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Suppression of Urinary Voiding “on Demand” by High-Frequency Stimulation of the S1 Sacral Nerve Root in Anesthetized Rats

Charly B.J. Brouillard, PhD; Jonathan J. Crook, PhD; Thelma A. Lovick, PhD

Objectives: High-frequency (kHz) stimulation of preganglionic pelvic nerve afferents can inhibit voiding in both anesthetized and conscious rats. The afferents travel via the S1 sacral nerve root, which is easier to access than the distal pelvic nerve fibers within the abdominal cavity. We therefore investigated whether voiding could be inhibited by high-frequency stimulation at S1 and how this compared to distal pelvic nerve stimulation.

Methods: Urethane-anesthetized rats were instrumented to record bladder pressure and abdominal wall electromyogram and to stimulate the distal preganglionic pelvic nerve bundle and S1 sacral root. Saline was infused continuously into the bladder to evoke repeated voiding. Stimulation was initiated within 1–2 sec of the onset of the steep rise in bladder pressure signaling an imminent void.

Results: In six rats, stimulation of the distal pelvic nerve bundle (1–3 kHz sinusoidal waveform 1 mA, 60 sec) suppressed the occurrence of an imminent void. Voiding resumed within 70 ± 13.0 sec (mean \pm SEM) of stopping stimulation. Stimulation (using the same parameters) of the S1 root at the level of the sacral foramen suppressed voiding for the entire stimulation period in three rats and deferred voiding for 35–56 sec (mean 44.0 ± 3.2 sec) in the remaining three. Stimulation at either site when the bladder was approximately half full, as estimated from previous intervoid intervals, had no effect on voiding.

Conclusions: This preliminary study provides proof-of-concept for the sacral root as an accessible target for high-frequency stimulation that may be developed as an “on demand” neuromodulation paradigm to suppress unwanted urinary voids.

Keywords: High-frequency stimulation, pelvic nerve, rat, sacral nerve, urinary voiding

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Sacral neuromodulation is the most commonly used, clinically effective intervention, for treating a number of urinary and bowel dysfunctions that are refractory to conservative management. Several recent evaluations (1–3) conclude that as experience grows, considerable levels of long-term therapeutic success (>50% improvement in main symptoms/leakage episodes) and improved quality of life can be expected in patients with urinary urge incontinence and urgency frequency. Nonetheless, adverse effects such as pain and the requirement for reintervention still remain problematic (1).

Current sacral neuromodulation procedures typically use continuous, low-frequency stimulation in the region of 10–15 Hz. The precise mechanism(s) underlying the effectiveness of this method is not understood completely, however, studies in large animal models have demonstrated an increase in bladder capacity (4,5). Although, this is certainly a major factor underlying efficacy in some patients with overactive bladder, continuous stimulation may not be optimal for all applications. For the patient with urinary urge incontinence, for example, an attractive refinement would be conditional or “on demand” stimulation (6,7). The ability to suppress unwanted voiding when urge occurs, thereby buying time to move to a suitable and socially acceptable environment to empty the bladder, would confer a

significant psychological advantage to the patient by restoring autonomy over control of their bladder. It would also have the additional benefit of increased device lifespan due to longer battery life (although *in-situ* rechargeable devices may obviate this need eventually).

With these provisos in mind, we developed an animal model in which imminent voids can be suppressed on demand. In anesthetized rats, initiating high-frequency (1–3 kHz) stimulation of the pelvic nerve at the onset of the bladder contraction signaling an imminent void aborts the void and maintains urinary continence during the stimulation period (8). The effect is rapid in onset, reproducible, and readily reversible. Voids could be similarly suppressed in chronically instrumented conscious rats without evoking any sign of discomfort or other adverse side effects (9).

These studies provided proof-of-concept for high-frequency stimulation of the pelvic nerve to control urinary continence “on demand.” However, a limitation to the translational potential of

Address correspondence to: Thelma Lovick, PhD, Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol BS8 1TD, UK. Email: thelma.lovick@bristol.ac.uk

Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK

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pelvic nerve stimulation is the invasive surgery (laparotomy) required to access the preganglionic pelvic nerve bundle. An alternative approach would be to access the pelvic nerve fibers outside the abdominal cavity as they approach the spinal cord. In Wistar rats, most pelvic nerve afferents enter the cord in the S1 spinal root (10). We therefore carried out a preliminary study in anesthetized rats to determine whether high-frequency stimulation at the S1 spinal root could inhibit voiding, and whether the effectiveness of stimulation at this site compares favorably with stimulation of the distal preganglionic pelvic nerve bundle within the abdominal cavity.

