Effects of a new selective β3-adrenoceptor agonist, vibegron, on bladder and urethral function in a rat model of Parkinson's disease

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Abstract

Objectives: Parkinson's disease caused by the loss of dopaminergic neurons induces not only motor dysfunction, but also lower urinary tract dysfunction. Patients with Parkinson's disease have recently been reported to experience both urge urinary incontinence (overactive bladder) and stress urinary incontinence, the latter of which occurs when the pressure of the bladder exceeds that of the urethra. Vibegron is a highly selective novel β_3-adrenoceptor agonist approved for the treatment of overactive bladder. However, how β_3-adrenoceptor agonists affect urethral function remains unclear. In a clinical report, the urethral function of patients with Parkinson's disease was shown to be degraded. The present study aimed to investigate the effects of vibegron on lower urinary tract activity in a rat model of Parkinson's disease.

Methods: In a rat model of Parkinson's disease induced by unilateral 6-hydroxydopamine injection into the substantia nigra pars compacta, we examined the effects of vibegron on bladder and urethral activity.

Results: Cystometric analysis revealed that compared with vehicle injection, intravenous injection of 3 mg/kg vibegron significantly increased the inter-contraction interval ($p < 0.05$) and reduced voiding pressure ($p < 0.01$). However, no significant effects on urethral function were observed.

Conclusions: The results of the present study provide corroborating evidence that bladder dysfunction is suppressed by the administration of vibegron in Parkinson's disease model rats, confirming that vibegron is effective for treating overactive bladder without further worsening urethral function. These findings may contribute to a better understanding of the mechanisms of β_3- adrenoceptor agonists.

Key words:

vibegron, micturition reflex, Parkinson's disease, dopaminergic mechanism

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease caused by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. By 2030, the number of patients with PD is expected to increase by 50% because of the aging population and longer life expectancy. The symptoms of PD include not only motor symptoms, but also various non-motor symptoms (NMSs) [1] such as sleep disturbance, constipation, dementia, depression, and lower urinary tract (LUT) dysfunction.[2] In regard to NMSs, patients with PD have been reported to have a high prevalence of LUT dysfunction, such as overactive bladder (OAB), which is noted from the early stage of PD.[3,4,5] Recent advancements in functional brain imaging studies have identified the mechanisms involved in controlling LUT symptoms,[6] showing that 72% of patients with PD had LUT symptoms, and 81% detrusor overactivity as indicated by urodynamic analysis. Most motor symptoms of PD can be favorably managed using various treatments. By contrast, NMSs of PD are under-recognized and poorly managed because of a lack of effective treatments. In patients with PD, NMSs usually increase the disease burden and affect quality of life more strongly than do traditional motor symptoms.[7,8]

Our group has been investigating the pathophysiology of LUT dysfunction using animal models of PD. Previous studies have shown that the micturition reflex was enhanced in a 6-hydroxydopamin (6-OHDA) induced PD model mimicking bladder overactivity in patients with PD.[9,10] Regarding the effects of various anti-parkinsonian drugs on the micturition reflex in PD model rats, a previous study showed that D_1 and D_5 receptor agonists can antagonize the micturition reflex (bladder overactivity), and that D_2 and D_4 play a role in stimulating the micturition reflex.[11]

OAB typically requires long-term pharmacotherapy treatment. However, to our knowledge, no study has thoroughly investigated pharmacotherapy treatment in patients with PD. Antimuscarinic agents have been proven to be efficacious in the treatment of neurogenic bladder dysfunction by controlling unwanted cholinergic bladder contractions (detrusor overactivity). Nevertheless, both patient persistence and adherence to most antimuscarinics are still relatively weak.[12]

An alternative option for the treatment of OAB is β_3-adrenoceptor (AR) agonists, which relax the detrusor smooth muscle, reduce afferent signaling, and increase bladder capacity. Mirabegron is the first approved β_3-AR agonist for the treatment of OAB. Considering the low level of associated adverse events, β_3-AR agonists may be promising as an initial OAB treatment that provides a distinct balance between efficacy and tolerability, contributing to greater persistence. Vibegron is a novel, highly selective β_3-AR agonist approved for the treatment of OAB. One of the advantages of vibegron over mirabegron is its lack of an inhibitory effect on

cytochrome P450 (CYP) enzymes, which are known to inhibit CYP2D6. Therefore, drug interactions should be considered in patients treated with mirabegron. However, again, to our knowledge, no studies focusing on treatment for OAB using vibegron in patients with PD have been reported.

