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PROSTATIC ISCHEMIA INDUCES VENTRAL PROSTATIC HYPERPLASIA IN THE SHR

Hypothesis / aims of study

Although there is increasing evidence that benign prostatic hyperplasia (BPH) and benign prostatic enlargement (BPE) is associated with cardiovascular disease, the pathogenesis of BPH/BPE is poorly understood and thought to be multifactorial[1)]. 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 the age[2)]. The prostate in the SHR is also known to be in a chronic ischemic condition[3)]. From these reports, one hypothesis that can be suggested is that mild hypoxia in the prostate induces up-regulation of hypoxia-inducible factor 1a (HIF-1a), the master regulator of oxygen homeostasis, and radical oxygen species (ROS), which subsequently activate TGF-b1 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 prostatic blood flow should inhibit the development of the prostatic hyperplasia. In the present study, we tried to investigate the effect of chronic administration of nicorandil, a vasodilator and K_{ATP} channel opener on the prostatic blood flow and hyperplasia in the SHR.

Study design, materials and methods

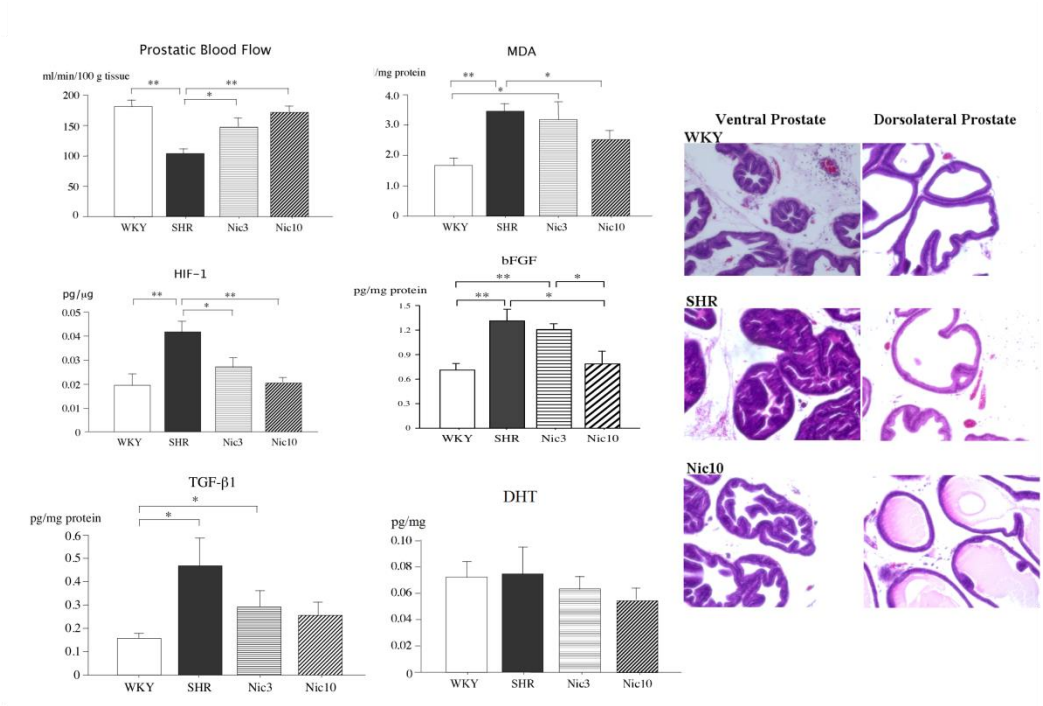
Twelve-week-old male SHRs were treated with nicorandil (0, 3 and 10 mg/kg, i.p.) for six weeks. Wistar-Kyoto (WKY) rats were used as normotensive controls. Six weeks after nicorandil treatment, blood pressure (the tail cuff method; BP-98A-L, Softron, Tokyo, Japan) and the prostatic blood flow (the hydrogen clearance method; PHG-301; Unique Medical Co., Tokyo, Japan) were estimated. Tissue levels of malondialdehyde (MDA, an oxidative stress marker) (NWLSSTM Malondialdehyde Assay, Northwest Life Science Specialties, LLC, Vancouver, WA) were determined by colorimetric assay. The tissue levels of HIF-1a□□□Enzyme-linked immunosorbent assay Kit for Hypoxia Inducible Factor 1 Alpha (HIF1a), USCN Life Science Inc, Wuhan, China), TGF-b1 (Quantikine® mouse/rat/porcine TGF-b1 immunoassay, R&D Systems, Inc., Minneapolis, MN), bFGF (Rat basic Fibroblast Growth Factor (bFGF) ELISA Kit, CUSABIO BIOTECH, Wuhan, China) and dihydrotestosterone (DHT) (DIHYDROTESTOSTERONE (DHT) ELISA, BioVendor LLC, Candler, NC) in the prostate were measured by the enzyme-linked immunosorbent assay (ELISA) method, and were normalized by protein contents. The histologic changes in the prostate were also evaluated in these groups.

