**414**

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# NICORANDIL AMELIORATES DETRUSOR OVERACTIVITY IN THE SHR

Hypothesis / aims of study

The overactive bladder (OAB) syndrome, characterized by urgency with or without incontinence, frequency, and nocturia is a common disorder. Antimuscarinic agents are the first-line pharmacotherapy for OAB. However, adverse events of antimuscarinics stop continuing medication, and another pharmacological therapeutics is required. The etiology of OAB is complicated, and various etiological factors have been suggested. Recently, several studies have suggested the bladder ischemia causes detrusor overactivity (DO). Spontaneously hypertensive rats (SHRs) develop bladder hyperactivity with pelvis ischemia, and the SHR is considered a valuable tool for exploring the pathogenesis of DO [1]. There are some reports indicated that α1-blockers improve DO via improvement of bladder blood flow in the rat with bladder outlet obstruction [2]. Nicorandil, a $K_{ATP}$ channel opener and nitric oxide (NO) donor, is used in the treatment of angina and acute heart failure. Kamiyama and his associates demonstrated that nicorandil significantly improved neurogenic and myogenic bladder overactivity [3]. Our hypothesis is that nicorandil could improve the hypertension-related DO via improvement of bladder blood flow. In the present study, we tried to investigate the effect of chronic administration of nicorandil on bladder overactivity in the SHRs.

Study design, materials and methods

Twelve-week-old SHRs started to receive six weeks of treatment by vehicle or nicorandil (3, or 10 mg/kg, i.p. every day). Wistar rats were used for normotensive controls. After 6 weeks of nicorandil treatment, blood flow in the bladder was estimated by hydrogen clearance method, and the bladder functions were estimated by voiding behavior studies and functional studies using carbachol and KCl. Tissue levels of nerve growth factor (NGF) were measured by ELISA method. Furthermore, the participation levels of $K_{ATP}$ channel pores were investigated by real-time PCR.

**Table 1. Voiding behavior studies in the experimental rats**

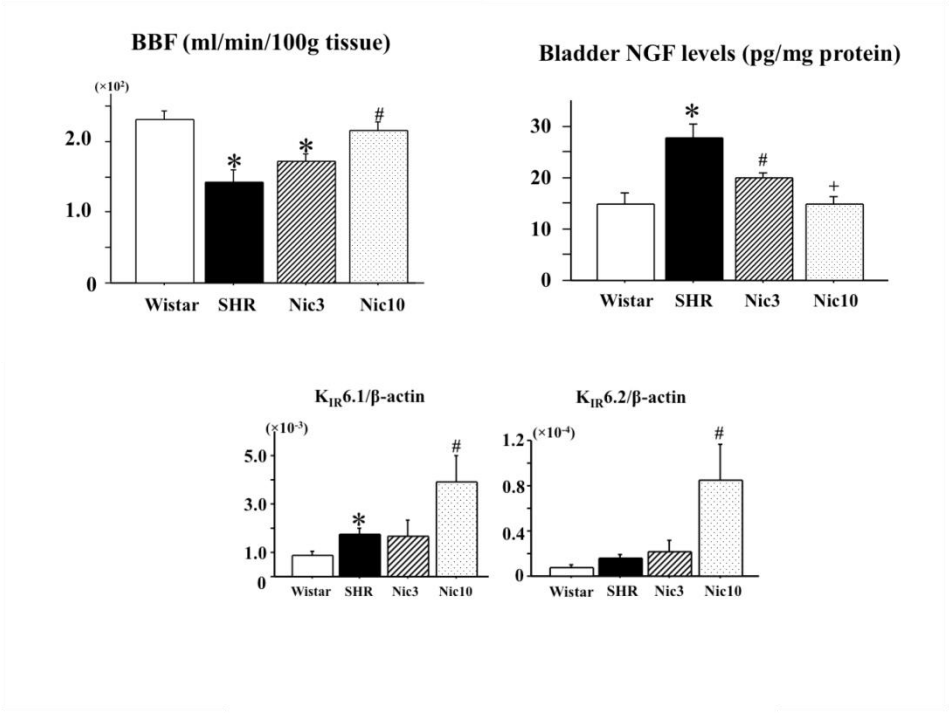
| Group | urine output (ml/d) | micturition frequency (/day) | single voided volume |
|---|---|---|---|
| Wistar | 17.2 ± 1.0 | 11.1 ± 1.1 | 1.43 ± 0.11 |
| SHR | 9.2 ± 0.8* | 19.4 ± 0.9* | 0.46 ± 0.03* |
| Nic3 | 9.5 ± 0.9* | 17.3 ± 1.8* | 0.52 ± 0.02* |
| Nic10 | 9.1 ± 1.5* | 14.0 ± 0.9† | 0.75 ± 0.13*† |

*) significantly different from the Wistar group ($p<0.05$). †) significantly different from the SHR group ($p<0.05$).

