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POST-STIMULATION INHIBITION OF BLADDER ACTIVITY INDUCED BY TIBIAL NERVE STIMULATION IN RATS

Hypothesis / aims of study

Percutaneous tibial nerve stimulation (TNS) has been used for the treatment of overactive bladder (OAB) symptoms. The efficacy of TNS is same as antimuscarinic drugs [1]. However, currently the possible mechanisms underlying tibial neuromodulation are not fully understood.

The purpose of this study is to develop an animal model for tibial neuromodulation and to investigate possible neural mechanisms underlying tibial neuromodulation.

Study design, materials and methods

Experiments were conducted in 29 female Sprague-Dawley rats under urethane anesthesia (1.2 g/kg). A catheter was placed into the bladder via the bladder dome to infuse the bladder with saline. A cuff electrode was placed around right tibial nerve for stimulation. In 24 rats, 3-5 cystometrogram (CMG)s were performed initially as control CMGs followed by one CMG with simultaneous application of TNS (5 Hz, 0.2 ms pulse width) at 2 to 4 times the threshold (T) intensity for inducing an observable toe movement. Then, the animals were divided into 2 groups. In the treated group (n=12), TNS (2-4T) was applied for 30 minutes with the bladder empty. In the control group (n=12), the animals with an empty bladder were rested for 30 minutes without stimulation although the electrode was placed on the tibial nerve. Following the 30 minute treatment, 5 CMGs were performed in about 1 hour period without stimulation to evaluate the post-stimulation effect. Bladder capacity (BC), voiding efficacy (VE), maximum voiding pressure (MVP), contraction duration (CD) and bladder compliance were measured from the CMGs. In 5 rats, electromyogram (EMG) was recorded during CMGs to investigate the effect of TNS on external urethral sphincter (EUS) activity. Two fine wire electrodes were inserted into EUS via perineum. The base-line and the maximal amplitude of EMG activity, bursting duration and frequency during micturition contraction were measured from the EMG recordings. For the repeated recordings, parameters were normalized to the measurement of first control CMG or EMG. The results are expressed as mean ± standard error (SE). Statistical significance ($P<0.05$) was detected by Student t-test or two-way ANOVA followed by Bonferroni multiple comparison.

Results

TNS applied during CMG had no effect on micturition reflex. However, 30 minute TNS induced significant post-stimulation effects including a 30-40% increase in BC (Figure 1) and a 20-30% increase in bladder compliance (Figure 2) during the 5 CMGs following the termination of TNS. There was no change in MVP, CD or VE during the following 5 CMGs. TNS did not induce significant changes of EUS EMG activity either during the stimulation or during the post-stimulation period.

Interpretation of results

Clinically a protocol of 30-minute TNS once per week for 12 consecutive weeks is used for treatment of OAB symptoms, suggesting a presence of post-stimulation inhibition of bladder activity. This study revealed that acutely applied TNS had no effect on bladder activity. However, TNS increased BC and bladder compliance after 30-minute stimulation. In a human study TNS is also reported to have no acute effect on CMG recordings [2]. Additionally, TNS did not change EUS activity in this study. It has been shown that low frequency electrical stimulation reduced afferent-induced excitatory postsynaptic potentials by 52% via N-methyl-D-aspartate and opioid receptors in rat spinal cord [3]. This suppression required 30 minutes to reach the maximal effect and lasted for more than 1 hour. Gradually appearing synaptic morphological and/or functional changes in the spinal cord is considered as the reason for the slow appearance of inhibition. Thus, it may be possible that synaptic interaction between tibial nerve and bladder sensory pathways occurs in the spinal level to induce the inhibitory effect on bladder activity. This interaction, which appears slowly and lasts for a long duration, may explain why 30-minute is required for TNS to induce the prolonged post-stimulation inhibition in this study. The tibial nerve and bladder pelvic nerve in rats are originated from L3–L5 and L6-S1 segments of spinal cord, respectively. Little is known about the intersectional interaction in the spinal cord on TNS inhibition in rats. Further study is needed to elucidate the site of action for TNS inhibition of bladder activity.

Concluding message

Our results suggest that TNS in rats has no acute effect but has significant post-stimulation inhibitory effect on micturition reflex. TNS has no effect on EUS activity. This animal model will be useful to further investigate the mechanisms underlying the tibial neuromodulation, including the sites of action and the neurotransmitters involved in TNS inhibition.

Figure 1. Changes in BC after 30-min TNS

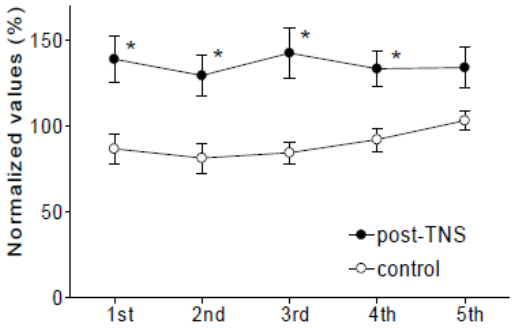
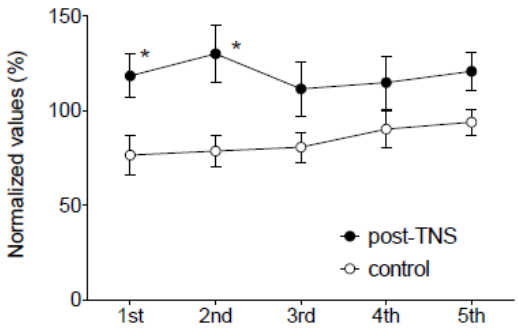


Figure 2. Changes in bladder compliance after 30-min TNS



Asterisk indicates significantly different from control group (determined by two-way ANOVA with post-hoc Bonferroni test).

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Disclosures

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