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A mathematical model of pregnancy recognition in mammals

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ABSTRACT

In this paper we develop a mathematical model of the luteal phase of the reproductive cycle in mammals with the aim to generate a systems understanding of pregnancy recognition. Pregnancy recognition is initiated by the production of interferon tau (IFNτ) by the growing conceptus. This ensures that the maternal corpus luteum (CL) remains viable to secrete progesterone, which is critical for providing a uterine microenvironment suitable for embryonic growth. Our mathematical model describes the interactions among the CL, the reproductive hormones and the hormone receptors in the uterus. It also characterises the complex interactions amongst the uterine oestrogen, progesterone and oxytocin receptors that control the sensitivity of the uterus to oestrogen, progesterone and oxytocin, respectively. The model is represented by a dynamical system and exhibits qualitative features consistent with the known experimental results in sheep. A key factor identified was a time-dependent threshold for the IFNτ signal below which the presence of the embryo might not be recognised and thus pregnancy would likely fail. Furthermore, the model indicated that if the IFNτ signal is later than around day 13 of the cycle, then pregnancy will not be recognised irrespective of the IFNτ concentration. The thresholds in the concentration and time of the IFNτ signal is a screening mechanism whereby only embryos of sufficient quality are able to prevent luteolysis (i.e. regression of the CL). The effect of progesterone secretion rate from the CL on pregnancy recognition was investigated. The model suggests that if the secretion rate is low then the initiation of the IFNτ signal is delayed, which in turn compromises the likelihood of a pregnancy being recognised by the CL. Furthermore, pregnancy recognition does not occur below a critical threshold in the progesterone secretion rate. In summary, the model can be used to identify the most favourable conditions for pregnancy recognition.

1. Introduction

Successful pregnancies in mammals require a precise sequence of endocrine and paracrine events to occur in the reproductive system. In particular, a successful pregnancy requires that a healthy oocyte is released at ovulation, is fertilised in a timely manner and that the embryo survives its intrauterine environment. Embryo survival is dependent on genetic, physiological and/or environmental factors such as nutrition, energy balance and hormones. In humans, around 30% of conceived pregnancies will proceed to live birth (Macklon et al., 2002). Evidence suggests that pre-clinical pregnancy loss (predominantly during preimplantation and the first week of implantation) is one of the major underlying causes for low fertility in humans (Macklon et al., 2002). In domestic animals a loss in fertility is one of the major issues for dairy cows (Diskin et al., 2006), which have been selected for milk production. Only around 40% of conceived pregnancies will proceed to live birth in dairy cows and a significant component of this is attributed to early embryo loss (Diskin et al., 2006). While fertilisation rates are around 90% (Sreenan and Diskin, 1983), one-third of embryos fail to survive the first 18 days of pregnancy (Sreenan and Diskin, 1983; Dunne et al., 2000). Reproductive losses in dairy cows due to early embryo death are therefore 3–4 times larger than losses due to fertilisation failure (Diskin et al., 2006). In sheep, between 20% and 40% of eggs shed at the time of mating do not proceed to live birth and the majority of these losses occur by day 18 of pregnancy (Ashworth, 1995). Fertilisation rate in sheep is normally near 100% (Diskin and Morris, 2008) and therefore early embryo loss is a significant component of reproductive failure in sheep. The causes of early embryo loss are only partly known although it involves an intricate interplay between reproduction, milk yield, nutrition, genetics and the environment.

A better understanding of the biological processes underlying the establishment of pregnancy can benefit assisted reproduction technologies and the management of breeding farm animals. During the last two decades, mathematical modelling has become a useful tool to compliment experimental studies in reproduction

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biology. There are several mathematical models of hormonal dynamics related to the growth of ovarian follicles in ruminants and humans (Blanc et al., 2001; Soboleva et al., 2004; Selgrade et al., 2009). Although these models address events during the follicular phase of the oestrous cycle, there are no models that address the hormone regulation of the luteal phase through to either a pregnancy or luteolysis (degradation of the corpus luteum (CL)) if fertilisation does not occur. Hormonal events during the luteal phase of the cycle prepare the endometrium for an anticipated arrival of an embryo if fertilisation is successful. A key factor in early embryo survival and implantation is a signalling process between the uterus and CL leading to pregnancy recognition. In the present paper, we use mathematical modelling and computer simulation to investigate the processes that immediately precede pregnancy recognition or luteolysis in mammals. In particular, our mathematical model describes the hormonal regulation of pregnancy recognition in sheep, which is often used as a model system for human reproduction and has a physiology that closely reflects that of mammals with a low ovulation rate phenotype.

