

Establishment of a bladder ischemia / reperfusion-induced bladder overactivity model and the effects of tamsulosin on bladder blood flow and bladder function in that model

Hypothesis / aims of study

Patients with benign prostatic hyperplasia (BPH) are known to show both voiding and storage symptoms. α_1 -Adrenoceptor antagonists, which are widely-used as a BPH therapy, reportedly improve not only voiding symptoms in patients with BPH, but storage symptoms as well. Bladder outlet obstruction (BOO) is widely thought to contribute to voiding symptoms; therefore, relaxation of the urethra and prostate via blockade of α_1 -adrenoceptors may be the main mechanism by which voiding function can be improved. Because storage symptoms are multifactorial, neither the mechanism responsible for the storage symptoms induced by BOO, nor that behind the improvement in symptoms seen with α_1 -adrenoceptor antagonists are clearly understood. In this study, focus was placed on bladder blood flow as one of the possible mechanisms causing the storage symptoms. To examine the influence of bladder ischemia / reperfusion on bladder function, a bladder ischemia / reperfusion model was established in rats. In addition, the effect of tamsulosin, the most common α_1 -adrenoceptor antagonist, on bladder function was examined in this model.

Study design, materials, and methods

A polyethylene catheter was inserted into the bladder via the external urethral orifice of pentobarbital- (bladder blood flow measurement) or halothane- (bladder function measurement) anesthetized female rats. Physiological saline (2 mL) was infused into the bladder at the rate of 0.1 mL/min to overdistend the bladder. Overdistension was maintained for 120 min, and then the bladder was emptied. Bladder blood flow before overdistension, immediately and 120 min after overdistension, and after bladder emptying (immediately, 30 min, 60 min, and 120 min after) were measured using a laser Doppler blood flowmeter. For the measurement of bladder function, rats were removed from halothane anesthesia concurrently with bladder emptying, and then allowed to awaken. Bladder function under water-loaded conditions (30 mL/kg, p.o.) was measured in a metabolic cage from 2 h to 6 h after bladder emptying (from 0 h to 4 h after water-loading), at which time the animals had completely recovered from the anesthesia. The mean voided volume was calculated using the following formula: mean voided volume = total voided volume / micturition frequency. Tamsulosin (1 μ g/kg/h) was continuously administered using a subcutaneously implanted osmotic pump from 1 week before the experiment. The effect of tamsulosin on bladder blood flow and bladder function was measured using the same methods.

Results

During bladder blood flow measurement, the numbers of animals in the control and tamsulosin-treated groups were 7 and 8, respectively. Bladder blood flow decreased significantly (approximately 40% of pre value) as a result of overdistension and continued throughout the distension period (120 min). This decrease in blood flow recovered partially (approximately 70% of the pre-distension value) after bladder emptying, which indicated that bladder ischemia / reperfusion is achieved by bladder overdistension and emptying. However, the reperfusion was found to be incomplete. Tamsulosin (1 μ g/kg/h, 1 week) increased bladder blood flow after emptying compared to the control group. In the bladder function study, the numbers of animals in the sham, control, and tamsulosin-treated groups were 10, 10, and 11, respectively. An increase in the micturition frequency and a decrease in the mean voided volume were observed in this rat model. The total voided volume was not affected by bladder ischemia / reperfusion. Tamsulosin improved the increase in the micturition frequency and decrease in the mean voided volume.

Interpretation of results

This is the first model which directly verify that bladder ischemia / reperfusion changes micturition patterns. Reduced bladder blood flow [1] or a prolonged ischemic period [2] have been reported in animals with BOO. Together, these observations indicated that BOO-affected bladders are ischemic. In the present study, bladder overdistension induced bladder ischemia with incomplete reperfusion after bladder emptying. In addition, from a bladder function perspective, bladder overactivity (increase in micturition frequency and decrease in mean voided volume) was observed in this model. Tamsulosin increased bladder blood flow during the reperfusion period, which led to an improvement in bladder overactivity. Therefore, the decrease in bladder blood flow may contribute to bladder overactivity in this model; however, the mechanism by which a decrease in bladder blood flow induces bladder overactivity remains unclear.

As in the animal models, a decrease in bladder blood flow has also been reported for patients with BPH [3], and it is widely recognized that these patients exhibit bladder overactivity (storage symptoms). The present study results may indicate a direct correlation between the decrease in bladder blood flow and bladder overactivity.

Concluding message

The results of this study indicate that bladder ischemia and incomplete reperfusion induces bladder overactivity, and that tamsulosin improves these symptoms by increasing bladder blood flow. Since reduced bladder blood flow has been reported in animal models with BOO, tamsulosin may improve bladder overactivity thus induced by increasing bladder blood flow. This may contribute to the elucidation of the mechanisms used by α_1 -adrenoceptor antagonists, which, in turn, may lead to the improvement of storage symptoms in BPH patients.

References

1. Neurourol Urodyn (2002) 21; 160-166
2. J Urol (2001) 165; 245-248
3. BJU Int (2007) 99; 831-835

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	Kinki University School of Medicine