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EFFECTS OF ANGIOTENSIN II RECEPTOR ANTAGONIST ON THE DETRUSOR OVERACTIVITY INDUCED BY BLADDER OUTLET OBSTRUCTION IN RATS

Hypothesis / aims of study

Clinically, Bladder outlet obstruction (BOO) caused by benign prostatic hyperplasia is associated with a reduced urine flow rate and increased detrusor pressure. The increased tension in the bladder is also associated with cellular and molecular alterations leading to functional changes, including detrusor overactivity (DO). Angiotensin II is a key biologic peptide of the renin-angiotensin system that regulates vascular tone, blood pressure, and sodium homeostasis. Angiotensin II acts on two subtype receptors, which are angiotensin II type 1 (AT1) and angiotensin II type 2 (AT2) receptors. Most of the physiological actions of angiotensin II including contractile effects are mediated by AT1 receptors. Recently, it has been reported that AT1 receptors are expressed in the urinary bladder and their presence may be related to DO. The aim of this study was to investigate the changes in the expression of both nerve growth factor (NGF) and the AT1 receptor in the urothelium and detrusor muscle in a rat model of BOO. We also determined whether the AT1 antagonist telmisartan alleviates the DO in rats with BOO through changes in NGF and AT1 receptor expression.

Study design, materials and methods

Male Sprague Dawley rats were randomly assigned to three groups. The control group (n = 10) included sham-operated rats. The animals in the BOO (n = 20) and telmisartan groups (n = 20) underwent partial BOO surgery. The telmisartan group also received a daily oral dose of telmisartan (3 mg/kg per day) for 14 consecutive days. A cystometrogram (CMG) was performed in all the three groups two weeks after the surgery. Urodynamic parameters were investigated, including intercontraction interval (CI), micturition pressure (MP, maximum bladder pressure during micturition), non-voiding contraction (NVC). After the CMG procedure was completed, the bladder of each rat was excised at the level of the ureteric orifices. The bladder body was cut open vertically and dissected under a microscope into urothelium and detrusor muscle. Immunofluorescent staining was performed to localize the expression of NGF and AT1 receptor in the urothelium and detrusor muscle. The immunoreactivity was expressed as mean ± SEM using a scoring system according to the degree of staining (5 = very strong, 4 = strong, 3 = intermediate, 2 = weak, 1 = very weak) by an urologist and a pathologist, respectively. Also, the expression levels of both NGF and AT1 receptor in the urothelium and detrusor muscle were quantified by western blotting.

Results

On CMG, the CI was markedly shorter in the BOO group, than in control group (4.1 ± 0.4 min, and 11.4 ± 0.8 min, respectively, $P < 0.05$). The mean number of NVCs was significantly greater in the BOO group than in control group (7.66 ± 3.59 / hr, and 0.75 ± 0.22 / hr, respectively, $P < 0.05$). The CI was significantly longer in the telmisartan group, compared with those in the BOO group (8.3 ± 0.4 min, vs 4.1 ± 0.4 min, $P < 0.05$). The number of NVC was reduced in the telmisartan group, compared with those in the BOO group (0.93 ± 0.54 / hr, vs 7.66 ± 3.59 / hr, $P < 0.05$).

Immunofluorescent staining indicated that NGF and AT1 receptor were localized in both the urothelium and detrusor muscles. Moreover, AT1 receptor was localized prominently in the urothelium. The immunoreactivities for NGF and AT1 receptor were upregulated in the BOO group, compared with the control group in both the urothelium (3.0 ± 0.2, 4.4 ± 0.3, vs 1.8 ± 0.2, 1.5 ± 0.5) and detrusor muscle (3.0 ± 0.4, 2.4 ± 0.3, vs 1.3 ± 0.2, 1.2 ± 0.1) ($P < 0.05$). Conversely, after the oral administration of telmisartan, the immunoreactivities for NGF and AT1 were downregulated compared with the BOO group in both the urothelium (1.8 ± 0.2, 1.2 ± 0.2, vs 3.0 ± 0.2, 4.4 ± 0.3) and the detrusor muscle (1.6 ± 0.3, 1.2 ± 0.2, vs 3.0 ± 0.4, 2.4 ± 0.3) ($P < 0.05$).

In western blot analysis, immunoreactive bands indicating expression of NGF (13 kDa) and AT1 receptor (45 kDa) were detected in both the urothelium and the detrusor muscle. In both the urothelium and the detrusor muscle, the expression of both NGF and the AT1 receptor were significantly greater in the BOO group than in the control group ($P < 0.05$). However, after the oral administration of telmisartan, the expression of NGF and the AT1 receptor were downregulated in the urothelium and the detrusor muscle ($P < 0.05$).

Interpretation of results

The results of this study suggest that the AT1 receptor plays a significant role in the pathogenesis of DO in rats with BOO. In these rats, oral administration of the AT1 antagonist telmisartan may prevent these changes.

Concluding message

We suggest that telmisartan has a beneficial effect on detrusor function, including the reduction of DO, reducing the expression of both NGF and the AT1 receptor in rats with BOO.

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