Abstract #672

Effects of vibegron, a β3-adrenoceptor agonist, on lower urinary tract dysfunction in diabetic rats

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Hypothesis / aims of study

Lower urinary tract dysfunction (LUTD) is caused by hyperglycemia-induced vascular endothelial damage in diabetes mellitus (DM). Moreover, chronic bladder ischemia induces bladder overactivity in the early stage and underactivity in the advanced stage in vascular endothelial dysfunction (1). Therefore, early treatment of bladder overactivity is important for patient health. Various pharmacotherapeutics, including anticholinergic agents, are used for the first-line treatment of detrusor overactivity in patients with DM at a risk of upper urinary tract damage. However, anticholinergic medications are not always effective, often causing adverse events, such as dry mouth and constipation. Vibegron, a new β3-adrenoceptor agonist, was approved for overactive bladder treatment in Japan in 2018. Notably, β3-adrenoceptor agonists, such as mirabegron, cause fewer clinical adverse events than anticholinergic medications (2). Moreover, vibegron suppresses bladder fibrosis in mice with spinal cord injury (3). These reports suggest vibegron as a potential therapeutic for LUTD in DM. However, specific effects of vibegron on DM-induced bladder dysfunction remain unknown. Therefore, in this study, we investigated the inflammatory and ischemic changes in the bladder of DM rats with or without vibegron treatment. To the best of our knowledge, this is the first study to determine the effects of vibegron on bladder activity due to DM.

