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PROTECTIVE EFFECT OF A RHO-KINASE INHIBITOR ON BLADDER DYSFUNCTION IN A RAT MODEL OF CHRONIC BLADDER ISCHEMIA

Hypothesis / aims of study

Recent studies have shown that lower urinary tract symptoms (LUTS) such as overactive bladder syndrome occur commonly in both men and women, with an age-related increase in both sexes. Epidemiologic studies have suggested that aging-associated changes in pelvic vasculature such as atherosclerosis eventually result in chronic bladder ischemia, which may play a key role in the development of LUTS[1)]. Currently, attention has focused on the role of the RhoA/Rho-kinase (ROK) pathway in neointimal formation of arteries. It has been shown that the RhoA/ROK pathway is substantially involved in the pathogenesis of atherosclerosis, and that inhibition of the RhoA/ROK pathway results in suppression of neointimal formation of arteries[2)]. On the other hand, there are many studies reporting that the RhoA/ROK pathway plays a central role in the pathogenesis of abnormal smooth muscle contractility, which may be a cause of bladder overactivity. However, it has not been established whether inhibition of the RhoA/ROK pathway affects bladder dysfunction in arterial occlusive disease-induced chronic bladder ischemia. Therefore, a previously described rat model of chronic bladder ischemia[3)] was used to investigate the effect of fasudil, a ROK inhibitor, on chronic ischemia-related bladder dysfunction.

Study design, materials and methods

Adult Sprague-Dawley male rats (16 weeks old) were divided into control, arterial endothelial injury (AI), and AI with fasudil treatment (AI/Fa) groups. The AI and AI/Fa groups underwent balloon endothelial injury of bilateral iliac arteries and received a 2% cholesterol diet for 8 weeks after AI. The AI/Fa group was given fasudil (30 mg/kg/day) orally once daily using a zonde for 8 weeks after AI. The control group received a regular diet for 8 weeks. After cystometrogram (CMG) recording in conscious rats from each group, they were euthanized, and the bladders and common iliac arteries were harvested for pharmacological and histological examinations.

Results

The body weight and bladder wet weight were not significantly different among the three groups. In the AI group, the iliac arteries showed obvious arterial wall thickening with neointimal formation (Figure 1). The mean arterial wall thickness was significantly greater in the AI group than in the control group. In the organ bath study, contractile responses of muscle strips to KCL, electrical field stimulation, carbachol (Cch) and ATP were significantly less after AI compared with controls (Figure 2). In the CMG, the bladder capacity and voided volume were significantly lower in the AI group than in controls (Figure 3, Table 1).

In the AI/Fa group, arterial wall thickening was suppressed compared with the AI group. A significant difference was observed between the AI and AI/Fa groups with respect to the mean arterial wall thickness. Furthermore, significant improvements were seen in muscle strip contractility and cystometric parameters in the AI/Fa group compared with the AI group

Interpretation of results

The present results suggest that arterial occlusive disease-induced chronic ischemia may lead to impaired muscle strip contractility and bladder hyperactivity. Chronic treatment with fasudil prevents neointimal formation and bladder dysfunction, resulting in improvement of bladder hyperactivity.

Concluding message

The results of the present study suggest that fasudil may be therapeutically useful in the prevention of atherosclerosis and chronic ischemia related bladder dysfunction.

Figure 1. Hematoxylin and eosin staining of cross-sections of common iliac arteries in the control, AI and AI/Fa groups(×100 magnification).
Bar graph shows arterial wall thickness. Scale bars represent 500μm

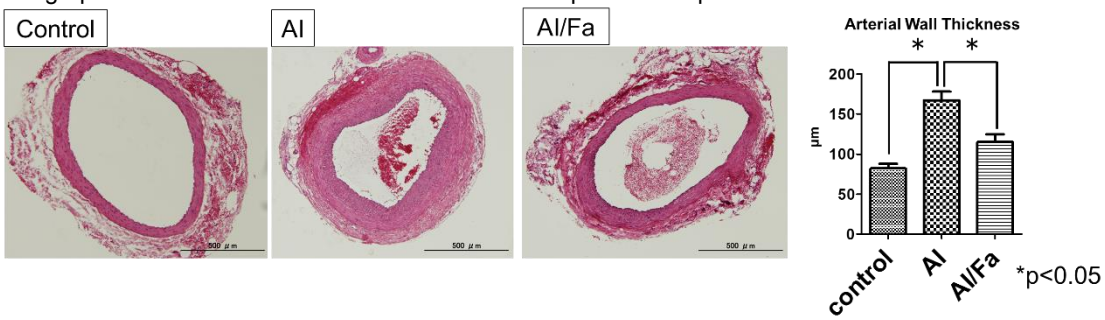

Figure 2.The contractile responses to 80mM KCL, electrical field stimulation, 1mM ATP and carbachol(Cch).

