Functional Prostaglandin E Receptors In Isolated Human And Rat Myometrium

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Prostaglandin (PG) E_2 acts through its receptors (EP_{1-4}) to promote angiogenesis, cell proliferation and to modulate uterine activity. Whilst it facilitates normal reproductive processes, such as sperm transport, ovulation and blastocyst implantation, aberrant PGE_2 output has been reported to reduce fercundity in women (Dixon *et al*., 2009) and in mice (Tilley *et al*., 1999). To assess the importance of PGE_2 in uterine motility, *ex vivo* PG profiles and *in vitro* responses to PGE_2 were characterised mid-cycle in non-gravid human myometrium. EP-mediated effects were also examined in the rat to determine its suitability as a model of human reproductive disorders.

Uterine samples were obtained from consenting pre-menopausal women undergoing hysterectomy for benign disorders (n=6) and from Lister Hooded rats (n=6). Studies were carried out in accordance with the Local Regional Ethics Committees and the Animals Scientific Procedures Act (1996)**.** For contraction recordings, myometrial strips were mounted in immersion baths under physiological conditions and attached to isometric force transducers. Following tissue equilibration, vehicle and concentration-effect curves (10^{-9}M to 10^{-5}M) were constructed for PGE_2, butaprost (an EP_2 agonist; Gardiner, 1986), L-902688 (an EP_4 agonist; Billot *et al*., 2003), ONO-D1-004 (an EP_1 agonist; Oka *et al*., 2003) and sulprostone (an $EP_{3/1}$ agonist; Schaaf *et al*., 1981). Stock solutions were prepared using ethanol. To assess endogenous PGs (n=9), human myometrial biopsies were extracted and quantified using liquid chromatography coupled with ionisation mass spectrometry (Nicolaou & Masoodi, 2006). Results were expressed as means ± S.E.M and analysed using ANOVA with Bonferroni's *post-hoc* test.

The results show that myometrial PGE_2 output was most abundant around ovulation relative to menses ($p<0.05$; Figure 1). In functional studies, compared to vehicle controls, PGE_2 produced bell-shaped responses with predominant utero-relaxant effects in the human ($p<0.001$) and excitatory effects in the rat ($p<0.01$). Exposure to butaprost evoked pronounced concentration-dependent inhibition of activity in human myometrial strips ($p<0.001$), whereas L-902688 stimulated activity at 10^{-5}M in the rat ($p<0.01$). Sulprostone further enhanced the amplitude and frequency of contractions in human ($p<0.01$) and rat tissues ($p<0.001$); ONO-D1-004, however, had little effect.

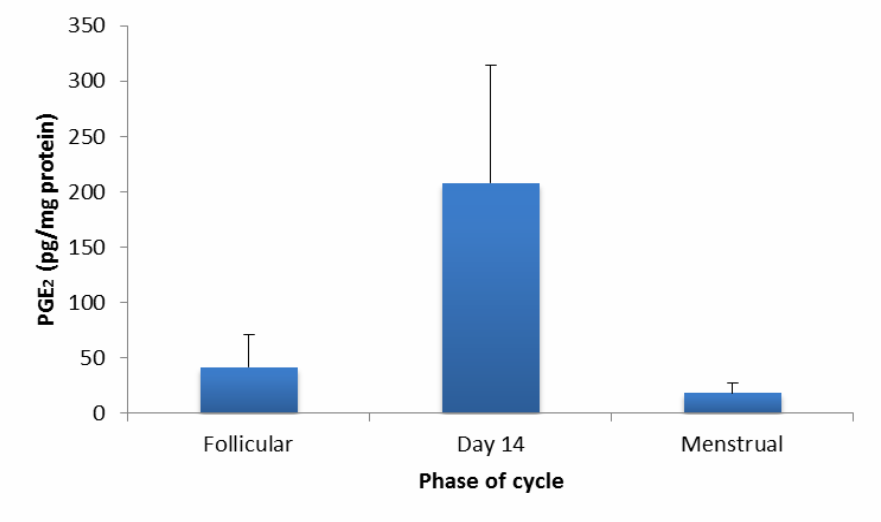

Figure 1: *Ex vivo* PGE_2 output in isolated myometrium obtained from non-gravid women with typical menstrual cycles (n=9); *$p<0.05$ for day 14 compared to the menstrual phase.

These findings indicate that the profound *in vitro* inhibitory effect of PGE_2 in human myometrium was mediated by the EP_2 subtype with some excitation achieved through a complement of EP_3 receptors. Utero-quiescence during the peri-ovulatory peak in PGE_2 may facilitate pregnancy. Even so, since PGE_2 in the rat was conversely uterotonic, it may not be easily transposed as a model of human uterine pathologies.

References:

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