414

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EFFECT OF A SELECTIVE ALPHA1A-ADRENOCEPTOR ANTAGONIST SILODOSIN ON PROSTATIC BLOOD FLOW AND PROSTATIC GROWTH IN THE SPONTANEOUSLY HYPERTENSIVE RAT

Hypothesis/aims of study

Prostatic vascular system plays an important role in the progression of benign prostatic hyperplasia/benign prostatic enlargement (BPH/BPE) [1]. Specifically, atherosclerosis and/or decreased prostatic blood flow can induce prostatic hyperplasia [2]. The spontaneously hypertensive rat (SHR) is a commonly used a genetically hypertensive rat model which shows chronic prostatic ischemia and prostatic hyperplasia [1]. The α_1-adrenoceptor antagonists are the most frequently used drugs for the treatment of BPH related lower urinary tract symptoms. Previously, administration of doxazosin, an α_1-adrenoceptor antagonist, restored the prostatic blood flow in the SHR [1]. In a recent study, a selective α_{1A}-adrenoceptor antagonist silodosin is known to increase the bladder blood flow, and as a result it managed to ameliorate the bladder dysfunction in the SHR model [1]. Thus, the effect of silodosin was investigated in the SHR prostate as a prostatic hyperplasia model focusing on the prostatic blood flow.

Study design, materials and methods

Twelve-week-old SHRs were treated with silodosin per orally (0, 100 or 300 μg/kg/day), once daily for another 6 weeks. Wistar-Kyoto (WKY) rats were used as normotensive controls treated with vehicle. The effect of silodosin on blood pressure, heart rate and prostatic blood flow were estimated by the tail cuff method and hydrogen clearance method, respectively. Furthermore, the prostates were removed and their weights were measured. The tissue levels of oxidative stress marker (MDA), inflammatory cytokines (IL-6, IL-8 (CXCL1/CINC1) and TNF-α), and growth factors (TGF-β1, bFGF and α-SMA) in the prostate were measured by using ELISA and western blot. The histological evaluation was performed by H&E staining.

Results

The SHRs demonstrated significant increases in blood pressure, prostate body weight ratio (PBR), and tissue levels of MDA, IL-6, CXCL1/CINC1, TNF-α, TGF-β1, bFGF and α-SMA in the prostate when compared to the WKY rats (Tables 1 and 2). Conversely, the SHR showed significant decreases in heart rate and prostatic blood flow when compared to the WKY rat (Tables 1 and 2). Moreover, the ventral prostate in the SHR showed the prostatic hyperplasia (Figure 1). Treatment with silodosin significantly improved the decreased heart rate and prostatic blood flow (Tables 1 and 2). On the other hand, it managed to decrease PBR, tissue levels of MDA, IL-6, CXCL1/CINC1, TNF-α, TGF-β1, bFGF and α-SMA, as well as the ventral prostatic hyperplasia in the SHR (Tables 1 and 2, and Figure 1).

Interpretation of results

The presented data showed that treatment with silodosin ameliorated the decreased prostatic blood flow, and the increased oxidative stress, inflammatory cytokines and growth factors, and prostatic hyperplasia in the SHR prostate. Prostatic ischemia could induce generation of reactive oxygen species and subsequent oxidative stress, which could be considered to play a role in the development of BPH [1]. The present study suggests that silodosin can inhibit the oxidative stress via the recovery of the prostatic blood flow in the SHR. Moreover, the inflammatory cytokines secreted from inflammatory cells could induce the proliferation, which results in the BPH/BPE [3]. Treatment with silodosin might improve the growth factors, PBR and prostatic hyperplasia via reducing the inflammatory cytokines.

Concluding message

The decreased prostatic blood flow can cause the prostatic hyperplasia via the oxidative stress, inflammatory cytokines and growth factors in the SHR prostate. Silodosin could ameliorate the prostatic hyperplasia through an increase in the prostatic blood flow.

