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Feasibility of deep brain stimulation for controlling the lower urinary tract functions: An animal study

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HIGHLIGHTS

- This study systematically explored deep brain stimulation (DBS) for controlling bladder functions in rats.
- Pedunculopontine tegmental nucleus (PPTg) DBS could stably evocate and inhibit bladder activity.
- PPTg might be a promising DBS target for developing new approaches to treat bladder dysfunctions.

ABSTRACT

Objective: To evaluate the feasibility of deep brain stimulation (DBS) and compare the potential of four DBS targets in rats for regulating bladder activity: the periaqueductal gray (PAG), locus coeruleus (LC), rostral pontine reticular nucleus (PnO), and pedunculopontine tegmental nucleus (PPTg).
Methods: A bipolar stimulating electrode was implanted. The effects of DBS on the inhibition and activation of micturition reflexes were investigated by using isovolumetric intravesical pressure recordings.
Results: PAG DBS at 2–2.5 V, PnO DBS at 2–2.5 V, and PPTg DBS at 1.75–2.5 V nearly completely inhibited reflexive isovolumetric bladder contractions. By contrast, LC DBS at 1.75 and 2 V slightly augmented reflexive isovolumetric bladder contractions in rats. DBSs on PnO and PPTg at higher intensities (2.5–5 V) demonstrated a higher success rate and larger contraction area evocation in activating bladder contractions in a partially filled bladder. DBS targeting the PPTg was most efficient in suppressing reflexive isovolumetric bladder contractions.
Conclusion: PPTg DBS demonstrated stable results and high potency for controlling bladder contractions. PPTg might be a promising DBS target for developing new neuromodulatory approaches for the treatment of bladder dysfunctions.
Significance: DBS could be a potential approach to manage bladder function under various conditions.

1. Introduction

Lower urinary tract (LUT) dysfunction is an increasingly common symptom worldwide. Neurological disorders are one of the main causes of LUT dysfunction. Specifically, aging-induced central neurodegeneration affects neurological control of bladder function. Since complex networks of the autonomic nervous system and central nervous system control micturition reflexes (Gómez-Pinilla et al., 2007), central neuromodulations are a potential approach for treating various troublesome of LUT disorders (Ju and Liao, 2016).

Deep brain stimulation (DBS) is a safe and effective neuromodulatory therapy for relieving various motor dysfunctions resulting

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from neurological disorders such as Parkinson's disease (Lozano Andres and Lipsman, 2013; Shih et al., 2014). On the other hand, therapeutic applications of DBS for treating other neurological and psychiatric disorders such as chronic pain have also been explored. DBS is carried out with implanting an electric electrode at a targeted brain region. The electric stimulation may immediately change the neuron activity of the targeted brain region directly and affect the related networks indirectly which resulted in the change of the associated pathological activity (Johnson et al., 2008). Various DBS targets exhibit different responsive characteristics and efficiencies. Identifying the appropriate targets is the first step in developing a DBS therapeutic approach. Hence, DBS targets have been extensively investigated for treating Parkinson's disease. DBSs on the subthalamic nucleus, sensorimotor internal globus pallidus, external globus pallidus, and pedunculopontine tegmental nucleus (PPTg) have effectively improved the motor function in patients with Parkinson's disease (Follett and Torres-Russotto, 2012). DBS would also be a promising approach for treating severe bladder dysfunction; however, until now, few studies have investigated DBS-related micturition regulation (Basiago and Binder, 2016).

The micturition reflex center in the brain stem is known as the pontine micturition center (PMC) (Blok and Holstege, 1997, 2000). The micturition pathways of the lower urinary tract system are composed of an afferent pathway from the urinary bladder to the PMC via the pelvic nerve and spinal cord, and an efferent pathway that projects from the PMC to the bladder via the sacral parasympathetic center of intermediolateral column cells (Sasa and Yoshimura, 1994). A schematic diagram is shown in Fig. 1. Several brain regions related to PMC modulate bladder activity, including the periaqueductal gray (PAG), locus coeruleus (LC), and rostral pontine reticular nucleus (PnO). The PAG is located between the forebrain and the lower brainstem and is responsible for the sensory inputs from the distended bladder-activated spinal–mid brain–spinal nerve circuit (Green et al., 2012). Lumbosacral neurons terminate strongly on neurons in the PAG (Blok et al., 1995), and this PAG region contains neurons projecting to the PMC (Blok and Holstege, 1994). PAG neurons are intensely activated during voiding (Tai et al., 2009), and the stimulation of the PAG elicits micturition (Skultety, 1959; Blok and Holstege, 1999). In a DBS study, PAG DBS in anaesthetized rats demonstrated inhibitory effects on micturition reflexes during cyclical voiding responses

