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Frequency Dependent Tibial Neuromodulation of Bladder Underactivity and Overactivity in Cats

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Abstract

Objectives—This study is aimed at determining if tibial nerve stimulation (TNS) can modulate both bladder underactivity and overactivity.

Methods—In a-chloralose anesthetized cats, tripolar cuff electrodes were implanted on both tibial nerves and TNS threshold (T) for inducing toe twitching was determined for each nerve. Normal bladder activity was elicited by slow intravesical infusion of saline; while bladder overactivity was induced by infusion of 0.25% acetic acid to irritate the bladder. Bladder underactivity was induced during saline infusion by repeated application (2–6 times) of 30-minute TNS (5 Hz, 4–8T, 0.2 ms) to the left tibial nerve, while TNS (1 Hz, 4T, 0.2 ms) was applied to the right tibial nerve to reverse the bladder underactivity.

Results—Prolonged 5-Hz TNS induced bladder underactivity by significantly increasing bladder capacity to $173.8 \pm 10.4\%$ of control and reducing the contraction amplitude to $40.1 \pm 15.3\%$ of control, while 1-Hz TNS normalized the contraction amplitude and significantly reduced the bladder capacity to 130–140% of control. 1-Hz TNS in normal bladders did not change contraction amplitude and only slightly changed the capacity, but in both normal and underactive bladders significantly increased contraction duration. The effects of 1-Hz TNS did not persist following stimulation. Under isovolumetric conditions when the bladder was underactive, TNS

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Authorship Statement:

All authors designed and conducted the study, including data collection and data analysis. All authors prepared the manuscript draft and approved the final manuscript. All authors had complete access to the study data.

Disclosures

Dr. Tai is the inventor of a patent application related to this study. The remaining authors have no conflicts of interest to disclose.

(0.5–3 Hz; 1–4T) induced large amplitude and sustained bladder contractions. In overactive bladders, TNS during cystometry inhibited bladder overactivity at 5 Hz but not at 1 Hz.

Conclusions—This study indicates that TNS at different frequencies might be used to treat bladder underactivity and overactivity.

Keywords

Tibial; Neuromodulation; Bladder; Underactivity; Cat

Introduction

Tibial neuromodulation is a FDA-approved therapy to treat overactive bladder symptoms (OAB). The efficacy of tibial neuromodulation in treating OAB has been demonstrated in large clinical trials [1,2]. Sacral neuromodulation is another FDA-approved therapy that can treat not only OAB but also non-obstructive urinary retention (NOUR) [3,4]. NOUR is one of the characteristics of underactive bladder (UAB) - a symptom complex consisting of prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream [5]. Currently, tibial neuromodulation is used to treat OAB; but because sacral neuromodulation can treat both OAB and UAB, it becomes logical to ask if tibial neuromodulation can also treat UAB.

The prevalence of UAB is about 25–40% in elderly population [6,7] and as many as 45% of elderly people show detrusor underactivity during urological evaluation [8,9]. Currently, there is no medication approved by FDA for the treatment of UAB [10,11]. It is a great challenge for clinicians to treat UAB leaving many patients untreated. When urinary retention occurs, intermittent self-catheterization is used to drain the bladder [5,12]. In comparison to the extensive literature dealing with OAB, relatively few basic research studies have focused on UAB despite the significant clinical need for new UAB treatments.

Our recent preclinical animal studies in cats discovered that electrical stimulation of superficial peroneal nerve or saphenous nerve at 1 Hz can trigger an excitatory reflex to bladder and treat bladder underactivity produced by prolonged tibial nerve stimulation (TNS) at 5 Hz [13,14]. These findings raise the possibility that 1 Hz TNS may also be able to reverse the bladder underactivity produced by 5 Hz TNS. If this reversal occurs in animals, then tibial neuromodulation might be used clinically at different stimulation frequencies to treat either UAB or OAB. To test this hypothesis in the current study, prolonged TNS at 5 Hz was used to produce an UAB condition during saline distention of the bladder in anesthetized cats; and then TNS at 1 Hz was applied to reverse the UAB activity. In addition, the effects of 1 Hz and 5 Hz TNS were also examined during bladder overactivity induced by acetic acid irritation of the bladder. The results suggest that tibial neuromodulation could be useful in the treatment of not only OAB but also UAB.

