An insight into maternal recognition of pregnancy in mammalian species

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Abstract Pregnancy loss especially at the early state of gestation is a major cause of infertility in both human and animal species. This has been attributed to the impaired interaction between the maternal endometrium and the developing embryo and/or inadequate hormonal support for the pregnancy continuation. Progesterone is the hormone of pregnancy and is essential for establishment and sustainance of pregnancy in most mammals. It is principally produced by the corpus luteum which undergoes regression mostly due to luteolytic action of prostaglandins F_2alpha at certain period of the oestrous cycle. Maternal recognition of pregnancy (MRP) is the phenomenon through which luteolysis of corpus luteum is abrogated for continuous production of progesterone in a conceptive cycle and is achieved by different agents in different mammalian species. It is interferon tau in ruminant, oestrogen in pig, while it is human chorionic gonadotropin in human. In mare, the MRP agent remains ambiguous and was speculated to be some protein and prostaglandins E_2. It is the purpose of this review to highlight the MRP signals in domestic mammals with emphasis on ruminant while discussing their mechanisms of action. Given the importance of progesterone in supporting pregnancy in all mammalian species, understanding the physiology of these mechanisms through which luteolysis is nullified will aid approaches necessary to correct pregnancy loss associated with defective MRP in one hand and may also lead to developing a novel contraceptive on the other hand.

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1. Introduction

Pregnancy loss during the early stage of gestation has been recognised as one of the major causes of infertility in cattle and other ruminants (Diskin and Morris, 2008). This has been attributed to impaired communication between the blastocyst and the maternal endometrium, and insufficient hormonal support (Dey et al., 2004). Progesterone otherwise known as hormone of pregnancy is essential for establishment and sustainance of pregnancy in all mammals. Its roles in (i) promoting uterine secretion for conceptus growth and development, (ii) initiating window of receptivity, (iii) inducing quiescence and non-contractility of myometrium to avoid abortion and (iv) protection of embryo against maternal immunosystem (Bazer, 1975; Lewis, 2003; Soloff et al., 2011) during pregnancy are beyond the scope of this review.

Progesterone is produced principally by the corpus luteum (CL) which undergoes regression at a certain period of reproductive cycle (Noakes et al., 2009) usually due to luteolytic action of prostaglandins F2 alpha (PGF2α). As pregnancy advances, the placenta also commences to produce progesterone using the maternal cholesterol. In some species such as sow, goat and camel, CL is required throughout the period of gestation because placenta cannot produce enough to sustain the pregnancy (Table 1). On the other hand, at certain period of gestation such as about 50 and 210 days in sheep and cow respectively, regression of CL will not cause pregnancy loss because placenta is capable of producing sufficient progesterone (Senger, 2005).

For obvious ethical reason, our understanding on the mechanism underlying pregnancy processes and events in human is far from being complete (Aplin et al., 2008). Certainly, most of the acknowledged concepts on these subjects are based on animal models especially mouse. Studies of implantation particularly in sheep have contributed immensely towards understanding the molecular mechanisms underlying implantation generally in mammalian species (Lee and DeMayo, 2004; Spencer et al., 2004) because of a number of reasons peculiar to pregnancy in this species. Firstly, the protracted peri-implantation period in sheep of about 15 days (Spencer et al., 2004) unlike 4 days in mouse that has made it suitable to understand the mechanism of event during early gestation. Secondly the superficial mode of implantation in this species that also enables better elucidation of the mechanism involved, since the micro-architectural transformations undergone by the endometrial luminal epithelia (LE) and trophoblast during the implantation process are retained and can be studied in detail unlike in mouse where this is erased due to haemochorial placentation (Senger, 2005).

In a conceptive cycle, there is a need for continued production of progesterone through abrogation of luteolytic mechanism. The phenomenon through which this is achieved is known as maternal recognition of pregnancy (MRP). It is accomplished by different agents in different mammalian species (Table 1). The agent of MRP in ruminants is interferon tau (IFNτ). It is human chorionic gonadotropin (hCG) in humans and oestrogen (E2) in pigs, while that of mare remains subject of speculation. It is the purpose of this review to highlight MRP signals in domestic mammals and human as well as discussing their mechanism of paracrine ‘luteostatic’ actions with emphasis on ruminants.

Table 1  Time of production and agents of maternal recognition of pregnancy (MRP) in mammals.

