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DESENSITIZATION OF THE BLADDER INHIBITORY RESPONSE TO TIBIAL NERVE NEUROMODULATION IN THE RAT

Hypothesis / aims of study

Tibial nerve (TN) stimulation is less effective and has a shorter duration of response relative to that produced by spinal nerve stimulation (1). We report on a further characterization of time course of the bladder inhibitory response to sustained TN stimulation and recovery from apparent desensitization to repeated stimulation in the rat model of bladder rhythmic contraction (BRC).

Study design, materials and methods

In anesthetized female rats (urethane, i.p. 1.2g/kg), stainless steel wires were placed independently under each TN. A cannula was placed into the bladder via the urethra and the urethra was ligated to ensure an isovolumetric bladder. Saline infusion induced the BRC. To evaluate the time course of the bladder inhibitory response, electrical stimulation at a fixed frequency of 10 Hz (pulse-width 0.1 ms), which has been shown to be optimal for inhibition of bladder contractions by both low and high intensity stimulation (1), was applied for 15 min continuously or for 5 min twice with variable length of 5-20 min intervals without stimulation inserted. Frequency/interval of the BRC was analysed to evaluate effects of TN stimulation on bladder contractions.

Results

The threshold current (T_{mot}) at which first visible motor contraction occurred to TN stimulation was 0.18 ± 0.01 mA (n=156). Figure 1A shows typical results of bilateral electrical stimulation of the TN on BRC ($3xT_{mot}$, 10 Hz, 15 min). The reduction in bladder activity occurred rapidly following the onset of the electrical stimulation. On the other hand, contractions began to re-appear well before the 15 min stimulation was terminated. Data in figure 1B and 1C demonstrate that TN stimulation inhibited the BRC frequency in a similar manner for both unilateral and bilateral stimulation. If stimulation was applied continuously for 15 min, the contraction frequency returned to pre-stimulation values prior to the termination of stimulation. By 10 min, the frequency was not significantly different from controls even in the presence of continued stimulation (Figure 1B). When tested across a range of stimulation intensities, TNS induced a brief, significant inhibition for the initial 5 min of time (the maximum inhibition attained was 54.69 ± 13% control, figure 1C), but the response grew smaller with duration of stimulation.

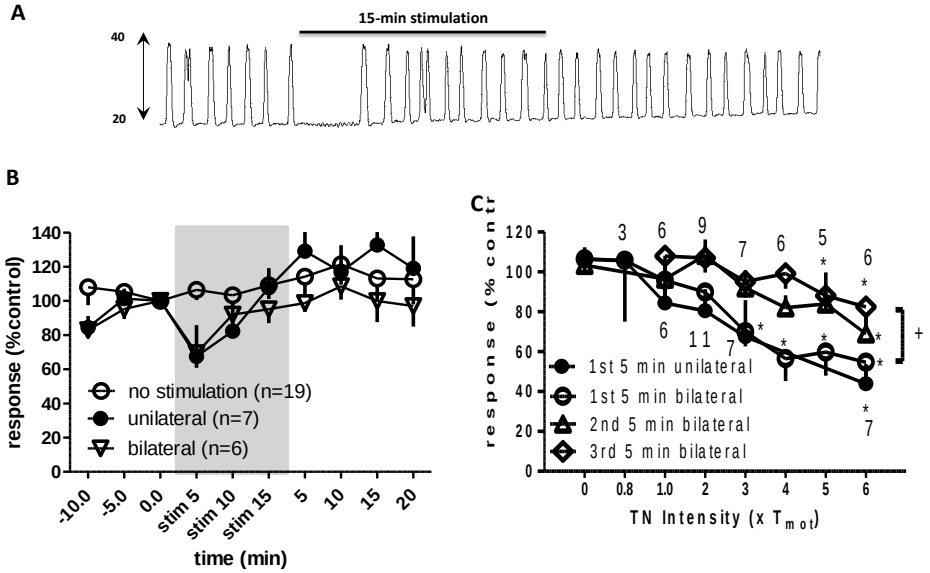

Figure 1. Time course of bladder inhibitory response to sustained 15 min tibial nerve stimulation on the frequency of bladder rhythmic contractions (% control). **A.** Typical record showing bladder contractions (mmHg) to 15 min bilateral stimulation ($3xT_{mot}$) at the time indicated. **B.** Time course of bladder inhibitory responses to unilateral and bilateral stimulation ($3xT_{mot}$). **C.** Intensity-dependent effects of three segments of sustained tibial stimulation. The number of animals is indicated either under (unilateral) or over (bilateral) each symbol. * p<0.05, stimulation vs. control; +, p<0.05, 1st 5 min vs. 3rd 5 min, Student's t-test.