Materials and Methods

The protocol and animal use in this study were approved by the Animal Care and Use Committee at the University of Pittsburgh.

Experimental setup

A total of 10 cats (5 male and 5 female, 2.6–4.2 kg; Liberty Research, Waverly, NY) were used in this study. The animals were anesthetized with isoflurane (2–5% in oxygen) during surgery and then switched to α -chloralose anesthesia (initial 65 mg/kg intravenous and supplemented as needed) during data collection. Left cephalic vein was catheterized for administration of anesthetics and fluid. A tracheotomy was performed and a tube was inserted to keep the airway patent. A catheter was inserted into right carotid artery to monitor systemic blood pressure. Heart rate and blood oxygen were monitored by a pulse oximeter (9847V; NONIN Medical, Plymouth, MN) attached to the tongue. Through an abdominal incision, the ureters were isolated, tied, and cut for external drainage. A double lumen catheter was inserted into the bladder via a small cut in the proximal urethra and secured by a ligature around the urethra. One lumen of the catheter was connected to a pump to slowly infuse (1–2 ml/min) the bladder with saline or 0.25% acetic acid (AA). The other lumen was connected to a pressure transducer to measure the pressure change in the bladder.

The tibial nerves were exposed at the left and right ankles. Tripolar cuff electrodes (NC223pt, MicroProbe, Gaithersburg, MD) were implanted on each tibial nerve for stimulation. Each cuff electrode was connected to an electrical stimulator (S88; Grass Medical Instruments, Quincy, MA) via a constant voltage stimulus isolator (SIU5; Grass Medical Instruments). The temperature of the animal was maintained at 36–38°C using a heating pad during the experiments. The surgical incisions including the skin and muscle layers were closed with sutures.

Stimulation protocol

Uniphasic rectangular pulses (0.2 ms pulse width) were delivered via the cuff electrodes. At the beginning of the experiment, the intensity threshold (T) for inducing observable toe movement was determined by gradually increasing stimulation intensity at 1 Hz on the right tibial nerve and 5 Hz on the left tibial nerve. Multiples of the threshold intensity were then used during the experiment. The left tibial nerve was only stimulated at 5 Hz. The right tibial nerve was always stimulated at 1 Hz except when different stimulation frequencies (0.5–30 Hz) were applied to examine frequency response relationships.

At the beginning of the study, repeated cystometrograms (CMGs) were performed by slowly infusing the bladder with saline to determine bladder capacity which was defined as the volume required to induce a reflex bladder contraction of large amplitude (>30 cmH₂O) and long duration (>20 seconds). Once bladder capacity stabilized, an additional 2 CMGs were performed during TNS (1 Hz, 0.2 ms, 4T intensity) applied on the right side (N=9 cats). For the first CMG, TNS was applied intermittently (60 second off and 30 second on) starting at the beginning of the CMG and ending with the onset of the micturition reflex at which time the stimulation was switched to continuous stimulation that continued for the duration of the micturition contraction. This stimulation pattern (intermittent-continuous) is termed TNSi-c in this study (see Fig. 1). For the second CMG, continuous TNS (TNSc) was applied at the beginning and maintained until the end of the CMG. The purpose of testing TNSi-c was to determine if prolonged TNSc during the storage phase produces fatigue and therefore has less effect on bladder capacity than TNSi-c which might be expected to produce less fatigue.

Following the two CMGs with TNS, another control CMG was performed without TNS to determine any post-stimulation effect. During the repeated CMG tests, a 2–3 minute resting period was always inserted between the CMGs.

