

# Conditioning Stimulus Can Influence an External Urethral Sphincter Contraction Evoked by a Magnetic Stimulation

Bjoern Wefer,<sup>1,2\*</sup> André Reitz,<sup>1</sup> Peter A. Knapp,<sup>1</sup> Andreas Bannowsky,<sup>2</sup>  
Klaus-Peter Juenemann,<sup>2</sup> and Brigitte Schurch<sup>1</sup>

<sup>1</sup>Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Zurich, Switzerland

<sup>2</sup>Department of Urology, Campus Kiel, University Hospital of Schleswig-Holstein, Germany

**Aims:** To study the effect of a conditioning stimulus on an external urethral sphincter (EUS) contraction evoked by a magnetic stimulation at different time intervals. **Methods:** Seven healthy male volunteers underwent EUS pressure measurement. At baseline, magnetic stimulation of the lumbosacral spinal cord above the motor threshold was performed and evoked EUS pressure responses were recorded. The lumbosacral magnetic stimulation was repeated with same intensity, while a selective electrical dorsal penile nerve stimulation below the bulbocavernosus reflex (BCR) threshold was preceding at five different intervals (10, 20, 30, 50, 100 msec). The protocol was performed with empty and full bladder (BLA), and baseline responses were statistically compared to those with combined stimulation. **Results:** When the dorsal penile nerve electrical stimulation preceded the lumbosacral magnetic stimulation by 20 msec ( $P = 0.0048$ ), 50 msec ( $P = 0.0039$ ), or 100 msec ( $P = 0.0002$ ), the amplitudes of the EUS pressure response with empty BLA were significantly reduced compared to lumbosacral magnetic stimulation alone. With a filled BLA, the amplitudes of the EUS were significantly reduced only at an interval of 50 msec ( $P < 0.0001$ ). **Conclusions:** A conditional sensory pudendal stimulation seems to have the capacity to inhibit the external urethral sphincter contraction induced by a magnetic stimulation. The inhibitory effect seems to depend on the latency between the peripheral and lumbosacral stimulation as well as on the degree of BLA filling. It remains to be proved if the neuromodulative effect of the conditional stimulus occurs at a spinal or supraspinal level. *NeuroUrol. Urodynam.* 24:311–317, 2005.  
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**Key words:** afferent; pathways; transcutaneous electric nerve stimulation; urinary retention; urodynamics

## INTRODUCTION

In humans, urinary continence depends on an intact urethral sphincter mechanism. The external urethral sphincter (EUS) is voluntary controlled and ensures sufficient urethral closure and continence during the storage phase of bladder (BLA) function. Intra-abdominal pressure rises (e.g., caused by coughing) lead to a reflexive contraction of the EUS, which prevents an urinary leakage. Micturition normally starts with relaxation of the EUS followed by detrusor pressure [Garry et al., 1959; De Groat and Steers, 1990; Park et al., 1997].

Disturbances of sphincter system can result either in urinary incontinence or urinary retention. Urinary retention may be due to reduced detrusor contractility, an obstruction to their outflow, or a combination of these. An obstructed outflow can have an anatomical or a functional basis [DasGupta and Fowler, 2003]. Treatment options like alpha-blockers, muscle relaxants, antidepressants, urethral distension and BLA neck incisions often showed poor results and usually these patients are depending on indwelling catheter or clean intermittent catheterization [Aboseif et al., 2002].

Initially used in patients with urgency/frequency syndrome and urinary incontinence who failed to conservative treatment sacral neuromodulation was also applied to previously unsuccessfully treated patients with urinary retention with some [DasGupta and Fowler, 2003].

The exact mechanism of action by which sacral neuromodulation is working especially in urinary retention is still unknown but it seems that afferent neurons play an important role in modulation of excitatory and inhibitory neurons between spinal cord and pelvic organs [DasGupta and Fowler, 2003].