Table 1. The general features in the experimental animals

	WKY	SHR	SHR+Sil100	SHR+Sil300
Body weight (g)	402 ± 5	326 ± 16*	336 ± 12*	327 ± 8*
Prostate weight (mg)	630 ± 35	926 ± 31*	863 ± 54*	920 ± 44*
PBR (×10^{-3})	1.57 ± 0.09	2.86 ± 0.07*	2.56 ± 0.11#	2.82 ± 0.12*
Heart rate (bpm)	338.0 ± 9.6	302.4 ± 3.9*	324.0 ± 9.8	323.2 ± 2.0#
Mean blood pressure (mmHg)	106.5 ± 1.1	166.0 ± 5.9*	154.7 ± 4.5*	159.3 ± 2.6*

PBR: Prostate body weight ratio.; WKY: 18-week-old WKY rats treated with vehicle, p.o.; SHR: 18-week-old SHRs treated with vehicle, p.o.; SHR+Sil100: 18-week-old SHRs treated with silodosin at a daily dose of 100 μg/kg, p.o.; SHR+Sil300: 18-week-old SHRs treated with silodosin at a daily dose of 300 μg/kg, p.o.; Quantitative data are presented as means ± SEM of eight separate determinations and were compared among multiple experimental groups using analysis of variance and Fisher's multiple comparison tests.

*: significantly different from the WKY group ($P < 0.05$) #: significantly different from the SHR group ($P < 0.05$)

Table 2. Measurements the blood flow, and the markers of oxidative stress, inflammatory cytokines and growth factors in the prostate

	WKY	SHR	SHR+Sil100	SHR+Sil300
Prostatic blood flow (ml/min/100 g tissue)	139.75 ± 9.23	88.26 ± 6.68*	131.01 ± 7.08#	135.86 ± 8.38#
MDA (nmol/mg protein)	1.28 ± 0.17	2.86 ± 0.34*	1.68 ± 0.26#	1.81 ± 0.17#
IL-6 (pg/mg protein)	9.21 ± 1.54	34.98 ± 7.06*	6.61 ± 4.26#	16.82 ± 3.06#
CXCL1/CINC1 (pg/mg protein)	17.95 ± 4.28	81.76 ± 30.54*	20.54 ± 4.83#	24.58 ± 2.84
TNF-α (pg/mg protein)	67.69 ± 11.20	223.16 ± 51.05*	83.60 ± 16.96#	103.87 ± 14.51#
TGF-β1 (pg/μg protein)	0.11 ± 0.02	0.27 ± 0.07*	0.12 ± 0.02#	0.12 ± 0.03
bFGF (pg/μg protein)	0.14 ± 0.05	0.90 ± 0.23*	0.28 ± 0.06#	0.26 ± 0.04#
α-SMA/β actin (%)	100.00 ± 0.00	127.20 ± 3.86*	100.27 ± 3.78#	101.92 ± 6.32#

MDA: Malondialdehyde; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; TGF-β1: Transforming growth factor-beta1. bFGF: Basic fibroblast growth factor. α-SMA: Alpha-smooth muscle actin. Quantitative data are presented as means ± SEM of eight separate determinations and were compared among multiple experimental groups using analysis of variance and Fisher's multiple comparison tests.

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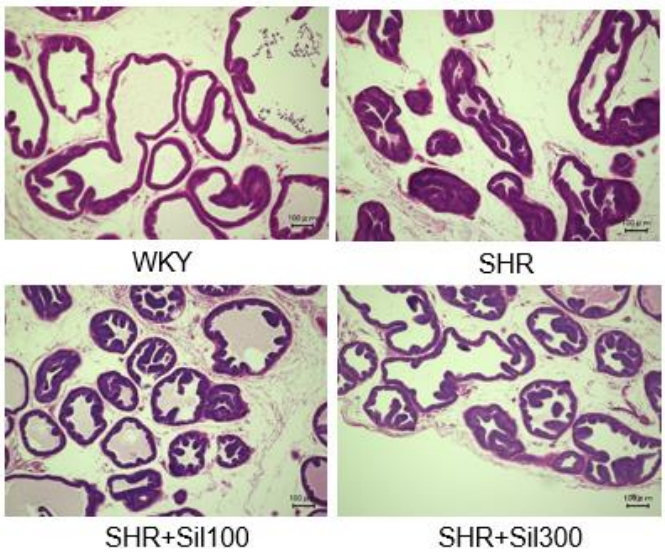
Figure 1. Histological changes in the ventral prostate of the SHR animals.
Original magnification: 100. The scale bar is 100 μm.



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Disclosures

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