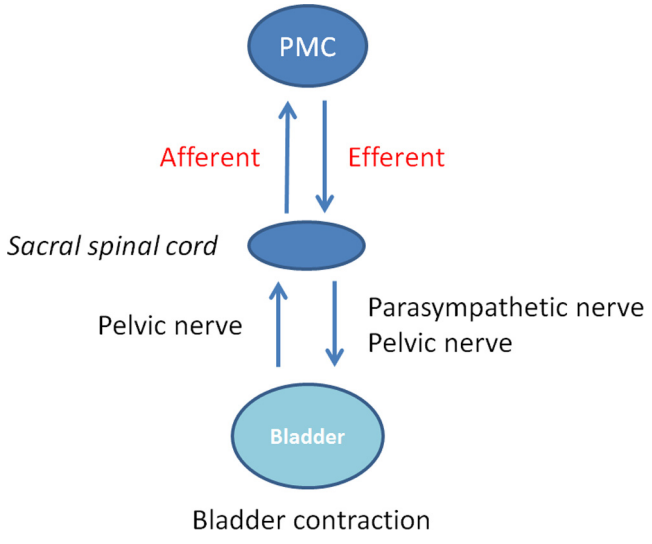

Fig. 1. The micturition pathways of the lower urinary tract system are mainly composed of afferent and efferent pathways between the pontine micturition center (PMC) and the urinary bladder.

(Stone et al., 2015). The LC is a nucleus located in the rostral pons and is considered the critical reactive part of the PMC (Sasa and Yoshimura, 1994). Electrical stimulation on the LC induced the firing of the preganglionic neurons in the sacral cord (Noto et al., 1989). Bladder distention increased the spontaneous discharge rate of the LC (Page and Valentino, 1994). Furthermore, chemical stimulation of the LC induced bladder contractions in animals (Sasa and Yoshimura, 1994). The PnO is ventrocentral to the PMC and is considered a pontine micturition inhibitory area (Sugaya et al., 2005). Chemical activation of the PnO inhibited bladder contractions in animals (Nishijima et al., 2005). However, the potential benefits of LC and PnO DBSs in micturition control have yet to be determined.

The PPTg is a new experimental brain target for managing severe Parkinson's disease. However, during therapy, a study reported that PPTg DBS may induce detrusor contraction, which resulted in urinary incontinence in patients (Aviles-Olmos et al., 2011). Thus, the PPTg may also be involved in the regulation of micturition, and neuromodulation of the PPTg may be a potential stimulation target for treating patients with micturition disorders.

Until now, few studies have systematically explored and compared these possible DBS targets for the control of bladder function. According to our review of the relevant literature, this is the first study to evaluate the effects of conducting DBS on four potential targets, namely the PAG, LC, PnO, and PPTg, on bladder activities. Isovolumetric intravesical pressure (IVP) recordings under fully (100%) and partially (33%) filled bladder conditions were used to investigate the DBS effects on the inhibition and activation of micturition reflexes, respectively.

2. Methods

2.1. Animals

In total, 54 female Sprague–Dawley rats, weighing 240–260 g were used in this study. All animal care and experimental protocols were reviewed and approved by the Institutional Animal Care and Use Committee of Taipei Medical University (LAC-2013-0199).

Forty-eight rats were equally allocated to two animal experimental groups: the inhibition group and the activation group of micturition reflexes. The animals in each experimental group were further equally divided into four subgroups for evaluating the effects of four possible DBS targets, namely the PAG, LC, PnO, and PPTg, on bladder activities (n = 6, each subgroup).

2.2. Brain surgical procedures

Rats were anesthetized using urethane (1.25 g/kg, subcutaneously). The bregma point was exposed, and the targeted areas were located according to the bregma point: the ventral LC (AP − 9.8 mm, L + 1.4 mm, DV − 7.0 mm), ventral PAG (AP − 8.3 mm, L + 0.8 mm, DV − 6.0 mm), rostral PnO (AP − 8.0 mm, L + 1.0 mm, DV − 7.5 mm), and ventral PPTg (AP − 7.3 mm, L + 2.0 mm, DV − 7.5 mm). Moreover, a hole was drilled into the bone, after which a bipolar concentric cylindrical electrode (SS80SNE-100, MicroProbes, Gaithersburg, MD, USA) was implanted in a targeted brain point with the aid of a stereotactic instrument (Stereotaxic, Stoelting, IL, USA). The bipolar electrode was electrically isolated between the inner and outer stainless steel conductors using polyimide tube. The inner and outer stainless steel conductors of the electrode were 0.2 mm and 0.4 mm in length, respectively, and totally 1 mm in interval. The detail configuration specification of the stimulating electrode is shown in Fig. 2. Due to the voltage distributions in the brain affected by the impedance of the electrode-tissue interface, the impedance of the stimulating electrode was