Abbreviations: BLA, bladder; BCR, bulbocavernosus reflex; EMG, electromyography; EUS, external urethral sphincter.  
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\*Correspondence to: Bjoern Wefer, MD, Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, Forchstrasse 340, 8008 Zurich, Switzerland. E-mail: bjoern.wefer@balgrist.unizh.ch  
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The aims of the study were *first* to answer the question what happens to lumbosacral magnetic evoked EUS contraction when a low current stimulation from strictly afferent nerve fibers precedes it? *Second*, at which time period should the preceding afferent stimulation happen to evoke greatest effects? *Third*, is there any change in the evoked EUS response measured after combined magnetic and electrical stimulation according to the degree of BLA filling?

## PATIENTS AND METHODS

### Subjects

The local ethics committee approved the experimental procedure. Seven male healthy volunteers (mean age 29 years, range, 22–44 years) gave their fully informed consent and were included in this study. None of the subjects took any drugs affecting the lower urinary tract or had urogenital surgery in his medical history. Immediately before and 24–48 hr after the experiment, urine screening tests were done to exclude urinary tract infection.

### Urodynamic Measurement

Prior to the experiment, the volunteers were asked to empty their BLA normally. During the experimental procedure, the subjects were in supine position on a fluoroscopy table. Rectal and anal sphincter pressure were measured using a rectally placed two-channel microtip pressure transducer catheter. Another two-channel microtip pressure transducer catheter was inserted into the urethra. The pressure transducers were positioned into the BLA and the EUS and anatomical landmarks using fluoroscopy and the obtained pressure values ensured correct position.

### Electrical Stimulation

Penile skin was degreased by alcoholic solution. Pudendal electrical stimulation was applied to the dorsal penile nerve using self-adhesive surface electrodes. Single electrical impulses were generated by a conventional electromyography (EMG) system (Dantec, Keypoint™, Copenhagen, Denmark). Square-wave single impulses 0.2 msec in duration were applied starting with an intensity of 5 mA. Then the current was increased slowly until clear motor responses of the EUS were recorded. This current was noted and electrical stimulation intensity was reduced until no more motor response of the EUS was measured. In the following protocol, electrical pudendal stimulations were performed with intensities above sensory and below motor threshold for the pudendal-EUS reflex.

### Magnetic Stimulation

Magnetic stimulations were generated with a commercially available stimulator (MagPro X100, Dantec®, Copenhagen,

Denmark) and applied by a liquid cooled magnetic coil (Dantecreg; MCF-125). The 14-cm diameter coil was placed midline over the lumbar spinal cord at the level of L1. Biphasic magnetic single pulses with durations of 0.2 msec were applied starting with 20% of maximal stimulator output of 1.8 T. The applied magnetic field strength was increased until a clear motor response of the EUS was measured which occurred usually between 40% and 70% of the maximum magnetic output.

### Experimental Protocol

Baseline stimulations were performed for both the dorsal penile and sacral magnetic stimulation separately. To ensure reproducibility of the motor responses both stimulations were repeated six consecutive times. To avoid any habituation of the reflexes or fatigue of the muscle, an interval of 20–30 sec between consecutive stimulations was kept carefully.

After baseline stimulations, combined electrical and magnetic stimulations were applied. The Dantec® Keypoint device generated the dorsal penile nerve stimulation, which was applied directly to the subject. Simultaneously a trigger was given from the Dantec® Keypoint device to the Mag Pro X100 device. Within the configuration of the Mag Pro X100 device, it was possible to delay the magnetic stimulus with a predefined latency. Using this technique, the electrical pudendal stimulation below motor threshold preceded lumbosacral magnetic stimulation above motor threshold. In five different experiments, the electrical pudendal stimulation was applied 10, 20, 30, 50, and 100 msec before lumbosacral magnetic stimulation. As described for the baseline measurements, the stimulation was repeated six consecutive times for every latency.

Combined electrical and magnetic stimulations were first performed at empty BLA. Thereafter, the BLA was filled with body warm saline solution until the volunteers reported a full BLA and desire to void and the entire protocol was repeated.

