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Prostaglandin F2α induced G protein signalling in human myometrium

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Introduction: Human labour, both at term and preterm, is preceded by inflammatory activation within the uterus, leading to myometrial activation, fetal membrane remodelling and cervical ripening (1). Prostaglandins are significant contributors to these processes (2). Prostaglandin F2α (PGF2α) is a potent stimulator of myometrial contractions and also contributes to uterine activation prior to labour. PGF2α receptor mainly couples to $G_{\alpha q}$ subunit but also has been shown to signal through $G_{\beta\gamma}$ protein pathway involving $G_{\alpha i}$ subunit (3, 4). To gain insight into molecular mechanism underlying the pro-inflammatory effects of PGF2α, such as the activation of NF-κB and MAPKs and subsequent expression of COX-2 and P-cPLA$_2$, we investigated the role of different G proteins involved in PGF2α signalling.

Method: Primary myometrial cells were isolated from biopsies obtained from non-labouring women undergoing elective caesarean section at term. Myocytes were incubated with either 1μM UBO-QIC ($G_{\alpha q}$ inhibitor) for 2hours or with 200ng/ml of pertussis toxin (PTX; $G_{\alpha i}$ inhibitor) for 12hours prior to stimulation with PGF2α (1μM) for 5, 15, or 30minutes or 2, 4, or 6hours. Activation of NF-κB and MAPKs and expression of COX-2 and P-cPLA$_2$ were assessed using Western blot.

Results: Treatment of myometrial samples (n=3) with UBO-QIC, resulted in reduced PGF2α-induced activation of p38 (81±14% decrease at 15 min; 83±5% decrease at 30 min) and also reduced the expression of COX-2 (60±6% decrease at 4h; 65±8% decrease at 6h). UBO-QIC had no effect on PGF2α-induced activation of p65 or P-ERK. Treatment of myometrial cells with PTX reduced the PGF2α-stimulated upregulation of COX-2 (50±5% decrease at 4h; 49±16% decrease at 6h) but did not have an effect on p65, p38 or P-ERK activation.

Conclusion: Both $G_{\alpha q}$ and $G_{\alpha i}$ seem to be involved in PGF2α-induced COX-2 expression where $G_{\alpha q}$ signalling seems to involve activation of p38. Further work is needed to determine which signalling pathways are involved in $G_{\alpha i}$-mediated COX-2 expression. This work provides insight into PGF2α inflammatory signalling in the initiation of parturition which could lead to identification of potential targets for management of preterm labour.

References:

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