Dynamic Regulation of Prostaglandin Receptors FP, EP2, EP3 and EP4 by Interferon Tau at the time of Maternal Recognition of Pregnancy in Bovine

Arosh JA[1], Banu SK[1], Kimmins S[2], Chapdelaine P[1], MacLaren LA[2] and Fortier MA[1]
[1]*Ontogénie et Reproduction, Centre de Recherche en Biologie de la Reproduction,Centre de Recherche du CHUL, Université Laval, GIV 4G2, Canada.*[2]*Department of Plant and Animal Sciences, Nova Scotia Agricultural College, , Nova Scotia, Canada, B2N 5E3.*

Early embryonic mortality remains as the major single cause of infertility in bovine. Up to 40% of early embryonic losses occur between days 8 and 17 of pregnancy and days 15-17 are considered the "critical period." The success of early pregnancy relies on the reversal by a viable embryo of the default maternal luteolytic signal. In ruminants, interferon tau (IFNτ) is considered as the embryonic antiluteolytic signal at the time of maternal recognition of pregnancy (MRP). Endometrial prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is considered as the luteolytic hormone and PGE_2 is thought to play an opposite role in establishment of pregnancy as temporary luteotrophic signal and/or immunomodulator. The actions of $PGF_{2\alpha}$ and PGE_2 are mediated through G protein-coupled receptors FP, EP1, EP2, EP3 and EP4. FP and EP1 are contractile receptors, EP2 and EP4 are relaxant receptors and EP3 is an inhibitory receptor. The objectives of the present study were to evaluate the expression and modulation of $PGF_{2\alpha}$ (FP) and PGE_2 (EP2, EP3 and EP4) receptors in endometrium and myometrium during the "critical period" in cyclical and IFNt treated animals. Beef heifers (19 $\pm$1 cycle length) were used in this study. Estrus was synchronized using double PG regimen (500 μg cloprostenol, Estrumate®) at 11 days apart. Then, animals were observed for one regular estrous cycle and the day of estrus was considered as day 0. Treatments were started on day 15 (6 pm) of the estrous cycle. Control group (n=4) received 4 doses of 0.5% BSA (5 ml /dose) and IFN group (n=4) received 4 doses of recombinant ovine interferon tau (roIFNt) (0.25 mg /dose-5 ml) intra-uterine at 12 h intervals. On day 17 of the estrous cycle (2 pm) all animals were slaughtered and uteri were collected. Uterine horns ipsi-and contra lateral to the corpus luteum were identified and endometrium and myometrium were separated. Total RNA was extracted using TRIzol. Expression of FP, EP2, EP3 and EP4 mRNA was studied by RT-PCR/Southern blotting. In control, FP and EP3 were undetectable in endometrium but expressed in myometrium, EP2 was expressed in both endometrium and myometrium and EP4 was undetectable in either endometrium or myometrium. In IFNτ group, the level of expression of FP, EP2 and EP3 were higher than those of control group in both endometrium and myometrium. In endometrium, absence of FP in control and presence in IFNτ treated animals suggest that $PGF_{2\alpha}$ regulates its own receptor. Presence of FP in myometrium of both control and IFNτ treated animals indicates that myometrium is a target site for $PGF_{2\alpha}$, besides corpus luteum, to effect uterine contractility and thus early embryonic loss and /or return to new estrous cycle. Presence of EP2 in endometrium of control and IFNτ treated animals militates in favor of a role for PGE_2 at the maternal-fetal interface at MRP. Presence of EP2 and EP3 in myometrium suggests the role of PGE_2 in uterine quiescence, uterine receptivity and establishment of pregnancy. Collectively, these results indicate that IFNτ exerts dynamic regulation of $PGF_{2\alpha}$ and PGE_2 receptors in uterus at MRP. Furthermore, treatments targeting $PGF_{2\alpha}$ and PGE_2 receptors might be a useful therapeutic tool in future to reduce early embryonic mortality or to improve the conception rate in bovine.

Key words: FP, EP2, EP3, EP4, Interferon Tau, MRP, Bovine.