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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, α1-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 pressure and residual urine volume were measured. Furthermore, chronic administration of silodosin, hydroxyfasudil and nicorandil significantly decreased micturition frequency compared with the SHR group. Moreover, silodosin, fasudil and nicorandil significantly decreased micturition frequency per day, single voided volume and total urine output per day in each rat. Single voided volume and micturition frequency per day in each rat. In voiding behavior studies, all drugs ameliorate single voided volume and micturition frequency to the control level. Silodosin and hydroxyfasudil normalize voided volume in the cystometries. Moreover, bladder NGF concentrations compared 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.

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 cystometries. Moreover, bladder NGF concentrations compared 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

Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: tottori university

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