<table>
<thead>
<tr>
<th>Species</th>
<th>Gestation length (days)</th>
<th>Placental takeover (days)</th>
<th>Agent of MRP</th>
<th>Day of production</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewe</td>
<td>150</td>
<td>50</td>
<td>oIFNτ</td>
<td>9/10–21</td>
<td>Flint et al. (1994)</td>
</tr>
<tr>
<td>Cow</td>
<td>270</td>
<td>180–240</td>
<td>bIFNτ</td>
<td>12–38</td>
<td>Flint et al. (1994)</td>
</tr>
<tr>
<td>Sow</td>
<td>114</td>
<td>11–30</td>
<td>Oestradiol</td>
<td>11–30</td>
<td>Geisert et al. (1990)</td>
</tr>
<tr>
<td>Human</td>
<td>270</td>
<td>60–70</td>
<td>hCG</td>
<td>11</td>
<td>Ticconi et al. (2007)</td>
</tr>
<tr>
<td>Mare</td>
<td>330</td>
<td>70</td>
<td>Proteins/oestrogen?</td>
<td>14–16; 15–30</td>
<td>Ziecik et al. (2011)</td>
</tr>
<tr>
<td>Dog, cat</td>
<td>60</td>
<td>–</td>
<td>None</td>
<td>–</td>
<td>Pineda and Dooley (2003)</td>
</tr>
</tbody>
</table>

Legend: MRP, maternal recognition of pregnancy; oIFNτ, ovine interferon tau; bIFNτ, bovine interferon tau; hCG, human chorionic gonadotropin.
2. Agents of MRP

2.1. MRP in ruminant

The MRP in ruminant is IFN\(\tau\). IFN\(\tau\) acts on the endometrium in a paracrine manner to prevent luteolysis, thereby maintaining the CL and production of progesterone (Roberts, 1989b). Originally, it was known as ovine trophoblast protein in sheep and bovine trophoblast protein in cattle, the name interferon tau was given to it by International Interferon Society. There are different types of IFN and IFN\(\tau\) is unique to ruminants (see review Roberts et al., 2008). IFN\(\tau\) is a Type I interferon with potential antiviral, antiproliferative and some immunomodulatory biological activities (Roberts, 1989a). This implies that apart from being the signal for MRP, IFN\(\tau\) plays other roles in early pregnancy in ruminants. These include protection of the conceptus or uterus against viral infection and modulating the maternal immune response towards tolerating the apparently foetal ‘semiallograft’.

The transfer of trophoblastic vesicles into cyclic ewes culminates into maintenance of the CL (Martal et al., 1979). Therefore, IFN\(\tau\) originates from the conceptus and not the endometrium. In sheep, secretion of IFN\(\tau\) is observed from days 10 to day 21 (day 0 = mating) with maximum levels between days 16 and 18. Likely by days 22–23, the synthesis of IFN\(\tau\) has ceased (Martal et al., 1979). The size of the blastocyst is a factor that determines the amount of IFN\(\tau\) produced which may necessarily not tally with the quantity of IFN\(\tau\) mRNA expressed by the blastocyst. This phenomenon was observed in cow (Robinson et al., 2006). Ovine embryos in vitro do not expand after hatching, however, they were reported to produce a small amount of IFN\(\tau\). In a related study, embryo harvested on day 8 of gestation produced 11 ± 3 ng/ml of IFN\(\tau\) into the culture media after 24 h of culture (Lo and Summers, 2002).

IFN\(\tau\) injection on days 11–15 post-oestrus decreased concentrations of oestrogen and progesterone receptors (PGR) in sheep endometrium on day 16 when compared with serum protein-infused control ewes, whose corpora luteal were undergoing regression on days 14–16 (Mirando et al., 1993).

What is the mechanism of action of IFN\(\tau\)? There are many schools of thought as regards the mechanisms of action of IFN\(\tau\). One common ground to the various opinions is that oxytocin (OT) is responsible for episodic release of PGF\(_{2\alpha}\) from the endometrium and this requires OT coupling with its receptor (OTR). One school of thought posits IFN\(\tau\) action on inhibition of oestrogen receptor (ER) expression, which in turn, abrogates OTR expression on the LE (Spencer et al., 1995). Whether in pregnant or cycling ewe, downregulation of progesterone receptor (PGR) will occur on day 11 in the LE and day 13 on the superficial glandular epithelia (GE). However, in a pregnant ewe, progesterone action in the endometrium is mediated via the stroma that expresses PGR positive during this period and 0 throughout the period of gestation (Wathes and Hamon, 1993). IFN\(\tau\) acts locally in a paracrine manner to suppress the expression of ER on the LE and superficial GE (Spencer et al., 1995). This in turn forestalls the formation of OTR on these endometrial epithelia. The consequence is that the endometrium fails to produce the luteolytic agent PGF\(_{2\alpha}\) because of failure of OT to couple with OTR which is essential for PGF\(_{2\alpha}\) synthesis (Fig. 1). Therefore, luteolysis does not occur and CL is sustained for continuous production of progesterone. Progesterone has a negative feedback on ER, whereas oestrogen has a positive feedback on OTR and PGR. This implies that downregulation of PGR in the epithelia is required for expression of ER genes, while ER is required for OTR upregulation.

