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Classification of α_1-adrenoceptors on the porcine superior vesical artery

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Introduction

- The bladder vasculature has become an area of focus in the quest to understand the pathophysiology of bladder dysfunction and LUTS. Hypoperfusion-induced hypoxia can produce bladder dysfunction (1,2) and enhancing perfusion can ameliorate dysfunction in experimental studies (3).
- Vascular smooth muscle tone is regulated via noradrenaline acting at α_1-adrenoceptors to cause vasoconstriction. There are 3 cloned subtypes of α_1-adrenoceptor (α_{1A}-, α_{1B}- and α_{1D}-), and the functional phenotype of the α_{1A} receptor, the $\alpha_{1A/L}$-adrenoceptor (4).
- Which functional subtype regulates vasoconstriction of the superior vesical artery supplying the porcine bladder is currently unknown.
- **The aim was to classify the α_1-adrenoceptor subtype mediating vasoconstriction of the porcine superior vesical artery.**

Methods

- Sections (~4mm) of porcine superior vesical artery (SVA) (internal diameter ~1mm) were isolated from 6-month old pigs and mounted on stirrups in tissue baths containing gassed Krebs-bicarbonate solution at 37℃.
- Developed tension of the circular smooth muscle was recorded via force transducers connected to a PowerLab using LabChart software.
- Contractions to noradrenaline, phenylephrine and the α_{1A}-adrenoceptor selective agonist A-61603 were recorded. Concentration-response curves to phenylephrine were obtained in the absence and presence of α_1-adrenoceptor antagonists silodosin and RS-100329(α_{1A}-selective), BMY-7387(α_{1D}-selective) and prazosin (α_{1A}>α_{1L}-selective). Experiments were performed in the presence of desipramine (1μM), corticosterone (1μM) and propranolol (1μM) to block neuronal & extraneuronal uptake and β & α_2 receptors.
- Control experiments without antagonists were performed to correct for time dependent changes in tissue sensitivity.

Results

Responses of SVA to agonists

- Noradrenaline, phenylephrine and A-61603 caused concentration-dependent contractions of the SVA (Fig. 1). A-61603 was more potent, with the relative potency of agonists A-61603 > phenylephrine ≥ noradrenaline (Table 1).

Table 1: Responses of superior vesical artery to agonists

Agonist	*n*	Potency (pEC_{50})	Maximum Response (g/mg)
A-61603	6	7.33±0.15**	1.71±0.11
Phenylephrine	9	5.83±0.20	1.76±0.14
Noradrenaline	6	5.47±0.15	2.14±0.11

Data is mean ± SEM. **p<0.01 vs phenylephrine & noradrenaline (ANOVA plus Tukey)

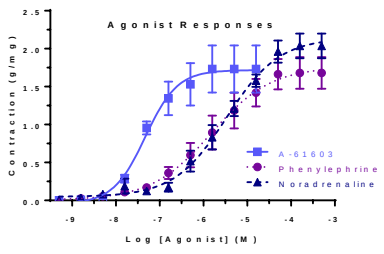

Figure 1: Responses of superior vesical artery to agonists Data is mean ± SEM, normalised to tissue weight. **p<0.01 vs phenylephrine & noradrenaline (ANOVA plus Tukey).

Effect of antagonists

- The α_{1D}-selective antagonist BMY7378, at relatively high concentrations up to 30μM, failed to antagonise responses to phenylephrine (Fig. 2A). However the α_{1A}-selective antagonists RS-100329 and silodosin produced rightward shifts of phenylephrine curves, at 10nM and 30nM ($p<0.01$ *vs* control) (Fig. 2B) and 1nM and 10nM ($p<0.05$ *vs* control) (Fig. 2C). Maximal responses to phenylephrine were not significantly affected by RS-100329 or silodosin and the pK_D estimates were 8.48±0.25 and 9.47±0.18, respectively.
- Prazosin shifted phenylephrine concentration-response curves without significantly affecting the maximal response, and with a relatively low affinity (pA_2) of 8.63 and pK_D estimate of 8.02±0.06 (Fig. 2D & E).

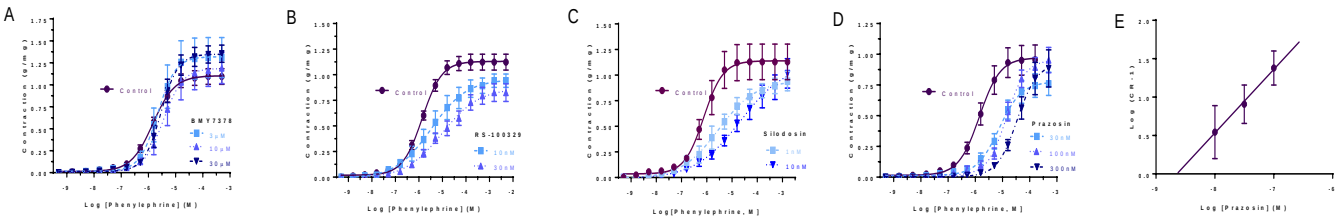

Figure 2: Responses to phenylephrine in the absence and presence of BMY7378 (A) RS-100239 (B) silodosin (C) and prazosin (D), with Schild plot for prazosin (E). Data is mean ± SEM, normalised to tissue weight. (n=6).

Conclusion

- The high potency of the agonist A-61603 suggests the presence of functional α_{1A}-adrenoceptors in the porcine superior vesical artery. This is supported by the antagonist data where silodosin and RS-100329 (α_{1A}- vs α_{1B}-selective), but not BMY-7378 (α_{1D}-selective), antagonised phenylephrine responses.
- The relatively low affinity estimate for prazosin suggests the presence of the low affinity functional phenotype of the α_{1A}-adrenoceptor.
- In conclusion, contraction of the porcine superior vesical artery is mediated via the low affinity form of the α_{1A}-adrenoceptor (i.e. the $\alpha_{1A/L}$-adrenoceptor), the same subtype known to mediate contraction of the prostate and erectile tissue.

References

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