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High frequency electrical conduction block of the pudendal nerve

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Abstract

A reversible electrical block of the pudendal nerves may provide a valuable method for restoration of urinary voiding in individuals with bladder–sphincter dyssynergia. This study quantified the stimulus parameters and effectiveness of high frequency (HFAC) sinusoidal waveforms on the pudendal nerves to produce block of the external urethral sphincter (EUS). A proximal electrode on the pudendal nerve after its exit from the sciatic notch was used to apply low frequency stimuli to evoke EUS contractions. HFAC at frequencies from 1 to 30 kHz with amplitudes from 1 to 10 V were applied through a conforming tripolar nerve cuff electrode implanted distally. Sphincter responses were recorded with a catheter mounted micro-transducer. A fast onset and reversible motor block was obtained over this range of frequencies. The HFAC block showed three phases: a high onset response, often a period of repetitive firing and usually a steady state of complete or partial block. A complete EUS block was obtained in all animals. The block thresholds showed a linear relationship with frequency. HFAC pudendal nerve stimulation effectively produced a quickly reversible block of evoked urethral sphincter contractions. The HFAC pudendal block could be a valuable tool in the rehabilitation of bladder–sphincter dyssynergia.

1. Introduction

During normal micturition, voiding occurs by synchronized bladder contraction and urethral sphincter relaxation. Spinal cord injury and other neurological disorders can result in detrusor-sphincter dyssynergia (DSD), where bladder and urethral contractions become uncoordinated [1]. DSD can result in significant medical complications such as urinary tract infections, autonomic dysreflexia and renal failure. An efficient and quickly reversible means to block the pudendal nerve and reduce urethral sphincter contractions would provide an effective tool for restoration of urinary voiding in individuals with DSD.

Nerve activation in applications for functional electrical stimulation is usually restricted to frequencies below 50 Hz. Frequencies above 100 Hz have been termed ‘high frequency’ by

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various investigators [2, 3]. Such frequencies have often been reported to result in the failure of evoked neural responses [4, 5]. The blocking effects of high frequency alternating current (HFAC) waveforms have been variously reported since 1939 [6]. Considerable controversy about the actions and mechanisms of HFAC has prevailed since then. Bowman and McNeal evaluated the effect of voltage-controlled biphasic rectangular pulses between 100 Hz and 10 kHz and achieved a nerve conduction block above 4 kHz [7]. There appears to be a boundary frequency below which a true conduction block does not occur. A recent systematic review of HFAC stimulation and electrical nerve block demonstrates that in the kHz range, HFAC can produce a complete block of nerve conduction [8].

An electrical nerve block provides the advantages of quick onset and reversal, together with minimal side effects. Many investigators have focused on devising blocking methods for application to the lower urinary system [9, 10]. The anatomically distinct and reciprocal innervation of the urinary bladder (storage organ) and the urethra (exit conduit) lend themselves well to electrical control schemes. Sweeney *et al* [11] explored uni-directional impulse propagation for 'collision block' of the pudendal nerve. Stimuli at 300 Hz applied to the pudendal nerves have been reported to show pressure reduction by 30 to 45% [12]. Li *et al* have used 200–300 Hz stimuli to cause sphincter fatigue prior to evoked voiding [13, 14]. Applied frequencies of 600 Hz have been claimed to produce a conduction type block [15]. Tai *et al* have shown that in the pudendal nerve, isolated from the spinal cord, evoked responses could be blocked with HFAC above 7 kHz [16]. They pointed out that the effectiveness of HFAC to produce block should be evaluated in animals with intact pudendal nerves, to allow the external urethral sphincter (EUS) to respond to both direct pudendal evoked responses and to centrally generated reflexes.

The objective of this study was to quantify the stimulus parameters and effectiveness of high frequency alternating current sinusoidal waveforms that produce a reversible pudendal nerve block and reduce evoked external urethral sphincter pressure. We tested a range of sinusoidal HFAC inputs from 1 to 30 kHz to explore the HFAC block on the pudendal nerves in anesthetized, neurologically intact animals. Our results demonstrate that a complete reversible conduction block of the pudendal nerve can be achieved in this range of frequencies.

2. Materials and methods

2.1. Experimental preparation

This study was conducted on six sexually mature, non-neutered male cats with average body weight of 3.0 kg. Anesthesia was induced with ketamine hydrochloride (Fort Dodge Laboratories, Fort Dodge, IA), 30 mg kg^{-1}, IM and maintained with alpha-chloralose (Sigma, St. Louis, MO) 60 mg kg^{-1}, IV by a cephalic venous line, continued at 15 mg kg^{-1} as required. Animals were intubated and respiration maintained with a pressure-regulated respirator and expired pCO_2 monitor. The level of anesthesia was supervised by monitoring blood pressure through a central arterial line, heart rate and withdrawal and blink reflexes. Warm 0.9% saline with 8.4 mg ml^{-1} sodium bicarbonate and 5% dextrose was administered at 10–20 mL kg^{-1} h^{-1}, and body temperature was maintained at between 37 and 39 °C with a thermal blanket. Gentamycin sulfate (Phoenix Scientific, St. Joseph, MO) 5 mg kg^{-1} IM was given pre-operatively.

