High-frequency blockade of the pudendal nerve using a transcutaneously coupled stimulator in a chronically implanted cat

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Abstract

A loss of voluntary drive to the external urethral sphincter (EUS) as a result of spinal cord injury (SCI) often causes EUS hyperreflexia and an inability to empty the bladder. High-frequency (HF) electrical stimulation of the pudendal nerve (PN) has been demonstrated by a number of investigators to produce a fast acting and reversible block of action potential propagation providing the ability to block unwanted EUS contractions.

We have previously shown in terminal experiments that a passive, transcutaneously coupled stimulus delivery system, or “stimulus router system” (SRS), can transmit HF pulse trains leading to blockade of proximally generated action potentials in the PN. We now report on our first experiences with a chronically implanted system. One cat was implanted with the SRS on the PNs bilaterally. Multiple evaluations under anesthesia over the course of two months have confirmed the effectiveness of HF stimulation in blocking ongoing EUS contractions. In addition, HF stimulation has been performed in the awake animal and was well tolerated. These results suggest that the SRS combined with HF stimulation could form the basis of a simple neuroprosthesis to aid in the management of EUS dysfunction after SCI.

1 Introduction

Bladder and EUS dysfunction often occur as a result of SCI and other conditions of both neurogenic and non-neurogenic origin. Normally, activity of the bladder and EUS is coordinated by supraspinal centres and assumes one of two states. During continence, active inhibition of the bladder and contraction of the EUS allows bladder filling without leakage. During micturition, bladder contractions accompanied by relaxation of the EUS allow low-pressure emptying of the bladder. After SCI, concomitant contraction of the bladder and EUS can prevent voiding and lead to elevated intravesical pressures and upper urinary tract deterioration.

Many attempts to develop neural prostheses to restore bladder and sphincter function after SCI have been made [1]. However many of the resulting devices have been either ineffectual or poorly tolerated. One recent effort to develop neural prostheses for bladder and sphincter control has focussed on using HF stimulation of the PN (which innervates the EUS) to block ongoing EUS contractions by blocking neural conduction [2, 3]. We are investigating the feasibility of using a stimulation technique using transcutaneous coupled electrodes [4] to achieve HF blockade of the PN. The SRS uses inexpensive implanted components coupled to an external stimulator. We have previously demonstrated the effectiveness of this system in eliciting PN blockade in terminal experiments, and here report on our experiences with this system in a chronically implanted animal.

2 Methods

A chronic implant targeting the PNs was performed in one adult male cat. The cat was anesthetized with a mixture of isoflurane (2-3%) in carbogen, at a flow rate of 1-2 L/min. Respiration and heart rate were monitored throughout the procedure. Body temperature was maintained using a heating pad.

The bladder was exposed and a custom made silicone catheter was inserted and secured to the bladder wall. The catheter was routed subcutaneously to a Luer fitting embedded in an acrylic headpiece. The PNs were exposed bilaterally and nerve cuffs containing one proximal monopolar electrode and one distal bipolar electrode pair were positioned on them. The cuff electrodes were part of a custom made implant and were connected to an array of three SRS pickup electrodes mounted in a silicone
substrate. The arrays of pickup electrodes were positioned in the subcutaneous space near the lumbar vertebrae on each side. Figure 1 shows a schematic of the implant.

![Figure 1: Schematic diagram of the left and right implants. The pickup electrodes were 1 cm in diameter and were spaced 3 cm apart. Each pickup electrode was connected to a corresponding electrode in the nerve cuff as indicated in the diagram.](image)

Evaluation sessions were performed with the cat anesthetized. The skin over each pickup electrode was shaved and adhesive gel surface electrodes (Kendall H69P) were applied. An additional adhesive gel electrode (Kendall H49P) was positioned over the base of the tail to act as the indifferent (anode) electrode during monopolar stimulation.

During HF blockade testing, LF stimulation trains (20 Hz, monophasic, voltage-controlled, 200 μs pulse width) were generated by a Grass SD9 stimulator connected to the most proximal electrode (L1). LF pulse trains were used to generate EUS contractions which could be blocked by distal HF stimulation. The HF stimulation trains were current-controlled sinusoids in a bipolar configuration over pickup electrodes L2 and L3. HF pulse train amplitude and frequency were varied from trial to trial.

Bladder and intraurethral pressures (side-port catheter infusion method) were monitored to determine the effect of LF and HF stimulation on bladder and EUS function. An automated analysis of the intraurethral pressure traces was performed to extract four measures of the performance of a particular set of HF stimulation parameters: percentage nerve block, onset amplitude, 90% maximum block time, and recovery percentage. These four measures were selected to provide quantitative information regarding the completeness of the block, the size of the onset response, the time required to establish the block and the effect of the block on subsequent neural and muscular function.

