038P PRELIMINARY STUDIES USING A PUTATIVE FP-RECEPTOR ANTAGONIST, AL-8810, ON ISOLATED MOUSE UTERUS

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We have previously demonstrated the presence of prostanoid FP-receptors on isolated mouse uterus (Knights *et al.,* 1992). The aim of this study was to investigate further the mouse uterine FP-receptor population using AL-8810 (Griffin *et al.,* 1999) a putative FP-receptor antagonist against rat thoracic aorta vascular smooth muscle and Swiss mouse 3T3 fibroblast cells. The agonists used were the parent prostanoid $PGF_{2\alpha}$, 17-phenyl$PGF_{2\alpha}$ (a selective FP-agonist) and U46619 (stable TP mimetic) to examine the selectivity of the antagonist. Virgin, sexually mature BKW female mice (25 – 36g) were sacrificed and a vaginal lavage was taken for histological assessment of the phase of the oestrous cycle. Each horn of the duplex uterus was excised, and dissected then set up in an 8ml jacketed organ bath containing Krebs buffer at 37°C, pH 7.4, with 1μM indometacin and gassed with 95%O_2/CO_2 (Chen *et al.,* 1998). After equilibration and establishment of myogenic activity, single doses of test agonist were applied, when the antagonist was used it was incubated with the tissue for 30 mins prior to the addition of agonist. Only one concentration effect curve was generated on each tissue. A concentration of $PGF_{2\alpha}$ (10^{-6}M) was applied to each tissue to provide a reference contraction. Excitatory potency was expressed as EC_{50} values, n=5 in all cases. Concentration effect data were analysed using one-way ANOVA with Dunnett's t-test.

The phase of the oestrous cycle had no effect upon the responsiveness of the tissues used in this study. All agonists were shown to elicit concentration-related contractions, the order of excitatory potency being 17-phenyl $PGF_{2\alpha}$>U46619> $PGF_{2\alpha}$. AL-8810 (10^{-5}M) alone tended to enhance myogenic activity. In the presence of AL-8810 (10^{-5}M) the concentration effect curve to $PGF_{2\alpha}$ was shifted rightwards and the maximum response was not significantly different to $PGF_{2\alpha}$ alone. The antagonist also depressed the concentration effect curve to 17-phenyl $PGF_{2\alpha}$ and the maximum response with the agonist alone could not be restored at the agonist concentrations available. In the presence of AL-8810 (10^{-5}M) the concentration effect curve to U46619 was also depressed up to 10^{-6} M U46619.

Table 1. Mean pEC_{50} values (nM) for $PGF_{2\alpha}$, 17- phenyl $PGF_{2\alpha}$ and U46619 on isolated mouse uterus alone and in the presence of AL-8810 (10^{-5}M). *P<0.05 significantly different from agonist alone.

Agonist	pEC_{50} (± s.e.m.)	
	Alone	+ AL-8810
$PGF_{2\alpha}$	1.72(0.152)	2.36(0.035)*
17-phenyl $PGF_{2\alpha}$	1.72(0.259)	2.42(0.292)
U46619	1.51(0.181)	2.02(0.179)*

The results of this study suggest that AL-8810 does antagonise the FP-receptor mediated response in isolated mouse uterus. The stimulation of myogenicity seen when the antagonist was used alone may be a sign of partial agonism via another stimulatory prostanoid receptor possibly the FP-receptor or even the TP-receptor. This is supported by the results attained with $PGF_{2\alpha}$ and U46619.

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Griffin, BW *et al.,* (1999). *J. Pharmacol. Exptl. Therap.* **290,** 1278-1284.
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