The urinary bladder was exposed through a suprapubic midline incision. Both ureters were exposed, ligated close to the trigone and transected proximal to the ligation. External drainage tubes were placed close to the proximal portion of the transected ureters. A 3.5F catheter (Sherwood Medical, St. Louis, MO) with a side and end port was placed in the

dome of the bladder and secured by a sero-muscular purse string suture. The abdominal incision was closed in layers and the skin sutured.

The pudendal nerve (PN) trunk after its exit from the sciatic notch was exposed through a postero-lateral gluteal approach. A molded tripolar nerve cuff electrode fabricated in this laboratory was implanted on the distal part of the nerve trunk before it branched, for the HFAC block (figure 1, the block electrode, BE). A shorter cuff electrode was placed on the proximal part of the nerve trunk, bipolar in three animals and tripolar in three (proximal stimulation electrode, PSE). The urinary bladder was emptied and drained by the suprapubic catheter. All animal care and experimental procedures were conducted after prior approval by the institutional animal care and use committee.

2.2. Electrical stimulation

A constant current stimulator (6bp-a, Pulsar, Bowdoinham, ME) was used with the PSE and pudendal nerve recruitment curves were recorded for the evoked EUS responses. Stimulus pulses (100 μs wide at supramaximal amplitude) at frequency 1 Hz were applied for evaluating twitch responses or at 20 Hz for testing tetanic responses. The tripolar BE was connected to a waveform generator (Wavetek 395, Fluke, Everett, WA) to generate a voltage-controlled high frequency sinusoidal wave train. A 3 μF capacitor was placed in series on both lines of the waveform generator to minimize dc leakage. All pulse trains were manually initiated during each trial.

2.3. Signal transduction

The suprapubic bladder catheter was connected to a programmable infusion pump (Genie, Kent Scientific, Litchfield, CT) for bladder filling and to an external pressure transducer (DPT-100, Utah Medical, Midvale UT) for recording the bladder pressure. External urethral sphincter pressures (P_{EUS}) were recorded with a micro-transducer mounted 3.5F catheter (AR4F2, Medical Measurements Inc., Hackensack, NJ) positioned at the location of maximum urethral pressure. All transducers were zeroed and calibrated before each experimental session. Pressure signals were conditioned with a set of universal amplifiers (G4615–58, Gould, Valley View, OH), amplified and low pass filtered (cutoff frequency = 300 Hz). Channels were sampled at 2.5 to 10 kHz on a digital data acquisition system (CDAT16, Cygnus Technologies, Delaware Water Gap, PA) and also recorded on a paper chart recorder (TA-11, Gould, Valley View, OH).

2.4. Experimental procedure

A preliminary set of trials with frequencies in the range of 1 to 30 kHz at 10 V was performed randomly to explore the block response (‘V’ indicates peak to peak voltage of the sinusoidal waveform). Each trial was run by applying the sinusoidal HFAC wave train to the BE on one pudendal nerve and recording the sphincter pressure. Depending on the block response, four HFAC stimulus frequencies with four amplitudes each were then selected for a randomized set of repeated trials.

For each trial, low frequency stimulation was started through the PSE and continued through the duration of the trial. After 5 s, the high frequency stimulus on the BE was begun and maintained for 20–30 s. Proximal stimulation pulses were continued for at least 5 s after the cessation of the HFAC block. An interval of about 2 min was given between successive trials. In 21 of these 131 trials, a hand-held bipolar hook electrode (distal stimulation electrode, DSE, figure 2) was used to apply stimulation to the pudendal nerve distal to the blocking electrode BE. Low frequency stimulus was started on the PSE and after at least 5 s, the HFAC was applied to the BE. While the HFAC was being applied, a 0.5 Hz low frequency stimulus was applied to the hook electrode DSE. This stimulus at the DSE, by

evoking EUS twitches during HFAC at the BE, ruled out fatigue of the EUS, thereby indicating a localized nerve conduction block at BE.

Another set of 33 trials was carried out with a 20 Hz suprathreshold stimulus applied proximally to produce tetanic contraction of the EUS. The HFAC sinusoidal stimulus was applied to the blocking electrode BE, as in the previous trial set. Additional 70 trials were conducted without any proximal or distal stimulus to record the sphincter response to the HFAC stimulus alone.

In four animals, voltage thresholds for the HFAC block were determined. The threshold was defined as the lowest voltage of the sinusoidal waveform that maintained the complete block. 1 Hz suprathreshold stimulus was applied to the PSE to produce sphincter twitches. The HFAC sinusoidal input to the block electrode BE was then started at 10 V to produce a block of the proximally evoked twitches. The HFAC amplitude was reduced in steps of 1 V until responses to the proximal stimulus reappeared. The lowest voltage at which the complete block persisted was identified as the block threshold for that particular frequency.

