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# Age depresses $\alpha_1$-adrenoceptor mediated vasoconstriction of the porcine superior vesical artery

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## 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 underlaying mechanisms are unclear (2).
- We have shown that vasoconstriction of the porcine superior vesical artery is mediated via the low affinity form of the $\alpha_{1A}$-adrenoceptor (i.e. the $\alpha_{1A/L}$-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 $\alpha_1$-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 stirrups in tissue baths containing gassed Krebs-Henseleit solution at 37ºC. Contractions developed by circular smooth muscle was recorded to a PowerLab using Labchart software.
- Cumulative concentration-responses to phenylephrine, noradrenaline, methoxamine and A-61603 were recorded. Responses to KCl 60mM were also recorded.
- Responses of phenylephrine were obtained in the absence and presence of $\alpha_1$-adrenoceptor antagonists BMY-7378($\alpha_{1D}$-selective), RS-100329 ($\alpha_{1A}$-selective), prazosin($\alpha_1$>$\alpha_{1L}$-selective), RS-17056($\alpha_{1A}$>$\alpha_{1L}$-selective), tamsulosin($\alpha_{1A/D}$-selective) and silodosin ($\alpha_{1A/L}$-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-61603 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-61603).
- 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).

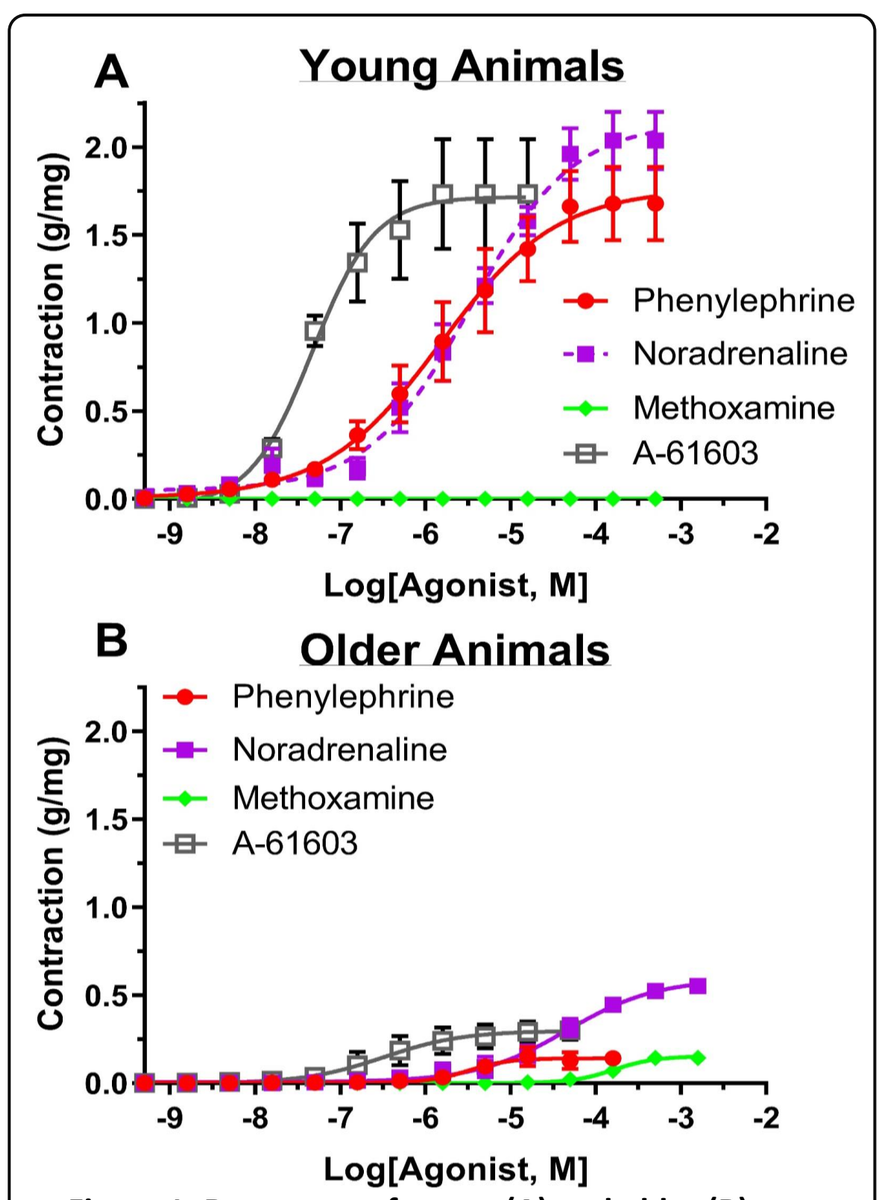


**Figure 1: Responses of young (A) and older (B) superior vesical arteries to α1-adrenoceptor agonists.** Data is mean ± SEM, normalized to tissue weight.

**Table 1: Contractile responses of young vs older porcine superior vesical artery to agonists**

| Agonist | Young | | | 3-Year Older | | |
|---|---|---|---|---|---|---|
| | n | Potency ($pEC_{50}$) | Max. Response (g/mg) | n | Potency ($pEC_{50}$) | Max. Response (g/mg) |
| Phenylephrine | 6 | 5.83±0.20 | 1.76±0.14 | 5 | 5.57±0.11* | 0.20±0.01** |
| Noradrenaline | 6 | 5.47±0.15 | 2.14±0.11 | 5 | 4.34±0.14* | 0.59±0.05** |
| Methoxamine | 6 | No Response | | 5 | 3.78±0.10* | 0.15±0.02* |
| A-61603 | 6 | 7.33±0.15* | 1.71±0.11 | 5 | 6.49±0.28* | 0.30±0.04** |

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 <0.01 vs Young A-61603

### Effects of $\alpha_1$-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 $\alpha_{1A}$-adrenoceptor and the phenotypic receptor $\alpha_{1L}$-adrenoceptor, both significantly antagonised phenylephrine responses. Both antagonists have a higher affinity for the $\alpha_{1A}$-adrenoceptor than the $\alpha_{1L}$-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).

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

| Agonist | Young | | 3-Year Older | |
|---|---|---|---|---|
| | n | $pK_D$ | n | $pK_D$ |
| BMY-7378 | 5 | 5.68±0.16 | 6 | No Shift |
| Tamsulosin | 6 | 9.99±0.27 | 5 | 9.85±0.39 |
| Silodosin | 5 | 10.1±0.27 | 5 | 10.19±0.33 |
| RS-100329 | 5 | 8.82±0.32 | 6 | 9.2±0.09 |
| RS-17056 | 5 | 8.16±0.12 | 4 | 9.52±0.38*** |
| Prazosin | 6 | 8.09±0.09 | 6 | 9.41±0.21** |

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

## Conclusion

- Age depresses $\alpha_1$-adrenoceptor-mediated contractile responses of the porcine superior vesical artery.
- Prazosin and RS-17056 affinity data suggest that in older animals vasoconstriction of the porcine superior vesical artery may be mediated by the $\alpha_{1A}$-adrenoceptor, different to that found in the young animals ($\alpha_{1L}$-adrenoceptor).

## References

[1]R, Dmochowski, *Ther Adv Urol*, 2009, 1(4), 209-221.
[2]M, Michel; R, Chess-Williams, S, Hegde, *Naunyn-Schmiedeberg's Arch Pharmacol*, 2015, 388, 687-694.
[3]B, Davis; M, Weiner; C, Chapple; R, Chess-Williams, *Auton Autacoid Pharmacol,* 2015, 34(3-4), 41-49.