Presented at the 63rd Annual SRI Conference – March 16-19, 2016 – Montreal, CANADA

Preterm Labor-OBE001

[T-071] The OTR Antagonist, OBE001, Inhibits OT-Driven Proinflammatory Effects in Both Human Myometrium and Amnion.

Sung Hye Kim, Oliver Pohl, Andre Chollet, Adam Fairhurst, Phillip R Bennett, Vasso Terzidou. Parturition Research Group, IRDB, Imperial College, London, United Kingdom; ObsEva, ObsEva SA, Plan-les-Ouates, Geneva, Switzerland

INTRODUCTION: Oxytocin (OT) is one of the strongest uterotonic agents known to stimulate uterine contractions and plays a key role in the initiation and regulation of both term and preterm labour (PTL). We have recently demonstrated an additional pro-inflammatory role of OT in human gestational tissues, thus suggesting that tocolytics that target OT/OTR system to inhibit premature uterine contractions should ideally inhibit both uterine contractions and inflammatory activation. Oxytocin receptor (OTR) antagonists such as Atosiban have been used therapeutically for the treatment of PTL. We have previously shown that Atosiban not only fails to inhibit the pro-inflammatory effects of OT in human amnion, but Atosiban alone activates NF-κB and MAPKs as well as upregulating downstream pro-labour gene expression, such as COX-2, p-cPLA$_2$, IL-6 and CCL5.
METHODS: In this study we treated prelabour amniocytes and myocytes with OT (10nM) and increasing doses of the orally active OTR antagonist, OBE001, in order to investigate its effect on the OT-driven activation of inflammatory response in human gestational tissues.
RESULTS: In contrast to our findings with Atosiban, presence of OBE001 led to significant inhibition of OT-induced NF-κB and p38 kinase activation at the lowest dose of 1μM in both myometrial and amnion cells. This led to subsequent decreases in OT-induced expression of COX-2 and p-cPLA$_2$, which was reflected in PGE$_2$ synthesis. Successful inhibition of NF-κB activation by OBE001 also translated to suppression of OT-induced NF-κB-regulated pro-labour gene expression including COX-2, IL-6, IL-8 and CCL2. Moderate reduction of OT-induced p-ERK activation was observed in both gestational tissues but it did not reach significance. Unlike Atosiban, OBE001 alone had no significant effect on the activation of NF-κB and p38 kinase, or downstream pro-labour gene expression.
CONCLUSIONS: In conclusion, these data suggest that OBE001 is a promising candidate tocolytic, which ensures effective inhibition of myometrial contractility and suppresses the OT-driven pro-inflammatory effects. This raises the possibility that such an agent could be used not only in the acute clinical situation but for prophylactic or maintenance therapy.