Selective Small Nerve Fiber Activation by Anodal Block – a Chronic Study

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Introduction

Following spinal cord injury, the control of bladder and bowel functions is commonly lost. One of the methods to restore bladder and bowel functions is through functional electrical stimulation. The most widely used, commercially available system for assisted emptying of the bladder and the bowel in SCI patients is the Finetech-Brindley bladder system [1]. To obtain voiding, it uses the technique of poststimulus voiding. Poststimulus voiding is an artificial micturition pattern, which causes voiding in spurts at supranormal bladder pressures. To accomplish more natural voiding, it would be necessary to avoid activation of the external urethral sphincter (EUS). That can be achieved by selectively activating only small diameter parasympathetic fibers. Anodal block is a stimulation technique that allows activation of small parasympathetic fibers without co-activation of large somatic fibers innervating the external urethral sphincter (EUS) and the external anal sphincter (EAS). The principle of anodal block is that both small and large fibers are activated and that the propagation of action potentials (APs) in the large fibers is blocked distal to the activation site. To obtain an anodal block, a tripolar cuff electrode is most commonly used. The central contact is the cathode and the lateral contacts are the anodes. The fibers are excited close to the cathode and the APs of large nerve fibers are blocked close to the anodes.

Anodal block for selective detrusor activation has been achieved in chronic experiments on animals [2,3] and in acute experiments on humans [4]. Selective rectum activation using anodal block was achieved only in acute experiments [5]. Although chronic studies have already been performed with anodal block, data on the performance of stimulating parameters under chronic implant, which are necessary to demonstrate the efficiency of the given method, are scarce. The aim of this study is to investigate the temporal stability of stimulating parameters of chronically implanted cuff electrodes. Anodal block is applied both for selective detrusor activation without co-activation of the EUS and for selective rectum activation without co-activation of the EAS.

Methods

Animal preparation

Experiments were performed on 7 nonspinalized female mini-pigs, weighting about 25 kg. Anaesthesia was induced by Isoflurane (1 ml/10 kg). The animals were intubated and mechanically ventilated (40% O2 and 60% N2O). Saline was administered intravenously.

A sacral laminectomy was performed in sterile conditions and the dura was opened to the entire length of the laminectomy to expose the sacral roots. Individual nerve roots were identified by their size and by responses of several muscle groups to stimulation with a bipolar hook electrode. In six pigs a split cylinder cuff electrode was implanted extradurally around the whole nerve root (S2 or S3) and in one pig intradurally around the whole S2 nerve root. Cuff electrodes were additionally closed with sutures. Lead wires were tunnelled on the side, proximally under the skin. Experiments were performed three to four weeks after cuff implantation and repeated every three to four weeks. In aseptic conditions, a small skin incision was made, the percutaneous electrode connector was taken out and connected to the stimulator.
Stimulation and Recording

A split cylinder cuff electrode with three contacts was placed around the nerve. Separation between the contacts was 3 mm, contact width was 0.5 mm and the length of the whole cuff was about 1.2 cm. Lead wires made of a Teflon-coated multi-stranded stainless steel (Cooner wire®, Chatsworth, CA) were spot-welded to the cuff platinum contacts. The subcutaneous connector was made of gold-covered contacts spot-welded to the lead wires, placed in Teflon and dipped in diluted silicone. The stimulator consisted of two synchronized current sources with a common cathode. The stimulating parameters were adjusted on a computer by means of custom-made software. Stimulation was performed with square and quasi-trapezoidal monophasic pulses with plateau duration from 100 \( \mu \text{s} \) to 1000 \( \mu \text{s} \) with a pulse train 25 Hz, 5 s.

The anal pressure was measured in the high-pressure zone of the EAS with a 9-F abdominal balloon catheter (100 ml, Life-Tech, UK). Rectal pressure was measured about 10 cm proximally from the EAS with a 12-F abdominal balloon catheter (300 ml, Medtronic, USA). Both balloons were filled to 70% of their volume. Intravesical pressure was measured with an 8-F bladder catheter (Rüsch, Kernen, Germany) with an additional 5 ml balloon to occlude the bladder and prevent the catheter from moving. Intraurethral pressure was measured with three open tip 4-F catheters (Vygon, Ecouen, France) fixed with a suture to the bladder catheter. The openings of the catheters were 1 cm apart. The most proximal one had the opening 2 cm below the bottom of the balloon catheter.

The catheters were perfused with a continuous flow of 3 ml/h. The sites of pressure measurement are referred to, starting from the most proximal, as U1, U2 and U3. Before starting the recording the bladder was manually evacuated with a syringe and then filled with 100 ml saline at body temperature (approximately 39°C). In some experiments wire electrodes were placed in the anal sphincter for recording of EMG. The impedance between the electrode contacts was measured with an impedancemeter using a sine wave at 1 kHz.

For displaying and recording pressures BioBench (National Instruments) was used. The sampling frequency was 10 samples/s. The amplified (5000x) and filtered (20-200 kHz) EMG was visualized by a portable oscilloscope (Fluke) and transmitted to an on-line PC for displaying and recording the data in custom made software developed in LabView (National Instruments).