### Data Analysis/Statistics

The BLA and EUS pressures were recorded continuously at 1,000 Hz sampling rate by a PC-based measurement system and further analyzed using a software for physiological research (Soleasy™ ALEA Solutions GmbH, Zurich, Switzerland).

The amplitudes of the EUS pressure responses obtained during the baseline stimulation (sacral magnetic stimulation alone) and the combined stimulation (sacral magnetic stimulation preceded by dorsal penile nerve stimulation) were measured at both empty and full BLA.

We also measured the latencies from the pressure responses after stimulation above motor threshold after electrical and magnetic stimulation. The latency was defined as the time between stimulation and onset of pressure response.

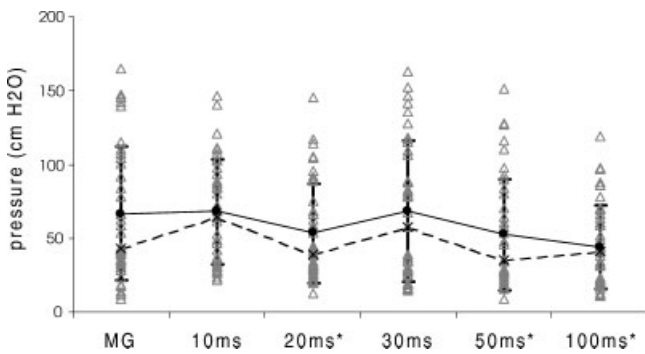
Both conditions were analyzed separately. The measured EUS amplitudes during the five experiments with combined stimulation (latency between dorsal penile and sacral magnetic stimulation: 10, 20, 30, 50, and 100 msec) were compared to the baseline EUS amplitudes by an analysis of variance for repeated measures. For the pair-wise comparisons,  $\alpha$  was corrected for the number of comparisons made ( $\alpha = 0.05/6 = 0.0083$ ).

**RESULTS**

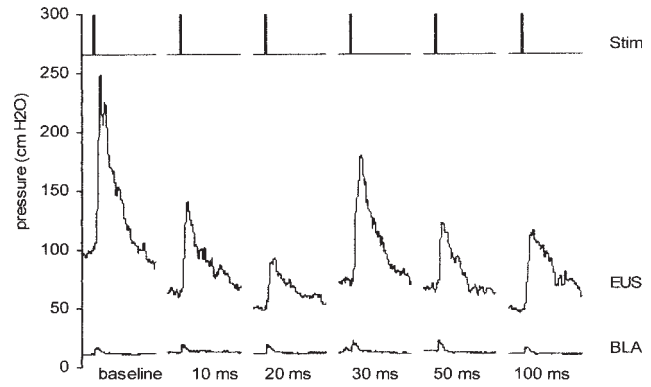
Electrical pudendal nerve and sacral magnetic stimulation was well tolerated by all volunteers. Urine screening tests before and after the protocol showed no urinary tract infection. No subject reported on any discomfort neither after electrical pudendal nor lumbosacral magnetic stimulation.

**Empty BLA**

After lumbosacral magnetic stimulation alone, a mean EUS pressure of 67 cm H<sub>2</sub>O (median 43 cm H<sub>2</sub>O) was calculated. By combining pudendal electrical stimulation and lumbosacral magnetic stimulation, an increase of the mean EUS pressure was observed by pudendal nerve stimulation preceding lumbosacral magnetic stimulation by 10 and 30 msec—this was however not significant. As opposed pudendal electrical stimulation preceding lumbosacral magnetic stimulation by an interval of 20 msec (mean 53 cm H<sub>2</sub>O,  $P = 0.0048$ , median 38 cm H<sub>2</sub>O), 50 msec (mean 52 cm H<sub>2</sub>O,  $P = 0.0039$ , median 35 cm H<sub>2</sub>O), and 100 msec (mean 44 cm H<sub>2</sub>O,  $P = 0.0002$ , median 40 cm H<sub>2</sub>O) led to significant decrease of the mean EUS pressure (see Fig. 1). An example of the pressure amplitudes during different experimental conditions and with empty BLA is shown in Figure 2.