After testing the TNS in normal bladders, the effect of 1 Hz TNS on bladder underactivity was further examined (N=8 cats). The animal's bladders were made areflexic or poorly reflexic by repeated application (2–6 times) of 30-minute TNS (5 Hz, 4–8T, 0.2 ms) to the left tibial nerve until the post-TNS CMG showed either no bladder reflex during filling up to intravesical pressures of 30–40 cmH₂O, or a bladder reflex that occurred at >150% of control capacity. Our previous study in cats [15] revealed that the post-TNS inhibition of reflex bladder activity persists for at least two hours. Once this type of bladder underactivity was achieved, 3 CMGs were performed: (1) CMG during 1 Hz TNSi-c applied on the right side; (2) CMG during 1 Hz TNSc applied on the right side; and (3) Control CMG to examine any post-stimulation effect. TNS (1 Hz) was terminated in some experiments before the reflex contraction ended to prevent bladder over distension when the contraction duration reached more than 2.5 times the control contraction duration.

After testing 1 Hz TNS during CMGs, the frequency and intensity effect of TNS on bladder underactivity were further tested under isovolumetric conditions with the bladder fully distended (N=4 cats). TNS of short duration (30 seconds) was applied to the right tibial nerve at different frequencies (0.5–30 Hz at 4T) or different intensities (0.25–4T at 1 Hz) with an interval of >60 seconds between any two applications.

At the end of the study, the effect of 1 Hz and 5 Hz TNS on bladder overactivity was examined (N=6 cats). Repeated CMGs were performed by infusing 0.25% AA to irritate the bladder and induce bladder overactivity, which markedly reduced the bladder capacity. Once the irritated small bladder capacity stabilized, 3 CMGs were performed during AA infusion: (1) CMG during continuous 1 Hz TNS (4T intensity) applied to the right tibial nerve; (2) CMG during continuous 5 Hz TNS (4T intensity) applied to the left tibial nerve; and (3) Control CMG to examine any post-stimulation effect.

Data analysis

The control bladder capacity for each animal was determined by averaging the 2–3 saline CMGs before each group of TNS CMGs. The treatment bladder capacities were measured during each CMG and normalized to the averaged control capacity in each experimental group. The bladder capacity measured during AA irritation was normalized to the saline control capacity before any TNS application. The amplitude and duration of the micturition contractions were also measured in each CMG and normalized to the averaged measurements of the control CMGs. If no micturition reflex occurred during a CMG, the bladder capacity was measured as the infused volume that generated the bladder pressure of 30–40 cmH₂O and the contraction amplitude and duration were counted as zero. During isovolumetric rhythmic bladder contractions, the area under the contraction curve was measured during each 30-second TNS and was normalized to the maximal response for comparison among different TNS frequencies and intensities. The data from different animals are presented as mean ± standard error. Statistical significance ($p < 0.05$) was

determined by repeated-measures one-way ANOVA followed by Dunnett multiple comparison.

Results

Effect of 1 Hz TNS on normal bladder reflex activity

1 Hz TNS (4T, 0.2 ms) had no effect on bladder capacity when it was applied intermittently (TNSi-c) during saline infusion (Fig. 1), while on average the bladder capacity was slightly increased when 1 Hz TNS was applied continuously (TNSc) (Fig. 2A). Neither TNSi-c nor TNSc altered the amplitude of the micturition contraction (Fig. 1 and Fig. 2B). However, the duration of the micturition contraction was significantly ($p<0.01$) increased to $180.7\pm18.5\%$ and $160.4\pm25.5\%$ of control duration by TNSi-c and TNSc, respectively (Fig. 1 and Fig. 2C). The effects produced by TNSi-c and TNSc on contraction duration were not significantly different (Fig. 2).

