

Fan Zhang^{1,2}, Abhijith D. Mally¹, P. Dafe Ogagan¹, Bing Shen¹, Jicheng Wang¹, James R. Roppolo³, William C. de Groat³, and Changfeng Tai¹

1. Department of Urology, University of Pittsburgh, Pittsburgh, Pennsylvania 2. Department of Urology, China Rehabilitation Research Center, School of Rehabilitation Medicine, Capital Medical University, Beijing, China 3. Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, Pennsylvania

INHIBITION OF BLADDER OVERACTIVITY BY COMBINATION OF TIBIAL NEUROMODULATION AND TRAMADOL TREATMENT IN CATS

Hypothesis / aims of study

To determine if a low dose (i.e., less adverse effect) of tramadol can significantly enhance the inhibitory effect of tibial neuromodulation on bladder overactivity in cats.

Study design, materials and methods

Total 17 cats were used under α -chloralose anesthesia. Bladder overactivity was induced by 0.25% acetic acid (AA) irritation during repeated cystometrograms (CMGs). Tibial nerve stimulation (TNS) of 5 Hz frequency at 2-4 times the threshold intensity for inducing observable toe movement was applied during CMG to inhibit bladder overactivity. Tramadol (0.3-7 mg/kg, i.v.) was used to enhance the TNS inhibition.

Results

AA irritation significantly ($P < 0.0001$) reduced bladder capacity to $24.8 \pm 3.3\%$ of the capacity measured during saline infusion. TNS without tramadol inhibited the bladder overactivity and significantly ($P < 0.01$) increased the bladder capacity to 50-60 % of the saline control capacity. Tramadol (7 mg/kg) without TNS could also significantly ($P < 0.01$) increase the bladder capacity to about 60% of the saline control capacity. However, at a lower dose of tramadol (1-3 mg/kg) a full recovery of bladder capacity to saline control was achieved when TNS was also applied during the CMG (fig.1).

Interpretation of results

This pre-clinical study has shown that TNS in combination with a low dose of tramadol (1-3 mg/kg) can fully restore the small capacity of the irritated bladder to the saline control level. It also induces post-stimulation inhibition with 3-7 mg/kg tramadol lasting more than 1.5-2 hours (fig.2). These results indicate a potential new strategy for OAB treatment by combining TNS with a low dose of tramadol.

Concluding message

The results suggest a novel treatment strategy for OAB by combining tibial neuromodulation with a low dose of tramadol. This combined treatment strategy is minimally invasive with potentially high efficacy and less adverse effect.

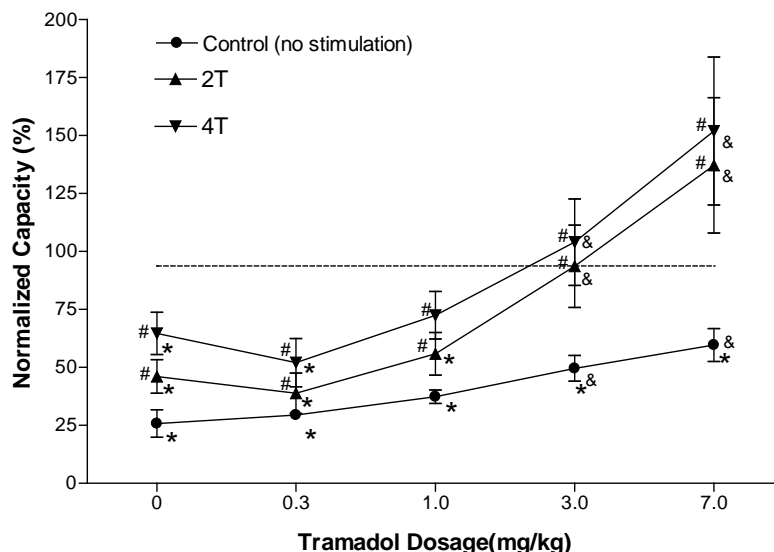


Figure 1. Inhibition of bladder overactivity by combination of TNS and tramadol treatment. Data for control (no stimulation) are obtained from another 6 cats with no TNS applied between each dose of tramadol. & indicates significantly different from the bladder capacity measured before tramadol treatment (i.e. at 0 mg/kg) under different conditions [control (before stimulation), 2T, 4T, or control (no stimulation)]. * indicates significantly different from the saline control capacity (indicated by the dashed line). # indicates significantly different from the control (no stimulation) at different tramadol dosage. Stimulation: 0.2 ms pulse width, T = 0.35-4.5 V.

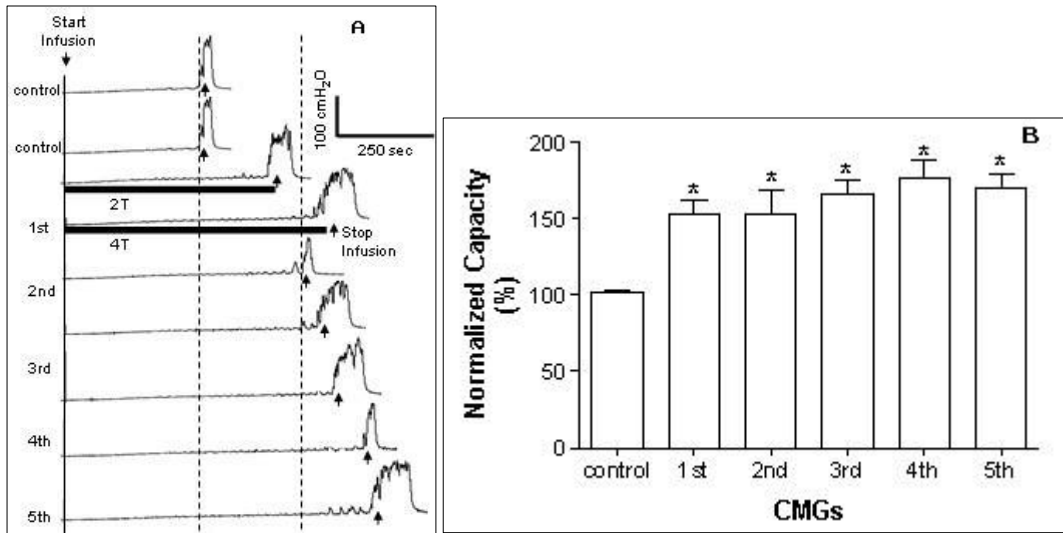


Figure 2. Post-stimulation inhibition of AA-induced bladder overactivity .A. Repeated CMG traces showing that after 7 mg/kg tramadol the increased bladder capacity by 2T and 4T TNS ($T = 0.35$ V) was maintained in the following 5 consecutive CMGs. B. Summarized results showing a significant (*) increase in bladder capacity during the 5 CMGs that lasted for about 1.5-2 hours. Stimulation: 0.2 ms pulse width, $T = 0.35$ -1.2 V. $N = 6$ cats.

References

1. Pandita RK, Pehrson R, Christoph T, Friderichs E, Andersson KE. Actions of tramadol on micturition in awake, freely moving rats. *Br J Pharmacol* 2003; 139: 741-8.
2. Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of idiopathic detrusor overactivity: a double-blind, placebo-controlled, randomized study. *Br J Clin Pharmacol* 2006; 61(4): 456-63.
3. Tai C, Chen M, Shen B, Wang J, Roppolo JR, de Groat WC. Irritation induced bladder overactivity is suppressed by tibial nerve stimulation in cats. *J Urol* 2011; 186(1): 326-30.

Disclosures

Funding: no **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Cat **Ethics Committee:** the ethics committee of University of Pittsburgh