MATERIALS AND METHODS

Experiments were carried out under the U.K. Animals (Scientific Procedures) Act 1986, project license PPL30/3200. Female Wistar rats (245–283 g) were anesthetized with urethane (0.7 mL/100 g 20% solution i.p.). Rectal temperature was maintained at 37°C using a thermostatically controlled heating blanket. With the animal supine, the left femoral artery and left femoral vein were cannulated in order to measure blood pressure and for intravenous fluid replacement, respectively, as needed. A midline abdominal incision was made to expose the bladder and a polythene catheter inserted into the bladder through the dome and secured in place with 6.0 silk suture (8). The left pelvic nerve was then located and a miniature bipolar cuff electrode (11) positioned on the preganglionic nerve bundle just proximal to the pelvic ganglion. The functional integrity of the nerve to bladder connection was confirmed by stimulating the nerve at low frequency (10 Hz, 1 mA for 10 sec) and observing a rise in bladder pressure, typically accompanied by a small rise in blood pressure (8–17 mmHg) as reported previously (8). The abdominal incision was then closed, and the bladder catheter and leads from the electrode exteriorised via the flank. In three rats, two needle electrodes, orientated rostro-caudally 10 mm apart, were inserted into the external oblique muscle on right side approximately 1 cm lateral to the midline to measure electromyogram (EMG). This enabled us to assess the contribution of the abdominal musculature to voiding under anesthesia and to determine whether stimulation of the pelvic nerve or S1 root evoked contraction of the abdominal wall.

The preparation was then turned prone and a midline incision made to expose the lumbar and sacral vertebrae. The paravertebral muscles were reflected and a clamp was applied to the L6 vertebra to stabilize the spine. The S1 foramen was located on the left side (Fig. 1) (12) and soft tissue cleared from the bone to allow a bipolar silver wire electrode (inter-electrode distance 1 mm) to be positioned on the foramen. The tail was lifted so that drops of fluid expelled from the urethra could be observed and counted. Correct positioning of the electrode was confirmed by repetitive twitching of the tail and perineal region evoked in response to stimulation at 10 Hz. In contrast to the effects of low-frequency stimulation of the pelvic nerve, no change in blood pressure and only a minimal increase in bladder pressure (0–2 mmHg) were evoked by this procedure. Once the electrode was positioned correctly, the exposed tissue was flooded with warm liquid paraffin to prevent it drying and to prevent electrical shorting between the electrode poles due to accumulation of tissue fluid.

Once the surgery had been completed, the preparation was left to stabilize for 30–60 min. Saline was then infused into the bladder at 6 mL h⁻¹ using a syringe pump (PHD 2000, Harvard

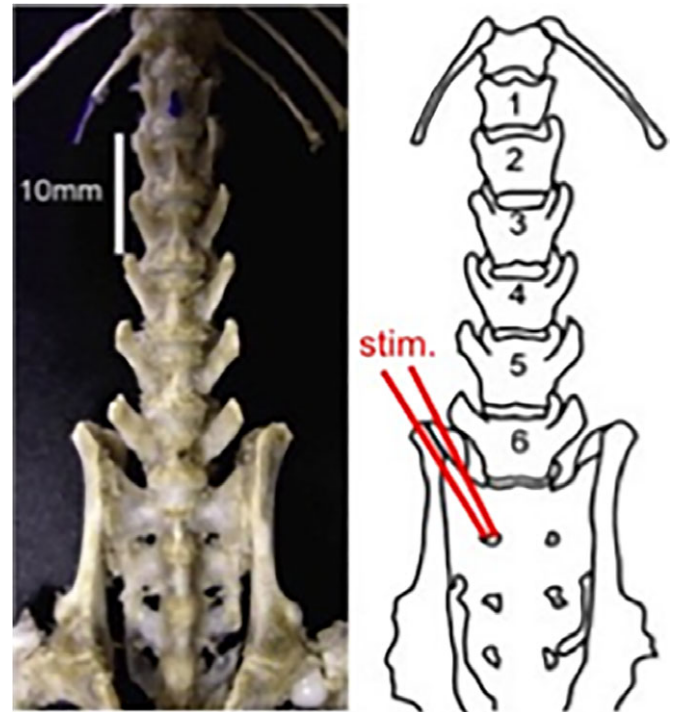


Figure 1. Location of stimulating electrodes on S1 foramen. Image of rat spine reproduced from (12) with permission from Elsevier publisher. [Color figure can be viewed at wileyonlinelibrary.com]

