The effect of mirabegron on bladder blood flow in a rat model of bladder outlet obstruction

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ABSTRACT

Introduction

We have evaluated the effects of mirabegron, a β3-adrenoceptor agonist on bladder blood flow in a rat model of bladder outlet obstruction (BOO).

Methods

Adult female Sprague-Dawley rats were divided into 3 groups: sham, BOO, and BOO + mirabegron. In the BOO and BOO + mirabegron groups, rats underwent an operation to establish partial BOO. After the surgery, the BOO + mirabegron group was treated with mirabegron (0.3 mg/kg/h, subcutaneously 14 days. The following experiments were performed after the 14 days-treatment: (1) continuous cystometry; (2) bladder blood flow; (3) hematoxylin-eosin staining of bladder tissue; and (4) malondialdehyde (MDA) measurement in bladder tissue.

Results

(1) continuous cystometry: The BOO group showed significantly higher baseline and peak pressure, more residual urine volume, lower voiding efficiency, and more frequent non-voiding contractions in comparison to the sham group (p = 0.04, < 0.001, 0.007, 0.02, 0.01, respectively). The BOO + mirabegron group had significantly fewer non-voiding contractions than the BOO group (p = 0.04).

(2) bladder blood flow: The bladder blood flow was significantly different at 0.4 mL intravesical volume among three groups in the following order: sham > BOO + mirabegron > BOO groups

(3) hematoxylin-eosin staining: The bladder tissue in the BOO group had a tendency to contain more hypertrophic detrusor muscle and inflammatory cells when compared to those of the control group, while mirabegron treatment suppressed these histological changes.

(4) MDA measurement: In the BOO group significantly increased MDA levels were detected, as compared to the sham group (p = 0.02). Moreover, significantly decreased MDA was observed in the BOO + mirabegron than the BOO group. (p = 0.04)

Conclusions

Mirabegron treatment significantly improved BOO-induced bladder dysfunction through the amelioration of bladder blood flow.

METHODS

Adult female Sprague-Dawley rats were divided into 3 groups: sham, BOO, and BOO + mirabegron. In the sham group, rats underwent a sham operation, whereas in the BOO and the BOO + mirabegron group, rats underwent an operation to establish partial BOO. After the surgery, the BOO + mirabegron group was treated with mirabegron (0.3 mg/kg/h, subcutaneously) using an osmotic pump for 14 days, whereas the sham and the BOO groups were similarly treated with the vehicle. The following experiments were performed after the 14 days-treatment: (1) continuous cystometry in awake state; (2) measurement of bladder blood flow with a 2D laser blood flow imager (OMEGAZONE); (3) hematoxylin-eosin staining of bladder tissue; and (4) malondialdehyde (MDA) measurement in bladder tissue.

RESULTS

The bladder weight was significantly increased in the BOO group than the sham group (p < 0.001), whereas the BOO + mirabegron group showed significantly decreased bladder weight than the the BOO group (p = 0.02). There was no significant differences in blood pressure among 3 groups.

(1) *Continuous cystometry in awake state*

The BOO group showed significantly higher baseline and peak pressure, more residual urine volume, lower voiding efficiency, and more frequent non-voiding contractions in comparison to the sham group (p = 0.04, < 0.001, 0.007, 0.02, 0.01, respectively). In addition, the BOO + mirabegron group showed significantly higher peak pressure, more residual urine volume and lower voiding efficiency than the sham group. The BOO + mirabegron group had significantly fewer non-voiding contractions than the BOO group (p = 0.04).

(2) *Measurement of bladder blood flow*

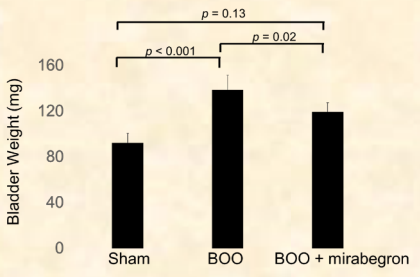
There was no significant difference among the three groups, regarding the bladder blood flow with intravesical volume at 0 mL. In contrast, at 0.4 mL intravesical volume, the BOO and BOO + mirabegron group had significantly decreased bladder blood flow than the sham group (p < 0.001 and 0.006), whereas the BOO + mirabegron group showed significantly (p = 0.01) increased bladder blood flow, as compared to the BOO group.