To date, a previous study on the urethral closure function in patients has reported that the sympathetic nervous system dominates in regard to maintaining the tonus in the urethra[13]. Throughout the entire length of the urethra, the administration of noradrenaline or β_2-AR agonist results in a contractile response. Kummeling et al. recently reported that β_3-AR is expressed in the human female urethra.[14] However, little research has been conducted on the effects of β_3-AR on the urethra given these background, we aimed to evaluate the effects of vibegron on bladder and urethral function in a PD rat model.

Methods

Animals

In this study, we used female Sprague Dawley rats (n=14; age range, 14–20 weeks, weight, 292.0–348.5 g). All experiments conformed to the National Institutes of Health animal care guidelines. This study was approved by the Hokkaido University ethics committee (approval No. 21-0104) and conformed to the ARRIVE guidelines. One of the most commonly used PD models is the 6-OHDA animal model, which was established in the late 1960s by Ungerstedt.[15] 6-OHDA neurotoxin is extensively used to lesion the nigrostriatal DA system as a model of PD. Although the exact mechanism by which 6-OHDA causes neurodegeneration is not fully understood, it is known as a DA analogue that targets the DA transporter to access the cytosol of DA neurons, where it induces mitochondrial respiratory dysfunction, leading to high levels of oxidative stress, subsequent neuronal dysfunction, and even death within the nigrostriatal pathway.[16]

PD model rats

Rats were intraperitoneally injected with 60 mg/kg of pentobarbital (Kyoritsuseiyaku Corp., Tokyo, Japan) before surgery to produce unilateral 6-OHDA-induced lesions. 6-OHDA (8 μg in 2 μL of 0.9% saline containing 0.3% ascorbic acid) was microinjected unilaterally into the left substantia nigra pars compacta of the brain at a point 5.3 mm posterior to the bregma, 8.0 mm ventral to the dura, and 2.2 mm laterally. Additionally, 6-OHDA (10 μg) was injected into the lateral striatum of rats before intravesical pressure was measured to obtain a rat model of unilateral PD. Motor dysfunction was confirmed in these animals to establish PD. All efforts were made to minimize animal suffering.[17]

Measurement of inter-contraction interval (ICI), voiding pressure (VP), baseline pressure (BP), threshold pressure (TP), and post-void residual volume (PVR)

The inter-contraction interval (ICI), voiding pressure (VP), baseline pressure (BP) and threshold pressure (TP) for micturition were measured using cystometry, as previously reported.[18] ICI was defined as time-to-contraction under constant filling conditions, VP was defined as the maximum intravesical pressure during detrusor contraction for micturition, BP was defined as the starting intravesical pressure at filling, and threshold pressure was defined as the ending intravesical pressure at filling. In addition, post-void residual volume (PVR) was measured by withdrawing intravesical fluid through the catheter using gravity before drug injection, and at the end of the micturition reflex after drug administration. The bladder was emptied using a syringe after micturition to measure PVR. For cystometry, a catheter from the bladder was connected via a three-way stopcock to a pressure transducer for monitoring bladder pressure. Saline at room temperature was continuously infused into the bladder using a syringe pump (TE-332S; Terumo, Tokyo, Japan) at a constant rate (3 mL/h). These parameters were monitored by a pressure amplifier, incorporated into a personal computer via a PowerLab system analog-to-digital (AD) converter (AD Instruments, Nagoya, Japan), and recorded using chart data acquisition software at a sampling rate of 400 Hz. Cystometry to assess the effects of drug administration was initiated after stable baseline data of bladder pressure were obtained for 60 min. Rats were anesthetized with isoflurane (Pfizer Japan Inc., Tokyo, Japan) and urethane (1.1 g/kg subcutaneous injection; Wako Pure Chemical Industries, Ltd., Osaka, Japan).[19] The lower abdomen was dissected, polyethylene tubing (Becton Dickinson, Franklin Lakes, NJ, USA) was inserted into the bladder dome to record bladder filling and pressure, and then ligated using thread. After confirming that no liquid was leaking from the bladder dome, the abdominal wound was sutured. Rats were allowed to stabilize for approximately 2 h before the experimental protocol was initiated.