3 Results

Figure 2 shows an example of HF blocking. The LF train was on for 35 s and after 10 s, the HF stimulator was turned on for 15 s. The LF train elicited a large contraction of the EUS resulting in an increase in intraurethral pressure. Bipolar HF stimulation completely abolished the EUS contraction, returning the intraurethral pressure to baseline. In both monopolar and bipolar HF stimulation cases, there was virtually no onset response (EUS contraction at the onset of HF stimulation) and the intraurethral pressure recovered to pre-block levels immediately after the HF train was stopped. This indicates that the blocking was not the result of EUS fatigue. Monopolar stimulation did not work as well as bipolar stimulation, although it may work well enough to be functionally useful.

![Figure 2: Intraurethral pressure traces during both monopolar and bipolar HF blocking. LF stimulus parameters: 20 Hz, 15 V, 200 μs pulse width, monophasic square wave. HF stimulus parameters: 6 kHz, 9 mA sinusoid.](image)

Figure 3 shows averaged data of the four measures of HF block efficacy collected over multiple sessions for each combination of stimulation amplitude and frequency. The most complete blocking was obtained with stimulation amplitudes from 7-10 mA and frequencies from 4-10 kHz (Fig. 3A). Because of the SRS, only a portion of the current (usually ~10%) delivered by the stimulus flows between the nerve cuff electrodes. All stimulation amplitudes reported here represent the output of the stimulator itself. At nearly all amplitudes and frequencies, the recovery of intraurethral pressure after HF stimulation was stopped approached 100% of the pre-block value (Fig. 3D). In addition, the onset response was minimized at frequencies > 5 kHz and amplitudes > 7 mA (Fig. 3B). The time taken...
for the intraurethral pressure to reach 90% of its minimum value during HF blocking was < 1 s for frequencies > 5 kHz and amplitudes > 9 mA (Fig. 3C).

Figure 3: Plots of the measures used to quantify the HF block performance at different stimulation frequencies and amplitudes. Shaded circles are plotted at each frequency/amplitude combination examined. Data is the average of four recording sessions. (A) Maximal block percentage obtained during a 5 s HF train. (B) Amplitude of the initial pressure response that occurred when the HF stimulation train was turned on. (C) Time required to establish the block. The circles show the delay between the onset of the HF stimulus train and the time when the intraurethral pressure reached 90% of the minimum blocking pressure. (D) Extent to which the intraurethral pressure recovered during the 10 s of LF stimulation after HF stimulation was stopped.

In addition to the results from anesthetized trials presented above, several HF stimulation trials were performed in the awake animal to evaluate possible aversion responses that might occur. Intraurethral pressure could not be recorded in the awake animal. At a constant frequency of 6 kHz, the stimulation amplitude was varied from 2 to 10 mA. The first visible response to the stimulation occurred at 5 mA. At stimulation amplitudes greater than 5 mA, there was a clear aversive response, but only at the onset of HF stimulation. The response was mild and consisted of a small whole body twitch-like reaction. No vocalizations occurred at any stimulation amplitude. This indicates that although there is a sensory volley transmitted through the PN coincident with the HF stimulation onset, no further unpleasant sensations are associated with HF stimulation.

4 Discussion and Conclusions

We have previously demonstrated the efficacy of using the SRS in combination with HF stimulation to block PN activity during terminal experiments in anesthetized animals. We have now shown that such a system can be implanted chronically and remains effective for at least two months. A functionally useful stimulation parameter range (frequency: 4-10 kHz, amplitude: 7-10 mA) was established in this animal, within which reductions in intraurethral pressure to baseline levels were achieved. The immediate and complete recovery of intraurethral pressure to pre-block amplitudes suggests that the observed results were not due to EUS fatigue. We have also demonstrated that an awake cat can tolerate HF stimulus trains at amplitudes and frequencies suitable for producing a complete PN blockade.

Although we have not directly addressed the long term safety issues associated with HF stimulation, we have seen no evidence of damage to the PN. During any given experimental session, from 4 to over 8 minutes of HF stimulation were delivered over the course of several hours.

The ultimate goal of HF blockade of the PN is to promote micturition in people with SCI. The main objective of future work will be to transfer these results into functional outcomes such as improved micturition. The simplicity of the technique and the lack of significant aversive responses to HF stimulation trains suggest that continued investigation could lead to clinical implementation of a device based on these techniques.

References


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