2.5. Block ratios

Block ratios were used to quantify block effectiveness. The block ratio was 1 for the complete block, decreased for the incomplete block and was 0 for no block as shown in figure 3. For the block trials without stimulation applied to the PSE, the degree of block was computed as [1 – (change from baseline at minimum reached during HFAC stimulus/pre-block basal pressure in the EUS)]. For the block trials with 1 Hz proximal stimulation, the degree of block was computed as a ratio of average pre-block proximally evoked pressure in the EUS spikes to the average evoked pressures during the HFAC block. The minimum pressure during the block was used when no proximal spikes could be detected during the block. For the block trials with 20 Hz tetanic proximal stimulation, the degree of block was computed as a ratio of average pre-block evoked pressure in the EUS to the minimum pressure during the HFAC block.

2.6. Data analysis

Digitized data sets were processed using commercial software programs (MATLAB, Math Works, Natick, MA and IGOR Pro, Wave Metrics Inc., Lake Oswego, OR) to derive the required data variables. Extracted data were analyzed using a commercial statistical software package (JMP, SAS Institute, Cary, NC). A one-way fixed effects analysis of variance (ANOVA) model was applied to the data sets to test the null hypothesis of equality of means, to determine the influence of each of the independent parameters as well as interactions between the parameters on the response variables. The control variables were: animal ID, trial number, side of tested nerve (right or left), HFAC frequency, HFAC voltage and type of proximal stimulus (1 Hz, 20 Hz or none). For the randomized trial sets, the output EUS response variables were (a) pre-trial baseline pressure, (b) average evoked pressure from five proximal stimulus pulses before application of the HFAC block, (c) maximum pressure response to HFAC, (d) minimum pressure during the block (or average of proximal stimulus induced spikes during partial block), (e) time to minimum during block and (f) average evoked pressure from five proximal stimulus pulses after termination of the HFAC block.

3. Results

The EUS typically responded to the onset of HFAC stimulation by a large magnitude pressure spike from baseline levels (figure 2). This was usually followed by a variable decay phase to a minimum value. This decay response often showed a repetitive activity pattern,

particularly when the block was incomplete. The block of the proximally generated EUS contractions became apparent when the pressure decayed low enough to reveal an absence of the twitch response. When a 1 Hz stimulus was applied to the proximal nerve trunk, the HFAC response was preceded and followed by EUS twitches from this proximal input. The block of EUS response to proximally generated twitches was achieved in all the animals within the range of frequencies tested between 1 and 30 kHz. The voltage range for the block varied between 1 and 10 V. Proximally evoked twitch responses usually reappeared within the first second of cessation of the HFAC stimulus.

For each trial run, the baseline pressure was determined from the EUS pressure records before the onset of input stimulus to the electrodes. The mean baseline pressure was 25.7 cm of water over all trials (range from 53.6 to 0.41 cm of water), establishing the basal urethral closure pressure under experimental conditions. The average baseline pressures were different between the experimental animals ($p < 0.01$), but the difference was not significant across the tested blocking frequencies over all the trials ($p < 0.15$).

3.1. Response to HFAC

The means of the absolute onset responses and the evoked peak above baseline to HFAC stimulus were 148.8 cm of water (S.E = 5.48, $n = 234$) and 123.1 cm of water (S.E. = 5.70), respectively over all trials. The differences in the maximum pressures were significant at $p < 0.01$ between the experimental animals. A linear fit of peak response to input frequency showed an inverse relationship with both the input frequency, significant at $p < 0.001$ and with the applied voltage ($p < 0.001$). The mean time to reach minimum pressure from the onset of HFAC was 12.6 s (S.E. = 0.77, range from 72.83 s to 0.11 s). This time course of decay is the same as the time to block onset (where the block could be complete or incomplete). There were significant differences between the experimental animals in the time to minimum pressure ($p < 0.01$) and the necessary applied voltage ($p < 0.1$), but not the applied blocking frequency ($p < 0.99$). The average pressure from pre-HFAC proximal stimulation and the pressures at minimum did not show any significant relationship to the applied HFAC frequency ($p < 0.83$ and $p < 0.69$ respectively).

3.2. Block effectiveness

The complete block of evoked sphincter responses was achieved in every animal tested. The HFAC block was observed over all the tested frequency range. For the block trials without stimulation applied to the PSE, the average block ratio was 1.055 ± 0.410 ($n = 70$, median = 0.997, range: 0.110–1.682, figure 3(a)). For the block trials with 1 Hz proximal stimulation, the average block ratio was 0.803 ± 0.517 ($n = 131$, median 1.01, range: 0.058–1.456, figure 3(b)). For the block trials with 20 Hz tetanic proximal stimulation, the average block ratio was 1.009 0.142 ($n = \pm 3$ (c)). The 33, median = 1.04, range: 0.515–1.160, figure frequency range at which maximum block could be obtained varied between the animals. The differences in the block ratios between the experimental animals were significant at $p < 0.03$, but not significant for the applied blocking frequencies ($p < 0.43$) or with the applied voltages ($p < 0.77$).