Urethral pressure (UP) measurement

We assessed urethral function as previously reported.[20] All assessments were performed under isoflurane (Pfizer Japan Inc., Tokyo, Japan) and intraperitoneal injection of 1.1 g/kg urethane anesthesia (Wako Pure Chemical Industries, Ltd.). At 4 weeks after 6-OHDA injection, urethral pressure (UP) was measured. Briefly, midline incisions of the lower abdomen were made to expose the rat ureters and bladders while in the supine position, after which, the ureters were ligated. A microtransducer-tipped catheter (3.5 Fr nylon SPR-524; Millar Instruments, Houston, TX, USA) attached to a pressure control unit (PCU-2000; Millar Instruments) was

inserted into the middle urethra of each rat 12.5–15.0 mm from the urethral orifice. We used a Power Lab AD converter (AD Instruments) with chart data acquisition to measure active urethral responses at a sampling rate of 400 Hz.

Drug administration

Vibegron (Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan) was intravenously administrated in the PD rats. Vibegron was dissolved in 60% polyethylene glycol 400, 20% ethanol, and 20% saline in a volume of 0.2 ml/kg for intravenous administration before use. Regarding the dosage, 0.3, 1, and 3 mg/kg were used for intravenous administration. Doses were set based on previous reports.[21] Saline (0.1 mg/kg) was administrated intravenously as vehicle.

Statistical analysis

The results of urinary variables, such as ICI, VP, and UP, were expressed as the mean ± standard error, and data from the PD model were statistically analyzed using repeated analysis of variance and Tukey's test. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were conducted with the JMP® 16 (SAS Institute Inc., Cary, NC, USA) for Macintosh.

Results

A rat PD model induced by an injection of 6-OHDA into the substantia nigra was confirmed bladder overactivity as previously reported.[11] Table 1 shows the ICI and VP following the administration of vehicle or vibegron (0.3, 1, and 3 mg/kg). In 6-OHDA lesioned rats, intravenous injection of 3 mg/kg vibegron led to a significantly longer ICI than did vehicle injection ($p < 0.05$; Table 1 and Figure 1). Vibegron (0.3 and 1 mg/kg) did not significantly affect ICI. In addition, VP after the administration of vibegron (3 mg/kg) was significantly lower than vehicle injection ($p < 0.05$). Vibegron (0.3 and 1 mg/kg) did not significantly affect VP. There was no significant decrease in baseline and threshold pressure was observed.

And PVR at the end of the micturition reflex after drug administration was not changed significantly. In the study of urethral function, no significant changes in UP were found after either dose of vibegron administration (Table 1 and Figure 2).

Discussion

To the best of our knowledge, this study provides the first direct evidence that the administration of vibegron, in a PD rat model improves bladder overactivity without significant effect on the urethral function or any increase in PVR.

