EFFECT OF SILODOSIN ON DETRUSOR OVERACTIVITY IN THE MALE SPONTANEOUSLY HYPERTENSIVE RAT

Hypothesis / aims of study
Among aging males, benign prostatic hyperplasia (BPH) is becoming one of the most common diseases with lower urinary tract symptoms (LUTS) which are attributed to bladder outlet obstruction (BOO) from an enlarged prostate. However, since LUTS occur in females and LUTS patients are not always prostate related, the evidence for a direct link between benign prostatic enlargement (BPE), BOO and LUTS is weak and unclear. Alpha 1-blockers are the first line therapy for LUTS in BPH, and several $\alpha_1$ adrenoceptor antagonists have been developed. Silodosin is a new alpha 1-blocker with high selectivity for $\alpha_{1A}$ receptor subtype, which predominates in the male bladder neck, urethra and prostate. Some clinical studies demonstrated that silodosin statistically significantly improved storage and irritative scores compared to placebo [1]. However, the mechanism of improvement of silodosin on storage symptoms is not well investigated and still unclear. Our hypothesis is that silodosin could improve the hypertension-related detrusor overactivities (DO) via improvement of bladder blood flow (BBF). The spontaneously hypertensive rat (SHR) is reported to be a valuable tool for exploring the pathogenesis of DO [2]. The aim of this study is to investigate the effect of chronic administration of silodosin on hypertension-related DO in male SHRs.

Study design, materials and methods
Twelve-week-old male SHRs received 6 weeks of treatment by vehicle or silodosin (100 $\mu$g/kg, perorally every day). Wistar rats were used for normotensive controls. As the silodosin dose recommended by the FDA is 8mg orally once a day, we used the doses of 100 and 300 $\mu$g/kg, perorally, 6 weeks every day for our preliminary experiments. The results from these experiments showed that there were no significant differences of micturition frequency and some parameters between SHRs treated with the two different doses of silodosin. Thus, in the subsequent experiments we decided to use only one dose of 100 $\mu$g/kg per day. After 6 weeks of silodosin treatment, blood pressure was estimated by tail cuff method, BBF was estimated by hydrogen clearance method, and the bladder functions were estimated by voiding behavior studies and cystometric studies. Tissue levels of nerve growth factor (NGF) and calcitonin gene-related peptide (CGRP) in the bladder were measured by ELISA method. Furthermore, the participation levels of $\alpha_1$ adrenoceptor subtypes in the bladder tissue were investigated by real-time PCR method.

Results
SHRs showed significant increases in blood pressure, micturition frequency, tissue levels of NGF and CGRP in the bladder. The mean blood pressure in the Wistar, SHR and Silodosin groups were 95.6±2.3, 167.7±4.2 and 156.3±3.5mmHg, respectively. Moreover, there were significant decreases in bladder blood flow as well as single voided volume in both metabolic cages and cystometrograms in the SHR compared to the Wistar rat. Treatment with silodosin significantly ameliorated hypertension-related alterations of these parameters. The expression levels of $\alpha_1$ adrenoceptor subtype mRNAs were similar and their rank order was $\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$ in all groups. However, there were no significant differences of expression of $\alpha_{1A}$ adrenoceptor subtype mRNAs between any groups except for those of $\alpha_{1D}$ adrenoceptor mRNAs between the SHR and Wistar groups.

Table 1. The result of voiding behavior studies in the experimental rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Urine output (ml/day)</th>
<th>Micturition frequency (/day)</th>
<th>Single voided volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar</td>
<td>17.2±1.0</td>
<td>10.4±0.9</td>
<td>1.50±0.11</td>
</tr>
<tr>
<td>SHR</td>
<td>12.3±2.0</td>
<td><em>19.5±0.7</em></td>
<td><em>0.55±0.05</em></td>
</tr>
<tr>
<td>Silod 100</td>
<td>10.7±1.2*</td>
<td>15.4±0.8*</td>
<td>0.85±0.11*</td>
</tr>
</tbody>
</table>

*1) significantly different from the Wistar group (p<0.05). *#) significantly different from the SHR group (p<0.05).

Table 2. The result of cystometric studies in the experimental rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Pdet (cmH2O)</th>
<th>Single voided volume (ml)</th>
<th>Post voiding residual urine (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wistar</td>
<td>31.6±3.5</td>
<td>0.765±0.063</td>
<td>0.144±0.067</td>
</tr>
<tr>
<td>SHR</td>
<td>34.9±1.8</td>
<td><em>0.245±0.038</em></td>
<td>0.174±0.021</td>
</tr>
<tr>
<td>Silod 100</td>
<td>35.4±5.7</td>
<td><em>0.342±0.018</em></td>
<td>0.147±0.048</td>
</tr>
</tbody>
</table>

Pdet; maximum detrusor pressure,
*1) significantly different from the Wistar group (p<0.05). *#) significantly different from the SHR group (p<0.05).
Blood flow in the bladder; *) significantly different from the other groups. Bladder NGF and CGRP levels; *) significantly different from the other groups. p < 0.05 is the level of significance.

Expression of α1 adrenoceptor subtypes in the bladder; *) significantly different from the Wistar group. p < 0.05 is the level of significance.

Interpretation of results
In the present study, we demonstrated that silodosin prevented to develop DO in the SHR estimated by several parameters. In addition, NGF and CGRP are possible biomarkers of OAB. Treatment with silodosin significantly normalized up-regulated bladder NGF and CGRP levels to the control levels. Moreover, in the present study, the expressions of α1 adrenoceptor subtypes in the bladder are α1A > α1D > α1B in the all groups. It is reported that relative subtype composition in the vesical artery was α1A > α1D > α1B in both control rats and tamsulosin mediated rats under the use of bladder outlet obstruction rat models[3]. This report is corroborating to our present real-time PCR data in the bladder. Therefore, it is possible that silodosin improves the decreased BBF in the SHR via α1A adrenoceptor subtype in the bladder vessels.

Concluding message
Silodosin prevents hypertension-related DO in the SHR. One possible mechanism of the efficacy of silodosin to the DO includes the improvement of the BBF in the bladder.

References
1. BJU Int 2006; 98:1019-1024.
3. Urology 2010; 75; 235-240.

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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 09-Y-68