3.3. Validation of the conduction block

In 21 of the 131 trials with proximal 1 Hz stimulus, low frequency stimulus was applied during HFAC stimulus by a hook electrode (DSE) on the deep perineal branch distal to the blocking cuff BE (figure 2). Twitches were evoked in the EUS, by the DSE stimuli, during the HFAC block input above 1 kHz to the BE. This demonstrated that the reduction in the EUS response during the HFAC block was not due to neuro-muscular junction fatigue at the nerve terminals.

3.4. Recovery following block

With applied proximal low frequency stimuli, there was a linear relationship ($p < 0.0001$, R^2 0.758) between average evoked pressure before application=of HFAC and the average evoked pressure after cessation of the HFAC block. The quick reversibility of the HFAC block was demonstrated by the recovery of the proximally generated response by 75% within the first 5 s of cessation of HFAC.

3.5. Block thresholds

Block thresholds were determined for sets of frequencies in four of the six experimental animals (figure 4). There was a linear relationship ($p < 0.0001$, $R^2 = 0.6045$, $n = 65$) applied sinusoidal between the block threshold voltage and the frequency. In some of the trials, block thresholds could not be determined at the highest frequencies because they were above the 10 V range of the equipment.

4. Discussion

This study showed that high frequency stimulus in the range from 1 to 30 kHz applied to the pudendal nerve could block external urethral sphincter contractions. Complete, reversible block of the pudendal nerves was obtained in all six experimental animals. Action potential transmission is an all-or-none phenomenon. The partial block of a peripheral nerve trunk implies the block of a subset of its axon population. We derived block ratios to quantify the degree of the block in each trial, with or without proximal stimulation, so that in each case 100% block was indicated by an index of 1 and no block by 0. The block ratios were 1 or greater (complete block) in 54% of the 234 individual trials. Our results demonstrate that the complete block could be achieved at varying stimulus amplitudes (range 1 V to 10 V), over the tested frequency range of 1 to 30 kHz. The optimum frequency window for the complete block over the tested range varied between animals. The HFAC conduction block has been previously reported in the cat pudendal at frequencies over 7 kHz [16] and the rat common peroneal nerve at frequencies above 10 kHz [17, 18].

This study used randomized, repeated trials to characterize the stimulus parameters and effectiveness of HFAC sinusoidal waveforms to produce the reversible pudendal nerve block and reduce evoked external urethral sphincter pressure. Such a study design allowed us to quantify the variability of the block response and amplitude–frequency relationship. An improved understanding of the pudendal nerve block is required to conduct functional voiding studies that may require bilateral block.

We utilized an experimental preparation in neurologically intact animals, without disruption of the spinal connections of the pudendal nerves, to allow the EUS to respond to direct pudendal evoked responses and also to centrally generated reflex activation, although the latter could be affected by the administered anesthetic [19]. This preparation allowed us to determine if the HFAC or the proximal stimulus signals traveling into the cord would initiate reflex contractions through the contralateral pudendal nerve. The presence of contralateral reflex contractions could affect the ability to produce the urethral sphincter block and achieve voiding. In our experiments, there were no apparent differences in the minimum EUS pressure during the complete block when compared to the pre-baseline pressure. These results appear to show that when the ipsilateral pudendal block was achieved, HFAC stimulation was not activating pathways that generate contralateral pudendal signals. Whether the absence of reflex activity was due to the specific properties of the onset response or to the specific experimental conditions (e.g. degree of bladder filling) is unknown and requires further study.

Our results demonstrated that the amplitude threshold for the HFAC block increased with stimulus frequency (figure 4). The data showed that the voltage–frequency relationship could be linear down to 1 kHz. Previously, we have shown that the voltage–frequency relationship for the block threshold in the rat sciatic nerve was linear over 10–30 kHz [17]. The ANOVA showed that the effect due to frequencies gave a probability <0.0001 (F = 46.89), whereas the variability due to animals was p <0.3292 (F = 1.1684). The threshold values in the cat pudendal were approximately 2.5–3 V higher than in the rat sciatic nerve, although the electrodes used in these two studies were essentially identical. This could be due to differences in the average nerve diameter (larger nerves are likely to require higher voltage to block [18]), fiber type (smaller fiber diameters should be more difficult to block [23, 24]) or to other experimental factors not yet identified.

The HFAC stimulus resulted in an onset response. This was characterized by a period of repetitive firing of the axons and resulted in a peak EUS pressure followed by a variable time decay to baseline pressure. The block was testable after this point and the block could be complete or incomplete depending on the frequency and amplitude parameters. The mean time to reach the minimum pressure was 12.6 s. We have shown previously in amphibian experiments that the block occurs extremely fast and with minimal continued activity of the nerve. However, the mammalian HFAC block has larger onset responses and longer initial activity, as previously shown in the rat sciatic nerve [18]. The onset response could be functionally undesirable in some applications. However, in producing micturition, a few seconds delay before the sphincter block is achieved may not affect voiding over the ensuing period. However, if the HFAC block is applied to a mixed nerve, it could result in a large sensory volley. Therefore, it would be desirable to minimize the onset response as much as possible.

