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EVALUATION OF PULSE WIDTH OF SPINAL NERVE STIMULATION IN A RAT MODEL OF BLADDER MICTURITION REFLEX

Hypothesis / aims of study

The optimal stimulation frequency and intensity of neuromodulation have been identified for spinal nerve stimulation (SNS) induced inhibition of the bladder rhythmic contraction (BRC) in the rat under isovolumetric conditions1 (1). In this study, the SNS evoked motor threshold (T_{mot}) response across different pulse widths (PWs) was first explored. A subset of selected stimulation PWs at T_{mot} intensity were then further tested on the BRC.

Study design, materials and methods

Wire electrodes were placed bilaterally under each of the L6 spinal nerves in anesthetized female rats (urethane, i.p. 1.2g/kg). A cannula was placed into the bladder via the urethra, and the urethra was ligated to ensure an isovolumetric bladder. Saline infusion was used to induce BRC. The T_{mot} was plotted against PW to elucidate the effect of PW on motor function. The rheobase (the minimal intensity of infinite PW) and chronaxie (the minimum PW required for an intensity double the rheobase) were calculated according to the equation Y=(Y0-NS)*exp(-K*X) + NS, where Y is T_{mot} response, X is PW, and Y0, the maximal vale is T_{mot} value when PW is close to 0. NS is the rheobase. K is the rate constant in inverse units of PW. The half-life (chronaxie) equals the ln2 divided by K (2). For effect of PW on BRC, 10 Hz, T_{mot} intensities of nerve stimulation was applied for 10 min at a given PW.

Results

Plotting T_{mot} current intensities against corresponding stimulation PWs (Figures 1A) illustrates that the T_{mot}s are lower as the pulse widths are increased. The monoexponential nonlinear regression analysis gives chronaxie of 0.04 ± 0.002 ms. The rheobase values were 0.12 ± 0.02 mA. The maximal values (Y0) were 0.71 ± 0.13 mA. The T_{mot}s to shorter PW stimulation of 0.02 ms, 0.03 ms or 0.06 ms are significantly higher in comparison to each of tested longer PWs (e.g. PW = or > 0.18 ms, one-way ANOVA, $p<0.05$). Figure 1B summarized the activation charge threshold (T_{mot}, nC) to different PW stimulation. One-way ANOVA analysis demonstrates significantly lower charge values to shorter PWs of 0.02 ms, 0.03 ms or 0.06 ms in comparison to each of tested longer PWs (e.g. PW = or > 0.15 ms, $p<0.05$). Statistical differences are also obtained for comparisons between other pairs, 0.09 ms vs = or > 0.21 ms, 0.12 ms vs = or >0.27 ms, 0.15 ms vs 0.3 ms, and 0.18 ms vs 0.3 ms.

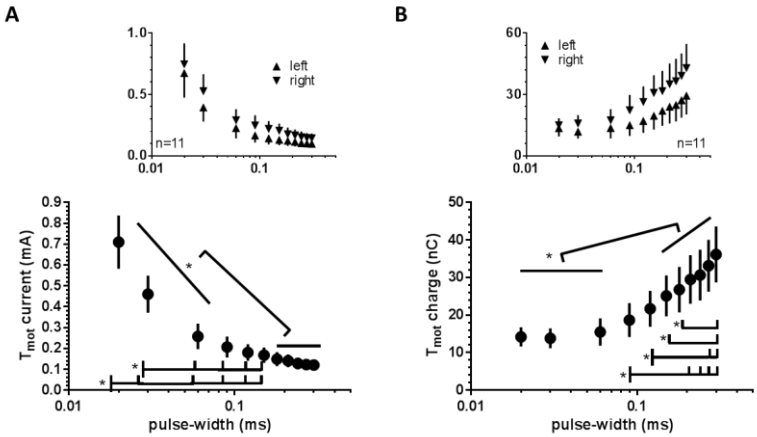

Figure 1. Summary data of visual motor threshold (T_{mot}) responses to graded pulse width of bilateral spinal nerve stimulation. **A.** Stimulation current intensity at T_{mot} (mA). B. Stimulation charges at the T_{mot} (current*pulse-width, nC). Inset illustrates the T_{mot} on the two sides of the spinal nerve which are independently expressed. * $p<0.05$, ANOVA Bonferroni post test.

