature data on outcomes.

HOW DIFFERENT ARE DIFFERENT FORMS OF NEURAL STIMULATION?

The mechanism and site of action of the different forms of neural stimulation and which ones are best suited to treat the different causes of detrusor overactivity or voiding dysfunction is unclear. The type of nerves stimulated by different forms of neural stimulation (usually unilateral) could be a key to their mechanism of action and the form of overactivity and hypersensitivity they are best suited to inhibit. SNS through the S3 foramen, and PNS near the transgluteal or ischial-rectal region, stimulate mixed somatic, and visceral nerves. Low amplitude stimulation (just below the threshold for an anal “wink”) is used to capture large somatic A α - and A β - and midsize A δ -afferents. Midsize B-fibers, which include visceral sympathetic and parasympathic efferents, may also be stimulated but not small C-fibers which have thresholds 50 times greater than A δ -and B-fibres.¹⁶ Therefore, nociceptive afferents may be less affected by these two forms of neural stimulation than mechanosensitive afferents and visceral efferents which may favor OAB wet. Alternatively, percutaneous posterior tibial nerve stimulation (PPTNS) near the heel or medial malleolus will stimulate mainly somatic nerves and, since 1.5–3 times the threshold to produce extensor flexion (without discomfort) is employed, this may also capture C-fibers and favor OAB-dry.¹⁷

The outcome is affected by stimulation parameters. High frequency (>20 Hz) stimulation cause detrusor contractions in non-obstructive urinary retention and low frequency (5–10

Hz) stimulation inhibits detrusor activity in OAB. This variable response depends on pelvic efferent activation via the pelvic ganglion and not on adrenergic pathways.¹⁸

DO LABORATORY ANIMAL STUDIES PROVIDE MORE ANSWERS?

Various animal models have been used to investigate the lower urinary tract (LUT) effects of the different forms of neural stimulation in order to discern their mechanisms of action and improve stimulation techniques for better patient outcomes. However, SNS,¹⁹ PNS,²⁰ and tibial nerve stimulation (TNS)¹⁷ have only been studied acutely. PNS has been proposed as a method of improving bladder emptying by modulating afferents innervating the urethra. It has the benefit that there are generally positive results in those who fail to respond to SNS and it can be administered transcutaneously using noninvasive surface electrodes. The mechanism of action is still unclear however and long-term studies are lacking in animals and humans. PTNS is the newest treatment route for neural stimulation. It has the advantages that it can be administered transcutaneously and has a persistent benefit on LUT symptoms following cessation of treatment.²¹ In rats, PTNS has a lower efficacy compared to SNS,²² however, PTNS may be elicited through remodeling of central pathways which would not be evident in acute studies.

The Kanai lab has been successful in using chronic TNS to suppress irradiation-induced detrusor overactivity in mice for at least 3 days after the final round of stimulation. TNS (10 Hz, 2 ms, 15–20 V) is administered (1 hr/day for 6 days), starting 1 week after focal irradiation (10 Gray; 1 Gy = 100 rads) of the bladder—as presented at the 2013 ICI-RS meeting in Bristol, UK. The persistent inhibition of detrusor overactivity can be demonstrated on cystometrograms from decerebrate mice, but not in isolated bladder sheets excised with their associated spinal roots. This suggests that the sites where TNS-induced changes occur are not in the forebrain or periphery, but in the brainstem (among others also location of the pontine micturition center) and spinal cord. Since the beneficial effects of SNS and PNS cease when stimulation stops, these indicate involvement of different mechanisms and sites of action with real-time stimulation of inhibitory neuronal circuits rather than their long-term remodeling as may occur with TNS. Accordingly, this mouse model is well suited to characterize TNS where sustained inhibition will allow in vivo testing of inhibitors to determine the neurotransmitters involved, and in vitro isolation and serial-sectioning of the midbrain and spinal cord to determine neurotransmitter sites of action.

Neurotransmitters are thought to play a role in neural stimulation, which could lead to combination therapies using drugs and electrical stimulation to increase their effectiveness. A number of acute animal studies have demonstrated a putative involvement of glutamate, serotonin, and opioid receptors in the effect of neural stimulation on control or irritated bladders. Glutamate receptors probably are involved in PNS-²³ and PTNS-mediated²⁴ inhibition of bladder overactivity in cats. Serotonin receptors are also suggested to be involved in PNS-mediated bladder inhibition,²⁵ however, the serotonin reuptake inhibitor, duloxetine, did not exhibit additive benefits during TNS in cats.²⁶ Opioid receptors, particularly type μ , were suggested to be involved in the effects of SNS and PNS in normal cat bladders. Together with glutamate receptors, they are also reported to produce synergic

effects in TNS of acetic acid irritated bladders.²⁷ However, the opioid receptor antagonist, naloxone, failed to decrease PNS-induced inhibition of detrusor overactivity in irritated bladders²³ and TNS-induced inhibition of reflex bladder contractions in control cats.²⁷ Thus, the types of neurotransmitters and their role in neural stimulation is still unclear but their elucidation may benefit from the use of the chronic TNS mouse model described above.