The linear fit of the peak of the onset response to input frequency showed an inverse relationship with both the input frequency and with the applied voltage. This was similar to our characterization of the rat sciatic nerve response to the HFAC block in the 10 kHz to 30 kHz range where the amount of repetitive activity as measured by gastrocnemius muscle force was minimal at combinations of high frequency and high amplitudes [17].

EUS twitches evoked with the distal stimulating electrode (DSE) during HFAC (figure 2) demonstrate that the reduction in the EUS response during the HFAC block was from a localized nerve block and not due to neuromuscular junction fatigue at the nerve terminals. Neuromuscular junction fatigue does occur below 1 kHz, and therefore it is important to verify a true conduction block experimentally. Other investigators have used a similar test to verify the conduction block [8, 17,18] or by recording from single fibers [7]. In addition, the HFAC block was quickly reversible as evident by the response to proximal stimuli immediately after the termination of the HFAC. The conduction block may be preferable over EUS fatigue for chronic applications.

There did not appear to be a common ideal frequency for the complete block among different animals. The degree of block varied between experiments over the frequency range. Our results seem to indicate that the frequency window for the complete block and the onset response were sensitive to the nerve–electrode interface, depending on electrode geometry and placement. We fabricated the nerve cuff electrodes used in this study with an internal diameter of 1 mm to closely conform to the feline pudendal nerve trunks at their exit from the sciatic notch. This helped to reduce required stimulus amplitudes and prevent excessive current leakage outside the cuff [20]. Tai *et al* have used electrodes with an internal diameter of 2 mm on the cat pudendal to study HFAC block responses [21]. Their published results show block of evoked responses above 7 kHz and absence of block below that frequency. Our previous experience with the HFAC block of the rat sciatic nerve

showed the importance of the electrode, specifically its size, conformity and stability [17]. Our observations suggest that electrode conformity could be an important influencing factor for the effectiveness of the HFAC block. Further experiments are needed to confirm this hypothesis.

The mechanism by which HFAC blocks nerve conduction has not been determined experimentally. We have previously reported modeling results of the HFAC block in the mammalian axon model [8] which showed incremental depolarization of the nodal and paranodal regions with each successive cycle of the sinusoidal block waveform until all the nodes showed a dynamic depolarization profile with a peak at the node nearest to the electrode. We identified this widespread depolarization as a likely mechanism of block [8] and some of the characteristics showed similarities to the direct current depolarization block [22]. Other investigators have alluded to the same depolarization mechanism [18, 23]. Tai *et al* [24] proposed a mechanism based solely on potassium inflow. Further research must be conducted in order to identify the true mechanism responsible for the HFAC conduction block.

Block ratios greater than 1 were obtained, suggesting that EUS residual tone could be decreased with HFAC. However, the EUS pressure records often showed a baseline shift between the HFAC block trials. We attempted to eliminate any shift due to change in the urethral position of the micro-transducer catheter by fixing it to the prepuce. However, we could not rule out perineal and pelvic floor movements contributing to the baseline drift following HFAC application. Although we could observe the absence of twitches to proximal stimulus of the external anal sphincter (EAS) during the HFAC block, we did not simultaneously transduce EAS pressures. The differences in the block ratios between the experimental animals were significant at $p < 0.03$, primarily because of the results from one animal. There were no significant differences in the blocking frequencies ($p < 0.43$) or applied voltages ($p < 0.77$) among all the animals.

Data regarding the chronic effects of HFAC are not yet available. Sinusoidal electrical waveforms by the nature of their geometry are symmetrically charge balanced and the total charge is independent of frequency. Important stimulus parameters that contribute to the safety of electrical stimulation at neural tissue interfaces are charge density, charge per phase and frequency. The impedance of electrodes of this design is approximately 1.5 kOhm at 10 kHz. Therefore, the peak to peak current for the 10 V maximum stimulus amplitudes used for these studies is calculated to be approximately 7 mA. This gives rise to a maximum charge of 1.1 μC per phase at 1 kHz (charge density of 0.37 μC mm^{-2}), which is within the reported range of safety limits [25]. However, it is not clear that the previously established safety limits, which were determined for frequencies below 50 Hz, can be directly applied to the HFAC block. In our experiments, the HFAC block was quickly reversible as is evident by the return of the EUS response to proximal stimuli immediately after the end of the HFAC, and no decreases in nerve conduction were observed over several hours of testing, suggesting that HFAC does not acutely cause damage. Furthermore, relatively low duty cycles of HFAC are required for clinical voiding systems and will have an impact on the safety of its application.

Complete, quickly reversible EUS block could provide a valuable tool for the treatment of voiding dysfunction in individuals with DSD. This study demonstrated that complete block could be achieved in neurologically intact animals with active sphincter reflexes. High frequency pudendal block could be an alternative for external sphincterotomy, which is a mainstay in the management of DSD [26]. One approach toward a functional neural prosthetic device to produce voiding in individuals with DSD would be to combine the pudendal block with sacral root stimulation for bladder voiding, similar to that by Sweeney

et al [11] who tested the collision block of the pudendal nerves. The pudendal block may also be combined with reflex afferent activation [27] for producing controlled bladder evacuation. The block characterization data presented in this study may be used to design such voiding studies.

