Table 1. General Features in the experimental rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight (g)</th>
<th>Prostate Weight (mg)</th>
<th>PBR (×10^-3)</th>
<th>Heart rate (/min)</th>
<th>Blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WKY</td>
<td>400 ± 4</td>
<td>662 ± 34</td>
<td>1.66 ± 0.09</td>
<td>326 ± 11</td>
<td>128.1 ± 1.2</td>
</tr>
<tr>
<td>SHR</td>
<td>305 ± 6*</td>
<td>581 ± 34</td>
<td>1.99 ± 0.06*</td>
<td>329 ± 22</td>
<td>198.0 ± 3.7*</td>
</tr>
<tr>
<td>Nic3</td>
<td>306 ± 6*</td>
<td>617 ± 12</td>
<td>2.03 ± 0.04*</td>
<td>336 ± 10</td>
<td>191.3 ± 5.1*</td>
</tr>
<tr>
<td>Nic10</td>
<td>282 ± 4*#</td>
<td>541 ± 24*§</td>
<td>1.93 ± 0.13</td>
<td>300 ± 10</td>
<td>188.3 ± 4.5*</td>
</tr>
</tbody>
</table>

PBR: Prostate Body weight Ratio. WKY; 18-week-old Wistar-Kyoto rat group. SHR; 18-week-old SHR group. Nic10; 18-week-old SHRs treated with nicorandil at a daily dose of 10mg/kg, i.p. Data are shown as means ± S.E.M. of eight separate determinations in each group. *: Significantly different from the WKY group (P<0.05 is level of significance). #: Significantly different from the SHR (P<0.05 is level of significance). §: Significantly different from the Nic3 (P<0.05 is level of significance).

Interpretation of results
The present study demonstrated that although the tissue levels of DHT were not changed, SHRs showed significant increases in blood pressure, tissue levels of MDA, HIF-1α, TGF-β1 and a-MMA, and a significant decrease in the prostate blood flow. Although treatment with nicorandil failed to decrease the blood pressure, it significantly ameliorated these factors and inhibited the development of ventral prostate hyperplasia without alterations of DHT levels. Our data indicated that development of ventral prostate hyperplasia in the SHR depends on prostate blood flow but not on tissue levels of DHT.

Possible mechanism of development of BPH

Concluding message
We propose that the development of prostate hyperplasia is related to prostate tissues, which nicorandil prevents via its ability to increase the blood flow in the prostate via inhibition of ROS and HIF-1α-TGF-β1 and bFGF pathways, and that it does not depend on tissue levels of antigens.

References

Hypothysis / aims of study
Although there is increasing evidence that benign prostate hyperplasia (BPH) and benign prostate enlargement (BPE) are associated with cardiovascular disease, the pathophysiology of BPH/BPE is poorly understood and thought to be multifactorial. Spontaneously hypertensive rats (SHRs), a commonly used model of genetic hypertension, have been found to exhibit hyperplastic morphological abnormalities in the ventral prostate, which are observed as early as 15 weeks of age. The prostate in the SHR is also known to be in a chronic ischemic condition. From these results, the hypothesis can be suggested that not only hypertrophy in the prostate induces up-regulation of hypoxia-inducible factor 1α (HIF-1α), the regulation of oxygen homoeostasis, and radical oxygen species (ROS), which subsequently activates TGF-β1 and bFGF in the prostate, leading to stromal proliferation, transdifferentiation and extracellular matrix production. This is one of possible mechanisms in the development of BPH/BPE. If this hypothesis is true, normalization of the prostate blood flow should inhibit the development of the prostate hyperplasia. In the present study, we tried to investigate the effect of chronic administration of nicorandil, a vasodilator and K_+ channel opener on the prostate blood flow and hyperplasia in the SHRs.

Study design, materials and methods
Twelve-week-old male SHRs were treated with nicorandil (0.3 and 10mg/kg, i.p.) for six weeks. Water-Kyoto (WKY) rats were used as normotensive controls. Six weeks after administration, blood pressure (tail cuff method; BP-90A-L, Sphyga, Tokyo, Japan) and the prostate blood flow (the hydrogen clearance method; PHG-30; Unique Medical Co., Tokyo, Japan) were measured. Tissues levels of malondialdehyde (MDA), an oxidative stress marker (Wako Pure Chemicals, Osaka, Japan) and GSH levels (Wako Pure Chemicals, Osaka, Japan) were measured using the enzyme-linked immunosorbent assay (ELISA) method, and were normalized by protein contents. The prostate samples (20 μg) were subjected to SDS-polyacrylamide gel electrophoresis (10% gradient gels), and were electrophoretically transferred to polyvinylidene difluoride (PVDF) membranes blocked with Tris-Buffered Saline (TBS), 6.1% Tween 20 (TBS-T) containing 5% nonfat dried milk, washed with TBS-T, and incubated overnight at 4°C for antibodies against a-SMA (1:400) and anti-α-smooth muscle actin (1:800) in TBS-T containing 5% nonfat dried milk. The bands were visualized with ECL Plus (Amersham). Western blots were performed in triplicate. The significance of the difference was determined using enhanced chemiluminescence reagent. The histological changes in the prostate were also evaluated in these groups.

Results
SHRs showed significant increases in blood pressure, tissue levels of MDA, HIF-1α, TGF-β1 and a-MMA, and a significant decrease in the prostate blood flow. Although treatment with nicorandil failed to decrease the blood pressure, it significantly ameliorated these factors. There were no significant differences in tissue levels of HIF-1α among groups. The ventral prostate in the WKY group showed regular, unaltered, compactly packed acini formed by low cellular cells showing a uniform monolayer arrangement. In contrast to the WKY group, the ventral prostate in the SHR group showed epithelial cells being dwarfed in shape with irregularities in the nuclear arrangement. Treatment with nicorandil normalized these abnormalities. However, alterations in the dorsal prostate were not found in all groups.