836

Wada N[1], Suzuki T[1], Shimizu N[1], Shimizu T[1], Takai S[1], Takaoka E[1], Tyagi P[1], Kakizaki H[2], Yoshimura N[1]
1. *The Department of Urology, Pittsburgh University,* ***2.*** *The Department of Renal and Urologic Surgery, Asahikawa Medical University*

PROTECTIVE EFFECTS OF MIRABEGRON AGAINST IMPAIRED DETRUSOR CONTRACTILITY AND BLADDER FIBROSIS IN RATS WITH BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study

Impaired detrusor contractility is one of the important comorbidities in patients with bladder outlet obstruction (BOO). Mirabegron, a β3-adrenoceptor agonist, is widely used as new medication for patients with overactive bladder (OAB). Some clinical studies demonstrated that mirabegron is effective for patients with secondary OAB due to BOO and that impaired detrusor contractility was improved after mirabegron treatment. We also previously reported that mirabegron improved bladder fibrotic changes in spinal cord injured rats. The aim of this study is to investigate the effect of mirabegron on bladder contractility and bladder fibrosis in rats with BOO.

Study design, materials and methods

Eight weeks-old female Sprague-Dawley rats were divided into 4 groups; A: intact rats (n=7), B: 6-week BOO rats without treatment (n=8), C: 6-week BOO rats with 2 weeks treatment of mirabegron (n=6), and D: 6-week BOO rats with 4 weeks treatment of mirabegron (n=7). BOO was induced by a 4-0 silk ligature tied tightly around the proximal urethra along with a 1.1mm diameter steel rod, followed by the removal of the rod. Mirabegron was subcutaneously administered at 0.2 mg/kg/hr continuously during the treatment period using an osmotic pump. The bladder was excised and dissected into 4 longitudinal strips for an isometric organ-bath assay. Contractile responses of bladder strips to 3 levels of electrical field stimulation (EFS; 2, 8, and 32 Hz), carbachol (20μM), and potassium chloride (KCl; 120mM) were determined in each group. The remaining bladder tissue was used for collagen and elastin analyses.

Results

The contractile responses to three kinds of stimulation methods (EFS, carbachol, and KCl) in the group B (untreated BOO rats) were significantly decreased ($P<0.05$) compared to the group A (intact rats). The contractile responses to different stimulation methods were improved with the significant difference ($P<0.05$) in the response to 2 Hz of EFS in the group D (BOO with 4-weeks mirabegron), but not in the group C compared to the group B (Figure 1).
The elastin level in the bladder was not different among the groups. However, the collagen concentration in the group B was significantly higher than that in the group A; however, it was significantly decreased in the group D compared to the group B (Figure 2).

Interpretation of results

In 6-week BOO rats, contractile responses to EFS, muscarinic stimulation and potassium were impaired compared to the normal rats, indicating the impaired bladder contractility after BOO. Collagen deposition in the bladder of untreated BOO rats was increased compared to the normal rats, indicating the bladder fibrosis after BOO. The 4-weeks mirabegron treatment, but not 2-weeks treatment, in BOO rats improved contractile responses to these three stimulations with a significant increase in the responses to 2 Hz of EFS compared to untreated BOO rats. The increased collagen concentration was also improved in 4-weeks treatment BOO rats compared to untreated BOO rats. Thus, BOO-induced collagen deposition in the bladder seems to be involved in the reduction in bladder contractile force. Mirabegron had the beneficial effects on both bladder contractility and bladder fibrotic changes in BOO rats.

Concluding message

Mirabegron counteracted the decrease in bladder contractile force and the increase in bladder collagen levels induced by BOO. Thus, mirabegron could have the protective effects against impaired bladder contractility and bladder fibrosis induced by BOO.