Figure 1. Intraurethral pressure responses \( P_{U1}-P_{U3} \) (U1 being the most proximal) and anal pressure response \( P_A \). Stimulation with 600 \( \mu \text{s} \) square pulses, with a pulse train 5s, 25 Hz. Pig AV6, two months after implantation.
Results

Cuff electrodes were chronically implanted in 7 pigs. A total of 11 cuff electrodes were implanted, with 9 on sacral root S2 and 2 on sacral root S3. Inner electrode diameters ranged from 1.8 mm to 3.2 mm. There were no responses from two electrodes and two electrode connectors were broken at the first experiment. The chronic experiments lasted from 2 to 8 1/2 months. Anodal block was achieved in 4 pigs. The somatic fibers in the sacral roots of two pigs had a very high excitation threshold (4 mA for a 600 µs square pulse) and in one pig it was not possible to avoid some leakage of current outside the cuff.

As anodal block should be applied to large nerve fibers, the nerve roots which upon stimulation gave the highest intraurethral and anal pressure responses were chosen. In two pigs in which anodal block was achieved, the same nerve root contained parasympathetic fibers innervating the detrusor muscle and the rectum together with somatic fibers innervated the EUS and the EAS. Temporal stability of various parameters is given in Table 1.

<table>
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<tr>
<th>Impedance</th>
<th>Decreased during the first 2-4 months, then increased or remained stable. If the impedance remained low, no anodal block was achieved. In only one pig, after 4 1/2 months, impedance became higher than during the implantation.</th>
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<tr>
<td>Excitation threshold</td>
<td>Increased while the impedance decreased, decreased with increase of the impedance. Increase was more pronounced in somatic than in parasympathetic fibers (pig AV1 excitation threshold 3 ½ months after the implantation: parasympathetic 0.8 mA, 600 µs, somatic 1.2 mA, 600 µs). The somatic fibers innervating the EUS and the EAS initially had the same excitation threshold but started to differ with time.</td>
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<td>Blocking threshold</td>
<td>Increased by time. Square or quasi-trapezoidal pulses applied (plateau duration 400-800 µs, exponential decay 400 µs, amplitude 1-3.8 mA). In some cases anodal block was not possible during first several months after the implantation. The increase of the blocking threshold was less than increase of the excitation threshold</td>
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<td>Pressure response</td>
<td>Remained stable or decreased by time. Compared to the initial pressure, intraurethral pressure responses in the zone of the EUS varied from 23 % to 100 % and anal responses varied from 0 % to 70 % (results from 4 pigs, electrodes implanted 3 ½ to 8 months).</td>
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Table 1

Figure 1 shows that somatic nerve fibers innervating the EUS (P_{U2}) and the EAS (P_{A}) have different excitation thresholds (EUS 1.5 mA, EAS 1.7 mA). It also shows that somatic fibers innervating the EUS in two intraurethral measurement points (P_{U2} and P_{U3}), have different excitation thresholds (1.5 mA for U2 and 1.7 mA for U3) and that muscles that are innervated by these nerve fibers behave differently to nerve stimulation: intraurethral pressure P_{U2} increased and intraurethral pressure P_{U3} (distally from P_{U2}) decreased. The current amplitude was too low to excite the efferents innervating the smooth muscle of the urethra in the high-pressure zone (P_{U1}). Figure 2 shows anodal block of somatic fibers of the S2 nerve root of the pig AV5, innervating the EUS and the EAS, 4 1/2 months after the cuff implantation.

Histopathological analysis

Histopathological analysis showed perineurial thickening and increased endoneurial connective tissue. Collagen existed between single nerve fibers in the fascicles even when nerve fibers were well preserved, and excitation and blocking thresholds were low (pig AV3). In the nerve which had a very high excitation threshold (pig AV2), demyelination of nerve fibers was noticed. In the same pig, nerve cross-sections distally from the cuff showed a decrease of connective tissue and increased number of myelinated axons. Nerves on which anodal block was achieved showed much thinner perineurium and endoneurial connective tissue. A large number of lymphocytes and plasma cells, as well as foreign body giant cells, were noticed.
Discussion

This study shows that it is possible to obtain anodal block during a period of several months. The nervous tissue had a strong inflammatory response to implanted cuff electrodes, which produced a thick layer of connective tissue. The thickness of perineurium and endoneurial connective tissue could be decreased by using a less stiff electrode. Decrease of the impedances caused increase of excitation and blocking thresholds. Increase of excitation threshold in the first months after the cuff implantations was also induced by a decreased number of myelinated axon. Nerve damage was partially induced during the implantation procedure, and in some cases recovery was noticed after several months. Experiments with an implanted stimulator would probably allow a longer duration of experiments and better recovery of nerves.

![Figure 2. Anodal block of somatic fibers innervating the EUS and the EAS with a quasi-trapezoidal pulse (plateau 600 µs, exp. decay 400 µs, 1.4 mA) and excitation with a square pulse (1.4 mA, 100 µs). Pulse train 5s, 25 Hz. Bars indicate stimulation. Pig AV5, 4 ½ months after cuff implantation.](image)

References


Acknowledgments: This work was supported by Danish Technical Research Council. The authors wish to thank Li Haisheng MD, Qingyun Xue MD and Zou Xuenong for assistance during experiments, to Claus Mosdal MD, for intradural cuff implantation and Karsten Nielsen MD for histopathological analysis.