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EXPANDING TRANSLATIONAL VALUE OF IN VIVO PRECLINICAL MODELS IN NEUROMODULATION OF BLADDER CONTROL: STIMULATION PARAMETER OPTIMIZATION

Hypothesis / aims of study

Exploratory testing in cats and dogs established early evidence for the use of sacral neuromodulation (SNM) for detrusor overactivity (1). However translational value of preclinical models has not been fully evaluated and the optimal stimulation of SNM therapy has not been studied in detail. Only recently have significant advances been made for acute parameter optimization in the rat isovolumetric bladder contraction model. Results from this work suggest similar stimulation parameters optimally attenuate bladder contractions in both rodent testing and in human clinical use (2, 3). In this study we link the work of isovolumetric bladder contraction model with cystometric quantification in acute anesthetized rats as well as in conscious unanesthetized sheep. The hypothesis tested in this study was that stimulation parameters differentially modify bladder capacity in the rat model of acetic-acid induced cystitis as well as in normal conscious sheep.

Study design, materials and methods

Rodent cystometry: Male rats (n=9) were anesthetized (urethane, IP 1.2 g/Kg) and cannulated with a bladder catheter which was placed via the bladder dome for 0.3% acetic acid infusion (3 ml/hr) and intravesical pressure monitoring. Two teflon-coated stainless steel electrodes were placed bilaterally under each of the L6 spinal nerve and current stimulation was controlled independently by two Grass stimulators. Five parameters (1 Hz, 10 Hz, and 50 Hz at motor threshold intensity, T_{mot}, or 10 Hz at $0.5xT_{mot}$ and $2xT_{mot}$) at 0.1 ms pulse-width were tested during one urinary void cycle in every two voids randomly; the same tests were repeated 2-3 times to get a mean response.

Sheep cystometry: Female sheep (n=4) were surgically instrumented bilaterally with InterStim II devices and leads in the sacral foramina (S2 or S3) under anaesthesia and allowed to recover for 2 wk before cystometry. In conscious, sling-restricted sheep, a bladder catheter was inserted through the urethra for saline infusion (30 ml/min). Ten void cycles were performed weekly. SNM (10 Hz, 0.21 ms pulse-width) was applied at T_{mot} or maximum tolerable (T_{Max}) intensity. SNM was delivered during the 4^{th}-5^{th}, 2 bladder voids or 4^{th}-10^{th}, 7 voids.

Results

In rats with intravesical acetic acid infusion (3 ml/hr), the average bladder inter-contraction interval (ICI) was 142.7 ± 25 seconds. Ten Hz stimulation at T_{mot} (0.26 ± 0.04 mA, n=18, right and left nerves in 9 rats) significantly increased the ICI (vs No Stim), but 1 Hz and 50 Hz stimulations were ineffective (Fig 1). The increased ICI is current intensity dependent. $0.5xT_{mot}$, T_{mot}, and $2xT_{mot}$ changed the ICI to 119.6±9 (p>0.05), 148.7±16 (p<0.05), and 192.6±27% of controls (p<0.05, vs 101.3±7%, No Stim).