The pathophysiology of LUT dysfunction in PD remains poorly understood. Patients with central nervous system disorders such as PD have been found to have a high incidence of OAB,[22] Although numerous experiments using animal models have been carried out to elucidate the pathophysiology of OAB,[23] "urgency," a key symptom of OAB, is a sensation that cannot be measured in animals; therefore, a perfect animal model for OAB has yet to be established.[24]

Anti-parkinsonian drugs may help treat LUT dysfunction in patients with PD.[25] Regarding the treatment sequence for the management of OAB in patients with PD, a lifestyle modification is a first-line treatment, followed by pharmacological treatment as a second-line treatment. Anticholinergic drugs have long been used as mainstays to treat OAB. However, many patients with PD experience severe constipation or undesirable side effects from anticholinergic drugs, and some cannot undergo treatment with antimuscarinic drugs because of severe side effects or inadequate efficacy.

OAB affects three β-Ars-β_1, β_2, and β_3-in the detrusor muscle and urinary tract epithelium. The β_3-AR subtype has been reported to enhance detrusor relaxation during the storage phase in the human bladder.[26] In addition, the pharmacological activity of vibegron has been confirmed both in vitro and in vivo.[27,28] Vibegron may have at least two mechanisms of action: decreasing the detrusor tone, which is regulated by cAMP, or inhibiting the release of ACh from cholinergic efferent nerve terminals and blocking the afferent activity pathway by inhibiting the release of ATP or increasing the release of NO from the urothelium. Moreover, multiple studies have been conducted to compare vibegron with placebo or antimuscarinic drugs for treating patients with OAB.[28,29,30] However, few studies have specifically investigated treatment for OAB in patients with PD. Furuta et al reported that the combination treatment of intravesical and intravenous administration of vibegron induced a significantly greater degree of bladder capacity increase compared to vehicle using rats induced by intravesical application of nonselective muscarinic receptor agonis.[31] And Fruta et al. reported that intravenous administration of vibegron (10 mg/kg) significantly increased intercontraction interval, voided volume and bladder capacity, and significantly decreased baseline, threshold and maximal voiding pressure compared to vehicle administration. In the current study, no significant decrease in baseline and threshold pressure was observed. At least two reasons are assumed for this discrepancy. The first is the model difference. And the

second is the difference in dosage of vibegron. Further investigation is required. The results of the present study confirm that vibegron increases the micturition reflex interval, and thus may improve OAB symptoms in the clinical setting. The LUT consists of two major components: the bladder and the urethra. The bladder is innervated for contraction and relaxation by cholinergic and noradrenergic fibers, respectively, and contains abundant muscarinic M_2 and M_3 receptors and β_3-ARs. The micturition reflex is known to be under the influence of nigrostriatal DA and GABA inhibitory pathways, and therefore, LUT dysfunction in patients with PD may reflect the degeneration of motor disorder-associated nigrostriatal DA cells. In other words, from a biological perspective, the degeneration of DA systems, i.e., the main pathogenetic mechanism of PD, also underlies the development of LUT dysfunction in patients with PD.[23,32] The bladder functions as a reservoir for storing urine as long as the UP is sufficient. LUT symptoms, including urinary incontinence, can occur upon disturbances in this coordinated function.

Kummeling et al. previously reported that β_3-AR is expressed in the human female urethra.[14] However, the potential roles of β_3-AR in the urethral function have not been fully explored. Now that selective β_3 agonists are currently available for treatment in patients with OAB, the question regarding whether and how UP is affected by these agents arises.

Urethral function in patients with PD remains to be elucidated. A previous study reported that patients with PD may experience both urge urinary incontinence (OAB) and stress urinary incontinence.[4] Stress urinary incontinence can occur if the pressure in the bladder exceeds that in the urethra because of exertion (e.g., upon sneezing or coughing), depending on the extent of static and dynamic urethral compressions. The reflexes involved in bladder storage and micturition originates in the urethra.[33] In addition, urine leakage into the urethra might stimulate, which can stimulate urethral afferents, thereby inducing an involuntary voiding reflex.[33,34] Ouchi et al. reported that DA depletion impaired urethral closure mechanisms in PD rats.[20] Moreover, DA D_1-like receptor activity in the central nervous system of PD rats has been suggested to compensate, at least in part, to urethral function negatively impacted by the lack of DA, whereas DA D_2-like receptor activity may exacerbate urinary leakage because of the negative effects on UP under increased intra-abdominal pressure.[20]

In the present study, urethral closure pressure was not significantly affected by vibegron. Moreover, for symptoms of OAB in patients with PD, vibegron was shown to be effective for treating OAB while not worsening urethral function. These findings suggest that vibegron can provide highly effective treatment for OAB in patients with PD. In addition, in terms of side effects, vibegron is considered desirable compared with anticholinergic drugs.