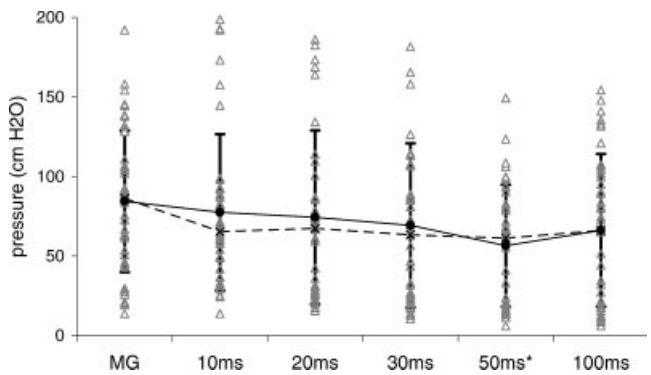
**Fig. 1.** Comparison of pressure amplitudes with magnetic stimulation alone and a combined stimulation at different time periods with empty bladder (combination: electrical pudendal stimulation below motor threshold preceding lumbosacral magnetic stimulation above motor threshold). Displayed are all values of volunteers as gray triangles. Mean values of all measurements including standard deviation are displayed as black circles connected with a continuous line; median values of all volunteers presented as black crosses connected with a broken line. Significance is marked with an asterisk (\*). MG, magnetic stimulation alone.



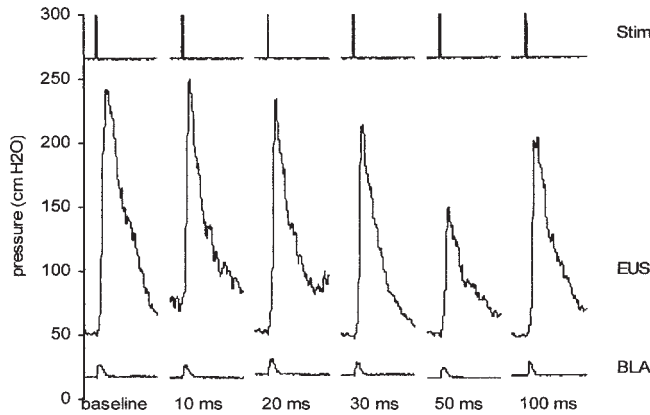
**Fig. 2.** Examples of pressure amplitudes of EUS and bladder (BLA) responses of one subject with magnetic stimulation alone above motor threshold (baseline) and at different time periods with an electrical pudendal stimulation below motor threshold preceding magnetic stimulation with the same currency with empty bladder.

**Full BLA**

With a filled BLA, the pressure amplitudes were generally higher than with empty BLA. Compared to lumbosacral magnetic stimulation alone (mean 84 cm H<sub>2</sub>O, median 86 cm H<sub>2</sub>O), all EUS pressure responses after a combined stimulation were lower. However, a significant EUS pressure reduction could only be seen at 50 msec (mean 56 cm H<sub>2</sub>O, median 61 cm H<sub>2</sub>O,  $P < 0.0001$ ) while at 10 msec (mean 77 cm H<sub>2</sub>O, median 63 cm H<sub>2</sub>O), 20 msec (mean 74 cm H<sub>2</sub>O, median 66 cm H<sub>2</sub>O), 30 msec (mean 69 cm H<sub>2</sub>O, median 63 cm H<sub>2</sub>O), and 100 msec (mean 66 cm H<sub>2</sub>O, median 66 cm H<sub>2</sub>O), the amplitudes were not significantly reduced (see Fig. 3). An example of the obtained pressure amplitudes during the experimental condition “full BLA” is shown in Figure 4 (same subject as in Fig. 2).