The hypothesis that nociceptive fibers promote OAB-dry and mechanosensitive ones OAB wet is feasible if second order A δ -fibers project to the periaqueductal gray region of the midbrain and their third order ones to the pontine micturition center to trigger micturition; while second order C-fibers project to the thalamus and insula and their third order ones to the cortex to signal bladder fullness. To test this hypothesis, work is on-going in the Kanai lab to develop viral constructs that express genetically encoded green and red fluorescent Ca²⁺ indicators driven by promoters unique to mechanosensitive or insensitive fibers. Since these viruses cross synapses, they can be injected into the detrusor to track bladder afferent fiber distribution in the brainstem and cortex. One important consideration is that not all A δ -fibers are mechanosensitive and not all C-fibers are nociceptive. Approximately half of the bladder afferents are A δ -fibers of which ~70% are mechanosensitive (80% high thresholds and 20% low threshold or silent requiring sensitization to respond) and 30% are mechanosensitive. On the other hand, essentially all C-fibers are high threshold and normally silent. However, half of them are noxious and half can respond to mechanical stimulation when sensitised.²⁸

PATIENTS PERSPECTIVE

One pilot study showed that highest scores for perception of a successful outcome and satisfaction with outcome were significantly more common in the 75 min group shared appointment group despite leaving objective measures of success unchanged when compared to office counseling only.²⁹ Others showed improvements in short-term patient knowledge about SNS using a Patient-Based Educational Video in comparison to manufacturer's video (MV).³⁰ Only patient's knowledge and no treatment outcome measures have been utilized in this study.

RESEARCH QUESTIONS AND STUDY OUTLINES

- **Basic Science**
 - Do the different forms of neural stimulation preferentially treat different types of bladder overactivity or hypersensitivity?
 - Test the different forms of neural stimulation with animal models of bladder overactivity (e.g., neurogenic, myogenic and mixed) and hypersensitivity (e.g., chemical, radiation, and bacterial cystitis).
 - Are different types of afferent nerves (i.e., mechanosensitive versus nociceptive) responsible for OAB wet and OAB-dry?
 - Inject the bladder wall with pseudorabies virus (PRV) containing genetically encoded green fluorescent protein or red fluorescent protein

(e.g., m-Cherry), driven by promoters unique to A δ - and C-fibers. This would be followed at an appropriate time by removal, serial-sectioning, and histological evaluation of the spinal cord, brain stem and cortex.

- Can developed refractoriness to neural stimulation be due to remodeling of neural circuits?
- Perform long-term neural stimulation followed by PRV tracing studies to evaluate remodeling in the periphery and CNS.
- **Clinical Studies**
 - Are there benefits to the combination of neural stimulation and pharmacotherapy in the “naïve” patients?
 - A randomized controlled trial (RCT), intention-to-treat comparing two group of patients;
 - ◆ SNS with or without pharmacotherapy at least 24 months in duration.
 - ◆ Outcome measures based on validated questionnaire and objective measures that is, pad test. Urodynamic parameters can be considered.
 - Do different stimulation sites or parameters have clinical significance in the treatment outcomes?
 - RCT comparing patients with unilaterally versus bilaterally implanted electrodes.
 - ◆ At least 3 months duration
 - ◆ Outcome measures as above
 - RCT comparing patients with S3 versus S4 lead placement
 - ◆ At least 3 months duration
 - ◆ Outcome measures as above.
 - Difficulties in standardization of precise electrode placing, diversity of human anatomy and electrode position flexibility, RCT trials investigating outcome impact of stimulation parameters, can only be done using the patient as its own control
 - ◆ At least 1–3 months duration of each period of stimulation with different parameters
 - ◆ Outcome measures as above
 - Does patient knowledge about the mechanism of action of neural stimulation improve outcomes?
 - A randomized controlled trial (RCT) comparing two group of patients

- ◆ Control Group; patients implanted with a standard office counseling
- ◆ Active Group; Patients with extensive pre implant interview with detail explanation of the mechanism of action of neural stimulation
- ◆ At least 24 months duration each period of stimulation with different parameters
- ◆ Outcome measures as above

CONCLUSIONS

It is obvious that our understanding of mechanism of action of different forms of neural stimulation is very superficial and more clinical and animal studies are needed to better comprehend how neural stimulation works. It is unclear if this lack of knowledge translates into the inferior benefits to the patients.

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