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FASUDIL, A RHO KINASE INHIBITOR, AMELIORATES HYPERPLASIA IN THE SPONTANEOUSLY HYPERTENSIVE RAT PROSTATE

Hypothesis/aims of study

The exact etiology and pathogenesis of benign prostatic hyperplasia/benign prostatic enlargement (BPH/BPE) remains to be fully elucidated. There are some evidence that the vascular risk factors and prostatic chronic inflammation, may be associated with the progression of the BPH/BPE [1]. The spontaneously hypertensive rat (SHR) is commonly used genetically hypertensive rat model which develops hyperplastic morphological abnormalities in the ventral but not dorsolateral prostate [1]. The rho kinase (ROCK) pathway is associated with various cellular functions, including smooth muscle contraction [1,2]. We investigated if administration of fasudil, a ROCK inhibitor, could reduce the levels of growth factors and an inflammatory marker, found to be relevant for the progression of prostatic hyperplasia in the ventral prostate of the SHR.

Study design, materials and methods

Twelve-week-old SHRs were treated with fasudil 0, 1 or 3 mg/kg/day, i.p. once daily for another 6 weeks. Wistar-Kyoto (WKY) rats were used as normotensive controls treated with vehicle. At 18 weeks of age blood pressure and heart rate were measured by the tail cuff method. Ultimately, the prostates were removed and their weight were measured. The tissue levels of ROCK activity, growth factors (TGF-β1 and bFGF), α-smooth muscle actine (α-SMA), an inflammatory cytokine (IL-6) in the prostate were measured by using ELISA and western blot. The histological evaluation was performed by H&E staining.

Results

The SHR showed a significant increase in blood pressure, prostate body weight ratio and tissue levels of ROCK activity, TGF-β1, bFGF, α-SMA and IL-6 when compared to the WKY rat (Tables 1 and 2). Conversely, there was a decrease in heart rate in untreated SHRs when compared to WKY rats (Table 1). Histological examination of the prostate showed the epithelial overgrowth in the SHR than in the WKY rat (Figure 1). Treatment with fasudil significantly improved the decreased heart rate, the heightened blood pressure and tissue levels of ROCK activity,TGF-β1, α-SMA, and IL-6 compared to the ones in untreated SHR (Tables 1 and 2). Histological examination of the prostate showed a lower degree of the epithelial overgrowth in the fasudil treated SHRs than in the untreated SHR (Figure 1).

Interpretation of results

Present data reveals that treatment of SHR with the fasudil reduces the heightened blood pressure, ROCK activity, growth factors, inflammatory cytokine as well as prostatic hyperplasia in the SHR prostate. ROCK medicated pathway plays a role in infiltration of inflammatory cells and cell proliferations in the various organs [1,2]. In the present study, fasudil mediated prostatic ROCK activity inhibition reduced the increased TGF-β1, bFGF and α-SMA in the SHR prostate. IL-6 is recognized as a potent growth factor for prostatic epithelial and stromal cells [3]. Fasudil could inhibit the prostatic hyperplasia by reducing the inflammatory cytokines including IL-6. Thus, the reduction of ROCK activity by fasudil maybe decrease the prostatic hyperplasia via the inhibition of growth factors and inflammatory cytokines in the SHR prostate.

Concluding message

These results suggest that fasudil mediated ROCK activity inhibition might be a good candidate for future treatment of prostatic hyperplasia progression.

Table 1. The general features in the experimental rats

	WKY	SHR	SHR+FAS1	SHR+FAS3
Body Weight (g)	395 ± 3	317 ± 17*	337 ± 4*	335 ± 7*
Prostate Weight (mg)	686 ± 29	929 ± 30*	998 ± 46*	949 ± 20*
PBR (×10^{-3})	1.74 ± 0.08	2.95 ± 0.07*	2.97 ± 0.14*	2.83 ± 0.05*
Heart rate (bpm)	328 ± 9	299 ± 3*	324 ± 4#	323 ± 2#
Mean Blood pressure (mmHg)	109.0 ± 0.8	173.0 ± 2.4*	163.6 ± 3.3*	154.5 ± 1.3*#

PBR: Prostate body weight ratio; WKY: 18-week-old WKY rats treated with vehicle, i.p.; SHR: 18-week-old SHRs treated with the vehicle, i.p.; SHR+FAS1: 18-week-old SHRs treated with fasudil at a daily dose of 1 mg/kg, i.p.; SHR+FAS3: 18-week-old SHRs treated with fasudil at a daily dose of 3 mg/kg, i.p.; 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.

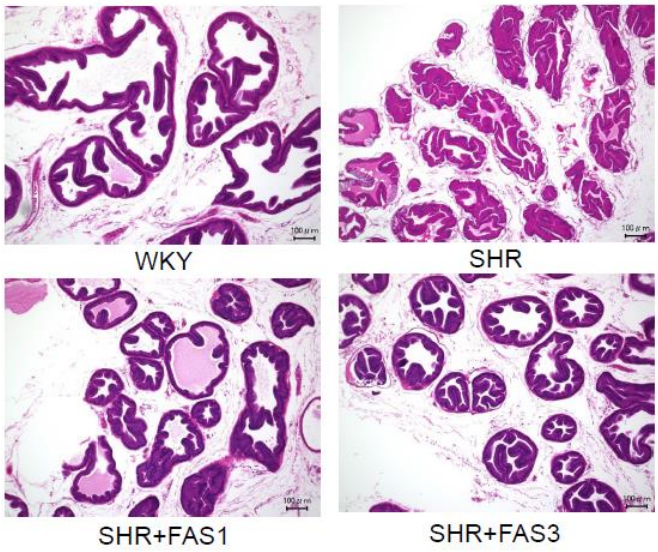
*: significantly different from the WKY group ($P < 0.05$) #: significantly different from the SHR group ($P < 0.05$).

Table 2. Measurements of the markers for ROCK activity, growth factors and inflammatory cytokine in the prostate

	WKY	SHR	SHR+FAS1	SHR+FAS3
ROCK activity (%)	100.00 ± 20.79	188.25 ± 28.80*	68.85 ± 17.00#	56.57 ± 14.43#
TGF-β1 (pg/μg protein)	0.10 ± 0.01	0.22 ± 0.04*	0.07 ± 0.01#	0.09 ± 0.01#
bFGF (pg/μg protein)	0.09 ± 0.03	0.20 ± 0.02*	0.14 ± 0.02	0.16 ± 0.02
α-SMA/β actin (%)	100.00 ± 0.00	112.23 ± 4.79*	85.90 ± 5.58*#	54.79 ± 18.02*#
IL-6 (pg/mg protein)	15.54 ± 4.63	27.21 ± 2.08*	19.60 ± 1.23#	16.73 ± 1.30#

ROCK: Rho kinase; TGF-β1: Transforming growth factor-beta1; bFGF: Basic fibroblast growth factor; α-SMA: Alpha-smooth muscle actin; IL-6: Interleukin-6; 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 ($P < 0.05$).

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



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Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The Animal Ethics Committee of Kochi University