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Preterm Labor-OBE001

[F-061] The OTR Antagonist, OBE001, Suppresses the Effects of OT on miRNA Expression in Human Myometrium.

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INTRODUCTION: MicroRNAs are small non-coding RNAs which modulate post-transcriptional gene expression. It is estimated that approximately 30% of the human genome is regulated by microRNAs. They have previously been shown to play a modulatory role in pathways leading to labor onset, and oxytocin (OT) was found to alter the expression of a unique set of myometrial miRNAs including hsa-miR-146a-5p, hsa-miR-196b-3p and hsa-miR-876-5p. Although hsa-miR-196b-3p and hsa-miR-876-5p have no experimentally validated gene targets reported to date, hsa-miR-146a-5p has been validated to target NF-κB activity as well as IL-8, TLR2 and TLR4 expression. These results suggest a further role for OT as a signalling molecule involved in the regulation of gene expression during parturition. Oxytocin receptor (OTR) antagonists have been used therapeutically for the management of labour. In this study we have investigated whether the orally active OTR antagonist, OBE001, can inhibit the OT-driven change in the expression of miRNAs hsa-miR-146a-5p, hsa-miR-876-5p and hsa-miR-196b-3p in human myometrial smooth muscle cells.

METHODS: QRT-PCR was used to quantify the expression of candidate miRNAs with the miRCURY LNA kit (Exiqon) with 0.05 ng complementary DNA. LNA assays were custom designed for miRNAs of interest: hsa-miR-146b-3p (204374), hsa-miR-196b-3p (204619), and hsa-miR-876-5p (204527). MiRNA expression data were normalized to 5S ribosomal RNA (203906).

RESULTS: Consistent with previous observations, OT down-regulated the expression of hsa-miR-146a-5p and hsa-miR-196b-3p after 2 h of stimulation, and hsa-miR-876-5p after 1 h. Presence of OBE001 reversed this effect of OT on all three miRNAs in a dose-dependent manner. Morever, prolonged exposure to OBE001 (4 h, 6 h and 24 h) led to slight increase in the expression of these miRNAs.

CONCLUSIONS: In addition to the typical role of OTR antagonists in inhibiting OT-driven myometrial contractions, OBE001 also reduced OT-induced changes in miRNA expression which target proinflammatory genes. This study shows the importance of an OTR antagonist being able to inhibit both the labour-associated inflammatory and contractile effects of OT.