



Review

Progesterone and reproduction in marsupials: A review

Felicity J. Bradshaw*, Don Bradshaw

School of Animal Biology M092 and Centre for Native Animal Research, The University of Western Australia, Perth, Western Australia 6009, Australia

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ABSTRACT

Progesterone (P4) profiles throughout pregnancy and the oestrous cycle are reviewed in a wide range of marsupial species, representing 12 Families, and focus on the *corpus luteum* (CL) and its functioning, compared with its eutherian counterpart. Physiologically, P4 subtends the same fundamental processes supporting gestation in marsupials as it does in eutherian mammals, from its role in stimulating the secretory endometrium, effecting nutritional transfer across the placenta and establishing lactogenesis. Before the formation of the CL, however, secretion of P4 is widespread throughout many Families and the dual roles of P4 in the induction of sexual behaviour and ovulation are exposed. In Dasyuridae, raised levels of P4 are linked with the induction of sexual receptivity and are also present around the time of mating in Burramyidae, Petauridae and Tarsipedidae, but their function is unknown. Only in Didelphidae has research established that the pheromonally-induced levels of pro-oestrous P4 trigger ovulation. This is principally the role of oestradiol in the eutherian and may be an important difference between the marsupial and the eutherian. The deposition of the shell coat around the early marsupial embryo is also a function of P4, but perhaps the most striking difference is seen in the time taken to form the CL. This is not always immediate and the maximum secretion of P4 from the granulosa cells may not occur until some 2 weeks after ovulation. The slower development of the CL in some species is linked with delays in the development of the embryo during its unattached phase and results in relatively long gestation periods. A common feature of these, in monovular species, is a short pulse of P4 from the newly-luteinised CL, which is all that is needed for the subsequent development of the embryo to term. Maternal recognition of pregnancy occurs soon after the formation of the blastocyst, with embryo-induced changes in ovarian production of P4 and the uterine endometrium. The embryo, similar to the eutherian, determines the length of the gestation period and initiates its own birth, but in direct contrast, the embryo of some marsupial species shortens the life-span of the CL. The evidence points to a different strategy; one of a reduction, rather than an expansion of the potential ovarian and placental support available during pregnancy. The marsupial mode of reproduction, where all species produce highly altricial young, receiving complex and extensive maternal care, has facilitated the adaptive radiation of this group and avoided the need for precociality.

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1. Introduction

A number of wide-ranging research programmes during the past twenty years has served to rehabilitate Australian marsupials from their former classification as 'inferior' or 'second-class' mammals and most biologists now accept their unique reproductive strategy as a valid alternative to that of the more widespread Eutheria (Kirsch, 1977; Low, 1978; Parker, 1977; Renfree, 1981; Renfree, 1993). The ubiquitous and uniform production of embryonic young throughout the Marsupialia (Fig. 1), however, is a startling feature of their mode of reproduction and is one that has, to date, eluded any convincing adaptationist interpretation (Tyndale-Biscoe, 2001; Tyndale-Biscoe and Renfree, 1987).

Attention has been drawn to the 'reptilian-like' features of early egg development, the short gestation periods, the preponderance of choriovitelline placentation, and an apparent lack of maternal recognition of pregnancy, in that the life span of the *corpus luteum* (CL) is not prolonged by the presence of an embryo. It was tempting to assume that there was hormonal equivalence between the pregnant and non-pregnant cycles (Sharman, 1970), the corollary of which, was the apparent incapacity of the marsupial placenta to secrete progesterone (P4). In some areas the suspicion still lingers that marsupials share a primitive mode of reproduction (Lowry, 2003), one that exerts a continuing phylogenetic constraint on their evolutionary potential (Lillegraven, 1975). In particular, it has been suggested that the basis for the metatherian-eutherian dichotomy stems from the apparent placental difference between the two groups, and that "...one of the essential changes that prolonged intrauterine gestation in the Eutheria was the evolution of

* Corresponding author. Fax: +61 8 6488 1029.

E-mail address: felicity.bradshaw@aapt.net.au (F.J. Bradshaw).



Fig. 1. Newborn joey of the quokka, *Setonix brachyurus*, less than 1 week-old, with a crown-to-rump measurement of 11 mm.

the responsiveness of the uterus to the progesterone secreted by the corpus luteum.” (Rothchild, 1981).

Progesterone, to date, has been measured throughout the reproductive phases of some 30 species of marsupial (Table 1). Although only a small fraction of the 210 extant species, it is perhaps an appropriate time to assess the significance of P4 in the seemingly parsimonious reproductive effort of the marsupial. This article will review P4 in all its roles throughout reproduction, and, where available, include: (i) the induction of oestrus and ovulation, (ii) establishment of the luteal phase, (iii) its profile of secretion throughout the reproductive cycle, (iv) its association with the rate of embryonic development, (v) in the initiation of parturition, (vi) the establishment of lactation, and (vii) evidence for maternal recognition of pregnancy.

We will suggest that all the basic physiological mechanisms that allow for the extended form of viviparity in the eutherian mammal can be accounted for in marsupials and that the marsupial’s minimalist approach to the production of their neonate is the result of a reproductive strategy underpinned by their extensive level of maternal care.