Apparatus, Cambridge, UK). A T-piece in the line enabled simultaneous recording of bladder pressure. Physiological variables were captured using a Powerlab 16/35 data acquisition system (AD Instruments, Oxford, UK) operating LabChart v8. Pelvic or sacral nerve stimulation was delivered via a constant current stimulator (STMISOLA, Biopac System Inc., Goleta, CA, USA). A sinusoidal waveform (0.5–10 kHz) was used to deliver a charge balanced stimulus with an intensity of 1 or 2 mA. In a previous study, we had found these parameters to be optimal for inhibiting voiding by stimulating the pelvic nerve (8). EMG activity was amplified (5000x) and filtered 50–5000 Hz using a Neurolog system (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). All values are given as means \pm SEM.

RESULTS

Experiments were carried out on 13 rats. Repeated voiding in response to continuous infusion of saline into the bladder was established in six animals. A void was defined as a coordinated contraction of the bladder accompanied by rapid expulsion of several drops of liquid from the urethra. Table 1 shows the urodynamic characteristics of voiding in these animals. During the filling phase bladder pressure increased gradually until a threshold was reached (15.8 ± 0.27 mmHg), whereupon the pressure rose sharply to reach a peak prior to expulsion of several drops of urine from the urethra (Fig. 2a).

A low level of tonic activity was present on the abdominal EMG signal during filling. In one animal phasic activity time-locked to respiratory expiration was superimposed on the tonic signal (13). When a void was imminent, there was a dramatic increase in abdominal EMG activity when bladder pressure reached 20.4 ± 0.3 mmHg, that is, immediately prior to attaining peak bladder pressure. The high level of activity was

Table 1. Urodynamic Parameters of Spontaneous Voids Induced by Saline Infusion (6 mL/h) for Each Rat. We Defined Baseline Pressure as the Pressure in the Bladder Prior to Starting Infusion of Saline; Void Threshold Was the Pressure at the Onset of the Sharp Rise in Pressure Signaling an Imminent Void; Contraction Pressure Was Maximum Pressure-Threshold Pressure.

Rat	Intervoid interval (sec)	Detrusor baseline pressure (mmHg)	Void threshold (mmHg)	Detrusor contraction pressure (mmHg)
1	184.3 ± 14.0	8.7 ± 0.1	15.9 ± 0.6	7.5 ± 0.2
2	81.3 ± 13.5	7.9 ± 0.3	11.0 ± 0.3	7.0 ± 0.3
3	86.0 ± 14.0	7.9 ± 0.4	13.9 ± 0.7	7.9 ± 0.7
4	108.2 ± 7.3	8.0 ± 0.3	17.1 ± 0.5	9.0 ± 1.0
5	214.8 ± 16.3	6.1 ± 0.2	16.1 ± 0.5	5.9 ± 0.4
6	193.9 ± 51.9	6.7 ± 0.1	19.1 ± 1.1	4.6 ± 0.4

sustained for 4.37 ± 0.19 sec during which time liquid was expelled via the urethra (Fig. 2a). In one of the rats, this burst of activity was preceded by an earlier (1.7 ± 0.28 sec prior) period of lower level abdominal EMG activity, which appeared when bladder pressure reached 16.9 ± 1.1 mmHg. In seven rats, integrated voids failed to establish reliably. Intravesicular pressure increased as saline was infused into the bladder and then remained stable at a high level while fluid dripped from the urethra at regular intervals (overflow). Because our experimental protocol required stable physiological voiding over a period of several hours in order to test the effects of sacral and pelvic nerve stimulation, the seven rats that developed overflow incontinence were discarded.

