# 056P A COMPARISON OF THE EFFECTS OF THE PUTATIVE $5HT_{1A}$ ANTAGONIST MM-77 WITH WAY-100635 ON THE MOUSE ISOLATED VASA DEFERENTIA

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1-(2-methoxyphenyl)-4-(4-succinimidobutyl) piperazine (MM-77) is a putative 5-$HT_{1A}$ antagonist with apparent specificity for postsynaptic $5HT_{1A}$ receptors (Mokrosz *et al*., 1994). However, we have reported that MM-77 displays some characteristics of a 5-$HT_{1A}$ agonist and an adrenoceptor antagonist (Arkle *et al*., 2004). The mouse vas deferens has a high density of adrenergic receptors (Kitchen, 1984) and our preliminary experiments showed that MM-77 produces concentration-dependent inhibition of contractile responses to submaximal electrical field stimulation, indicative of adrenergic inhibition. To further characterise this effect, we compared the effects of MM-77 and the selective 5-$HT_{1A}$ antagonist WAY100635 (Fletcher *et al*., 1996) on phenylephrine (PE)-stimulated contractions of mouse isolated vas deferens.

Adult male CFLP mice (b. wt. ~50g) were killed by exposure to $CO_2$ and cervical dislocation. Vasa deferentia were mounted in 15 ml organ baths in Krebs Ringer for isometric recording (Kitchen, 1984), incubated with $10^{-7}$-$10^{-6}$M MM-77 or WAY-100635 and then sequentially exposed to $10^{-6}$–$10^{-3}$M PE for 30s in a 3 min time cycle Schild plots were constructed from these data with dose ratios calculated at 25% of tissue maximal response ($E_{max}$).

MM-77 produced a rightward shift of concentration-responses curves to PE with a progressive decrease in $E_{max}$ (fig.1). Schild plots of these data were linear with a mean intercept of -6.8±0.1 and slope of 1.42±0.2, consistent with non-competitive antagonism at $\alpha_1$-adrenoceptors. By contrast, while WAY-100635 also caused a rightward shift of the PE concentration-response curves, there was no loss of $E_{max}$ except at the 1μM concentration (fig. 2). Schild plots of these data were linear with a mean intercept of -7.1±0.1 and slope of 1.0±0.1, consistent with competitive $\alpha_1$-adrenoceptor antagonism.

WAY-100635 has a 10 fold greater potency than MM-77 *in vivo* and this may explain the overt adrenergic antagonistic effects that we reported with MM-77 in behavioural studies (Arkle *et al*., 2004). Nevertheless, the action of these drugs at α-adrenoceptors may confound interpretation of selective 5-$HT_{1A}$ receptor effects in behavioural experiments.

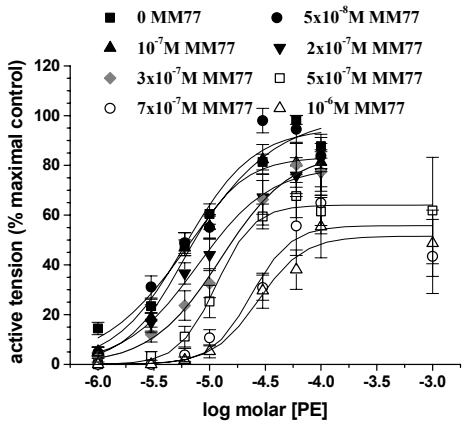


Fig.1. Effects of MM-77 on PE-stimulated contractile responses in vas deferens, n=7.

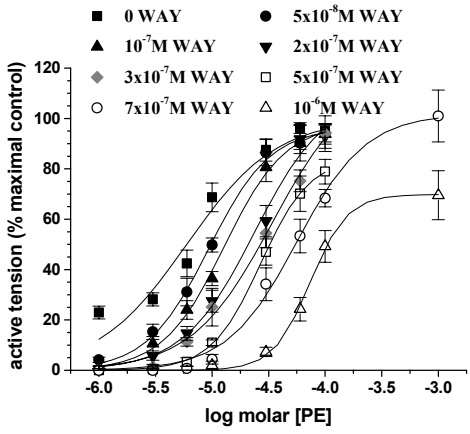


Fig.2. Effects of WAY-100635 on PE-stimulated contractile responses in vas deferens, n=6.

Arkle, M.J. *et al.*, (2004) *Proc. Br. J. Pharmacol*., in press.
Fletcher, A. *et al*. (1996). *Behav. Brain Res*., **73**, 337 – 353.
Kitchen, I. (1984) Textbook of *In Vitro* Practical Pharmacology, Blackwell, Oxford.
Mokrosz, J.J. *et al*. (1994) *J. Med. Chem*., **37**, 2754 – 2760.