Age depresses α₁-adrenoceptor mediated vasoconstriction of the porcine superior vesical artery

Damian Nilsson, Russ Chess-Williams, Donna J Sellers

Centre for Urology Research, Faculty of Health Science and Medicine
Bond University, Queensland, Australia

Introduction

• With the growing worldwide elderly population, the incidence of bladder dysfunction and incontinence is increasing (1).
• Age is not only a common risk factor for the development of lower urinary tract symptoms, but is also an independent risk factor for cardiovascular diseases such as atherosclerosis.
• Impaired blood flow, or ischemia of the bladder may play a role in the etiology of bladder dysfunction, although the underlying mechanisms are unclear (2).
• We have shown that vasoconstriction of the porcine superior vesical artery is mediated via the low affinity form of the α₁-adrenoceptor (i.e. the α₁AL - adrenoceptor), the same subtype known to mediate contraction of the prostate and erectile tissue.
• The aim of this study was to determine the effect of ageing on functional α₁-adrenoceptor subtypes of the porcine superior vesical artery.

Methods

• Superior vesical arteries from female pigs aged young 6-months old and older 3-years old were obtained. Sections (~4mm length, ~1mm internal diameter) of superior vesical artery were isolated and mounted on sttrips in tissue baths containing gassed Krebs-Henseleit solution at 37°C. Contractions developed by circular smooth muscle was recorded to a PowerLab using Labchart software.
• Cumulative concentration-responses to phenylephrine, noradrenaline, methoxamine and A-16603 were recorded. Responses to KCl 60mM were also recorded.
• Responses of phenylephrine were obtained in the absence and presence of α₁-adrenoceptor antagonists BMY-7378(α₁A-selective), RS-100329 (α₁D-selective), prazosin(α₁A,α₁L-selective), RS-17056(α₁A,α₁L-selective), tamsulosin(α₁D-selective) and silodosin (α₁L-selective).  
• Control experiments without antagonists were performed to correct for time-dependent changes in tissue sensitivity.

Results

Contractile responses on superior vesical artery

• Phenylephrine caused concentration-dependent contractions with maximal responses being significantly depressed in older animals (P<0.01 vs Young Phenylephrine), by approximately 88% (Figure 1, Table 1).
• Responses to noradrenaline were significantly depressed, and potency and maximal contractions were decreased in older animal arteries (Figure 1, Table 1).
• Superior vesical arteries from young animals did not respond to methoxamine, however it did produce a response in older animals, although it was significantly less potent than other agonists (Figure 1, Table 1).
• A-16603 was significantly more potent than other agonists in both age groups (P<0.05 vs Agonists). Potency and maximal contractile responses were significantly depressed in older animals (Figure1, Table 1) (P<0.05, P<0.01 vs Young A-16603).
• In contrast, contractile responses to KCl were not affected by age (0.68±0.13 in young arteries and 0.76±0.13 older arteries).

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Young (μg)</th>
<th>3-Year Old (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>5.8±0.20</td>
<td>1.76±0.14</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>5.7±0.11</td>
<td>1.74±0.11</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>0.4±0.25</td>
<td>0.3±0.15</td>
</tr>
<tr>
<td>A-16603</td>
<td>7.3±0.12</td>
<td>1.71±0.11</td>
</tr>
</tbody>
</table>

Data is mean ± SEM. *P<0.05 vs Young Agonists, †P<0.05 vs Older Agonists.
**P<0.01 vs Young Phenylephrine. ***P<0.01 vs Young Noradrenaline. 
*P<0.05 vs Young A-16603.

Effects of α₁-adrenoceptor antagonists on contractile responses

• BMY-7378, at relatively high concentrations, did not significantly shift phenylephrine responses in both age groups.
• Tamsulosin (3nM) and silodosin (1nM) significantly shifted phenylephrine curves yielding high affinity estimates (Table 2).
• RS-100329 antagonised phenylephrine curves yielding high affinity estimates for both age group (Table 2).
• Prazosin and RS-17056, two antagonists able to distinguish between α₁L adrenoceptor and the phenotypic receptor α₁L-adrenoceptor, both significantly antagonised phenylephrine responses. Both antagonists have a higher affinity for the α₁L-adrenoceptor than the α₁L-adrenoceptor. Prazosin yielded a lower affinity estimate in the young arteries compared to the older arteries (Table 2). Similarly RS-17056 had a significantly lower affinity in young arteries than in older arteries (Table 2).

Conclusions

• Age depresses α₁-adrenoceptor-mediated contractile responses of the porcine superior vesical artery.
• Prazosin and RS-17056 affinely data suggest that in older animals vasoconstriction of the porcine superior vesical artery may be mediated by the α₁L-adrenoceptor, different to that found in the young animals (α₁A-adrenoceptor).

Table 2: Antagonist Affinities in young and older porcine superior vesical artery

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Young (pK)</th>
<th>3-Year Old (pK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMY-7378</td>
<td>5.6±0.16</td>
<td>6.0 No Shift</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>9.9±0.27</td>
<td>9.85±0.39</td>
</tr>
<tr>
<td>Silodosin</td>
<td>10.1±0.27</td>
<td>10.19±0.33</td>
</tr>
<tr>
<td>RS-100329</td>
<td>8.8±0.32</td>
<td>9.2±0.09</td>
</tr>
<tr>
<td>RS-17056</td>
<td>8.16±0.12</td>
<td>9.52±0.38</td>
</tr>
<tr>
<td>Prazosin</td>
<td>8.09±0.09</td>
<td>9.41±0.21</td>
</tr>
</tbody>
</table>

Data is mean ± SEM. pK estimates for antagonists on phenylephrine-concentration dependent responses for both age groups. **P<0.01, ***P<0.001 vs Young

References