76. PROGESTERONE RECEPTOR EXPRESSION IS MODULATED BY PROSTAGLANDINS IN HUMAN MYOMETRIAL CELLS

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Progesterone withdrawal transforms the myometrium to a highly contractile state required for parturition. In human pregnancy, progesterone withdrawal is mediated functionally by a decrease in myometrial progesterone responsiveness. This is attributed to increased expression of progesterone receptor type A (PR-A), a repressor of progestin actions. Prostaglandins (PGs) are potent endogenous uterotonins and their administration at any stage of human pregnancy induces the full parturition cascade. We hypothesized that in human pregnancy PGs act, at least in part, by inducing functional progesterone withdrawal by modulating myometrial expression of PR-A relative to PR-B. To test this hypothesis, we determined whether PGE_2 and $PGF_{2\alpha}$ influence PR-A and PR-B expression in the PHM1-31 human myometrial cell line. PHM1-31 cells were exposed to PGE_2 and $PGF_{2\alpha}$ (1 pM to 10 nM each) for 24 h. Relative abundance (normalized to 18S rRNA) of mRNAs encoding total PR-A and PR-B were determined by real-time quantitative RT-PCR. Abundance of PR-A and PR-B mRNAs were differentially and dose dependently increased by PGE_2. PGE_2 more efficiently induced PR-A than PR-B expression. Consequently, the PR-A/PR-B expression ratio, which is thought to reflect the extent to which PR-A suppresses progesterone responsiveness, increased in response to low doses of PGE_2 (0.01 to 1 nM) and returned to basal levels in response to higher PGE_2 levels (1-10 nM). $PGF_{2\alpha}$ stimulated expression of PR-A but had no effect on PR-B. This increased the PR-A/PR-B expression ratio. These data show that PGE_2 and $PGF_{2\alpha}$ regulate PR-A and PR-B expression in human myometrial cells. Since progesterone responsiveness is inversely related to the PR-A/PR-B expression ratio, the increase in this ratio by PGE_2 (at low concentrations) and $PGF_{2\alpha}$ may cause functional progesterone withdrawal. These data suggest that PGs induce parturition in part by inducing functional progesterone withdrawal. Such a mechanism would explain why PGs alone can induce the full parturition cascade.

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