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PROTECTIVE EFFECT OF TADALAFIL ON ENDOTHELIAL FUNCTION OF BLADDER MICROVESSELS IN A RAT MODEL OF CHRONIC BLADDER ISCHEMIA

Hypothesis / aims of study

Vascular endothelial dysfunction and atherosclerosis, a common clinical problem in the elderly population, may lead to impaired lower urinary tract perfusion and have an important role in the development of lower urinary tract symptoms (LUTS) (1, 2). In male LUTS, the therapeutic effects of PDE5 inhibitors, such as tadalafil, sildenafil and vardenafil have been well documented. It has been suggested that the reduction of LUTS by PDE5 inhibitors is due in part to improvement of vascular endothelial function, resulting in increased bladder perfusion (1, 2). However, despite intensive clinical studies, it has not been established that PDE5 inhibitors can improve endothelial dysfunction of bladder microvessels. Thus, we used a previously described rat model of chronic bladder ischemia (3) to investigate whether chronic ischemia-induced bladder hyperactivity and change of eNOS expression in bladder microvessels can be prevented by chronic treatment with tadalafil.

Study design, materials and methods

Adult male Sprague-Dawley rats were divided into control, arterial endothelial injury (AI), and AI with tadalafil treatment (AI-tadalafil). AI and AI-tadalafil groups underwent endothelial injury of the iliac arteries and received a 2% cholesterol diet following AI. AI-tadalafil rats received tadalafil (2mg/kg/day) orally for 8 weeks after AI. The control group received a regular diet. After 8 weeks, urodynamic investigation was performed. Bladder tissues and iliac arteries were processed for histological and immunohistochemical examination

Results

Iliac arteries from AI and AI-tadalafil rats displayed neo-intimal formation and luminal occlusion. Average wall thickness of the common iliac arteries in the AI and AI-tadalafil groups was significantly greater than in controls (Fig1). In the AI group, the micturition interval was significantly shorter (5.4$\pm$ 0.5 vs 11.1$\pm$1.1 min), and bladder capacity and voided volume were less than in controls (Table 1). The AI bladders showed significantly increased collagen ratio and decreased eNOS expression in the microvessels compared with the controls (Fig 2). In the AI-tadalafil group, tadalafil significantly improved collagen ratio and eNOS expression, and there were significant improvements in cystometric parameters compared with the AI group (Table 1, Fig 2,).

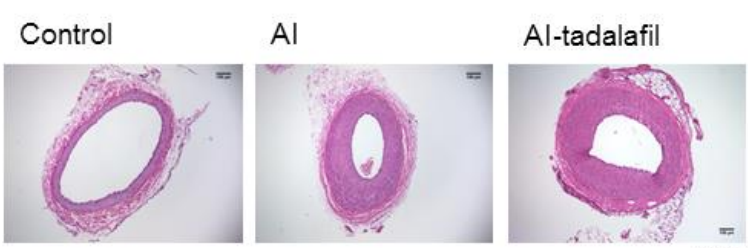
Interpretation of results

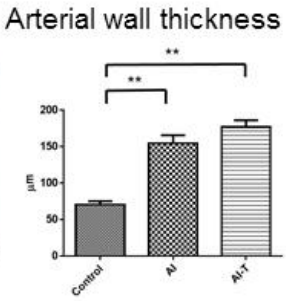
Arterial occlusive disease with a high cholesterol diet induced endothelial dysfunction of bladder microvessels and consequent bladder ischemia, resulting in fibrosis formation and bladder hyperactivity. A protective effect of tadalafil on neointimal formation in the damaged sites of the iliac arteries in this model was not observed. However, chronic treatment with tadalafil may protect bladder function and morphology by the improvement of endothelial function in the bladder microvessels.

Concluding message

Chronic bladder ischemia may be an important factor contributing to the development of LUTS. Our findings suggest that protection of vascular endothelial function and improvement of LUT perfusion as therapeutic strategies for LUTS may have beneficial effects on chronic ischemia-related bladder dysfunction in the elderly population.

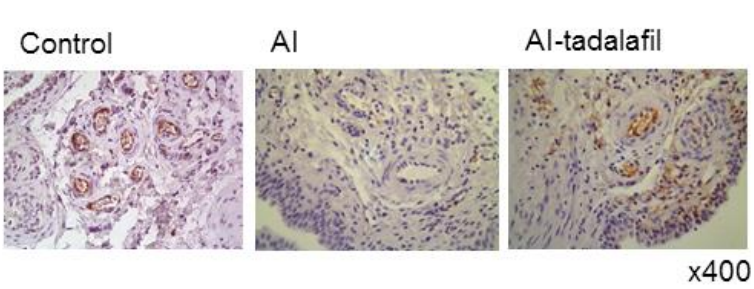
Fig 1. H&E staining of cross section of common iliac arteries

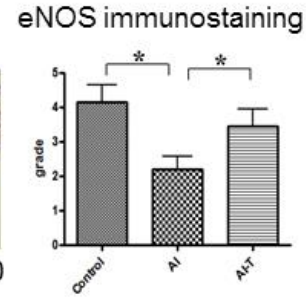




Control n=8, AI n=10, AI-T n=9,
**p<0.01.

Fig 2. Immunohistochemiacl staining of eNOS in bladder tissues





Control n=6, AI n=10, AI-T n=7,
* P<0.05.

Table1. Cystometric parameters at 8 weeks in the control, AI and AI-tadalafil groups

	Micturition interval (min)	Bcap (ml)	MV (ml)	RV (ml)	BP (cmH_2O)	TP (cmH_2O)	MP (cmH_2O)
Control (n=8)	11.1±1.1	1.85±0.19	1.78±0.15	0.11±0.02	7.5±1.1	24.2±1.7	43.4±3.4
AI (n=10)	5.4±0.5**	0.91±0.08**	0.80±0.10**	0.10±0.03	10.1±0.8	27.4±3.6	44.8±3.3
AI-tadalafil (n=9)	8.6±0.9#	1.44±0.15#	1.30±0.10#	0.14±0.03	11.5±3.59	32.2±4.9	52.9±6.4

Bcap; bladder capacity, MV; micturition volume, RV; residual volume, BP; basal pressure, TP; threshold pressure, MP; maximum pressure.
**p<0.01 vs control, #p<0.05 vs AI.

References

1. Cellek S, et al. Microvascular dysfunction and efficacy of PDE5 inhibitors in BPH-LUTS. Nat Rev Urol. 2014 Apr;11(4):231-41.
2. Andersson KE, et al. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. Neurourol Urodyn. 2011. 30. 292-301.
3. Nomiya M, et al. The effect of atherosclerosis-induced chronic bladder ischemia on bladder function in the rat. Neurourol Urodyn. 2013. 31. 195-200.

Disclosures

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