Modulation of Voiding by Stimulation of the Pelvic Nerve and S1 Sacral Root

Pelvic Nerve Stimulation

In each experiment, we first established that pelvic nerve stimulation inhibited voiding, as described previously (8). In every animal (6/6 rats), pelvic nerve stimulation was effective. Stimulation at 1 mA was initially tested and if this proved ineffective, the intensity was raised to 2 mA. Optimal effects were obtained using stimulation frequencies of 1 or 3 kHz, 1–2 mA for 60 sec (Figs. 2b and 3a). In 8/9 tests using optimal stimulation parameters, imminent voiding was suppressed completely by stimulation initiating within 1.0–2.4 sec (mean 1.44 ± 0.21 sec) of the onset of the preceding sharp rise in bladder pressure. Continence was maintained for the duration of the stimulus (Fig. 3a), and voiding resumed 70 ± 13.0 sec after the stimulation period ended. In the remaining test, the imminent void was initially suppressed; however, a void occurred after 36 sec, that is, before the end of the 60 sec stimulation period.

Sacral Nerve Stimulation

Once we had established the effectiveness of pelvic nerve stimulation, we investigated whether similar effects could be produced by stimulating the sacral nerve root at S1. In each rat (6/6 tested), imminent voiding was suppressed by stimulation at S1, initiated within 0.9–3.0 sec (mean 1.8 ± 0.16 sec) of the onset of the preceding steep rise in pressure, using stimulation parameters that were optimal for inhibiting voiding when stimulating the pelvic nerve in that animal (1 or 3 kHz, 1 mA, Fig. 2b). Typically,

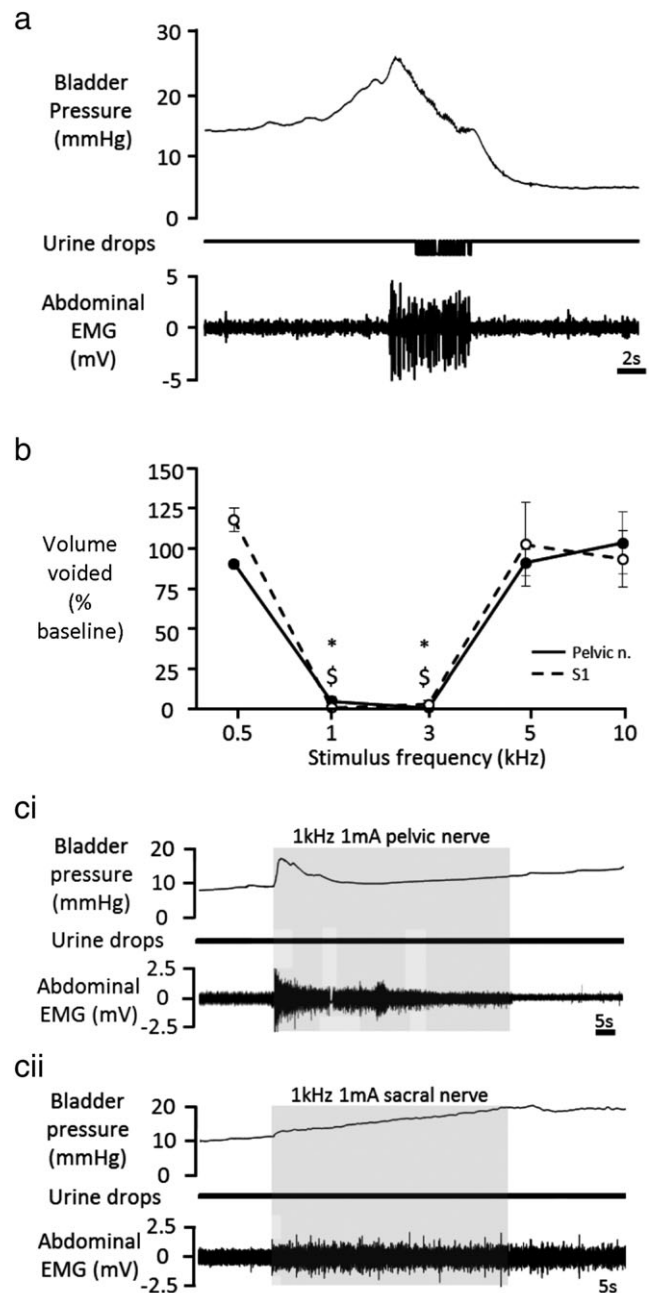


Figure 2. a. Change in bladder pressure and abdominal electromyogram during a spontaneous void. Urine drops channel indicates timing of drops of urine exiting the urethra. b. Effect of stimulus frequency on inhibition of voiding during the first 30 s of stimulating the pelvic nerve and S1 root (six rats). Voided volume during stimulation is plotted as a percentage of the mean of the previous three spontaneous voids (baseline). * $p < 0.05$ pelvic n.; § $p < 0.05$ S1 compared to baseline; Wilcoxon signed-rank test (ANOVA not possible due to incomplete data set for all frequencies). c. Effects of stimulating pelvic nerve (i) and S1 root (ii) during the filling phase in between voids. Data from the same rat using the same stimulation parameters that inhibited voiding when applied at the onset of an imminent void.