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References

[1]. de Groat WC. Anatomy and physiology of the lower urinary tract. Urol. Clin. North Am. 1993; 20:383–401. [PubMed: 8351765]

[2]. Andersen H, Nielsen JF, Sorensen B, Nielsen VK. Effect of ischemia and cooling on the response to high frequency stimulation in rat tail nerves. J. Peripher. Nerv. Syst. 2000; 5:22–6. [PubMed: 10780680]

[3]. Moser A, Gieselberg A, Ro B, Keller C, Qadri F. Deep brain stimulation: response to neuronal high frequency stimulation is mediated through GABA(A) receptor activation in rats. Neurosci. Lett. 2003; 341:57–60. [PubMed: 12676343]

[4]. Kiernan MC, Hales JP, Gracies JM, Mogyoros I, Burke D. Paraesthesiae induced by prolonged high frequency stimulation of human cutaneous afferents. J. Physiol. 1997; 501(part 2):461–71. [PubMed: 9192317]

[5]. Robinson LR, Nielsen VK. Limits of normal nerve function during high-frequency stimulation. Muscle Nerve. 1990; 13:279–85. [PubMed: 2355940]

[6]. Reboul J, Rosenblueth A. The blocking and deblocking effects of alternating currents on nerve. Am. J. Physiol. 1939; 125:251–64.

[7]. Bowman BR, McNeal DR. Response of single alpha motoneurons to high-frequency pulse trains. Firing behavior and conduction block phenomenon. Appl. Neurophysiol. 1986; 49:121–38. [PubMed: 3827239]

[8]. Kilgore KL, Bhadra N. Nerve conduction block utilising high-frequency alternating current. Med. Biol. Eng. Comput. 2004; 42:394–406. [PubMed: 15191086]

[9]. van Balken MR, Vergunst H, Bemelmans BL. The use of electrical devices for the treatment of bladder dysfunction: a review of methods. J. Urol. 2004; 172:846–51. [PubMed: 15310981]

[10]. Bhadra N, Grunewald V, Creasey GH, Mortimer JT. Selective suppression of sphincter activation during sacral anterior nerve root stimulation. Neurourol. Urodyn. 2002; 21:55–64. [PubMed: 11835425]

[11]. Sweeney JD, Mortimer JT, Bodner DR. Acute animal studies on electrically induced collision block of pudendal nerve motor activity. Neurol. Urodyn. 1989; 8:521–36.

[12]. Ishigooka M, Hashimoto T, Sasagawa I, Izumiya K, Nakada T. Modulation of the urethral pressure by high-frequency block stimulus in dogs. Eur. Urol. 1994; 25:334–7. [PubMed: 8056028]

[13]. Li JS, Hassouna M, Sawan M, Duval F, Elhilali MM. Electrical stimulation induced sphincter fatigue during voiding. J. Urol. 1992; 148:949–52. [PubMed: 1512865]

[14]. Li JS, Hassouna M, Sawan M, Duval F, Elhilali MM. Long-term effect of sphincteric fatigue during bladder neurostimulation. J. Urol. 1995; 153:238–42. [PubMed: 7966780]

[15]. Shaker HS, et al. Reduction of bladder outlet resistance by selective sacral root stimulation using high-frequency blockade in dogs: an acute study. J. Urol. 1998; 160(3 part 1):901–7. [PubMed: 9720585]

[16]. Tai C, Roppolo JR, de Groat WC. Block of external urethral sphincter contraction by high frequency electrical stimulation of pudendal nerve. J. Urol. 2004; 172(5 part 1):2069–72. [PubMed: 15540791]

[17]. Bhadra N, Kilgore KL. High-frequency electrical conduction block of mammalian peripheral motor nerve. Muscle Nerve. 2005; 32:782–90. [PubMed: 16124008]

[18]. Williamson RP, Andrews BJ. Localized electrical nerve blocking. IEEE Trans. Biomed. Eng. 2005; 52:362–70. [PubMed: 15759566]

[19]. Rudy DC, Downie JW, McAndrew JD. a-chloralose alters autonomic reflex function of the lower urinary tract. Am. J. Physiol. 1991; 261:R1560–R7. [PubMed: 1750580]

[20]. Mortimer, JT.; Bhadra, N. Peripheral nerve and muscle stimulation. In: Horch, K.; Dhillon, GS., editors. Neuroprosthetics: Theory and Practice. World Scientific; NJ: 2002. p. 638-82.