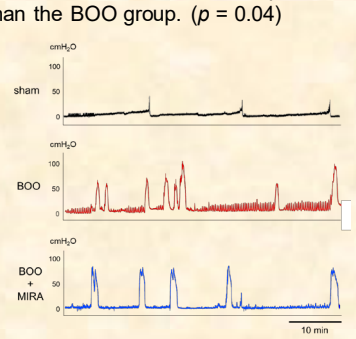
(3) Hematoxylin-eosin staining

The bladder tissue in the BOO group had a tendency to contain more hypertrophic detrusor muscle and inflammatory cells when compared to those of the control group, while mirabegron treatment suppressed these histological changes.

(4) *MDA measurement*

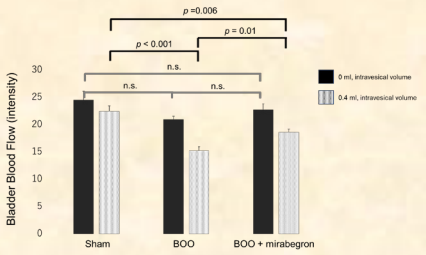
In the BOO group significantly increased MDA levels were detected, as compared to the sham group (p = 0.02). Moreover, significantly decreased MDA was observed in the BOO + mirabegron than the BOO group. (p = 0.04)

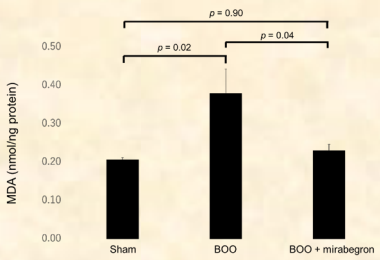


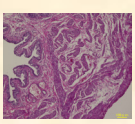


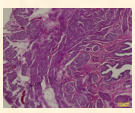
		B.P. (cmH_2O)	M.T. (cmH_2O)	P.P. (cmH_2O)	V.V. (mL)	R.V. (mL)	V.E.	Compliance (mL/H_2O)	B.C. (mL)	No of NVCs (n)	Amplitude of NVCs (cmH_2O)
Sham (S)		3.7 ± 0.3	8.9 ± 1.1	36.8 ± 3.6	0.78 ± 0.15	0.02 ± 0.01	0.97 ± 0.01	0.17 ± 0.02	0.80 ± 0.16	1.2 ± 0.8	1.9 ± 1.2
BOO (B)		5.6 ± 0.5	13.7 ± 2.2	81.5 ± 8.4	0.50 ± 0.14	0.28 ± 0.09	0.63 ± 0.10	0.09 ± 0.007	0.77 ± 0.20	6.1 ± 1.5	5.7 ± 1.0
BOO + MIRA (BM)		5.5 ± 0.5	12.6 ± 1.0	70.0 ± 8.0	0.43 ± 0.06	0.31 ± 0.11	0.59 ± 0.10	0.11 ± 0.04	0.71 ± 0.12	2.1 ± 0.7	4.4 ± 1.2
p-value	S vs B	0.04	n.s.	< 0.001	n.s.	0.007	0.02	n.s.	n.s.	0.01	n.s.
	S vs BM	0.05		0.01		0.006	0.001			0.85	
	B vs BM	0.99		0.50		0.97	0.44			0.04	

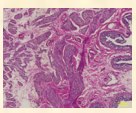
B.P.: basal pressure, M.T.: micturition threshold, P.P.: peak pressure, V.V.: voided volume, R.V.: residual volume, V.E.: voiding efficiency, B.C.: bladder capacity, NVC: non-voiding contraction, n.s.: not significant, MIRA: mirabegron











CONCLUSIONS

Mirabegron treatment significantly improved BOO-induced bladder dysfunction through the amelioration of bladder blood flow.

ACKNOWLEDGEMENT

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