Recent findings have disproved the above Spencer’s hypothesis that ER regulates OTR expression. According to Robinson et al. (2008), IFN\(\tau\) is capable of causing downregulation of OTR and hence attenuation of OT-induced PGF\(_{2\alpha}\) production without prior inhibition of ER. It remains debatable if ER is required for OTR up-regulation and which one precedes the other in the endometrial LE as soon as downregulation of PGR occurs (Spencer et al., 1998 vs Wathes and Hamon, 1993; Robinson et al., 2001). ER may stimulate OTR expression but is not essentially required for OTR upregulation. This hypothesis is supported by the spontaneous upregulation of OTR in bovine luminal epithelial cells in vitro in the absence of oestradiol (Leung and Wathes, 2000).

A third school of thought posits that the action of IFN\(\tau\) is based on alteration in the ratio of PGE\(_2\):PGF\(_{2\alpha}\) expression in the endometrium in favour of PGE\(_2\), which unlike PGF\(_{2\alpha}\), is known to be luteotrophic. It is believed that the endometrium produces PGF\(_{2\alpha}\) even during pregnancy but at a very low and insufficient rate to cause luteolysis. In bovine, IFN\(\tau\) causes downregulation of OTR as well as cyclooxygenase 2 (COX-2) expression and hence, reduced expression of PGF\(_{2\alpha}\) synthase (Xiao et al., 1999) because COX-2 is a rate limiting enzyme that determines the synthesis of PGF synthase, while the latter is responsible for the synthesis of PGF\(_{2\alpha}\). The final outcome is reduced expression of PGF\(_{2\alpha}\). On the contrary, Parent et al. (2002) reported reduced OTR expression as well as increased expression of COX-2 but simultaneous increased expression of PGE\(_2\) in bovine endometrial cells in vitro treated with IFN\(\tau\).

Figure 1 Proposed mechanism of action of Interferon tau abrogating luteolysis in ruminant.
In spite of the variation in COX-2 expression in these reports, it is certain the ratio of PGE2:PGF2α is in favour of PGE2. The luteotrophic action of PGE2 overrides the luteolytic tendency of PGF2α and finally, luteolysis fails to occur.

In human, MRP is the luteotrophic hCG. IFNα, unlike human hCG has no effect on PGR expression in the endometrial epithelia. Downregulation of PGR at the time of implantation is required for the expression of genes and transport of histotroph from the GE into the uterine lumen across all mammalian species. Endometrial expression of OTR is regulated by ER and PGR (Wathes and Lamming, 1995). PGR expression in the endometrial epithelia in a cycling and pregnant ewes do not differ between days 2 and 12, however, pregnant ewes do not show the general increased ER staining associated with luteolysis on days 14–1 of oestrous cycle (Wathes and Hamon, 1993). Certainly, it is erroneous to think that IFNα increases expression of PGR when there is convincing evidence that suggests otherwise (Mirando et al., 1993). It can be concluded that it is important for the endometrium to be exposed to IFNα before upregulation of OTR in a concepcive cycle, otherwise, it might be too late for luteolysis to be abolished.

2.2. MRP in sows

In sow, the MRP signal is oestrogen. For the pregnancy to be sustained by the action of oestrogen, at least two embryos, one in each of the uterine horns are required. Otherwise, the horn with no embryos will still produce PGF2α and this will initiate embryo loss (Senger, 2005). Pig conceptus produces oestrogen on day 14 and 18 as agent of MRP (Geisert et al., 1990). The oestrogen redirects the PGF2α synthesis towards the endometrial lumen (exocrine) rather than diffusing into the blood (endocrine) (Bazer, 2013). Therefore, PGF2α, produced by the endometrium fails to get to the ovary to cause luteolysis. In the endometrial lumen, PGF2α is metabolised and/or speculated to cause (local) contraction in the lumen. The latter is envisaged to aid even distribution of the embryos (being multiparous) within the available space in the uterus.