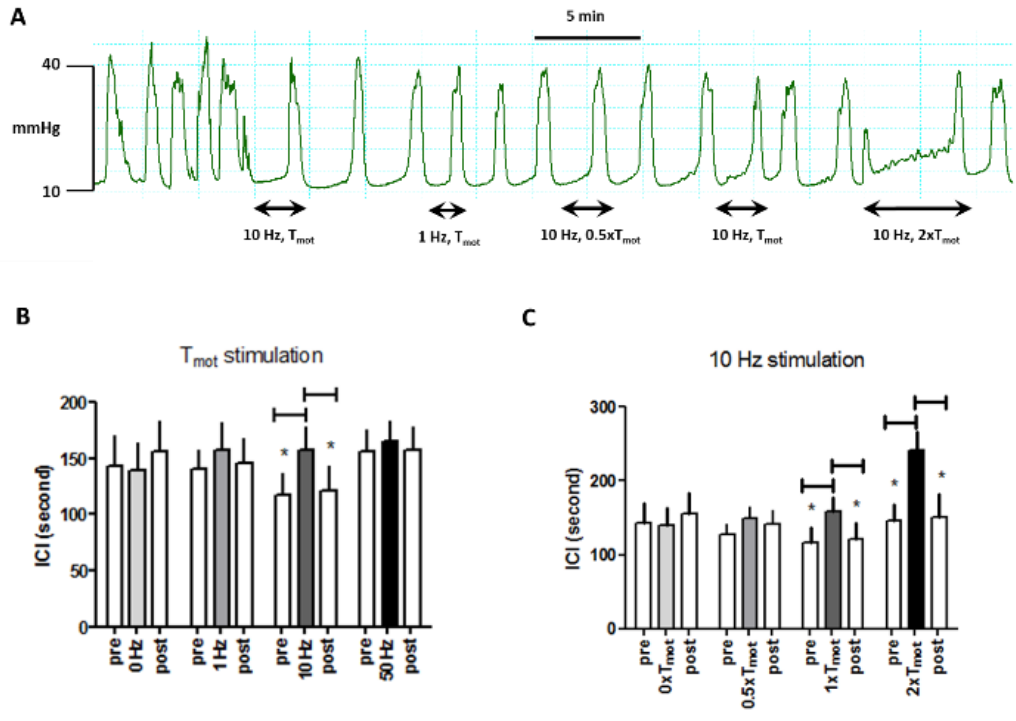
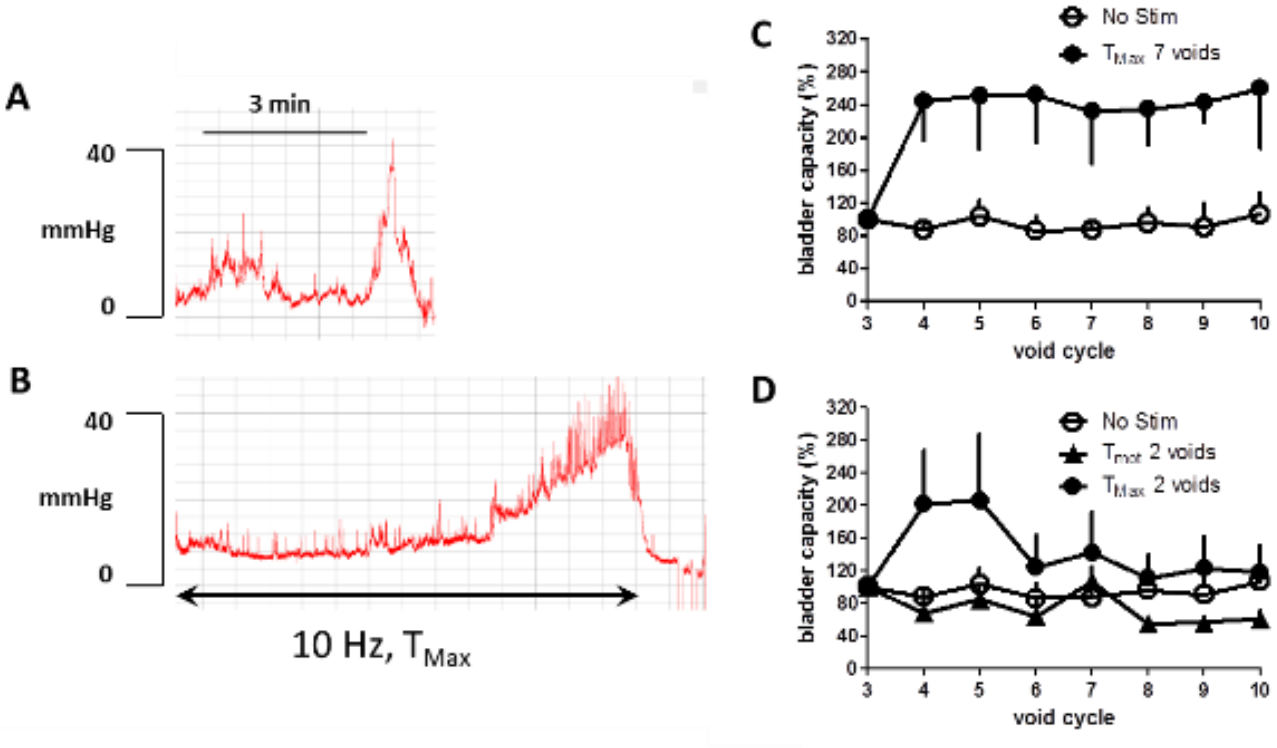


Fig 1. Cystometric effects of L6 spinal nerve stimulation in rats. **A.** Typical records of intravesical pressure showing one series of stimulation parameter tests (5 shown). **B & C.** Frequency and intensity-dependent effects. *P < 0.05, Student's t test.

In conscious sheep with intravesical saline infusion, the average bladder capacity was 144.9 ± 24 ml (n=4). There was no significant change in bladder capacity if electrical stimulation was not applied. T_{Max} (2.01 ± 0.44 V, n=8 in 4 sheep) SNM for 7 voids significantly increased bladder capacity to 245 ± 40% of control (vs 94±16%, No Stim, p=0.02, Fig 2C). Capacity during stimulation at T_{mot} (1.55 ± 0.35 V) and T_{Max} (2.23 ± 0.54 V) for 2 trials changed to 76 ± 1% (p=0.20) and 204 ± 60% of controls (vs 96±11%, No Stim,



p=0.18, Fig 2D), respectively.

Fig 2. Cystometric effects of SNM in sheep. **A & B.** Typical intravesical pressure recording prior to (A, 103 ml bladder capacity) and with 10 Hz stimulation at T_{Max} (B, 260 ml bladder capacity). **C & D.** Acute SNM applied for 7 (C, stimulation during 4th-10th, 7 voids) or 2 (D, stimulation during 4th-5th, 2 voids) bladder voids on bladder capacity. Responses are represented as a percentage of control (% control).

<u>Interpretation of results</u>

Neurostimulation induced cystometric increases in bladder capacity in both the rat acetic acid model and unanethetised sheep. (Fig 3). In rats the maximal increases in bladder capacity were observed using 10 Hz stimulation with larger effects seen at higher amplitudes. This frequency dependence is consistent with SNM therapy results observed clinically; 14 Hz (vs 5.2 Hz) in patients with overactive bladder syndrome (3). The same stimulation parameter dependency across these models strongly demonstrates the specific therapeutic action of neuromodulation in preclinical settings, suggesting those models are useful translational tools in the acute test of neuromodulation for the treatment of bladder dysfunction.