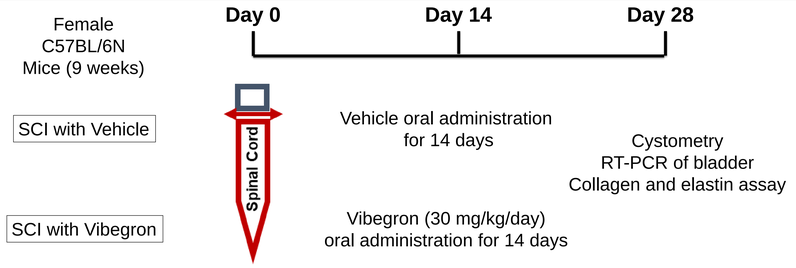
MP54-08 Effects of vibegron, a new β3-adrenoceptor agonist, on detrusor overactivity and remodeling in a mouse model of spinal cord injury (SCI)

Daisuke Gotoh[1], Nobutaka Shimizu[1], Naoki Wada[1], Katsumi Kadekawa[1], Tetsuichi Saito[1],
Shinsuke Mizoguchi[1], Masahiro Kurobe[1], Kazumasa Torimoto[2], Kiyohide Fujimoto[2], Naoki Yoshimura[1]
1, Department of Urology, University of Pittsburgh, Pittsburgh, PA, 2, Department of Urology, Nara Medical University, Nara, Japan

Introduction

- Neurogenic lower urinary tract dysfunction due to spinal cord injury (SCI) is characterized by detrusor overactivity (DO), low bladder compliance, and detrusor-sphincter dyssynergia (DSD).
- Vibegron is a new β3-adrenoceptor agonist that was approved for treating overactive bladder (OAB) in Japan in 2018. β3-adrenoceptor agonists including mirabegron cause fewer clinical adverse events than anticholinergic medication (1).
- Therefore, vibegron is potentially applicable for treating patients with neurogenic bladder dysfunction due to SCI. However, the effects of vibegron on bladder dysfunction and bladder wall remodeling after SCI have not been previously investigated. Therefore, the present study aimed to evaluate bladder activity, and fibrotic and ischemic changes in the bladder of SCI mice with or without vibegron treatment.

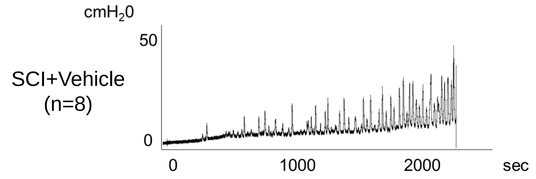
Methods

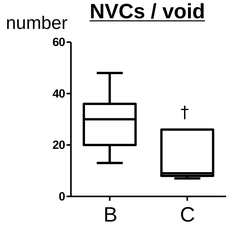


Animal: Female C57BL/6N mice (9 weeks old) were used (Group A spinal cord intact n=6; Group B vehicle-treated SCI n=8; Group C vibegron-treated SCI n=7).
Spinal cord injury: SCI mice underwent Th8-9 spinal cord transection.
Vibegron treatment: Vibegron was suspended in 20% polyethylene glycol. Then, the drug (30 mg/kg body weight) or vehicle was orally administered by gavage once a day in the morning for 2–4 weeks after spinal cord transection.
Cystostomy: Under isoflurane anesthesia, PE50 catheter was inserted into bladder dome, placed under the skin and pulled out from the back of the neck.
Analysis of the expression of fibrosis and ischemia markers: Gene expression of fibrosis markers such as collagen type 1 and 3, and transforming growth factor beta 1 (TGF-β1), and ischemia marker such as hypoxia-inducible factor 1 alpha (HIF-1α) was quantified using real-time PCR.
Collagen and elastin assay: We determined the levels of collagen and elastin in the bladder of each SCI mouse by dye-binding methods, using Sircol™ collagen and Fastin™ elastin assay kits, respectively (Biocolor Ltd., Carrickfergus, UK).
Ethical considerations: All animal experiments were conducted in accordance with the institutional guidelines approved by the University of Pittsburgh Institutional Animal Care and Use Committee.