This study have several limitations. First, we investigated the acute effect of intravenous administration of vibegron; thus, it was possible to confirm the effects of long-term administration. Second, although a common limitation of animal experiments, it was not possible to confirm changes in urgency, which is the primary symptom of OAB. Third, we investigated only static urethral function in this study, however it is important to examine the dynamic and static functions of the urethral function in order to examine urinary incontinence in clinical practice.

Conclusion

The results of the present study provide corroborating evidence that the administration of vibegron suppresses bladder dysfunction in PD model rats, and thus could contribute to a better understanding of the mechanisms of β_3-AR agonists in LUT function.

Acknowledgments Statement

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Conflicts of Interest Statement

Vibegron was provided by Kyorin Pharmaceutical Co., Ltd.

Data availability statement

The data that support the findings of this study are not openly available due to reasons of sensitivity human data and are available from the corresponding author upon reasonable request.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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Informed Consent Statement

Not applicable.

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Table 1 Intravenous administration of vibegron in a rat model of Parkinson's disease.

n=7	Mean (SE) ICI, sec	Mean (SE) VP, cmH_2O	Mean (SE) TP, cmH_2O	Mean (SE) PVR, mL
Vehicle	292 (48.1)	24.4 (1.77)	4.49 (4.31)	0.000 (0.00)
Vibegron 0.3 mg	394 (51.6)	21.8 (1.76)	4.34 (3.89)	
Vibegron 1 mg	335 (20.2)	21.3 (1.50)	3.81 (4.11)	
Vibegron 3 mg	464 (48.6)*	16.2 (0.61)**	3.71 (4.08)	0.004 (0.07)

n=7	Mean (SE) UP, cmH_2O
Vehicle	31.3 (4.11)
Vibegron 0.3 mg	30.8 (3.77)
Vibegron 1 mg	29.6 (3.93)
Vibegron 3 mg	25.5 (3.46)

ICI intercontraction interval, VP voiding pressure, TP threshold pressure, PVR post-voided residual volume, UP urethral pressure

