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CHARACTERIZATION OF CURRENT INTENSITY OF BILATERAL VERSUS UNILATERAL NEUROMODULATION IN A RAT MODEL OF BLADDER RHYTHMIC CONTRACTION

Hypothesis / aims of study

InterStim® Therapy, usually uses unilateral electrical stimulation of the sacral spinal nerve (SN, S3), to relieve symptoms of urge incontinence, increased frequency and urinary retention. Using the rat bladder rhythmic contraction (BRC) model, we 1) compared the relative effectiveness of unilateral, sequential unilateral or bilateral neuromodulation by stimulating the L6 spinal nerve (SN), 2) evaluated whether inhibition of BRC requires precisely timed stimulation pulses (e.g. phase locking on each side of the SN), and 3) characterized the relationship between stimulus intensity- and inhibition of the bladder micturition reflex by bilateral neuromodulation.

Study design, materials and methods

In anesthetized female rats (urethane, i.p. 1.2g/kg), a bared portion wire electrode was placed under either one or both of the L6 SN roots. A cannula was placed into the bladder via the urethra and the urethra was ligated, resulting in an isovolumetric bladder preparation. The urethral cannula was linked with a pressure transducer and the signal was amplified through a DC amplifier. Saline infusion induced the BRC reflex. Effect of SN stimulation on the BRC was evaluated.

Results

There was no significant change in the isovolumetric bladder contractions during a 45 min recording when no electrical stimulation was applied (n=21). At motor threshold intensity (Tmot intensity, at which first visible motor contraction occurred, 0.14 ± 0.01 mA, n=253), unilateral stimulation of the left SN or sequential stimulation of each side of the SN at 5 min per side alternatively for a total of 10 min or 20 min produced mild or no reduction of the frequency of bladder contractions during electrical stimulation. Bilateral electrical stimulation of the SN significantly attenuated bladder contractions (figure 1A). During electric stimulation, unilateral, 10 min sequential, 20 min sequential and bilateral SN stimulation decreased the frequency of contractions to 82.04 ± 7% (n=15, p>0.05), 61.85 ± 18% (n=7, p>0.05), 64.90 ± 16% (n=11, p>0.05), and 26.30 ± 14% of controls (n=10, p<0.05, vs. 98.52 ± 5%, control), respectively. Inhibition of the contraction frequency to bilateral stimulation was stronger than unilateral stimulation (p<0.05). To examine whether the inhibition of BRC requires precisely pulse locking on each side of the SN, bilateral neuromodulation was testing using pulse match (no delay between stimulation of right and left SN) and pulse mismatch (50-ms delay). Ten Hz pulse match stimulation at 0.8*Tmot or 1*Tmot showed an equal degree of bladder inhibition as pulse mismatch (figure 1B), which produced inhibition of BRC to 74.33 ± 14% (p>0.05) and 28.24 ± 11% (p<0.05), and 71.54 ± 11% (p>0.05) and 15.62 ± 9% (p<0.05) of controls, respectively.

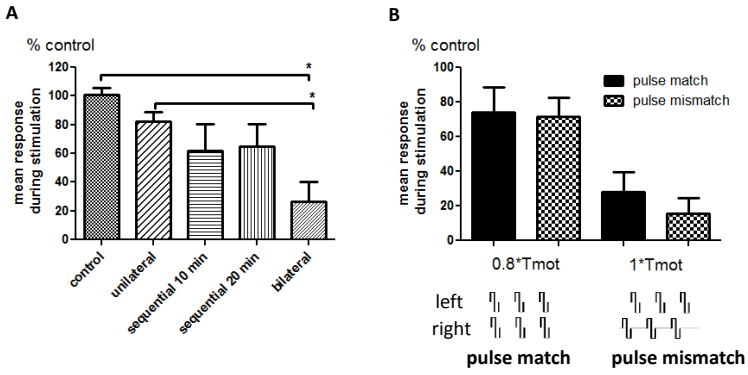

Figure 1. Effects of spinal nerve stimulation (10 Hz) on the frequency of the bladder rhythmic contraction during electric stimulation. Responses are represented as a percentage of control (%control). Tmot: motor threshold intensity. * p<0.05, student'st-test

Figure 2 summaries the frequency of BRC against the summation of total current intensity across the both sides of the SN to unilateral, balanced bilateral and unbalanced bilateral stimulations. The minimal effective intensities to attenuate bladder contractions were 2*Tmot unilateral stimulation, 1.6*Tmot bilateral stimulation (80% Tmot on each nerve) and 1.2*Tmot unbalanced bilateral stimulation (20% Tmot on one nerve and 100% on the other nerve), decreasing the frequency of the BRC to 53.21 ± 20% (n=12), 67 ± 14% (n=9), and 50 ± 16% of controls (n=7) during stimulation, respectively.

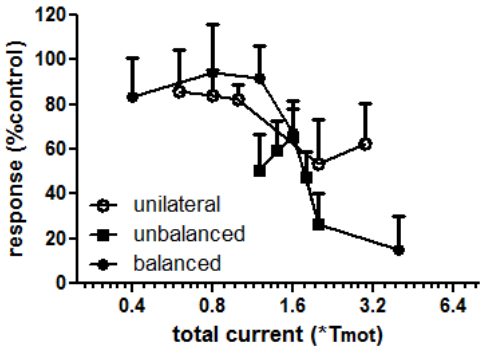

Figure 2. Intensity-dependent effects of spinal nerve stimulation on frequency of isovolumetric bladder contractions. The response of contraction frequency is the mean value as a percentage of control (%control) during stimulation. Total current is the summation of current intensity to both sides of the spinal nerve. Tmot: motor threshold intensity.

Interpretation of results

Bilateral stimulation was more effective in attenuating bladder contractions and the effective thresholds were 0.8*Tmot on each nerve (balanced stimulation), or 0.2*Tmot on one side SN and Tmot at the other side SN (unbalanced stimulation). Unilateral stimulation was less efficacious and the effective threshold was 2*Tmot. Unilateral left and right, sequential stimulation of both spinal nerves (e.g. 5 min per side alternatively for a total of 10 min or 20 min), a temporal summation manner, did not attenuate bladder contraction frequency. Therefore, spatial summation of simultaneous stimulation of both nerve roots even at subthreshold intensities may be effective in neuromodulation of bladder function. The inhibition of BRC does not require precisely pulse locking on each side of the SN.

Based on our data, in terms of bladder inhibition, unilateral sacral neuromodulation can be applied only at suboptimal stimulation parameters while bilateral stimulation can achieve effective bladder inhibition at intensities below the muscle twitch threshold using either equal (balanced) or unequal (unbalanced) intensities of bilateral SN stimulation.

Concluding message

Current InterStim® Therapy by unilateral neuromodulation might only achieve suboptimal efficacy in some patients because uncomfortable skeletal muscle contraction limits stimulation at optimal inhibitory intensities. The increased bladder quieting response to a given intensity of bilateral stimulation may allow increased therapeutic efficacy within a side-effect-limited therapy “window” (normally restricted by therapy threshold at the lower level and patients motor or sensation side effects at the upper). Lower intensity therapy may allow reductions of side effects such as patient sensation or unwanted muscle contractions.

Disclosures

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