

KETANSERIN SUPPRESSED DETRUSOR OVERACTIVITY IN SPONTANEOUSLY HYPERTENSIVE RATS, SUGGESTING A PATHOGENIC ROLE OF 5-HT_{2A} RECEPTOR

Hypothesis / aims of study

It has been well documented that spontaneously hypertensive rats (SHR) show detrusor overactivity and decrease in micturition volume. Activation of Rho-kinase pathway, angiotensin receptor and adrenaline receptor are supposed as factors involved in the pathogenesis of detrusor overactivity. Recently, a role of 5-HT_{2A} receptor on the onset of detrusor overactivity has been reported in rats with partial bladder outlet obstruction [1, 2]. However, its role in SHR is not known until today. The aim of this study is to elucidate the role of 5-HT_{2A} receptor in SHR.

Study design, materials and methods

A total of 27 rats were used in this study. Twelve-week old SHR or Wister Kyoto rats (WKY) were used. A cystometric study in awake SHR or WKY was performed with infusion rate of 0.04 ml/minute. Voided volume, residual volume, voiding efficacy, maximum voiding pressure and basal pressure were measured. Ketanserin, a 5-HT_{2A} receptor antagonist, was administered via left jugular vein. The effect of cumulative doses of ketanserin (0.01, 0.03, 0.1, 0.3 and 1 mg/kg) on the bladder activity and hemodynamics was examined. The body weight of SHR or WKY was measured just before the cystometric measurement. All values were indicated as mean ± standard error.

Results

The body weight of SHR was significantly lower than WKY (175.4 ± 1.6 g vs. 202.3 ± 1.8 g, $P < 0.0001$) (Figure 1). No significant difference was seen in heart rate between SHR and WKY. Although 1 mg/kg dose of ketanserin did not change the blood pressure of WKY, it significantly decreased systolic pressure of SHR (Figure 2). Ketanserin didn't change diastolic pressure of SHR or WKY. Therefore, following experiments were carried out with ketanserin doses under 1 mg/kg. Voided volume of SHR was significantly lower than WKY (0.66 ± 0.06 ml vs. 1.29 ± 0.10 ml, $P < 0.0001$) as a baseline value. Ketanserin increased voided volume of SHR in a dose-dependent manner. It was evident even when the voided volume was calculated as per body weight. Ketanserin didn't change residual volume, maximum contraction pressure and voiding efficiency.

Interpretation of results

Present study revealed that ketanserin decreased systolic blood pressure, and suppressed detrusor overactivity at the dose not to decrease blood pressure. Interestingly, inhibitory effects of ketanserin on the bladder smooth muscle were only seen in SHR. Thus, the role of 5-HT_{2A} receptor on the smooth muscle tonus is likely to depend on pathological condition such as hypertension. Ketanserin is thought to act on the bladder with hypertension. In a recent paper, an increase in inflammatory cytokines was found in the SHR bladder [3]. 5-HT_{2A} receptors might be a factor affecting bladder overactivity in patients with hypertension as 5-HT is known to be released from inflammatory cells and related to several pathophysiology.

Concluding message

These results indicate that ketanserin suppresses bladder overactivity in SHR. 5-HT_{2A} receptor might be a new target of bladder overactivity.

Figure 1 The body Weight of SHR and WKY

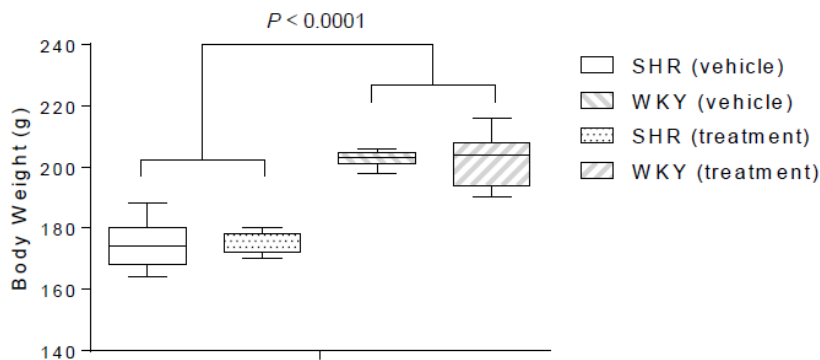
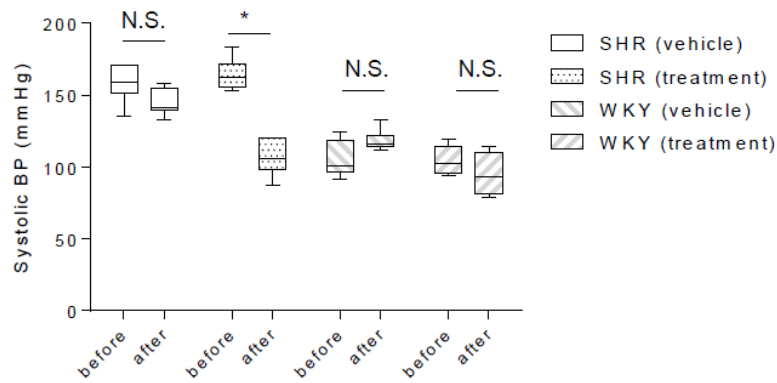
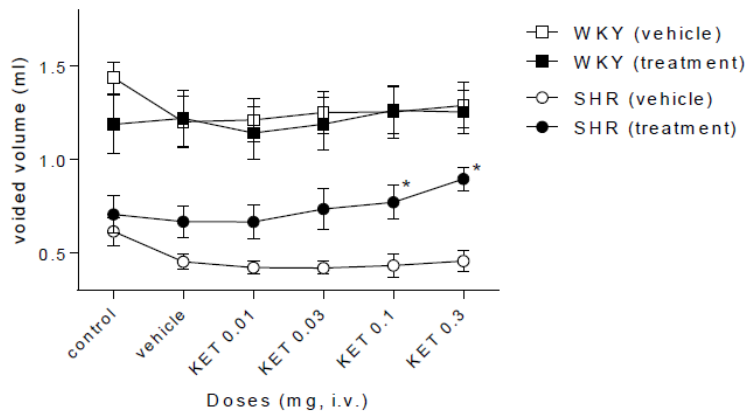


Figure 2
Effect of 1 mg/kg dose of ketanserin on systolic pressure in SHR or WKY



Ketanserin (1 mg/kg) significantly decreased systolic blood pressure in SHR. * indicates $P < 0.05$, determined by paired t -test. N.S. indicates statistically not significant.

Figure 3
Effect of ketanserin on voided volume in SHR or WKY



Ketanserin significantly increased voided volume in SHR with dose-dependent manner. * indicates $P < 0.05$, determined by one-way ANOVA with post-hoc Dunnett test.

References

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2. Sakai T, Kasahara K, Tomita K, et al. 5-Hydroxytryptamine-induced bladder hyperactivity via the 5-HT_{2A} receptor in partial bladder outlet obstruction in rats. *Am J Physiol Renal Physiol.* 2013 Apr 1;304(7):F1020-7.
3. Shen S, Xia CM, Qiao LY. The urinary bladder of spontaneously hypertensive rat demonstrates bladder hypertrophy, inflammation, and fibrosis but not hyperplasia. *Life Sci.* 2015 Jan 15;121:22-7.

Disclosures

Funding: None **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** The institutional animal care and use committee of University of Fukui