Abstract

We characterized two spinal reflexes between urethral sensory fibers in the pudendal nerve and the bladder in anesthetized cats. When the bladder contained a sufficient volume, activation of pudendal sensory nerve fibers innervating the urethra caused bladder contraction coupled with synergic relaxation of the urethral sphincter. These responses enabled voiding with an efficiency that was equal to or exceeded voiding obtained by distention-evoked reflex micturition. Stimulation of appropriate pudendal sensory nerve fibers may provide an alternative to sacral root stimulation for bladder emptying.

1 Introduction

Urological complications lead to significant morbidity and substantial decreases in quality of life in persons with neurological disorders including spinal cord injury, stroke, and multiple sclerosis. The long-term goal of this research is to develop a neural prosthesis to restore bladder function, including continence and micturition, in persons with neurological disorders, particularly spinal cord injury. We are pursuing an innovative approach using a single multi-electrode nerve cuff implanted on the pudendal nerve to maintain continence and produce micturition. This innovative approach differs substantially from existing approaches using electrical stimulation of the spinal roots in that it does not require a spinal laminectomy, does not require irreversible surgical transection of the sacral sensory nerve roots, and stimulates the afferent rather than the efferent side of the system [2].

The objective of the experiments reported herein was to characterize the bladder responses evoked by electrical stimulation of pudendal sensory nerve fibers innervating the urethra. We recorded the responses evoked by stimulation of the urethral sensory (US) branch of the pudendal nerve which innervates the proximal urethra and carries sensory information presumed to indicate urine flow [11][6] and by stimulation of the deep perineal (DP) branch of the pudendal nerve which innervates the mid-urethra and also carries sensory information presumed to indicate urine flow [13].

2 Methods

Experiments were conducted in adult cats anesthetized with ketamine and maintained with α-chloralose. A midline abdominal incision was made to expose the bladder, the ureters ligated, transected proximal to the ligation, and drained externally. Animals were instrumented to record bladder pressure and electroneurograms from the contralateral pudendal nerve and its branches in response to electrical stimulation of the US and DP branches of the pudendal nerve using trains of regulated current stimuli.

3 Results

We identified two spinal reflexes between urethral sensory fibers in the pudendal nerve and the bladder, and characterized these reflexes in adult cats anesthetized with α-chloralose.

The first reflex, between the urethral sensory (US) branch of the pudendal nerve, and the bladder was described by Shefchyk and Buss [10], and we have replicated and extended their results. Stimulation of the US produced volume-dependent excitation of the bladder (figure 1) such that US stimulation only produced bladder contractions above a threshold volume. Stimulation of the US nerve when the bladder was full enabled efficient voiding of 72±17% (mean±s.d., n=4) of the initial bladder volume (16-26 ml).
Figure 1: Generation of bladder contractions and voiding in cats by stimulation of urethral afferent nerve fibers in the urethral sensory branch (US) of the pudendal nerve. A. Bladder pressure during stimulation of the US (bars: 500µA, 100µs, 10s, 20Hz) and infusion of saline into the bladder at 1 ml/min illustrating the volume dependence of the urethra-bladder reflex. Initially, US stimulation evoked small, unsustained contractions (open bars). When bladder volume was increased to ≥ 10 ml, US stimulation produced sustained contractions of large magnitude (filled bars). When bladder volume was increased to ≥ 16 ml quasi-periodic distention-evoked reflex contractions occurred (*). US stimulation during a reflex contraction (**) led to large bladder pressure increases (peak is clipped). B. Bladder pressure during voiding produced by stimulation (black bar) of the US (500µA, 100µs, 20 Hz). The initial volume in the bladder was 26 ml and the animal voided 22 ml in response to stimulation (85% voiding efficiency). Note that following voiding, the same stimulation fails to evoke a bladder contraction (--) because the bladder volume is too small.

The second, previously undescribed reflex was between the deep perineal (DP) branch of the pudendal nerve and the bladder (figure 2). Similar to US nerve stimulation, stimulation of the DP nerve produced volume-dependent excitation of the bladder, and enabled efficient voiding of 78±13% (mean±s.d., n=12) of the initial bladder volume.

The two reflexes shared several important characteristics, and were differentiated only by the distal nerve branch that evoked them. Both reflexes exhibited strong state dependence, such that contraction of the bladder was only generated by pudendal urethral afferent stimulation when the bladder volume was above a threshold volume (figures 1, 2). Threshold volume for generating a contraction by urethral afferent stimulation was 78±17% of the volume threshold for distention-evoked reflex contractions (mean±s.d., n=4 cats with matched paired comparisons), and similar results were reported for fluidic stimulation of the urethra in the ewe [8]. Second, when the bladder volume was sufficiently large and the stimulation frequency > 20 Hz, stimulation of urethral sensory fibers led to an increase in bladder pressure coupled with a synergic reduction of activity in the external urethral sphincter, as described previously by Mazieres et al. [7] and Shefchyk and Buss [10]. Third, the excitatory reflexes between the urethra and bladder were preserved following spinal cord transection. However, due to different degrees of spinal shock the magnitude of reflex bladder contractions evoked following SCI was quite variable across animals.

Discussion and Conclusions

These results demonstrate the presence of robust excitatory reflexes between urethral
sensory fibers in the pudendal nerve and the bladder. Importantly, these reflexes were preserved following SCI and led to synergic relaxation of the urethral sphincter. Preliminary results suggest that these reflexes enable efficient bladder emptying. Bladder emptying achieved with by stimulation of urethral sensory nerves was greater than the 39±30 % (n=10 trials across 2 animals) of initial volume voided by distention-evoked reflex micturition. This difference most likely arose due to the dyssynergic contraction of the sphincter during distention-evoked reflex micturition that occurs under α-chloralose anesthesia [9][12], but the synergic relaxation of the sphincter during voiding evoked by stimulation of urethral sensory nerve fibers.

The traditional view holds that coordinated micturition (bladder contractions coupled with a reduction in activity of the external urethral sphincter) requires a spinal-brainstem-spinal reflex loop that is triggered by bladder distention. However, these and previous results support that coordinated bladder and sphincter responses can also be evoked by activation of urethral afferents [7][4][10]. Excitatory urethra to bladder reflexes have also been documented in humans. Slow infusion of fluid into the urethra in normal females resulted in micturition contractions when the bladder was full, but not when the bladder was at low volume [5][1], and we have demonstrated a bladder-volume-dependent excitatory reflex between the urethra and the bladder in humans with SCI by electrical stimulation of urethral sensory nerve fibers [3].

Restoration of bladder evacuation in persons with spinal injury results in clear benefits. However, the widespread application of existing technology using sacral anterior root stimulation is limited by the necessity of conducting a dorsal rhizotomy and the complex surgical implant procedure. Stimulation of peripheral nerve pathways in the pudendal nerve is a departure from conventional approaches to restoration of motor function with electrical stimulation. Rather than driving the efferent side of the system, we propose to drive the afferent side of the system and use the spinal reflex circuitry to control continence and micturition [2]. This approach may simplify the implant procedure and thereby increase the population of individuals who can benefit from neural prosthetic technology.

References

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