* $P < 0.05$ vs vehicle

** $P < 0.01$ vs vehicle

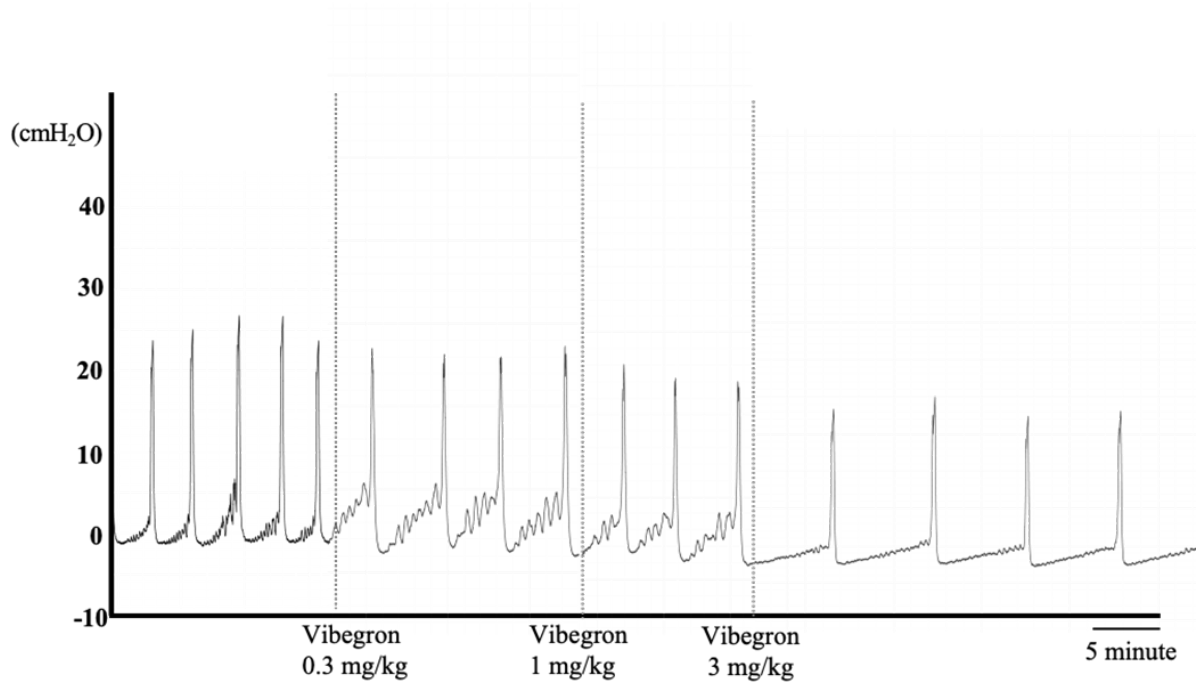

Figure 1

Representative cystometry in a rat model of Parkinson's disease treated with vibegron (3 mg/kg).

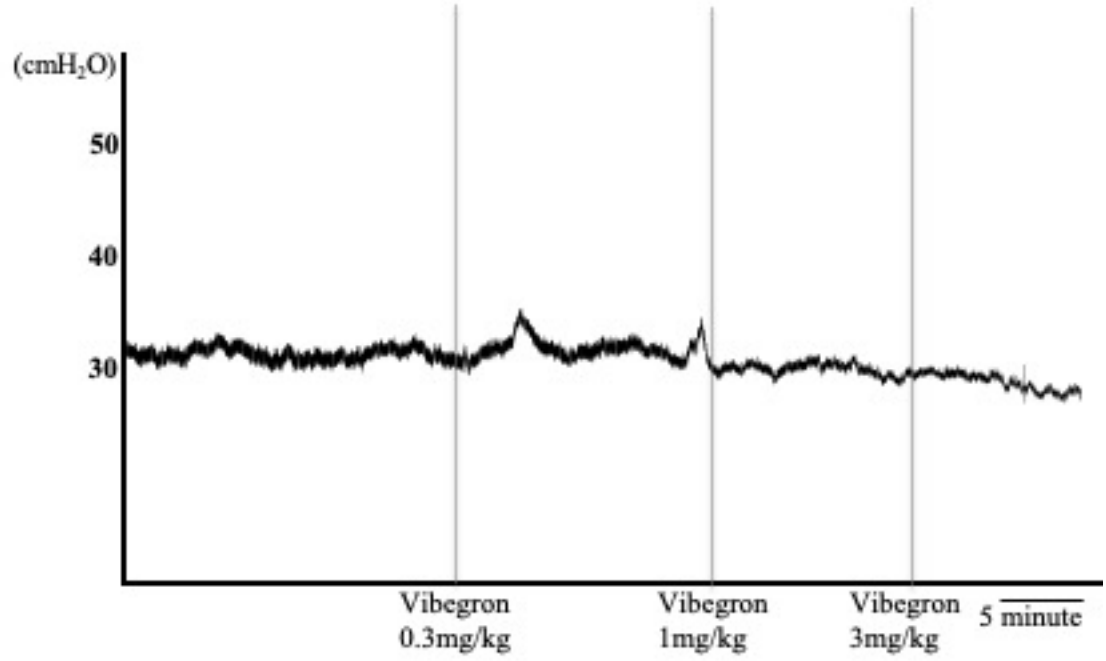

Figure 2

Representative urethral pressure in a rat model of Parkinson's disease after cumulative administration of vibegron (0.3, 1, 3 mg/kg).