**Fig. 3.** Comparison of pressure amplitudes with magnetic stimulation alone and a combined stimulation at different time periods with full bladder (combination: electrical pudendal stimulation below motor threshold preceding lumbosacral magnetic stimulation above motor threshold). Displayed are all values of volunteers as gray triangles. Mean values of all measurements including standard deviation are displayed as black circles connected with a continuous line; median values of all volunteers presented as black crosses connected with a broken line. Significance is marked with an asterisk (\*). MG, magnetic stimulation alone.



**Fig. 4.** Examples of pressure amplitudes of EUS and bladder (BLA) responses of same subject as in Figure 2 with magnetic stimulation alone above motor threshold (baseline) and at different time periods with an electrical pudendal stimulation below motor threshold preceding magnetic stimulation with the same currency with full bladder.

#### Latency of Pressure Responses

To evaluate origin of the evoked pressure response, we measured the latencies of the EUS pressure after magnetic stimulation. Mean latencies of onset of this pressure response after lumbar magnetic stimulation above motor threshold was about 35 msec (SD 17 msec). Compared to this the mean latency of the onset of the EUS pressure response after electrical pudendal stimulation above motor threshold approximately 45 msec (SD 14 msec).

#### DISCUSSION

Considering our results, we admit a widespread of our raw data (see Figs. 1 and 3). This is due to the wide interindividual spread of data. Like Bemelmans et al. [1992] report on EMG-latencies of external anal sphincter with magnetic stimulation of the cauda equina, our pressure data also show a great inter-individual variability. However, volunteers with high initial pressure amplitudes remained in high amplitudes throughout the end of the experiment. On the other hand, volunteers with low-pressure amplitudes like values around 20 cm H<sub>2</sub>O showed only slight differences in our experiment. What all volunteers had in common is a higher-pressure amplitude with filled BLA than with empty BLA. Despite these difficulties, we could demonstrate that spinal motoneurons innervating the EUS can be modulated by a peripheral stimulation of somatosensory afferents from the external genitalia. The modulating effect depends on the latency between the peripheral and sacral stimulation as well as on the degree of BLA filling.

When the sensory branch of the pudendal nerve is stimulated above the sensory threshold, the impulses travel via pudendal fibers and the sacral roots to the spinal cord and ascend further to the somatosensory cortex. Latencies of

pudendal somatosensory evoked potentials have been established to the lumbar spinal cord (around 11 msec) and more common to the cortex (around 40 msec) [Amarenco and Kerdraon, 1999; Choi et al., 2001; Perretti et al., 2003]. When the pudendal nerve stimulation exceeds the threshold for elicitation of the bulbocavernosus reflex (BCR), a response of the pelvic floor muscles can be recorded. Afferent impulses travel to the sacral segments S2 to S4, and after a polysynaptic processing activate pudendal motoneurons in Onuf's nucleus, which leads to a pelvic floor muscle contraction after around 35 msec [Podnar et al., 1999; Amarenco et al., 2002; Thor, 2003]. In our experiment, we found a latency of measured EUS response after pudendal nerve stimulation of about 45 msec that might be explained by the lack that we measured pressure latencies and not EMG.

The efferent motor pathway from the sacral spinal cord to the pelvic floor has been evaluated using sacral magnetic stimulation combined with electromyographic and/or EUS pressure recordings. Motor latencies to the pelvic floor could be established which range around 4–10 msec [Opsomer et al., 1989; Vodusek, 1996; Brostrom, 2003] for the electromyographic response depending on the method (surface or needle electrodes, electrical or magnetic stimulation, location of stimulation) and around 27 msec for the urethral pressure response [Schmid et al., 2001].