2.3. MRP in mare

In mares, the agent of MRP remains a mystery and yet to be clarified (Klein and Troedsson, 2011). Some scholars believe MRP in mare involves some glycoproteins, oestrogen and PGE2 even though these could not be substantiated (Klein and Troedsson, 2011). The study of Wilsher and Allen (2011) disproved oestrogen from being a likely agent for MRP in mares. Instead, administration of fractionated coconut or peanut oil on Day 10 postovulation provides an effective and practical method of extending luteal life span. What is certain in this species is the need for movement of the embryo from one horn to another (McDowell et al., 1988; Sharp et al., 1989). This movement is accomplished by simple peristalsis within the endometrium and the bi-partite shape of the mare uterus seems a physiological facilitator of this movement. The simulation of embryo movement from one horn to the other using a bead or ball procrastinates luteolysis and extends CL longevity (Rivera del alamo et al., 2008). Both conceptus and endometrium synthesised PGE2 during early pregnancy (Boerboom et al., 2004). It was then proposed that PGE2 by antagonising the luteolytic effect of PGF2α is the MRP in this species. This speculation was further corrobated by the study of Ealy et al. (2010). The presence of conceptus on day 15 pregnancy blocked the induction of COX-2, that determines the synthesis of PGs. Sequel to this is reduced expression of PGF2α and abrogation of luteolysis (Boerboom et al., 2004). This evidence remains to be clarified.

Unlike ruminant, horse conceptus or the uterine flushing on days 13–15 gestation failed to show antiviral activities of interferon (Sharp et al., 1989). Rather, the study of Herrler et al. (2000) confirmed the insulin growth factor 1 (IGF-I) binding activity and several IGF binding proteins in the pre-implantation equine conceptus. These are hypothesised to be essentially required to enhance embry development and so, indirectly partake in MRP.

2.4. MRP in dogs and cats

In dogs and cats, there is dearth of information on MRP or early pregnancy factor like on other species (Cavanagh, 1997; Lash and Legge, 1997). This may be attributed to the fact that MRP is not required for sustainance of pregnancy in these species. Whether is a concepcive or nonconcepcive, CL is retained for the same period of time (about 60 days). This culminates into exhibition of pseudo-pregnancy (Senger, 2005).

2.5. MRP in human

In human, the luteolytic agent is also PGF2α which is produced by the ovary instead of the endometrium in ruminant and pig (Aplin et al., 2008). The signal for MRP is hCG (Ross, 1978). hCG is luteotrophic and is produced by the blastocyst on days 4–5 as soon as the embryo descends from the oviduct into the endometrium. The mechanism of hCG inducing MRP in human is beyond the scope of this review but has been reviewed elsewhere (Tecconi et al., 2007). This explains the reason why detection of hCG in the serum/urine has been used as one of the earliest pregnancy diagnosis in woman (Johnson et al., 2009).

3. Conclusion

The communication between the conceptus and the maternal endometrium in the form of MRP is very crucial for pregnancy establishment and subsequent events such as luteostasis, apposition, adhesion and attachment that lay the foundation for blastocyst implantation and then placenta. Mamo et al. (2012) in their study captured this relationship with the phrase, ‘conceptus-endometrial cross talk’. One of the primary objectives of MRP is to abrogate luteolysis. Luteolysis is an important mechanism in female reproductive function. During the late luteal phase, there is a need for luteolysis to occur otherwise the animal will not return back to oestrus primarily due to inhibition of progesterone on the gonadotropins. In concepcive cycle, luteostasis which is achieved by the paracrine action of MRP agent(s) is crucial for continued production of progesterone. Understanding the physiology of the mechanisms underlying luteolysis and luteostasis is important for their therapeutic manipulation to either improve fertility or develop a novel contraceptive, that

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References


The essence of maternal recognition of pregnancy is to prevent luteolysis and sustained CL production of P allows that is essentially required for establishment and maintenance of pregnancy. The luteolytic agent in ruminants is PGF2α which is produced by the endometrium and requires OT coupling with its receptor, OTR on the endometrial LE. During pregnancy, IFNα is produced by the filamentous blastocyst (Bl) after binding to its receptor, IFNAR abrogates luteolytic action of PGF2α through one of the following mechanisms: (i) Inhibition of ER which in turn abrogates expression of OTR, leading to failure of OT-induced synthesis of PGF2α, (ii) IFN directly inhibits expression of OTR, and hence failure of OT to couple with OTR leads to abrogation of PGF2α synthesis from the endometrium, (iii) IFNα causes upregulation of COX-2 and PGE2 synthase which produces PGE2, that is luteotropic. Legends; AP; anterior pituitary, PP; posterior pituitary, CL; corpus luteum, OT; oxytocin, OTR; oxytocin receptor, Pα; progesterone, PGR; progesterone receptor, ER; oestrogen receptor, LE; luminal epithelia, PGF2α; prostaglandin F alpha; IFNα; Interferon tau, IFNAR; Interferon tau receptor, COX-2; cyclooxygenase, inhibition, stimulation. Inspired by (1) (Spencer et al. (1995), 2: Robinson et al. (2001), 3: Parent et al. (2002)/Xian et al. (1999).

Conflict of interest

The authors declare that there are no conflicts of interest.


