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INTERSTIM® THERAPY IN A RAT MODEL OF RHYTHMIC BLADDER CONTRACTION

Hypothesis / aims of study

Electrical stimulation of spinal nerves using Interstim® Therapy is a useful treatment in patients with overactive bladder. Using the model of rhythmic bladder contraction in rats, we have assessed this preclinical model for optimizing stimulation parameters and elucidating therapeutic mechanisms of spinal nerve stimulation.

Study design, materials and methods

In anesthetized female rats (urethane, i.p. 1.2g/kg), a wire electrode was placed under the L6 spinal nerves bilaterally and sealed with Kwik-Cast Sealant (WPI). A cannula was placed into the bladder via the urethra and the urethra was ligated to ensure an isovolumetric bladder. The urethral cannula was linked with a pressure transducer (ADI MLT844D), and the signal was amplified through a DC amplifier (ADI, ML228). Saline infusion (50 microliter per min followed by 10 microliter per min) induced rhythmic bladder contractions. In 8 rats, one jugular vein was cannulated with polyethylene tubing for intravenous administration of pancuronium before nerve stimulation. Total 32 rats were chronically treated with capsaicin (25 and 50 mg/kg at a 12-h interval on the 1st day and 50 mg/kg on the 2nd day; s.c.) or vehicle (10% ethanol and 10% Tween 80) 4 days prior to neurostimulation testing.

Results

Electrical stimulation of spinal nerves evoked hind-toe twitches and pelvic floor muscle contraction. Stimulation currents were adjusted for each animal as a function of motor threshold. Mean motor threshold was 0.18 ± 0.01 mA (n=62). Current was then decreased to a level at which the muscle contraction was just discernible in each animal. Stimulation using motor-threshold pulses (0.1 ms pulse width, 10 Hz, 10 minutes) slowly inhibited or decreased the frequency of rhythmic bladder contractions to a level that was 34 ± 11% (mean, SEM) of control (n=10, v.s. control, n=9, $p<0.05$, two-way ANOVA). Spinal nerve stimulation did not reduce the amplitude of bladder contractions. Stimulation at higher intensity (0.6 mA) caused a frequency-dependent attenuation of rhythmic bladder contractions; stimulation at 10 Hz completely abolished bladder contractions (n=7, $p<0.001$, two-way ANOVA). Inhibitory effects of high intensity spinal nerve stimulation (0.6 mA, 0.5 Hz) were not altered by pancuronium (1 mg/kg, i.v., 61 ± 14% of control, n=8, v.s. 39 ± 15% of control in 7 untreated rats). Finally in rats pretreated with capsaicin (125 mg/kg s.c.), high-intensity stimulation produced a stronger inhibition of bladder contraction frequency (18 ± 14% of control, n=6, v.s. 63 ± 17% of control in 7 vehicle pretreated rats, $p<0.05$, two-way ANOVA).

Interpretation of results

Consistent with clinical findings of sacral spinal nerve stimulation in humans, electrical stimulation of spinal nerves attenuated the frequency of urinary bladder contractions in the rat rhythmic contraction model. The optimal frequency of spinal nerve stimulation is 10 Hz. Inhibitory effects of high intensity stimulation were not via the stimulation-evoked skeleton muscle contraction since the degree of inhibition was not altered by pancuronium. However, higher intensity stimulation produced a stronger inhibition of rhythmic contractions in C-fiber desensitized rats, suggesting high intensity stimulation may have activated primary afferent C-fibers in vehicle pretreated rats, which may have attenuated the action of spinal nerve stimulation.

Concluding message

The rat rhythmic bladder model is useful for preclinical optimization of stimulation parameters and further elucidating the mechanism of action for spinal nerve stimulation. Exploring the differential effects of stimulation frequency and intensity is important for further understanding of neuromodulation for urinary bladder dysfunctions.

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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