2. A model of pregnancy recognition

Sheep are spontaneous ovulators that maintain regular 17-day oestrous cycles until the initiation of pregnancy (Spencer et al., 2004). A schematic diagram of the main components and interactions responsible for maintaining these oestrous cycles is depicted in Fig. 1. The progression of the oestrous cycles depends on the pituitary and ovarian hormones as well as the function of the uterus, which produces prostaglandin F2 alpha (PGF2α) that induces regression of the CL. In sheep PGF2α is synthesized by the endometrial luminal epithelium (LE) following CL-derived oxytocin (OX) binding to uterine oxytocin receptors (OR). Oxytocin is produced by the CL as a result of PGF2α binding to PGF2α receptors (PGFR). Thus, CL regression is triggered by a positive feedback loop between the CL and LE, which is initiated by increases in OR levels during the late luteal–early follicular phase. The OR levels are regulated by the actions of oestradiol acting via the uterine oestrogen receptor (ER). The source of the oestradiol is the developing ovarian follicles and this steroid is delivered to the uterus via the countercurrent transport mechanism from the ovarian vein to the uterine artery. Although sheep can have multiple ovulations, we assume for simplicity in this paper that a single ovulation takes place.

Progesterone acting via uterine progesterone receptors (PR) can also downregulate ERs (McCracken et al., 1999). Activated PR negatively regulates PR expression by decreasing PR gene transcription. The PR levels at oestrus (day 0) are regulated by oestradiol and the subsequent changes in PR are regulated by the circulating concentrations of CL-derived progesterone (P). After ovulation the CL increases in size during the early-mid luteal phase before undergoing regression as a consequence of the luteolytic PGF2α signal, if fertilisation and implantation do not occur.

After fertilisation, the early embryo produces interferon tau (IFNτ) that prevents the synthesis and release of PGF2α from the uterus (Ealy and Yang, 2009). This ensures that the CL continues to function and produces progesterone, which is critical for generating an environment suitable for embryonic growth.

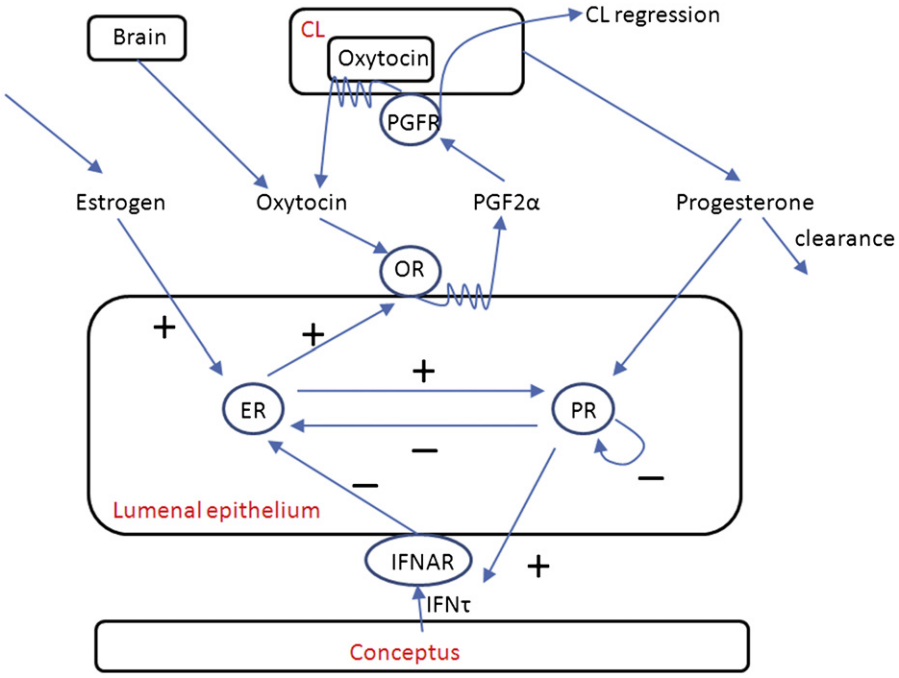

Fig. 1. Schematic diagram of the main components and interactions responsible for maintaining oestrous cycles and the maternal recognition of pregnancy. The oestrous cycles are dependent on the uterus, which produces luteolytic prostaglandin F2 alpha (PGF2α) that induces regression of the ovarian corpus luteum (CL). In sheep PGF2α is synthesized by the endometrial luminal epithelium (LE) as a result of oxytocin (OX) binding to OX receptors (OR). OX is produced by the CL as a result of PGF2α binding to PGF2α receptors (PGFR) and in small quantities by the brain. CL regression is triggered by a positive feedback loop between the CL and LE, which is initiated by an increase in OR levels late in the oestrous cycle. The OR levels are regulated by the oestrogen receptor (ER), which is in turn regulated by the levels of the oestrogen (*E*) and progesterone receptor (PR). Oestrogen is synthesized by the ovarian follicles and is transported via circulation to the uterus. Progesterone receptors also downregulate ERs and activated PR negatively autoregulates PR expression via a decrease in PR gene transcription. The PR level at oestrus (day 0) is regulated by oestrogen and the PR dynamics are in turn regulated by progesterone (*P*) in the uterus. Progesterone is synthesized by the growing CL and is rapidly removed from circulation predominantly by the liver. The CL increases in size over a cycle before rapidly regressing due to the luteolytic PGF2α signal. The conceptus produces interferon tau (IFNτ) to prevent the production of the luteolytic signal from the uterus. The anti-luteolytic action of IFNτ is mediated by the interferon tau receptor (IFNAR), which generates a signal to suppress ER expression. Progesterone is also able to modify the time and intensity of the IFNτ signal.