We also quantified the responsiveness to 5 min stimulation at variable durations following an initial stimulus. Data in figure 2 illustrate that for an interval of 10 min the inhibitory response to a second stimulation was suppressed or totally abolished. By 15 min following the initial stimulus the responsiveness returned to near normal (figure 2B). Summary data (figure 2C) demonstrate that responsiveness to the 2nd stimulation is significantly reduced for following the 1st 5 min stimulation (n=16, * p<0.05, repeated measures ANOVA, Bonferroni post test). At 5 min following the initial stimulation a second tibial stimulation produced no inhibition of bladder contraction. However by 20 min following a prior stimulation a second stimulation produced near normal inhibition (22.76 ± 9%, n=10, vs. -5.98 ± 12% control, n=16, 5 min interval, p=0.08, unpaired t-test).

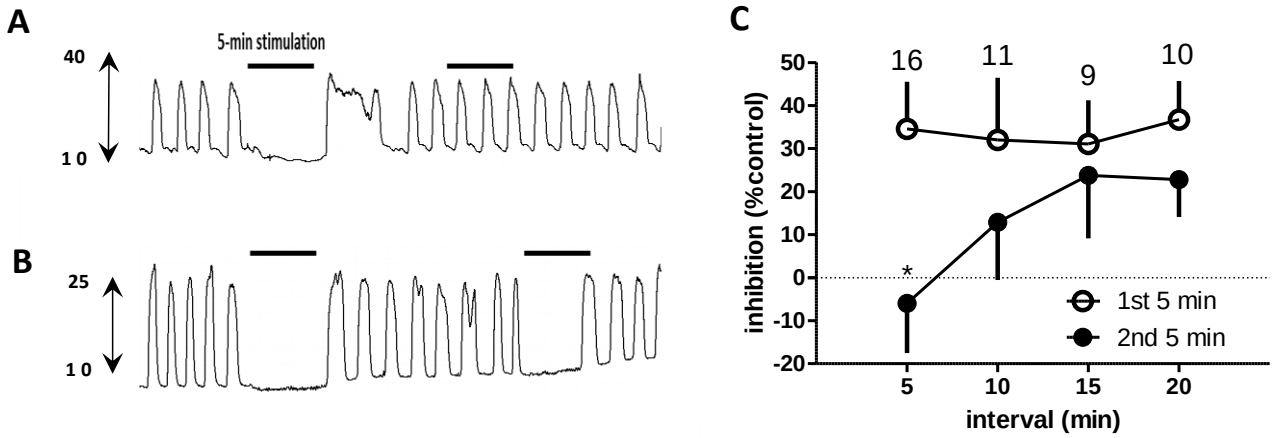

Figure 2. Reduced response of bladder inhibition following a prior stimulation and recovery from desensitization with time. **A** and **B**, Typical experimental recordings showing the bladder rhythmic contraction (mmHg) to two 5 min stimulations separated by 10 and 15 min respectively ($3xT_{mot}$). **C**. Recovery of responsiveness with time following an initial stimulation (% control). * $p<0.05$, repeated measures ANOVA, Bonferroni post test. The number of animals is indicated over each symbol.

Interpretation of results

Different from spinal nerve stimulation (2), in this model we find that the duration of the bladder inhibition to TN stimulation is short lasting relative to the stimulation duration. Additionally the reduced responsiveness that occurs during sustained stimulation is likely also seen following a previous stimulation. These time course data demonstrate an apparent desensitization of the response to continuous TN stimulation. These results may be a consequence of the more rapid stimulation induced desensitization to TN relative to spinal nerve stimulation.

Concluding message

Based on this rat model, the desensitization of inhibitory bladder appears during continuous TN neuromodulation and also following a prior stimulation. These results prompt further investigation and a potential area for improvement of TN stimulation for the treatment of patients with urinary bladder dysfunction.

References

1. Su X, Nickles A, Nelson DE. Comparison of neural targets for neuromodulation of bladder micturition reflex in the rat. Am J Physiol Renal Physiol, 303:F1196-F1206, 2012.
2. Su X, Nickles A, Nelson DE. Neuromodulation in a rat model of bladder micturition reflex. American Journal of Physiology-Renal Physiology, 302: F477-F486, 2012.

Disclosures

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