[21]. Tai C, Roppolo JR, de Groat WC. Response of external urethral sphincter to high frequency biphasic electrical stimulation of pudendal nerve. J. Urol. 2005; 174:782–6. [PubMed: 16006976]

[22]. Bhadra N, Kilgore KL. Direct current electrical conduction block of peripheral nerve. IEEE Trans. Neural Syst. Rehabil. Eng. 2004; 12:313–24. [PubMed: 15473193]

[23]. Tanner JA. Reversible blocking of nerve conduction by alternating-current excitation. Nature. 1962; 195:712–3. [PubMed: 13919574]

[24]. Tai C, de Groat WC, Roppolo JR. Simulation of nerve block by high-frequency sinusoidal electrical current based on the Hodgkin–Huxley model. IEEE Trans. Neural Syst. Rehabil. Eng. 2005; 13:415–22. [PubMed: 16200764]

[25]. Merrill DR, Bikson M, Jefferys JG. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J. Neurosci. Methods. 2005; 141:171–98. [PubMed: 15661300]

[26]. Reynard JM, Vass J, Sullivan ME, Mamas M. Sphincterotomy and the treatment of detrusor-sphincter dyssynergia: current status, future prospects. Spinal Cord. 2003; 41:1–11. [PubMed: 12494314]

[27]. Gustafson KJ, Creasey GH, Grill WM. A urethral afferent mediated excitatory bladder reflex exists in humans. Neurosci. Lett. 2004; 360:9–12. [PubMed: 15082166]

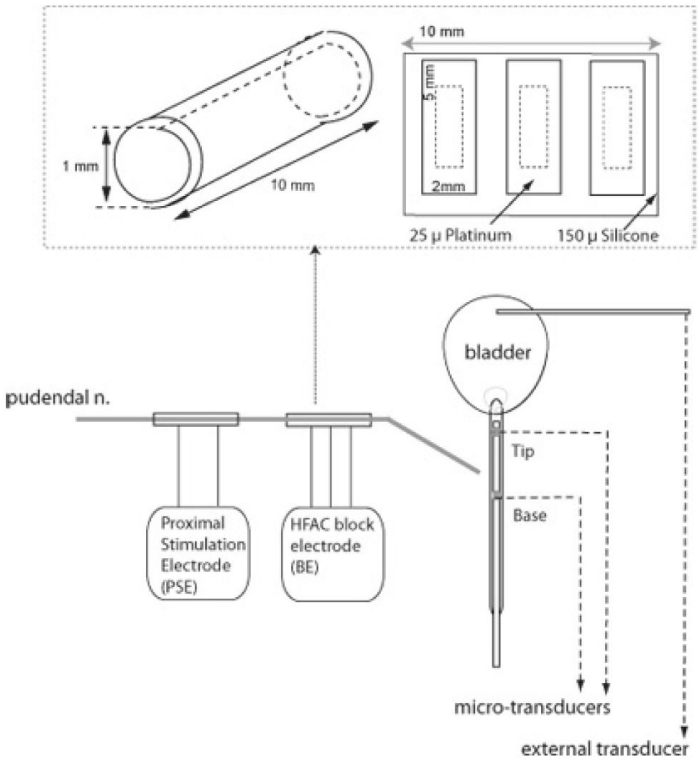

Figure 1.
Schematic of experimental setup with two nerve cuff electrodes on the pudendal nerve and instrumentation for pressure recording from bladder and EUS. Inset shows details of the nerve cuff electrode design used for the HFAC block.

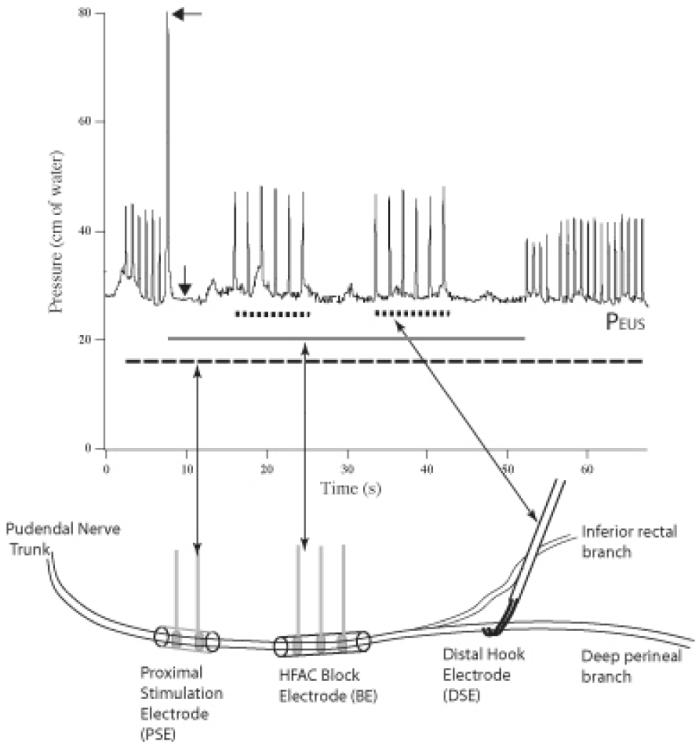

Figure 2.

