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ORIGINAL ARTICLE

Effects of pudendal neuromodulation on bladder function in chronic spinal cord-injured rats

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Background/Purpose: Few studies have investigated the feasibility of using pudendal neuromodulation to regulate bladder function in spinal cord-injured (SCI) animals. The present study aimed to determine the effects of electrical activation of the pudendal sensory branch on improving voiding functions in rats 6 weeks after a spinal cord injury and to explore the underlying neuromodulatory mechanisms.
Methods: Two urodynamic measurements were used to assess the effects of electrical stimulation (ES) on bladder and urethral functions: simultaneous recordings of the intravesical pressure (IVP)

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during continuous isotonic transvesical infusion (i.e., isotonic IVP) and external urethral sphincter (EUS) electromyography (EUS-EMG), and simultaneous recordings of transvesical pressure under isovolumetric conditions (i.e., isovolumetric IVP) and urethral perfusion pressure (UPP).
Results: Six weeks after the SCI, the rats showed voiding dysfunction, as indicated by abnormal cystometric measurements (e.g., increased volume threshold, increased contraction amplitude, and increased residual volume, and decreased voided volume). The voiding efficiency (VE) decreased to 13% after the SCI, but increased to 22—34% after applying pudendal afferent stimulation. In addition, pudendal stimulation significantly increased the EUS burst period and increased the difference between the UPP and the high-frequency oscillation (HFO) baselines, and changed the time offset between bladder and EUS activities. These findings suggest that pudendal afferent stimulation improved the VE by prolonging the micturition interval, decreased the urethral resistance, and recovered detrusor-sphincter dyssynergia during the voiding phase.
Conclusion: This study demonstrates the feasibility of using pudendal neuromodulation in chronic SCI rats. These results could aid in developing an advanced neural prosthesis to restore bladder function in clinical settings.

Introduction

The lower urinary tract (LUT) system comprises two components: the reservoir (i.e., urinary bladder) and the outlet [i.e., bladder neck, urethra, and external urethral sphincter (EUS)], which are regulated by a complex neural control system. The two components typically exhibit reciprocal activities that are coordinated by a descending projection from the pontine center.[1] A spinal cord injury above the lumbosacral level causes detrusor-sphincter dyssynergia (DSD) and induces simultaneous contractions of the bladder and the EUS during voiding, which obstructs evacuation of the urine from the bladder.[2—4] Chronic DSD may increase bladder pressure and may result in vesicourethral reflux and renal failure.[5] Daily urethral catheterization can aid patients in voiding urine from the bladder; however, catheterization can cause serious problems such as frequent urinary tract infections and a reduced quality of life.

Electrical neuromodulation such as sacral anterior root neuromodulation was successfully introduced to treat patients with a spinal cord injury and voiding dysfunction.[6] However, despite its clinical efficacy, sacral neuromodulation is not widely accepted by these patients because of the need for a dorsal rhizotomy, which can inhibit residual sensations and reflexes such as defecation, erection, ejaculation, and lubrication. Therefore, a more effective neuroprosthesis is required to restore bladder function in patients with a spinal cord injury and voiding dysfunction. Recent animal and human studies indicate that electrical stimulation (ES) of the pudendal nerve encourages the augmenting reflex, and thereby improves bladder voiding in patients with voiding dysfunction.[7—10] Thus, pudendal nerve modulation by ES could be an effective approach to treat voiding dysfunction.

Rats have gained great popularity as the primary species to investigate LUT functions. Therefore, SCI rats have been extensively used to investigate physiological changes in the regulation of urine storage and micturition reflexes.[11—13] However, to our knowledge, few studies have investigated the feasibility of using pudendal neuromodulation to regulate bladder function in a rat model of chronic spinal cord injury. Thus, this study primarily aimed to investigate the feasibility of electrically activating the pudendal sensory branch to improve bladder dysfunction in rats 6 weeks after a spinal cord injury and to explore the underlying neuromodulatory mechanisms.

Materials and methods

The experiment protocols involving the use of animals in this study were approved by the Institutional Animal Care and Use Committee of Taipei Medical University and Hospital (Taipei, Taiwan). Female Sprague—Dawley rats ($n = 60$) that weighed 250—300 g were used in the study. The rats were divided into two equal groups: the normal control (NC) group and the SCI group. The NC group rats received a sham operation with no damage to the spinal cord, whereas the SCI group rats received spinal cord transection. The spinal cord injury surgical procedures were performed, based on a previous report.[11] Spinal cord transections were performed under 2—2.5% isoflurane anesthesia using aseptic surgical techniques. After a T_8—T_9 laminectomy, the dura matter, spinal cord, and spinal roots were cut with fine scissors. The severed ends of the spinal cord typically retracted 1—2 mm. They were inspected under a surgical microscope to ensure complete transection. The overlying muscle and skin were sutured. Animals were treated with an antibiotic (ampicillin, 200 mg/kg, intramuscular) for 7—10 days. To prevent overdistension of the bladder, urine was expressed manually every 6—8 hours until automatic micturition developed at approximately 10—14 days postsurgery. The bladder was then expressed two to three times daily.

Urodynamic and electromyographic recordings

After a 6-week recovery period, all rats were anesthetized with subcutaneous urethane (1.2 g/kg). The sensory branch of the unilateral pudendal nerve was exposed through a posterior approach.[7,8] A bipolar cuff electrode was