bladder pressure continued to rise after the stimulation onset, reached a peak, and then reduced rapidly, stabilizing at a lower level for the remainder of the 60 sec stimulation period or until a void occurred (whichever was the shorter time) (Fig. 3b). Once the void had taken place, bladder pressure returned to baseline.

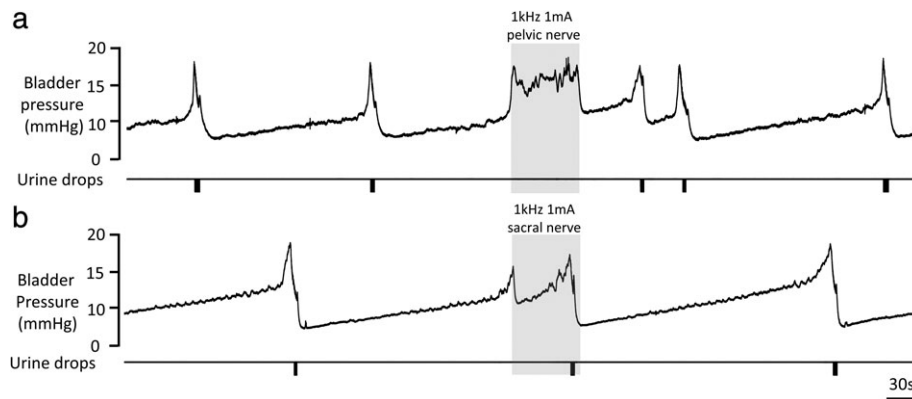


Figure 3. a. Stimulating the pelvic nerve (gray panel) suppressed voiding. b. In the same rat, stimulation of the S1 root deferred the imminent void until just before the end of the stimulation period.

In three of the rats, voiding was suppressed completely for the entire 60 sec stimulation period, resuming 10, 76, and 262 sec, respectively, after the stimulation ceased. On the other occasions in the same experiment and in all tests carried out in the three remaining rats, the imminent void was initially suppressed, however, a void occurred before the end of the stimulation period (35–56 sec, mean 44.0 ± 3.2 sec, after stimulus onset). Of the three rats in which stimulation at S1 suppressed voiding completely for the entire 60 sec stimulation period, the optimal stimulation frequency to produce this effect was 1 kHz in two rats and 3 kHz in the other one. For the three rats in which we were able only to defer voiding, changing the stimulation frequency did not improve the outcome.

Optimal Stimulation Parameters for S1 Stimulation

We chose initially to use stimulation parameters for sacral nerve stimulation that we had found previously to be optimal for inhibiting voiding by stimulating the preganglionic pelvic nerve bundle (8). However, we also tested the effect of stimulation over a range of frequencies (0.5–10 kHz). The range of stimulus frequencies that was optimal for suppressing voiding using S1 stimulation (1–3 kHz) was the same as for the pelvic nerve (Fig. 2b). The effect was intensity dependent. Stimulation at S1 using 0.75 mA ($N = 2$) did not suppress voiding, whereas increasing the current to 2 mA inhibited voiding effectively but produced significant movement artifact ($N = 3$); we therefore restricted stimulation to 1 mA in further tests.

Stimulation During the Filling Phase

No urine was ever expelled in response to stimulating either the pelvic nerve or S1 root during the filling phase, when the bladder was approximately half full. However, stimulation of S1 at frequencies that suppressed voiding did evoke a tonic increase in abdominal EMG activity, which lasted for the duration of the stimulation period (Fig. 2cii). There was also a small, transient increase in bladder pressure (2.2 ± 0.6 mmHg) at the onset of the stimulation. In contrast, stimulating the pelvic nerve at the same frequencies evoked only a transient increase in abdominal EMG activity at the onset of the stimulation (Fig 2ci), and a slightly larger, but transient, increase in bladder pressure (11.1 ± 3.6 mmHg).