Effect of 1 Hz TNS on the underactive bladder reflex activity induced by prolonged 5 Hz TNS

Repeated application (2–6 times) of 30-minute TNS (5 Hz, 4–8T, 0.2 ms) induced post-stimulation inhibition which blocked the large amplitude micturition reflex in 4 of 8 cats tested even when the bladder pressure reached 30–40 cmH₂O during a CMG (see the second CMG in Fig. 3). In the other 4 cats, the micturition reflex still occurred but the bladder capacity was increased to $>150\%$ of control capacity. On average the prolonged 5 Hz TNS significantly ($p<0.01$) increased the bladder capacity to $173.8\pm10.4\%$ of control (Fig. 4A) and reduced the contraction amplitude to $40.1\pm15.3\%$ of control (Fig. 4B), but did not significantly change contraction duration (Fig. 4C).

TNSi-c and TNSc (1 Hz, 4T, 0.2 ms) reversed the 5 Hz TNS-induced bladder underactivity by significantly ($p<0.01$) reducing the capacity to $130.9\pm5.8\%$ and $143.1\pm9.5\%$ of control (Fig. 4A) and restoring the contraction amplitude to $104.7\pm6.4\%$ and $96.7\pm5.6\%$ of control (Fig. 4B), respectively. The 1 Hz TNSi-c also significantly ($p<0.05$) increased the contraction duration to $171.7\pm27\%$ of control (Fig. 4C). In 2 cats, the 1 Hz TNSi-c was terminated early before the contraction ended since the duration of contraction reached $>250\%$ of control (see the third CMG in Fig. 3). In one cat, the 1 Hz TNSc was also terminated before the contraction ended due to a long duration of contraction. Within 10–15 minutes after the 1 Hz TNSi-c or TNSc the bladder underactivity returned (see the fifth CMG trace in Fig. 3 and control 3 bars in Fig. 4), indicating that the post-TNS inhibition induced by 5 Hz stimulation was long-lasting. In 2 of the 4 cats with areflexic bladders, a weak bladder reflex reappeared with a contraction amplitude less than 50% of control and a large bladder capacity during the post-stimulation period after the 1 Hz TNSi-c and TNSc (see the control 3 CMG in Fig. 5).

Frequency and intensity effects of TNS on bladder underactivity

The effects of various frequencies and intensities of TNS on bladder underactivity were tested under isovolumetric conditions when the bladder was fully distended and exhibited small or no reflex contractions (Fig. 5A). TNS (4T, 0.2 ms) of 30-second duration and in a

range of frequencies (0.5–3 Hz) induced significantly ($p<0.05$) larger contractions (Fig. 5B), while TNS at 1 Hz induced significantly ($p<0.05$) larger contractions when the intensity was at or greater than 1T (Fig. 5C).

Effects of 1 Hz and 5 Hz TNS on overactive bladder reflex activity

Infusion of 0.25% AA irritated the bladder and elicited bladder overactivity indicated by a significantly ($p<0.01$) reduced bladder capacity that was only $42.8\pm4.2\%$ of the control capacity measured during saline infusion before application of any TNS (Fig. 6). Subsequent 1 Hz TNS (4T) did not significantly change the bladder capacity. However, 5 Hz TNS significantly ($p<0.01$) increased bladder capacity to $85.2\pm8.2\%$ of saline control (Fig. 6). There was no post-TNS effect on bladder capacity. In addition, the amplitude and duration of bladder contractions were not significantly changed by either AA irritation or TNS when compared to the measurements during saline control conditions. The effect of 1 Hz TNS to smooth the contraction and increase the area under the contraction curve (see Fig. 6A) was only observed in 2 of the 6 cats tested.

