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THE VASODILATING DRUGS AMELIORATE DETRUSOR OVERACTIVITY VIA IMPROVING PELVIC BLOOD FLOW IN THE MALE SPONTANEOUSLY HYPERTENSIVE RAT.

Hypothesis / aims of study

The overactive bladder (OAB) syndrome, characterized by urgency with or without incontinence, frequency and nocturia is a common disorder and the incident rate increase with age. Antimuscarinic agents are currently the first-line pharmacotherapy for OAB. However, the adverse effects of antimuscarinics leading to medication withdrawal. Recently, decrease in bladder blood flow (BBF) has thought to be one of the main reasons for OAB. Several reports suggested that OAB patients have less BBF compared to those of controls measured by ultrasonography. Spontaneously hypertensive rats (SHRs) develop detrusor overactivity (DO), and they are considered as a valuable animal model for exploring the pathogenesis of DO. In this experiment, we select three drugs, $\alpha 1_{A}$-blocker; silodosin, Rho-kinase inhibitor; hydroxyfasudil, and ATP dependent K^{+} channel opener; nicorandil, whose roles are relaxation of vascular smooth muscles. Our hypothesis is that these three drugs could improve the hypertension-related DO via improvement of BBF due to relaxing bladder vessels. We investigated the effects of chronic administration of these drugs on DO in the SHRs.

Study design, materials and methods

All doses of drugs were effective for increasing BBF without any decrease in blood pressure proven by our preliminary experiment. Thus, we decided to use the dose of the agents described as below. Twelve-week-old male SHRs received 6 weeks of treatment by vehicle or silodosin (100 μg/kg, perorally every day), or hydroxyfasudil (1mg/kg, intraperitoneally every day), or nicorandil (10mg/kg, intraperitoneally every day). Wistar rats as normotensive controls and vehicle treated SHRs were used in each group. Six weeks after the treatment with these drugs, all rats were placed into metabolic cages individually and measured micturition frequency per day, single voided volume and total urine output per day in each rat. Subsequently, blood pressure was measured by tail cuff method without anesthesia, and cystometries were performed in the silodosin and the hydroxyfasudil group under urethane anesthesia (1.0g/kg intraperitoneally). In cystometries, maximum detrusor pressures during voiding, voided volume and residual urine volume were measured. Then BBF was measured with hydrogen clearance method in all groups. After these studies, bladders were cut into small pieces and the concentration of nerve growth factor (NGF) in the urinary bladder were measured by ELIZA method.

Results

In the SHR group, blood pressure, micturition frequency and bladder NGF concentration were significantly higher than those in the Wistar group. On the other hand, single voided volume and BBF were significantly lower than those in the Wistar group.
In voiding behavior studies, the single voided volume of silodosin, hydroxyfasudil and nicorandil groups was significantly higher than that in the SHR group (0.85±0.11 vs. 0.55±0.05 ml, 0.94±0.18 vs. 0.55±0.05 ml, 0.75±0.13 vs. 0.46±0.03 ml, respectively, $p<0.05$). Moreover, silodosin, fasudil and nicorandil significantly decreased micturition frequency compared to the SHR group. However, there were no significant changes in total urine output.
In cystometry, chronic administration of silodosin and hydroxyfasudil significantly increased voided volume compared with the SHR group (0.34±0.02 vs. 0.25±0.04 ml, 0.35±0.02 vs. 0.25±0.04 ml, respectively, $p<0.05$), but there were no significant differences in maximum detrusor pressure and residual urine volume.
The BBF of silodosin, hydroxyfasudil and nicorandil groups was significantly higher than that in the SHR group (172.5±8.2 vs. 107.9±5.2 ml/min/100g, 162.1±7.6 vs. 107.9±5.2 ml/min/100g, 214.5±13.5 vs. 142.0±17.5 ml/min/100g, respectively, $p<0.05$). Furthermore, chronic administration of these drugs significantly decreased the bladder NGF concentrations compared with the SHR groups.

Interpretation of results

In the voiding behavior studies, all drugs ameliorate single voided volume and micturition frequency to the control level. Silodosin and hydroxyfasudil normalize voided volume in the cystmetries. Moreover, bladder NGF concentration also recovers to the normal level in all groups. These results indicate that chronic administration of silodosin, hydroxyfasudil and nicorandil normalize hypertension-related DO in the SHRs, possibly via improvement of BBF.

Concluding message

The treatment with silodosin, hydroxyfasudil or nicorandil may be a potentially therapeutic strategy for treatment of the hypertension-related DO.

Disclosures

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