Results

SHRs showed significant increases in blood pressure, tissue levels of MDA, HIF-1a, TGF-b1 and bFGF, and a significant decrease in the prostatic 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 DHT among any groups. The ventral prostate in the WKY group showed regular, unfolded closely packed acini tapered by low cuboidal cells showing a uniform monolayered arrangement. In contrast to the WKY group, the ventral prostate in the SHR group showed epithelial cells being taller in the shape with irregularities in the nuclear arrangement. Treatment with nicorandil normalized these abnormalities. However, alterations in the dorsolateral prostate were not found in all groups.

Interpretation of results

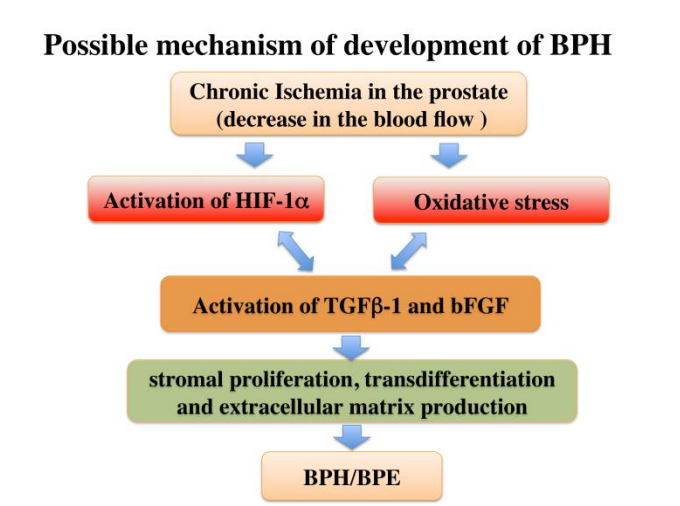
The present study demonstrated that although the tissue levels of DHT were not changed, SHRs showed significant increases in blood pressure, tissue levels of MDA, HIF-1a, TGF-b1 and bFGF, and a significant decrease in the prostatic blood flow. Although treatment with nicorandil failed to decrease the blood pressure,it significantly ameliorated these factors and inhibited the development of ventral prostatic hyperplasia without alterations of DHT levels. Our data indicated that development of ventral prostatic hyperplasia in the SHR depends on prostatic blood flow but not on tissue levels of DHT.



*WKY; 18-week-old Wistar-Kyoto rat group. SHR; 18-week-old SHR group. Nic3; 18-week-old SHRs treated with nicorandil at a daily dose of 3 mg/kg, i.p. Nic10; 18-week-old SHRs treated with nicorandil at a daily dose of 10 mg/kg, i.p. *) Significantly different between groups (P<0.05 is level of significance). **) Significantly different between groups (P<0.01 is level of significance).*

Concluding message

We propose that the development of prostatic hyperplasia is related to prostatic hypoxia, which nicorandil prevents via its ability to increase the blood flow in the prostate via inhibition of ROS and HIF-1a□TGF-b1 and bFGF pathways, and that it does not depend on tissue levels of androgens.



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Disclosures

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