Concerning the spinal magnetic stimulation, it is from the literature unclear that what exactly is stimulated by the magnetic coil. On one hand, a direct EUS response is possible as well as reflex EUS response via the afferent pathways. Most of the data are published for EMG recordings after magnetic stimulation [Brostrom, 2003]. Brodak et al. [1993] reported about latencies of the EUS and MEP of the bulbocavernosus muscle in spinal cord injured patients. He could measure mean sacral reflex latency of 37.9 msec and compared this to Opsomer et al. [1989] who recorded a mean sacral reflex latency of 31.4 msec in normal volunteers. As opposed, Snooks and Swash [1984] reported in 1984 about a 4.9 msec latency of the EUS in normal volunteers after transcutaneous electrical stimulation of L1 and L4. To our knowledge, Schmid et al. [2001] were the only one reporting about measurements of EUS pressure latencies after transcortical and lumbosacral magnetic stimulation in healthy volunteers combined with measurements of EMG latencies of the EUS using a catheter-mounted electrode. MEP latency after lumbosacral stimulation was 4.25 msec and EUS pressure latency was 27 msec.

According to these data and our measured pressure latencies, taking into account the different length of the nerve from the stimulation side to the spinal cord, the different way of stimulation (electrical vs. magnetic) and of recording (EMG vs. pressure), we believe that in our experimental setup we were stimulating mainly afferent fibers and that the recorded responses are reflexly mediated.

Taking into account the available knowledge about the latencies in the afferent and efferent limb of the sacral reflex

arc, we developed the experimental setup of the present study. The underlying idea was to study the pressure responses of the EUS to a lumbosacral magnetic stimulation alone and with a preceding peripheral dorsal penile nerve stimulation. The electrical stimulation of the dorsal penile nerve was set above the sensory but below the motor threshold for the sacral reflex arc. The peripheral sensory stimulation preceded the lumbosacral magnetic stimulation with five different latencies, three of them were within the sacral reflex latency of around 35 msec (10, 20, 30 msec), one right thereafter (50 msec), and one considerably later (100 msec).

First, the experimental protocol was performed with empty BLA and no desire to void and then repeated with full BLA and desire to void. Corresponding to BLA filling and an increased afferent input from tension receptors in the BLA wall, the activity of the pudendal motoneuron in the sacral spinal cord is known to increase overtime to close the urethral sphincter mechanism and maintain continence. These reflexes are known as guarding reflexes [Park et al., 1997; Bloom et al., 1998; Thor, 2003]. Siroky and Krane [1982] reviewed the data of 137 patients with detrusor hyperreflexia and a known neurological lesion. They found a loss of the guarding reflex in most of the complete spinal cord injured patients indicating that the control of the striated perineal musculature is a supraspinal function. Dyro and Yalla [1986] performed electrical dorsal penile nerve stimulation in 14 male patients and recognized that the reflex response was elevated in patients without neurological abnormalities but not in patients with upper motor neuron lesions during BLA filling with its normal increase in periurethral striated muscle sphincter activity indicating a supraspinal influence on this reflex. With respect to this pudendal motoneuron behavior, the entire protocol was then repeated when the subjects reported a full BLA and present desire to void.

Our data show that the pressure amplitudes of the EUS to lumbosacral magnetic stimulation were significantly lower compared to baseline (lumbosacral magnetic stimulation alone) when a sensory dorsal penile stimulation preceded the lumbosacral magnetic stimulation by 20, 50, and 100 msec with empty BLA and by 50 msec with filled BLA. This may demonstrate that the excitability of the sacral pudendal motoneurons and therefore the contractility of the EUS are modulated (inhibited) when a sensory pudendal input is present. Basically, when applied with a certain latency prior to a direct lumbosacral stimulation, an afferent input from the external genitalia seems to inhibit sacral pudendal motoneurons.

The origin of the modulative effect of the conditional stimulus at 50 and 100 msec remains unclear (spinal vs. supraspinal). While the result at the 50 msec interval is supposed to demonstrate a spinal reflex mechanism, the relaxation at 100 msec is supposed to have a supraspinal origin. The urethral relaxation at 50 msec could be an indirect reference of Barrington's 4th-reflex. Barrington's doubtful 4th-reflex is postulated to be elicited by flow through the urethra with the afferent and efferent limb in the pudendal nerve causing

a spinal mediated urethral sphincter relaxation [Morrison, 1987]. As opposed, sphincter relaxation seen after combined stimulation at the 100 msec interval and empty BLA might, in our opinion, only be explained by supraspinal inhibition of the sacral motoneurons. Increased pelvic afferent information at full BLA and strong desire to void are postulated to induce cortical inhibition of the supraspinal micturition centers [Blok, 2002]. Accordingly, sphincter relaxation observed after combined stimulation at the 100-msec interval is no more able to take place with full BLA and strong desire to void.