2. The luteal uterus

More than 100 years ago, Sandes (1903) identified the marsupial CL in the ovaries of the eastern quoll, *Dasyurus viverrinus*, and described it as ‘... a glandular structure with an internal secretion...’ that prevented ovulation during pregnancy. Studies in other marsupial species noted the origin of the glandular, luteinised cells as the *membrana granulosa* by both hyperplasia and hypertrophy (O’Donoghue, 1916) and their close association with a glandular uterus was first recorded (Hill, 1910; Hill and O’Donoghue, 1913). It was not until some 50 years later, that P4 was implicated when injections of the hormone into ovariectomised quokkas, *Setonix brachyurus*, not only increased glandular development (Waring et al., 1955) but also transformed the uterine endometrial cells from their cuboidal shape, with a central nucleus, to columnar with a small basally-situated nucleus, characteristic of a secretory cell (Sharman, 1955a; Waring et al., 1955). The concept of a luteal uterus in the marsupial was established.

2.1. The corpus luteum as origin

The first indirect evidence was obtained from the brushtail possum, *Trichosurus vulpecula*, in which pregnanediol, a urinary

metabolite of P4, reached maximal levels during the luteal phase (Pilton and Sharman, 1962) and the concentration of P4 in venous blood draining the ovary containing the active CL was raised during the luteal phase (Thorburn et al., 1971).

Investigating the ovary as the source of P4, gas chromatography identified the presence of P4 in ovarian tissue of the red kangaroo, *Macropus rufus* (Lindner and Sharman, 1966) and incubations of the luteinised ovary of the Virginia opossum, *Didelphis virginiana*, with radioactively-labelled cholesterol and pregnenolone demonstrated synthesis of P4 (Cook and Nalbandov, 1968). In addition, its synthesis was enhanced by ovine luteinising hormone (LH), thereby establishing its steroidogenic role in the marsupial. Active secretion from luteinised cells was identified from ultrastructural examination of ovaries of the brushtail possum, which correlated with levels of P4 during the life-span of the CL (Shorey and Hughes, 1973a; Shorey and Hughes, 1973b). In two other species, the red-necked wallaby, *Macropus rufogriseus banksianus*, (Walker et al., 1983) and the northern brown bandicoot, *Isodon macrourus* (Gemmell, 1979), the appearance of densely-staining granules in the CL, typical of P4 secretion in eutherian mammals (Gemmell and Stacy, 1979), was also associated with raised levels of circulating P4.

An incubation experiment in the tammar wallaby, *Macropus eugenii*, confirmed the CL as the origin when luteal tissue, incubated alone, synthesised P4 from the precursor, pregnenolone (Renfree et al., 1984; Renfree and Heap, 1977). Again in the tammar, the concentration of P4 that was extracted from CL throughout pregnancy showed a direct correlation with the mass and stage of development of the CL (Renfree et al., 1979). Finally, *in vitro* secretion of P4 by luteal tissue was demonstrated in both the tammar (Hinds et al., 1983; Kojima et al., 1993) and the quokka (Bradshaw and Bradshaw, 1992). In the quokka, secretion of P4 from the CL was enhanced when the luteal tissue received perfusate from the remaining ovarian tissue, thus demonstrating cooperativity between the CL and the ovarian interstitial tissue (Bradshaw and Bradshaw, 1992).

Further evidence for the steroidogenic capacity of luteal cells has come from more recent work in the brushtail possum by Whale et al. (2003), who isolated ovarian cellular RNA and, using *in situ* hybridisation, identified expression of mRNA for steroidogenic acute regulatory protein, cytochrome P-450 side-chain cleavage enzyme and 3 β -hydroxy-steroid dehydrogenase, as well as P4 receptor mRNA (Haydon et al., 2008), all of which are key factors involved in P4 synthesis (Niswender, 2002; Niswender et al., 2000).

The control over the CL appears to be intrinsic. Once formed, under the influence of LH acting on granulosa cells of the pre-ovulatory follicle (Stewart and Tyndale-Biscoe, 1982), the CL functions autonomously (Hearn, 1973), similar to the unstimulated CL in eutherian mammals (Rothchild, 1981).

2.2. Progesterone as the luteal agent

The intracellular action of P4 as an agent for cellular proliferation (Clarke and Sutherland, 1990) comes from investigations in three marsupial species. High-affinity binding of a synthetic progestin to a uterine cytosolic component was characterised in the quokka (Owen et al., 1982), the brushtail possum (Curlewis and Stone, 1986) and the tammar (Renfree and Blanden, 2000). In the possum, although cytosolic binding decreased by day 5 of the cycle, changes in ratios between RNA and DNA and between protein and DNA in the uterine cells, indicated an increase in cellular metabolic activity, which included secretion, and coincided with high plasma P4 levels (Curlewis and Stone, 1986). Using immuno-histochemistry, P4 receptor (PR) was located in the nuclei of the uterine stromal cells of the possum (Sizemore et al., 2004) and subsequent exposure to P4 stimulated the luteal changes in the endometrium.

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