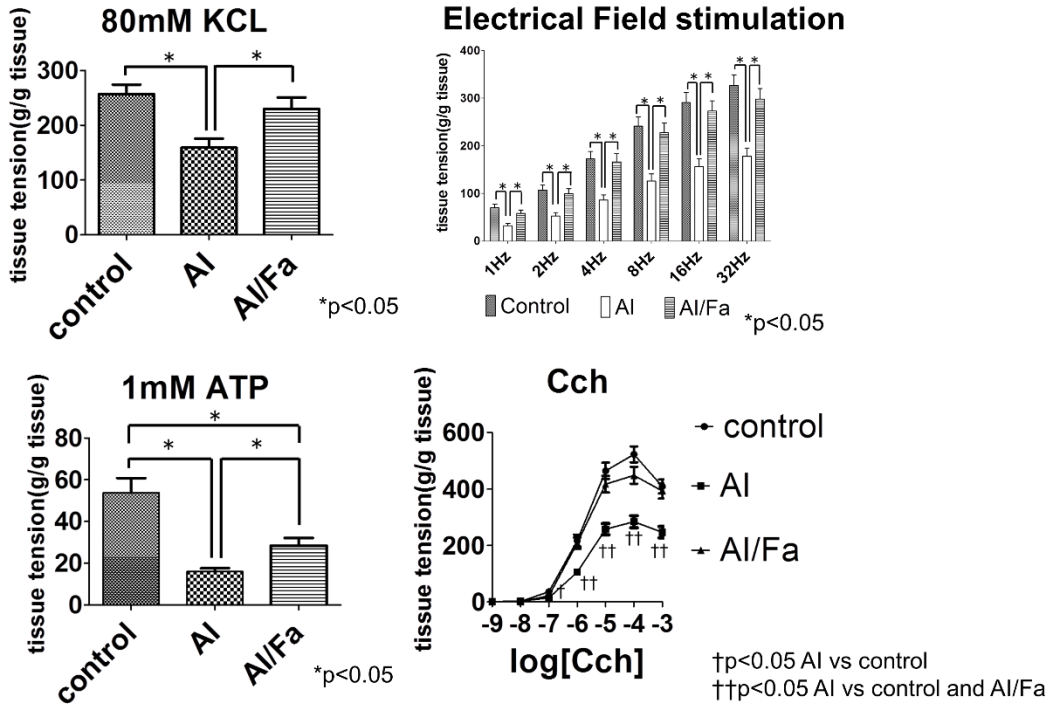

Figure 3. Typical cystometrogram recordings

Table 1. Cystometric parameters at 8weeks in control, AI and AI/Fa

Figure 3

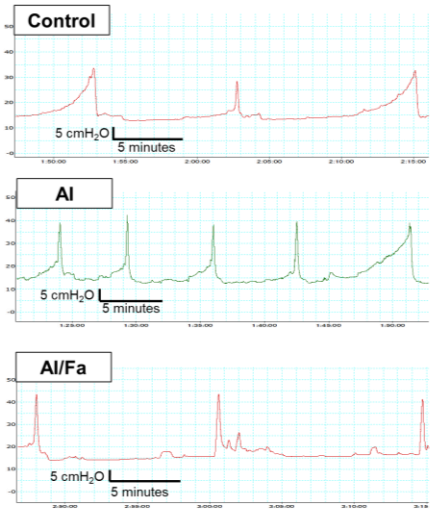

Table 1

	Control (n=10)	AI (n=10)	AI/Fa (n=9)
Bcap (mL)	2.01±0.53	1.19±0.33*	2.55±0.38***
V.V (mL)	1.92±0.61	1.15±0.34*	2.44±0.42**
R.V (mL)	0.14±0.12	0.06±0.06	0.12±0.09
BP (cmH_2O)	13.70±0.81	16.46±2.26	15.29±3.14
MP (cmH_2O)	41.64±3.72	44.32±9.77	48.50±5.11
Bcomp (mL/cmH_2O)	0.18±0.08	0.19±0.06	0.30±0.15***

Bcap: bladder capacity
V.V: voided volume
R.V: residual volume
BP: baseline pressure
MP: maximum pressure
Bcomp: bladder compliance

*P<0.05: vs control
**P<0.05: vs AI
***P<0.05: vs control and AI

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Disclosures

Funding: none **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Animal Experiments in Fukushima Medical University