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EFFECTS OF CHRONIC VARDENAFIL TREATMENT ON ISCHEMIC BLADDER CAUSED BY LIGATION OF BILATERAL INTERNAL ILIAC ARTERIES IN RATS

Hypothesis / aims of study

Recently it has been reported that the treatment of phosphodiestherase-5 (PDE-5) inhibitors are effective for lower urinary tract symptoms. However it is unknown whether the treatment of PDE-5 inhibitor is effective for voiding dysfunction caused by ischemic. In this study we investigated the effect of chronic administration of vardenafil, which is one of the PDE-5 inhibitors, on ischemic bladder model rats.

Study design, materials and methods

8-weeks-old female Spargue-Dawley rats were divided into five groups; two Control groups (1 week or 4 weeks), two Ligation groups (1 week or 4 weeks), or vardenafil (4 mg / kg / day) treatment group. Rats of Control groups were underwent sham operation and those of Ligation groups were ligated bilateral internal iliac arteries. vardenafil was given to ligated rats as oral administration once daily, for 3 weeks from 1 week after operation. Cystometry was performed in all rats to evaluate intercontraction interval and maximum voiding pressure. After cystometry, bladder was harvested to calculate bladder-to-body weight ratio and use immunohistchemistry of α-smooth muscle actin (α-SMA), endothelial nitric oxide synthase (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS).

Results

At 1 week after surgery, intercontraction interval in Ligation group was not significantly but longer than that in Control group. At 4 weeks, the interval in Ligation group was significantly longer than that in Control group ($P<0.05$). The interval in vardenafil treatment group was significangly shorter than that in Ligation group ($P<0.01$) and almost equal to that in Control group. At all periods there was no change in maximum voiding pressure between Control and Ligation groups. The pressure in vardenafil treatment group was not significantly but increased compared with Control and Ligation groups. (Figure)

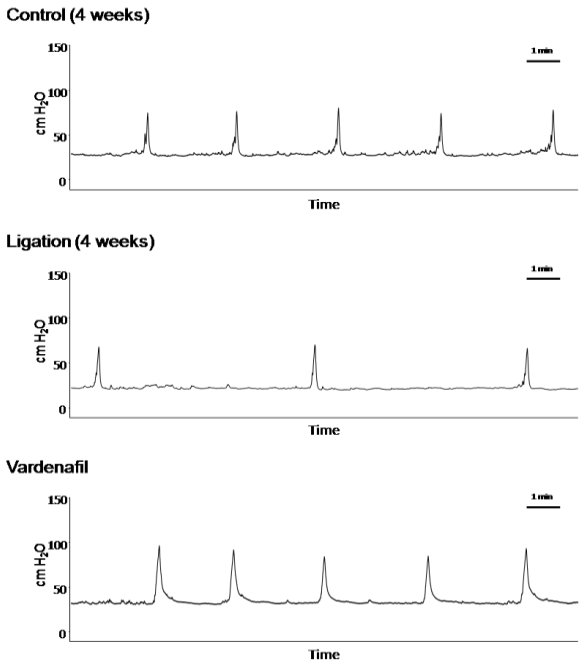

Figure The effect of chronic vardenafil treatment on voiding in each group at 4 weeks

At all periods, there was no difference in body weight between Control and Ligation groups. Bladder weight and bladder-to-body weight ratio in Ligation group at 1 week were significantly increased compared with Control group at 1 week ($P<0.05$). However, at 4 weeks those in Ligation group were almost equal to those in Control group. Vardenafil treatment had no effect on, body weight, bladder weight, and bladder-to-body weight ratio.

The integrity of localization of α-SMA was time-dependently lost in Ligation groups. At 1 and 4 weeks, the decreases of the expressions of eNOS and nNOS proteins were observed in Ligation groups compared with Control groups. However, vardenafil treatment prevented the loss of the integrity of α-SMA and the decreases of eNOS and nNOS. The expressions of iNOS in Ligation groups were increased compared with Control groups at 1 and 4 weeks. The increase of iNOS was prevented by vardenafil treatment.

Interpretation of results

Chronic vardenafil treatment was useful for voiding dysfunction by ligation of bilateral internal iliac arteries. Ligation of bilateral internal iliac arteries caused loss of integrity of smooth muscle, the decreases of the expressions of eNOS and nNOS, and the increase of the expression of iNOS. However vardenafil treatment prevented the loss of smooth muscle, the decreases of eNOS and nNOS, and the increase of iNOS. The improvement of voiding function by the chronic vardenafil treatment is thought to be the result of the preservation of smooth muscle and normalization of nitric oxide / cyclic guanosine monophosphate pathway.

Concluding message

Vardenafil treatment is effective for voiding dysfunction in rats with ligation of bilateral internal iliac arteries, and may be developed to become clinically useful treatments for voiding dysfunction by bladder ischemia.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**The Institutional Animal Care and Use Committee at Nagoya City University**