These points may help to explain why a stimulation of sacral afferent fibers is sometimes useful for patients with chronic urinary retention. These patients are usually present with a abnormal high EUS pressure in the urine storage phase and a relaxation failure during micturition. It was recently hypothesized that in patients with urinary retention, the abnormal activity of the striated urethral sphincter impairs its relaxation and, through the effect of sustained contraction, secondary effects on the detrusor and BLA sensation come up and deteriorate retention [Swinin et al., 2002].

Those secondary effects rely on the stimulation of afferent somatosensory fibers in the pudendal nerve, which have the capacity to influence autonomic pathways controlling the pelvic organs. The underlying reflex mechanism involves somatosensory afferent pathways from the external genitalia and efferent motor pathways to the pelvic floor muscles. In particular, pudendal afferent pathways are connected with autonomic fibers to BLA, BLA neck, and rectum by several reflex pathways [Reitz et al., 2003]. This reflex mechanism has been studied extensively in animals and more recently in humans. In a cat, an afferent pudendal nerve stimulation has been shown to inhibit the BLA by two spinal reflex mechanism [Lindstrom et al., 1983]. At low intravesical pressures corresponding to the filling phase, the spinal reflex response travels predominantly in the hypogastric nerve. An excitatory alpha-adrenergic response supports BLA neck closure and an inhibitory beta-adrenergic response relaxes the BLA itself. At higher BLA pressures, a second reflex mechanism appears with the pelvic nerve as its efferent limb. Pudendal afferents inhibit the BLA by inhibition of the spontaneous pelvic nerve activity [Grill et al., 2001]. A modulating effect of afferent pudendal fibers on sympathetic neurons controlling the BLA neck could be shown recently in spinal cord injured humans, which may suggest that the reflex mechanism described in cats act also in humans in a similar manner [Reitz et al., 2003].

Basically, all these reflexes promote continence by enhancing the urethral tone and relaxing the BLA. In patients with urinary retention, these mechanisms affect adversely the ability to empty the BLA and deteriorate finally the retention problem. A potential therapeutic intervention for retention patients should interrupt these inhibitory reflex mechanisms by eliminating the abnormal sphincter pressure as the underlying cause.

Electrical sacral nerve stimulation via needle electrodes or permanent leads have been established as an effective treatment for urinary retention [Goodwin et al., 1998; Shaker and Hassouna, 1998; Jonas et al., 2001; Swinn and Fowler, 2001; Jezernik et al., 2002]. Electrophysiological studies during sacral nerve stimulation in able-bodied and complete spinal cord injured humans showed that both efferent and afferent fibers are activated and that the responses of the anal sphincter are partially reflexively mediated [Fowler et al., 2000; Schurch et al., 2003].

There is still a controversial discussion about a potential involvement of supraspinal structures in the effect of a sacral nerve stimulation. From our results, we cannot determine whether the observed inhibitory effect of the afferent nerve stimulation on the pudendal motoneurons is mediated only by a spinal reflex mechanism or requires a supraspinal loop. A potential approach to answer this question would be to repeat the study in humans with a complete spinal cord injury on a suprasacral level. These experiments are planned for the future.

## CONCLUSION

Considering our results, we think that a sensory stimulation of somatosensory fibers of the pudendal nerve may have the capacity to inhibit pudendal motoneurons in the spinal cord, which potentially leads to a reduction of the sphincter tone. The reduced sphincter tone may prevent secondary inhibitory effects on the detrusor. The inhibitory effect depends on the latency between the peripheral and lumbosacral stimulation as well as on the degree of BLA filling.

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