Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst151P.pdf

Neither phentolamine nor prazosin behave as classical competitive antagonists against noradrenaline-induced contractions in the porcine isolated splenic artery

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Introduction: Activation of post-junctional α_1- and α_2-adrenoceptors is known to cause constriction of blood vessels. The porcine isolated splenic artery (PSA) possesses both alpha-adrenoceptor subtypes (Wright *et* al., 1995), and α_2-adrenoceptor-mediated contractions can be revealed by selective agonists and pharmacological manipulation (Roberts *et al*., 1999), but studies with subtype-selective antagonists and noradrenaline, only revealed α_1-adrenoceptors (Wright *et* al., 1995). We have compared phentolamine, a non-selective α-adrenoceptor antagonist, and prazosin, a selective α_1-adrenoceptor antagonist, against responses of PSA to noradrenaline and A61603, a potent, selective α_1-adrenoceptor agonist (Mills *et al*., 2008).

Methods: Pig spleens were obtained from a local abattoir. Isometric tension recordings were undertaken in vitro with 5mm ring segments of the PSA, that were first exposed to 60mM KCl. Cumulatively increasing concentrations of noradrenaline and A61603 were used to generate response curves (CRC) in the presence of phentolamine (10nM-10μM in half log unit increments) and prazosin (1nM-1μM in half log unit increments) and the pA_2 and slope of Schild plot determined. Cocaine (10μM), corticosterone (30μM) and propranolol (1μM) were included in the bathing solution when noradrenaline was used. All values were expressed as the mean ± standard error of the mean (SEM) in tissues from different animals (n). A Student's paired t-test was used to assess the statistical significance of deviation from unity of the slope of the Schild plot.

Results: Both agonists produced concentration-dependent contractions, with A61603 (pD_2 8.07±0.1, n=6) 100-fold more potent than noradrenaline (pD_2 5.90±0.05, n=7). Phentolamine and prazosin caused concentration-dependent, parallel, rightward shifts of the CRC against both agonists that, with the exception of the highest antagonist concentration, did not change the maximum response. The estimated pA_2 values for the antagonists were independent of the agonist, but the slopes of the Schild plot against noradrenaline were significantly different from unity (Table 1).

Table 1 Mean pA_2 (± sem) and Slope of Schild Plot for Prazosin and Phentolamine.

(* -Denotes that the slope of Schild plot is significantly different from unity ($p<0.05$)

Drug	Antagonist	pA_2	Slope of the Schild Plot	n
Noradrenaline	Phentolamine	8.1 ± 0.13	0.67 ± 0.05*	6
	Prazosin	9.50 ± 0.25	0.79 ± 0.06*	8
A61603	Phentolamine	8.5 ± 0.10	0.91 ± 0.03	6
	Prazosin	9.09 ± 0.23	1.02 ± 0.06	5

Conclusion: Based on the estimated pA_2 values prazosin was 3-30-fold more potent than phentolamine against A61603 and noradrenaline, respectively, consistent with the presence of only α_1-adrenoceptors. However, the slope of the Schild plot for both antagonists against the endogenous ligand was significantly different from unity. Presently, we have no explanation for the different results with the two agonists, but a role for post-junctional α_2-adrenoceptors seems unlikely.

References:

Mills K *et al*., (2008) *Br. J. Pharmacol*. **155**, 110-117

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