Among tested PWs of 0.03 ms (stimulation charge: 3.27 ± 0.70 nC), 0.06 ms (6 ± 1.31 nC), 0.09 ms (16.88 ± 2.64 nC), 0.12 ms (14.9 ± 4.14 nC), and 0.21 ms (34.34 ± 5.90 nC), all produced statically significant inhibition on bladder contractions. The amplitudes of inhibitory effects (changes between pre-stim and during stim) were not different among PWs tested ($p>0.05$, one-way ANOVA, Figure 2). SNS at 0.03 ms, 0.06 ms and 0.09 ms decreased bladder contraction frequencies from 103 ± 3%, 100 ±

4%, and 103 ± 4% of controls, to 52 ± 16% (n=8, p=0.02, paired t test), 56 ± 15% (n=11, p=0.02) and 40 ± 19% (n=10, p=0.01), respectively.

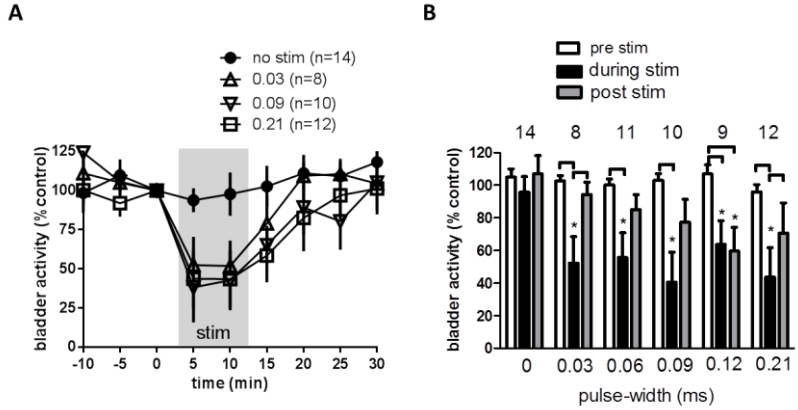

Figure 2: Effects of spinal nerve stimulation at different pulse widths (motor threshold, 10 Hz) on the frequency of the bladder reflex contraction. Responses are represented as a percentage of control (% control), where the baseline response before stimulation is defined as 100%. **A.** Time course response of frequency of the bladder reflex contraction to spinal nerve stimulation at pulse widths of 0.03 ms, 0.09 ms and 0.21 ms. The shaded areas is during 10 min stimulation (stim). The significance of differences between no stimulation (no stim) and to 0.09 ms (5 min and 10 min time points), and 0.21 ms (10 min time point) stimulation was demonstrated by ANOVA Bonferroni post test. **B.** Mean responses of 10 min contraction frequency under three conditions before (pre stim), during and post stimulation. The significance of differences was demonstrated by Student's t test. * $p<0.05$. The trial numbers are indicated over each bar set.

Interpretation of results

The chronaxie of L6 spinal nerve activation in the anesthetized rat is about 0.04 ms, much shorter than 0.1 - 0.21 ms typically used in previous preclinical and clinical studies. Interestingly, at fixed 10 Hz, T_{mot} intensity, shorter PWs SNS are equally effective in attenuation of the frequency of bladder contractions as the longer PWs.

Based on T_{mot} and PW response curve, short PWs correlate significantly to higher current intensity and lower charge values in comparison to longer PWs. Setting the stimulation intensity close to the chronaxie may allow that shorter PWs reduce the stimulation charge without sacrificing therapeutic effect. PW also affects the relative selectivity of stimulation among different types of nerve fibers (diameter). Preferential activation of large nerve fibers over small fibers can be more pronounced with a shorter PW stimulation (3). This pronounced ability to selectively stimulate certain fibers may lead to increased efficacy and reduced unwanted side-effects in clinical practice.

The current data show that the inhibitory effects of SNS on bladder contractions was equivalent across all PWs tested (T_{mot}), and the magnitude of the inhibition (40% to 60% inhibition) reported in this study is similar to other reports using the same intensity, T_{mot} stimulation at a fixed PW of 0.10 ms (1).

Concluding message

We have reported the chronaxie (0.04 ms) of SNS evoked motor response and demonstrated equally effective BRC inhibitory effects between short and long PWs of SNS in a preclinical model. Two advantages associated with shorter PWs in neuromodulation therapy are a potential decrease in battery-referred current consumption which subsequently, enhances device longevity, and a possibility to optimize treatment outcomes. For example, reduced discomfort with short PW nerve stimulation would allow a relatively higher therapy intensity that might enhance efficacy. Our initial work in this study should be confirmed in patients with neuropathological conditions, focusing directly upon the energy consumption, stimulus-induced sensations and clinical effectiveness of sacral neuromodulation with different pulses.

References

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Disclosures

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