Discussion

This study in anesthetized cats shows that the effects of TNS on bladder reflex activity are dependent on stimulation frequency and the state of the bladder reflex. When tested on a normal bladder, 1 Hz TNS significantly enhances the duration of the micturition contraction and induces a small increase in bladder capacity (Figs. 1–2). When tested on an underactive bladder, 1 Hz TNS significantly reduces bladder capacity and enhances the amplitude and duration of the micturition contractions (Figs. 3–4). However, when bladder is overactive the 1 Hz TNS has no significant effect on reflex bladder activity (Fig. 6). Meanwhile, the excitatory effect of TNS on the normal and underactive bladder can only be induced in a very low frequency range of 0.5–3 Hz (Fig. 5). In a higher frequency range of 5–30 Hz, TNS is ineffective in eliciting an excitatory effect (Fig. 5). However, in this higher frequency range TNS becomes very effective in inhibiting bladder overactivity (Fig. 6) or producing prolonged post-TNS inhibition resulting in bladder underactivity (Figs. 3–4) as shown in current study and in our previous study [13,14].

The frequency dependent effects of TNS on bladder activity suggest that tibial neuromodulation might be used to treat UAB in addition to OAB. Currently the FDA-approved tibial neuromodulation therapy for OAB uses 20 Hz frequency [1,2]. Our study indicates that a very low frequency (0.5–3 Hz) might be used to treat UAB in human subjects by enhancing the bladder contractions or reducing the bladder volume threshold for triggering the urge to void. Although the efficacy of low frequency TNS in treating UAB must be proven by a clinical trial, the advantages of applying tibial neuromodulation to treat UAB are obvious. Tibial nerve innervates the plantar surface of the foot. It can be stimulated by inserting a needle at the ankle [1,2] or by non-invasive skin electrodes attached to the plantar surface of the foot [16,17]. Therefore, tibial neuromodulation for UAB would be less invasive than FDA-approved sacral neuromodulation that requires surgically implanting a stimulator and an electrode on the sacral S3 root. Another treatment option for UAB is urethral catheterization (indwelling or intermittent) that is complicated by frequent urinary

tract infections [12,18]. While medications represent a non-invasive therapeutic modality, studies to date have shown limited efficacy of various agents, including parasympathomimetics and prostaglandins, such that their side effect profile often limits their use [19,20,21]. Therefore, there is a significant clinical need for a new UAB treatment and our study suggests a potential tibial neuromodulation therapy to meet this need.

The 1 Hz TNS at a stimulus intensity of 1–4T is effective in enhancing bladder activity in UAB conditions (Fig. 5). Since the tibial nerve consists of both motor and sensory nerve fibers, TNS at 1T intensity must have activated the largest group I motor axons and induced a direct motor response observed as toe twitching. At 4T intensity, TNS could activate the non-nociceptive group II afferent axons [22], while activation of the group III and IV afferent axons in the tibial nerve that can induce painful sensations, would require a stimulus intensity greater than 10T intensity [22]. Our study using 1–4T intensity only activated the large motor axons and the group II afferent axons that are non-nociceptive and therefore would not cause painful sensations if used in clinical applications.

This study in cats revealed that TNS in a low range of stimulation frequencies (0.5–3 Hz) not only enhances normal bladder contractions (Figs. 1–2) but also reverses bladder underactivity (Figs. 3–4). A previous study in cats [23] also showed the effectiveness of 2 Hz TNS in enhancing normal bladder contractions. Similar to the low frequency TNS, excitatory effects on reflex bladder activity were also elicited in our recent studies in cats [13,14] by 0.5–2 Hz saphenous nerve stimulation (SNS) or 1–3 Hz superficial peroneal nerve stimulation (SPNS). These low frequency stimulations enhanced the normal micturition reflex contraction by significantly increasing either the contraction duration (TNS and SNS) or the area under the contraction curve (SPNS). However, only the SPNS but not TNS or SNS significantly reduced the bladder capacity for inducing a normal micturition reflex (Fig. 1 and Fig. 2A). Furthermore, both SNS and SPNS completely reversed the increase in bladder capacity that occurred during the prolonged post-stimulation inhibition induced by repeated 5 Hz TNS, while 1 Hz TNS only partially reversed this increase (Fig. 3 and Fig. 4A). These results indicate that TNS might not be as effective as SNS or SPNS in the treatment of UAB. However, clinical trials will be needed in order to compare the efficacies of these potential neuromodulation therapies for UAB.