Electrodes on pudendal nerve (bottom) and responses (top) to applied proximal and distal stimulation with the HFAC sinusoidal block. Horizontal arrowhead points to the peak onset response. Vertical arrowhead points to the minimum pressure during block. Lower dotted line: proximal stimulus at 1 Hz applied with cuff electrode PSE on left. Solid line: HFAC applied with cuff electrode BE at center. Upper dotted lines: distal stimulus at 0.5 Hz with hook electrode DSE. The evoked EUS twitches from stimulus at the DSE, during HFAC input, ruled out fatigue of the EUS.

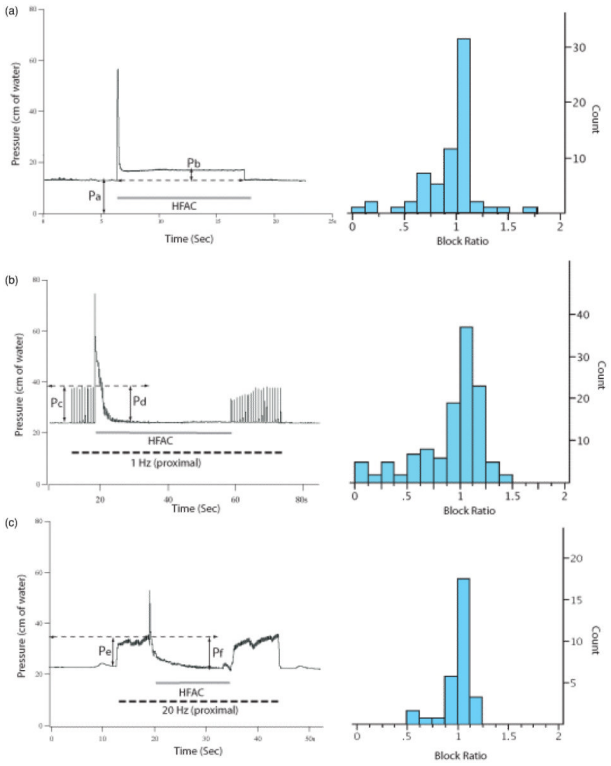

Figure 3.

Typical EUS pressure responses to HFAC are shown in the traces on the left, with histograms of block ratios on the right. In each case, 1 = complete (100%) block, 0 = no block. **(a)** Block ratio without proximal stimulation; $(1 - P_b/P_a)$ 1 – (minimum EUS pressure during block/pre block baseline pressure), $n = 70$, mean = 1.055 ± 0.410. (**b**) Block ratio with proximal 1 Hz stimulation; P_d/P_c = ratio (average pre block response–minimum response during block)/average pre block response; $n = 131$, mean = 0.803 ± 0.517. **(c)** Block pre block response; with proximal 20 Hz stimulation; P_f/P_e = (average pre block response–minimum response during block)/average pre block response; $n = 33$, mean = 1.009 ± 0.142.

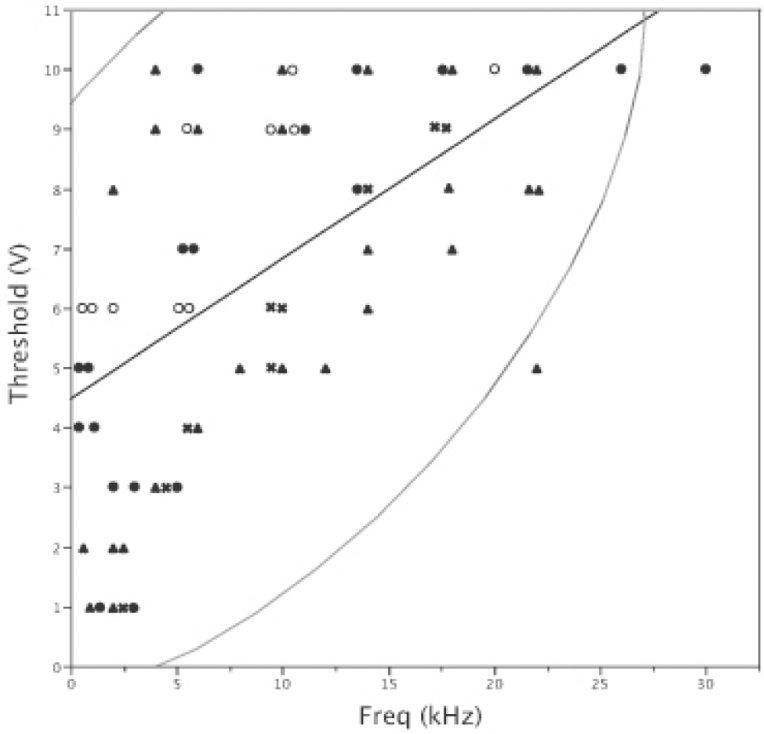

Figure 4.
Threshold voltage and HFAC frequency, with a linear regression fit line ($p < 0.0001$) and bivariate normal ellipse (p 0.950). The individual trials for each of the four test animals are= shown by different markers. The data show an increase in the voltage required to achieve complete HFAC block, with increasing frequency.