**Table 2. Functional studies in the experimental rat bladder strips**

| Group | $E_{max}$ values (g/mm$^2$) | $EC_{50}$ values (x $10^{-7}$M) | $E_{max}$/ 100 mM KCl | 100 mM KCl(g/mm$^2$) |
|---|---|---|---|---|
| Wistar | 2.42 ± 0.24 | 9.72 ± 0.99 | 1.64 ± 0.07 | 1.55 ± 0.17 |
| SHR | 3.95 ± 0.38* | 8.02 ± 0.96 | 1.63 ± 0.06 | 2.46 ± 0.25* |
| Nic3 | 3.64 ± 0.46* | 8.89 ± 1.10 | 1.74 ± 0.05 | 2.14 ± 0.28 |
| Nic10 | 2.39 ± 0.27†§ | 7.86 ± 0.80 | 1.63 ± 0.09 | 1.40 ± 0.15†§ |

*) significantly different from the Wistar group ($p<0.05$). †) significantly different from the SHR group ($p<0.05$). §) significantly different from the Nic3 group ($p<0.05$).




**Blood flow in the bladder;** *) significantly different from the Wistar group. #) significantly different from the SHR group. **Bladder NGF levels;** *) significantly different from the Wistar group. #) significantly different from the other groups. +) significantly different from the SHR and Nic3 groups. P<0.05 is level of significance. **Expressions of $K_{IR}$6.1 and $K_{IR}$6.2 messenger RNAs in the bladder;** *) significantly different from the Wistar group. #) significantly different from the Wistar and SHR groups. P<0.05 is level of significance.

Results

SHRs showed significant increases in blood pressure, micturition frequency, carbachol-induced and KCl-induced contractility and expressions of both $K_{IR}$6.1 and $K_{IR}$6.2 mRNAs, and a significant decrease in blood flow in the bladder. Although both doses of nicorandil failed to decrease in blood pressure, nicorandil significantly ameliorated increases in micturition frequency and carbachol- and KCl-induced hypercontractility, and decrease in blood flow in the bladder in a dose dependent manner. Tissue levels of NGF in the SHR were significantly higher than those in the Wistar, and treatment with nicorandil significantly ameliorated them in a dose dependent manner. The expression levels of $K_{IR}$6.1 mRNAs in the bladder were more than 100-fold of those of $K_{IR}$6.2 mRNAs in the Wistar and SHR groups. The low dose of nicorandil slightly and the high dose of nicorandil significantly up-regulated the expressions of both $K_{IR}$6.1 and $K_{IR}$6.2 mRNAs compared to non-treated SHRs.

Interpretation of results

In the present study, we clearly demonstrated that nicorandil prevented to develop OAB in the SHR in a dose-dependent manner estimated by several parameters. In addition, NGF is a possible maker of OAB [1]. Treatment with nicorandil significantly normalized up-regulated bladder NGF levels to the control levels. Two mechanisms of preventive effect of nicorandil on OAB have been suggested; one mechanism is direct effect on bladder smooth muscle, and the other one is suppressing the firing of capsaicin-sensitive C-fiber bladder afferents. From present data, we suggest the third mechanism of preventive effect of nicorandil on OAB; nicorandil improves DO via improvement of chronic ischemia in the bladder. The expressions of $K_{IR}$6.1 or $K_{IR}$ 6.2 were up-regulated in the SHRs, and treatment with nicorandil increased these up-regulated $K_{IR}$6.1 and $K_{IR}$ 6.2. However, it is still unclear which type plays major role in the detrusor smooth muscle in this condition.

Concluding message

Nicorandil prevents hypertension-related DO in the SHR via possible mechanisms, direct effect on detrusor smooth muscle, suppressing the firing of capsaicin-sensitive C-fiber bladder afferents and modulating blood flow in the bladder.

References

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| ***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*** | **the Tottori University Committee for Animal Experimentation** |