Cardiovascular Effects Evoked by High Frequency Pelvic Nerve or S1 Stimulation

Stimulating S1 at any of the frequencies tested (0.5–10 kHz) for their ability to suppress imminent voids produced only a very small change in blood pressure (mean of maximum response in each rat 5.2 ± 0.9 mmHg). This contrasts with pelvic nerve stimulation, which evoked an increase in blood pressure at the onset of stimulation. Interestingly, the maximum effect (18.3 ± 4.6 mmHg) was evoked at the lowest frequency tested (500 Hz), which in general was not effective in blocking voiding.

DISCUSSION

The present study was designed to compare the effectiveness of high-frequency stimulation of the S1 root and the pelvic nerve to inhibit voiding. As reported previously by us and by others, continuous infusion of saline into the bladder evoked repeated voiding (8,14,15). In addition, we observed contraction of the external oblique musculature of the abdominal wall during voiding. This has also been described in conscious rats (16,17) and may aid expulsion of urine by adding to the increase in intravesicular pressure generated as the bladder contracts.

In the present study, 48% of the rats prepared for cystometry voided reliably. This is rather lower than our past experience in which around 70% of urethane-anesthetized rats developed reliable voiding (8). The lower success rate in the present study may be linked to the more invasive surgery necessary to access both the sacral root and pelvic nerve, which included the added steps of closing the abdominal wall after exposing the bladder and pelvic nerve, turning the rat prone, and the further surgery to expose the S1 vertebra.

The use of anesthesia in the present study is another possible confound. However, voiding evoked during continuous cystometry under urethane anesthesia is similar to that seen in conscious rats, differing principally with respect to the volume and frequency of voids (9,18,19). Most importantly for the present investigation, the inhibitory effect of pelvic nerve stimulation is also similar in anesthetized and conscious rats (8,9). Urethane is therefore not a confounding factor likely to bias the response to S1 stimulation. Nevertheless, it will be important in the future to repeat the study in conscious, chronically instrumented animals.

High infusion rates (6 mL h^{-1} in our experiments), which are many times the rate at which the bladder fills naturally via the

ureters, are used routinely during cystometry in rats for the convenience of evoking voids every few minutes (e.g., 8, 14, 15, 19). In the present study, the infusion of saline into the bladder continued throughout the 1 min period of nerve stimulation, during which imminent voiding was suppressed. This continuing filling of the bladder, beyond the threshold for voiding, may pose a risk of myogenic damage due to overdistension of the bladder while voiding was suppressed. However, in another study on modulation of voiding, we continued to fill for up to 7 min while suppressing voiding by stimulation in the brain and observed no ill effects (15), suggesting that the detrusor had not been compromised. It is worth noting that a stimulation paradigm that is able to suppress voiding when the stimulus to void is above threshold, and continuing to increase rapidly, is likely to be even more effective when tested during more physiological filling rates.

The primary objective of the present study was to determine whether stimulation of S1 could inhibit voiding and how this compared with stimulation of the pelvic nerve. In agreement with our previous study (8), in each animal tested (6/6 rats), high-frequency stimulation of the pelvic nerve produced a rapid onset and readily reversible suppression of voiding. Stimulation at S1 also suppressed imminent voids in every rat. This represents a 100% success rate. However, in contrast to pelvic nerve stimulation, which suppressed voiding completely for the whole of the 60 sec stimulation period in every rat tested, stimulation at S1 suppressed voiding for the entire 60 sec stimulation period in 50% of animals. In the remainder, the imminent void was suppressed initially, but a void occurred toward the end of the stimulation period. At first sight, this suggests that stimulation at S1 is less effective than stimulation of the pelvic nerve. However, although pelvic nerve fibers project through the S1 root in Wistar rats (10) and would be activated by stimulation at this level, other fibers in the S1 root will also be activated, which may evoke responses that conflict with the effects of pelvic nerve stimulation. Another explanation for differential effects may relate to the type of electrodes we used for stimulating the pelvic nerve and S1 root (respectively, cuff on the pelvic nerve vs. bipolar needle electrode on the S1 foramen). The larger diameter of the S1 nerve trunk compared to the pelvic nerve, the difference in dimensions of the stimulating electrodes, and their proximity to the nerve bundle at the two stimulation sites would mean that current density in the sacral nerve bundle would be lower than for the pelvic nerve when identical currents were applied. Our exploration of the effectiveness of S1 stimulation at higher currents was limited by motor side effects. In future studies, the use of a custom-designed electrode more closely opposed to the sacral nerve root bundle should be able to resolve this limitation of the present experiments. Even so, this initial study does provide proof-of-concept for inhibiting voiding "on demand" by stimulation at S1.

