60

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INVOLVEMENT OF OXIDATIVE STRESS AND PROINFLAMMATORY CYTOKINES IN DETRUSOR OVERACTIVITY BY ATHEROSCLEROSIS-INDUCED CHRONIC BLADDER ISCHEMIA IN THE RAT

Hypothesis / aims of study

Epidemiological studies have demonstrated that lower urinary tract symptoms（LUTS）, including overactive bladder (OAB), occur commonly in both men and women, with an age-related increase in both sexes. Atherosclerosis is also common in the elderly. Recently, vascular risk factors for atherosclerosis were shown to play a role in the development of LUTS in both sexes. This indicates that arterial occlusive disease and concomitant chronic ischemia may produce detrusor overactivity (DO). However, the molecular mechanisms by which chronic bladder ischemia induces DO have not been completely understood. Thus, using a rat model, we investigated whether chronic bladder ischemia induces oxidative stress and up-regulation of proinflammatory cytokines in the bladder.

Study design, materials and methods

Adult (16-week old) male Sprague-Dawley rats were divided into arterial injury (AI, n=21), sham (n=19) and control groups (n=19). The rats in the AI group underwent balloon endothelial injury of the iliac arteries and received a 2% cholesterol diet. The rats in the sham group underwent only incised bilateral inguinal region and were given a 2% cholesterol diet. The age-matched rats in the control group were given a regular diet (0.09% cholesterol). After 8 weeks, cystometrograms (CMG) without anesthesia or restraint were performed for six rats from each group. Seven rats from each group were anesthetized, and bladder blood flow was measured with a laser Doppler blood flowmeter. The remaining rats from each group were anesthetized, and the bladders were rapidly removed for the determination of oxidative stress marker malondialdehyde (MDA) and proinflammatory cytokines (IL-6, IL-8 and TNF-α).

Results

At 8 weeks, the body and bladder wet weights were not significant different among the three groups. The CMGs showed that the mean micturition interval in the AI group decreased significantly compared with those in the other two groups (Figure1). In the measurement of bladder blood flow, in the empty bladder, there was no statistically significant difference among the three groups. Bladder filling caused a decrease in bladder blood flow in the three groups. At the bladder volume of 0.6ml and 0.9ml, the mean reduction rates in bladder blood flow in the AI group were significantly greater than those in the sham and control groups (Figure 2). Histological study showed that the iliac arteries in the AI group possessed thickening of intima as well as diffuse fibrosis media at the sites of balloon injury (Figure 3).The levels of oxidative stress marker (MDA) and proinflammatory cytokines (IL-6, IL-8, and TNF-α) in the AI group were significantly increased compared with those in the other groups (Table1).

Table 1: Animal and bladder wet weight, protein levels of proinflammatory cytokines and MDA.

	Body weight	Bladder wet weight	IL-8	IL-6	TNF-α	MDA
	(g)	(g)	(pg/mg protein)	(pg/mg protein)	(pg/mg protein)	(μM/mg protein)
control (n=6)	524±8.9	0.14±0.008	31.25±5.69	63.34±10.78	2.56±0.58	0.35±0.11
sham (n=6)	492±16.6	0.13±0.009	69.13±9.76	91.59±7.99	4.02±0.40	0.67±0.03
AI (n=8)	511±12.0	0.12±0.006	90.27±18.64*	145.69±26.62*	11.99±2.55**	2.27±0.42***

Each value represents the mean ±SEM. *P<0.05 versus control.
**P<0.01 versus control P<0.05 versus sham, ***P<0.01 versus control and sham.

Interpretation of results

The present study clearly showed that chronic bladder ischemia led to an increase in bladder proinflammatory cytokines as well as oxidative stress marker in the rat. In addition, DO was demonstrated in our rat model. Our findings suggest that DO may be associated with ischemia / reperfusion in micturition cycle, followed by increase of reactive oxygen species (ROS) and proinflammatory cytokines

Concluding message

Oxidative stress and proinflammatory cytokines in the bladder may be key factors in the development of DO and OAB by atherosclerosis-induced chronic bladder ischemia. Therefore, antioxidant and anti-inflammatory agents may potentially be useful for the treatment of DO and OAB.

Figure1 : Cystometrogram in conscious rats.

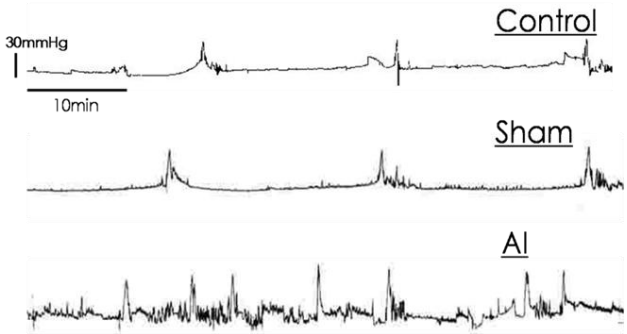
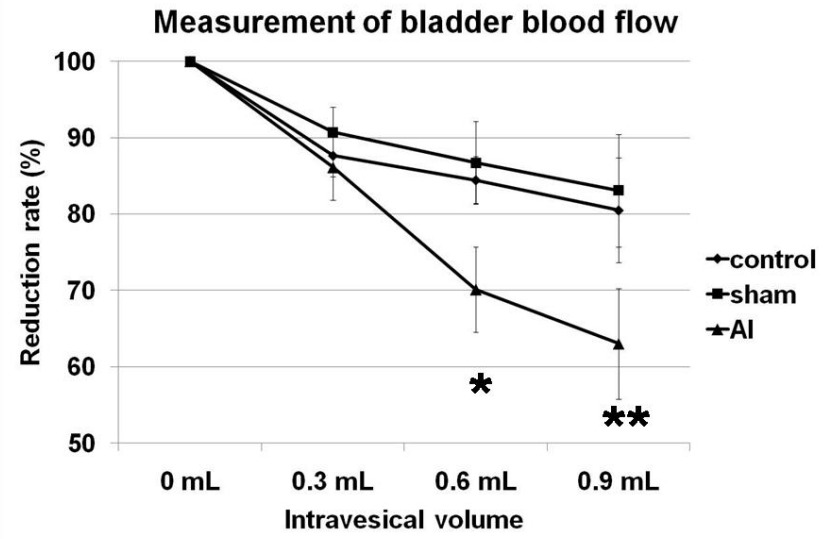
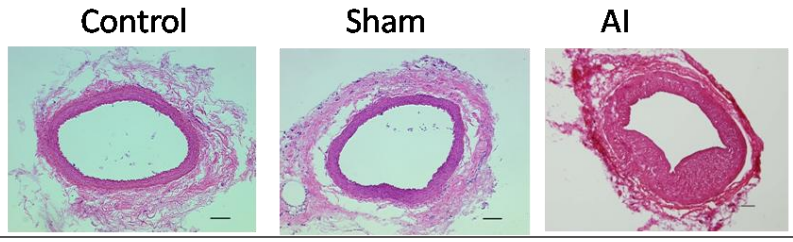


Figure 2 : Measurement of bladder blood flow in anesthetized rats.



*P<0.05 versus control and sham, **P<0.01 versus control and sham.

Figure 3 : H&E staining of cross section of iliac arteries (x100 magnification). Scale bars indicate 100 μm.



Specify source of funding or grant	None
Is this a clinical trial?	No
What were the subjects in the study?	ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	Yes
Name of ethics committee	Fukushima Medical University