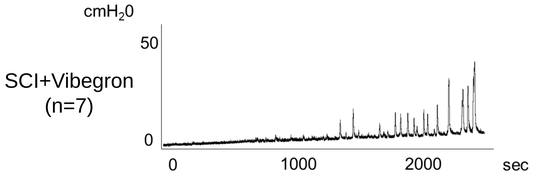
Results 1

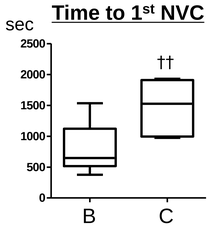
Cystometry





NVC = Non-voiding contractions during bladder filling

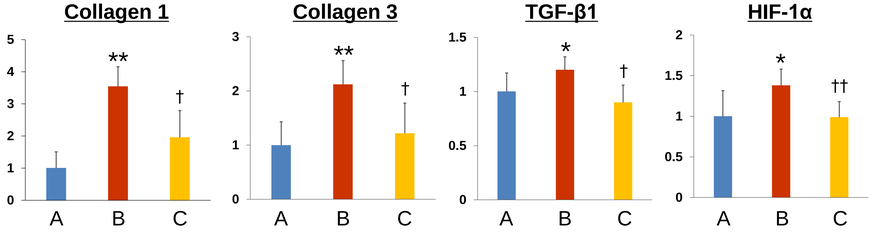




Comparison of other cystometric parameters

	Spinal cord intact (n=6)	SCI + Vehicle (n=8)	SCI + Vibegron (n=7)
Maximal micturition pressure (cmH_2O)	30.8 ± 9.7	47.4 ± 7.5**	45.3 ± 6.2**
Time to voiding (sec)	407.1 ± 141.1	2324.2 ± 886.1***	2133.9 ± 718.7**
Voided volume (mL)	0.06 ± 0.02	0.03 ± 0.02*	0.03 ± 0.01**
Post-void residual (mL)	0.00 ± 0.00	0.36 ± 0.14**	0.33 ± 0.12**
Bladder capacity (mL)	0.07 ± 0.02	0.39 ± 0.15***	0.36 ± 0.12**
Bladder compliance (mL/cmH_2O)	0.02 ± 0.01	0.04 ± 0.01*	0.03 ± 0.01**
Voiding efficiency (%)	95.0 ± 2.1	8.4 ± 3.3***	8.8 ± 5.0**

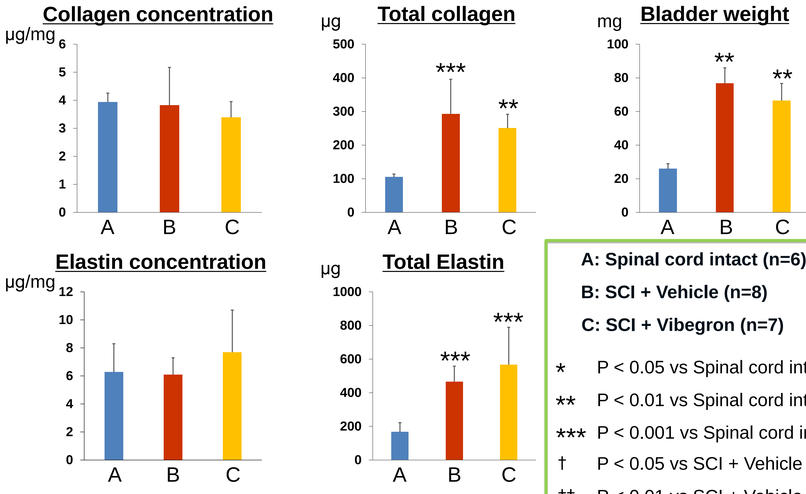
Real-time PCR



Fold changes compared to spinal cord intact mice.

Results 2

Collagen and elastin assay



A: Spinal cord intact (n=6)
B: SCI + Vehicle (n=8)
C: SCI + Vibegron (n=7)

*	P < 0.05 vs Spinal cord intact
**	P < 0.01 vs Spinal cord intact
***	P < 0.001 vs Spinal cord intact
†	P < 0.05 vs SCI + Vehicle
††	P < 0.01 vs SCI + Vehicle

Interpretation of results

- Previous studies in rodent SCI models demonstrated that the afferent limb of micturition reflexes inducing NVCs and voiding bladder contractions are controlled by C-fiber and Aδ-fiber afferent pathways, respectively, after SCI (2).
- In this study, because vibegron treatment decreased SCI-induced DO evident as reduced NVC, our results indicate that vibegron is useful for the treatment of neurogenic detrusor overactivity dependent on the activation of C-fiber bladder afferent pathways.
- Additionally, vibegron treatment improved the mRNA expression of type 1 collagen, type 3 collagen, TGF-β1 and HIF-1α although the protein level of collagen is not decreased yet at this stage of SCI (4 weeks).

Concluding message

- Vibegron, a new β3-adrenoceptor agonist approved for OAB, would be effective for reducing SCI-induced neurogenic detrusor overactivity and tissue remodeling in the bladder.

(1) Neurourol Urodyn. 36: 1097-1103, 2017
(2) Am J Physiol Renal Physiol. 313: F796-F804, 2017