Although the pathophysiology underlying UAB is currently not clear, it seems reasonable to classify UAB into 3 general categories as neurogenic, myogenic, or idiopathic [12]. Since the mechanisms underlying the bladder underactivity induced in this study by prolonged 5 Hz TNS are still unknown, it is difficult to classify our cat model of bladder underactivity. However, it is highly likely that tibial afferent input driven by 5 Hz TNS produces a long-lasting inhibitory effect in the CNS rather than in the bladder muscle, because our previous study showed that the prolonged post-TNS inhibition only occurred during saline infusion of the bladder but not during AA irritation of the bladder [24]. It is known that saline distention activates the non-nociceptive A δ -fiber mediated supraspinal micturition reflex pathway; while AA irritation also activates the nociceptive C-fiber afferent mediated spinal reflex pathway [25]. The selectivity of post-TNS inhibition on different micturition reflexes indicates a CNS site of action rather than a peripheral site of action. Therefore, it seems reasonable to classify our cat model of bladder underactivity as a neurogenic UAB model.

Despite the unknown mechanism of action, this cat model of bladder underactivity is very useful for testing neuromodulation effects produced by stimulation of different somatic afferent nerves such TNS, SNS, or SPNS [13,14]. Since the urethral outlet was closed in this study, the effect of TNS-induced bladder underactivity on voiding efficiency could not be examined. In addition, the effect of low frequency (0.5–3 Hz) TNS on the external urethral sphincter and the ability of the low frequency TNS to improve voiding efficiency were not investigated. Thus, further studies will be needed to evaluate voiding efficiency and urinary retention in this cat model of bladder underactivity.

Continuous and intermittent patterns of 1 Hz TNS (60-sec off and 30-sec on) were tested to determine if the excitatory effect of continuous TNS might fatigue during the prolonged period of bladder filling (Fig. 1 and Fig. 3). The intermittent TNS produced a significant increase in contraction duration when bladder was underactive; while the continuous TNS failed to produce a significant change (Fig. 4C). Meanwhile, the continuous TNS slightly increased normal bladder capacity; while the intermittent TNS did not (Fig. 2A). Therefore, it seems that intermittent TNS might be more effective in clinical applications if 1 Hz tibial neuromodulation is used to promote voiding in UAB patients.

This study reveals that the effects of TNS on bladder activity are dependent on stimulation frequency and the state of the bladder reflex (normal, underactive, or overactive). The results from this animal study suggest that the FDA-approved tibial neuromodulation therapy for OAB might be also effective at certain stimulation frequencies to treat UAB symptoms. However, since our animal model of UAB might only mimic one type of many different types of UAB that may occur in patients, the efficacy of low frequency (0.5–3 Hz) TNS in treating the general population of UAB patients still needs to be determined by clinical trials.

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Fig. 1.

Tibial nerve stimulation (TNS) applied during a saline cystometrogram (CMG) significantly increased the duration of the micturition contraction. TNSi-c – TNS was applied intermittently during the storage phase but was applied continuously once a micturition contraction occurred. TNSc – TNS was applied continuously from the beginning of the CMG. The black bar under bladder pressure trace indicates the duration of stimulation. TNS: 1 Hz, 0.2 ms, $4T = 8V$. T = threshold intensity for TNS to induce toe twitch. Infusion rate: 2 ml/min.

Fig. 2.