Stimulation of the S1 root at frequencies that blocked voiding evoked a sustained, but low level, contraction of the abdominal wall. While this is likely to reflect reflex activation of the abdominal musculature due to activation of S1 afferents from the uterus and colon (20–22), another possibility is that it might represent a viscerosomatic response to activation of nociceptive afferents (23). The latter explanation seems unlikely however because noxious colorectal distension under urethane anesthesia has been shown to be accompanied by a depressor response (23), while in the present study stimulation at S1 evoked a very small increase in blood pressure and only in some tests. Nevertheless, it will be

important to test the behavioral responsiveness to S1 stimulation in conscious rats, in order to resolve the question unequivocally.

Previous studies have demonstrated that low frequency (<20 Hz) stimulation of S1 in rats and S2 in larger mammals can increase bladder capacity and inhibit isovolumetric bladder contractions (24–26). The superiority of dorsal vs. ventral root stimulation indicated that the effect was mediated by activation of afferent fibers (24,26). High-frequency (1–3 kHz) stimulation of the pelvic nerve, which suppresses integrated voiding is also thought to be due to activation of afferent fibers (8). In the present study, stimulation at the level of the S1 foramen would most likely engage these same afferent fibers, although the stimulus would be less selective as afferents from other sources converging at the S1 root would be activated as well.

The mechanisms underlying the effectiveness of neuromodulation strategies to control bladder function are not fully understood. Recent thinking is that activation of afferents by low-frequency stimulation results in a change in bladder perception threshold and an increased bladder capacity, almost certainly mediated via a central mechanism (27–29). The effectiveness of high-frequency stimulation is also thought to be due to activation of afferent fibers, albeit likely via engagement of a different central mechanism (8). It has been proposed that stimulation of pelvic nerve afferents at frequencies in the kHz range may impose an unphysiological pattern of firing that leads to a functional occlusion of the central voiding circuitry, thereby preventing a void from being generated (8).

Devices for sacral nerve stimulation currently in clinical use are usually restricted to using continuously applied low (10's of Hz) frequencies, although a limited number of studies suggest that preprogrammed or patient-operated schedules of intermittent stimulation may also be effective (30,31). Novel stimulation paradigms applied to the pelvic nerve using frequencies in the kHz range developed by us (8,9) or using combinations of high and low frequencies (32) have the potential to produce sophisticated and flexible modulation to target different types of voiding dysfunction. The functional response to high-frequency stimulation of the S1 root and pelvic nerve described in the present study (total, immediate, and readily reversible suppression of imminent voids) differs from the functional response (increase in bladder capacity) produced by the low-frequency stimulation regimens in clinical use.

CONCLUSION

The results of the present study provide proof-of-concept for the development of high-frequency stimulation to suppress involuntary urinary voids "on demand" in humans. Although the distal pelvic nerve and the sacral roots are both effective stimulation sites, the sacral root provides the more accessible target. There is also a considerable body of clinical experience in implantation of stimulators at sacral level. For the individual with urinary urge incontinence, the opportunity to activate their stimulator at the onset of urge sensation and suppress imminent involuntary voids would restore autonomy over their bladder emptying. As implantable sensor technology develops (33,34), it may become possible to incorporate a stimulator into a device, which would detect bladder fullness and/or sharp rises in bladder pressure and then alert the individual to the need to empty their bladder while at the same time activating the stimulator to suppress the imminent void and prevent an incontinent episode. Such a "smart" device

could have applications for those with impaired bladder sensation, for example, after spinal cord injury, as well as patients with urinary urge incontinence.

Authorship Statements

Thelma A. Lovick conceived the study, obtained funding, and wrote the first draft of the manuscript. Charly B.J. Brouillard carried out most of the experimental work and analysis of the data with input from Jonathan J. Crook and Thelma A. Lovick. All authors approved the final version of the manuscript.

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