Figure 1

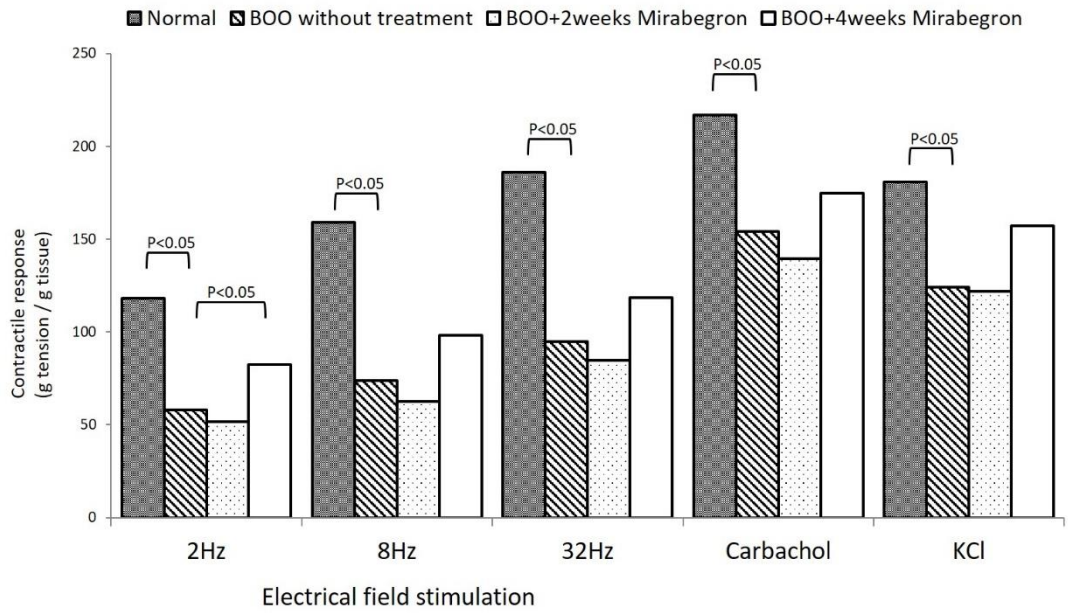
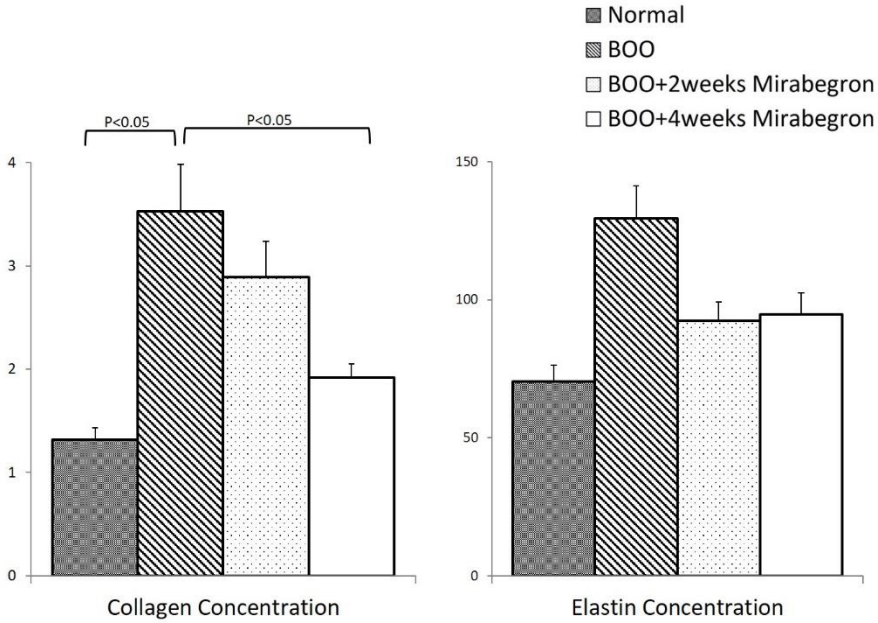


Figure 2



References
1. J Urol 2013; 190: 1320–7.
2. LUTS 2016; 8: 171-6

Disclosures
Funding: Mirabegron was provided by Astellas with the material transfer agreement. **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The University of Pittsburgh Institutional Animal Care and Use Committee