Effects of Sildenafil, a phosphodiesterase type 5 inhibitor, on the primary single afferent activity of the rat bladder

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Objectives
Phosphodiesterase type 5 inhibitors (PDE5 inhibitors) are primary medicine for the treatment of erectile dysfunction. Recently, several clinical studies demonstrate that these drugs have an effect also on improving male lower urinary tract symptoms (LUTS). However, the mechanisms involved in the effect of PDE5 inhibitors on LUTS have not been clarified. We investigated the direct effects of sildenafil on the single unit mechanosensitive afferent activities (SAAs) primarily originated from the bladder in the rat.

Materials & Methods
Preparation
Eleven female Sprague-Dawley rats under urethane anesthesia (1.5 g/kg i.p.)
Left pelvic nerve was put on an electrode for electrical stimulation
A catheter was inserted into the bladder dome, and a separate catheter was placed in the carotid artery and external iliac vein for monitoring of blood pressure and sildenafil-administration, respectively.
Laminectomy: L6 dorsal roots cut and left split until < 3 fibers
Aδ-fiber: conduction velocity (CV) ≥2.5 m/sec, C-fiber: CV< 2.5 m/sec

Measurement
The afferent activity originating from the bladder were identified by electrical stimulation of the pelvic nerve and by bladder filling (0.08 ml/min).
Then, sildenafil was administrated intravenously at three doses, 1, 3 and 10 mg/kg cumulatively.

Results
After Sildenafil-administration, bladder compliance increased and blood pressure decreased (Table).
Thirteen single units were isolated.
(Aδ-fibers: n=6, CV: 6.72±2.28 m/sec; C-fibers: n=7, CV: 1.88±0.15 m/sec)
SAA of Aδ-fibers significantly decreased in a dose-dependent manner, but SAA of C-fibers decreased significantly only at the highest dose used (Figures 1 and 2).

**P<0.01: significant difference from Base (Friedman test).

<table>
<thead>
<tr>
<th>Bladder compliance (ml/cmH2O)</th>
<th>Base (before)</th>
<th>After 1 mg/kg, i.v.</th>
<th>After 3 mg/kg, i.v.</th>
<th>After 10 mg/kg, i.v.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0197 ± 0.0009</td>
<td>0.0208 ± 0.0008</td>
<td>0.0217 ± 0.0008</td>
<td>0.0234 ± 0.001**</td>
<td></td>
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<thead>
<tr>
<th>Mean blood pressure (mmHg)</th>
<th>Base (before)</th>
<th>After 1 mg/kg, i.v.</th>
<th>After 3 mg/kg, i.v.</th>
<th>After 10 mg/kg, i.v.</th>
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<tr>
<td>79.12 ± 5.79</td>
<td>58.03 ± 4.39**</td>
<td>62.68 ± 4.32</td>
<td>56.66 ± 3.95**</td>
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</table>

Figure 1. Bladder pressure (Badder P.) and firing rate of Aδ-fiber (A) and C-fiber (B) during bladder filling with saline before and after sildenafil-administrations (1, 3 and 10 mg/kg, i.v.).

Figure 2. Responses to intravenous administration of sildenafil of the Aδ-fibers (left) and C-fibers (right) integrated during the whole filling phase. The values are expressed as a percentage of baseline activity (mean ± S.E.M.).

*P<0.05, **P<0.01: significant difference from Base (two-way ANOVA followed by Tukey’s test).

Conclusion
These results indicate that sildenafil can inhibit Aδ-fibers (partly also C-fibers) of the primary bladder mechanosensitive afferents of the rat although these effects may be partially influenced by systemic hypotension.