Effects of tibial nerve stimulation (TNS) on bladder capacity (A), contraction amplitude (B), and contraction duration (C) measured during saline cystometrograms. TNSi-c – TNS was applied intermittently during storage phase but was applied continuously once a micturition contraction occurred. TNSc – TNS was applied continuously from the beginning of the CMG. TNS: 1 Hz, 0.2 ms, 4T = 1.6–8 V. * significantly ($p < 0.05$) different from control 1 (one-way ANOVA). N = 9 cats.

Fig. 3.

During saline cystometrograms (CMGs) tibial nerve stimulation (TNS) of 1 Hz enhanced micturition contraction and reduced bladder capacity during the bladder underactivity produced by prolonged TNS of 5 Hz. At the end of Control 1 CMG, 5 Hz TNS of 30-minute duration was applied 3 times, which resulted in an areflexic bladder as shown in Control 2 CMG. TNSi-c – TNS was applied intermittently during storage phase but was applied continuously once a micturition contraction occurred. TNSc – TNS was applied continuously from the beginning of the CMG. After testing TNSi-c and TNSc, Control 3 CMG showed that the bladder was still underactive with a large capacity and a small contraction amplitude. The black bar under bladder pressure trace indicates the duration of stimulation. TNSi-c/TNSc: 1 Hz, 0.2 ms, 4T = 2.4 V. T = threshold intensity to induce observable toe twitch. Repeated 30-minute TNS: 5 Hz, 0.2 ms, 30 minutes × 3 times, 4–8T, T = 0.3 V. Infusion rate = 2 ml/min.

Fig. 4.

Effects of 1 Hz tibial nerve stimulation (TNS) on bladder capacity (A), contraction amplitude (B), and contraction duration (C) during the bladder underactivity produced by prolonged 5 Hz TNS. The definitions for control 1, 2 and 3 are same as Fig. 3 TNSi-c – TNS was applied intermittently during storage phase but was applied continuously once a micturition contraction occurred. TNSc – TNS was applied continuously at the beginning of the CMG. TNSi-c/TNSc: 1 Hz, 0.2 ms, 4T = 1.6–8V. Repeated 30-minute TNS: 5 Hz, 0.2 ms, 30 minutes repeated 2–6 times, 4–8T, T = 0.2–0.7 V, * significantly ($p < 0.05$) different from control 1 (one-way ANOVA). # significantly ($p < 0.05$) different from control 2. N = 8 cats.

Fig. 5.

Bladder pressure responses to different frequencies (0.5–30 Hz) and intensities (0.25–4 T) of tibial nerve stimulation (TNS). T – threshold intensity for TNS to induce toe twitch. A: bladder pressure traces from the same cat. The black bar under the pressure trace indicates the duration (30 secs) of TNS. TNS: 4T = 6.4 V, 0.2 ms for top trace; 1 Hz, 0.2 ms for bottom trace. B: Normalized area under curve for different frequencies of TNS (4T = 1.6–6.4 V, 0.2 ms). C: Normalized area under curve for different intensities of TNS (1 Hz, 0.2 ms). * significantly ($p < 0.05$) different from the response at 30 Hz in B or at 0.25 T in C (one-way ANOVA). N = 4 cats.

Fig. 6.

Effects of 1 Hz and 5 Hz tibial nerve stimulation (TNS) on bladder overactivity induced by acetic acid (AA) irritation. A. Intravesical infusion of dilute (0.25%) AA irritated the bladder and caused bladder overactivity resulting in a smaller bladder capacity. TNS at 1 Hz did not change the small bladder capacity, but at 5 Hz increased the bladder capacity. 1 Hz and 5 Hz TNS: 4T = 2.4 V, 0.2 ms. Infusion rate = 2 ml/min. B. Summarized results from 6 cats. 1 Hz TNS: 4T = 1.6–8 V, 0.2 ms. 5 Hz TNS: 4T = 0.8–2.4 V, 0.2 ms. * significant ($p < 0.05$) different from control 1 (one-way ANOVA). # significantly different from ($p < 0.05$) control 2 (one-way ANOVA).