Study design, materials and methods

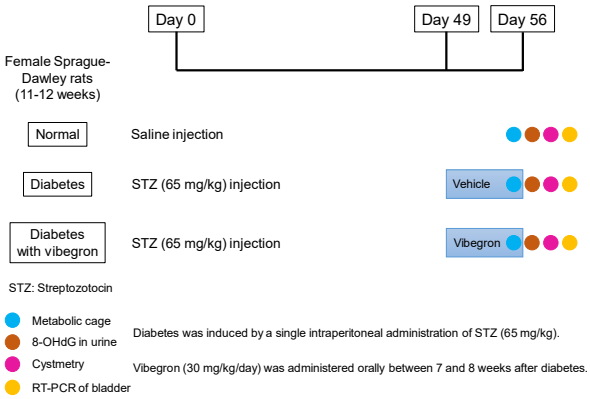


Fig. 1 Experimental protocol

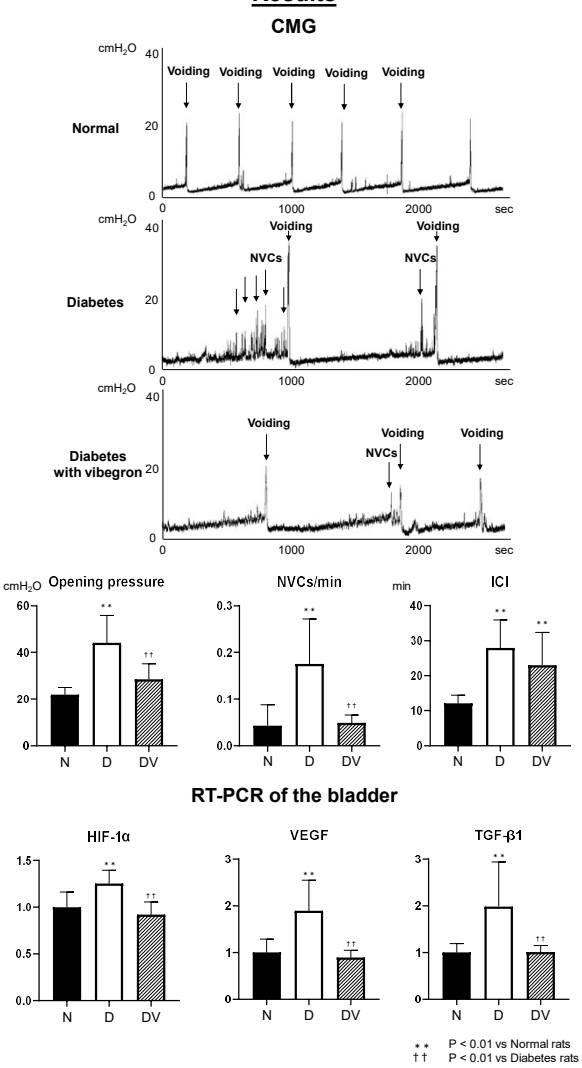
Female Sprague–Dawley rats (age: 11–12 weeks old; weight: 250–300 g) were used in this study. All rats were divided into three groups: non-diabetic (N), diabetic (D), and vibegron-treated diabetic (DV) groups (n = 12 rats/group). Diabetes was induced via a single intraperitoneal injection of streptozotocin (65 mg/kg). Experiments were performed 8 weeks after diabetes induction (Fig. 1). 24-h voiding assays were performed to evaluate the urodynamic parameters of all groups via awake cystometry/cystometrogram (CMG). Subsequently, 8-hydroxydeoxyguanosine (8-OHdG) levels in urine and mRNA expression levels of ischemia-related and inflammatory markers in bladder tissues were evaluated. Several parameters, including opening pressure (pressure at which the urethra opens and urine flows), intercontraction intervals (ICIs), number of non-voiding contractions (NVCs) per voiding, post-void residual (PVR) urine volume, bladder capacity, bladder compliance, and voiding efficiency (VE), were measured in CMG. NVC is defined as > 8 cm H_2O increase in intravesical pressure above the baseline. All values are expressed as the mean ± standard deviation.

Results

	Normal	DM + vehicle	DM + vibegron
Body weight (g)	261.5 ± 10.5	237.0 ± 13.5**	262.3 ± 12.9††
Blood glucose (mg/dL)	140.5 ± 21.8	487.5 ± 30.6**	479.2 ± 51.0**
Total voided volume (mL)	14.1 ± 2.1	165.3 ± 47.6**	141.6 ± 34.8**
Tidal voided volume (mL)	0.9 ± 0.3	3.4 ± 0.4**	3.1 ± 0.5**
Frequency (number)	16.0 ± 4.0	47.8 ± 11.5**	44.7 ± 5.7**
Water intake (mL)	27.5 ± 5.2	187.5 ± 51.8**	166.7 ± 34.2**
8-OHdG in urine (ng/mg・Cr)	25.2 ± 10.5	93.6 ± 18.2**	63.8 ± 17.2**†

** P < 0.01 vs Normal rats
† P < 0.05 vs Diabetes rats
†† P < 0.01 vs Diabetes rats

Results



Interpretation of results

Compared to normal rats, diabetic rats exhibited higher urinary oxidative stress indicated by increased 8-OHdG levels in the urine. Furthermore, NVCs, micturition pressure, and residual urine volume increased but VE decreased in diabetic rats, indicating the exacerbation of urinary storage and micturition symptoms. Reverse transcript (RT)-PCR revealed increased bladder ischemia and inflammatory marker levels in diabetic rats. Our results suggest that vibegron alleviates urinary oxidative stress by reducing the bladder ischemic inflammatory marker levels, which improves the bladder micturition pressure and reduces NVCs, thereby improving LUTD.

Conclusions

Vibegron, a new β3-adrenoceptor agonist approved for overactive bladder treatment, reduces the NVCs, opening pressure, and mRNA expression levels of *HIF-1α*, *VEGF*, and *TGF-β1* in early-stage DM (at 8 weeks), acting as a potnetial candidate for DM-induced detrusor overactivity treatment and bladder remodeling.

References

(1) J Urol. 182: S8-S13, 2009
(2) Neurourol Urodyn. 36: 1097-1103, 2017
(3) Neurourol Urodyn. 39: 2120-2127, 2020

COI disclosure

The authors have no financial conflicts of interest to disclose concerning the presentation.