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Review Article

Luteal regression vs. prepartum luteolysis: Regulatory mechanisms governing canine corpus luteum function☆

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ARTICLE INFO

Article history:
Received 13 May 2013
Accepted 30 November 2013
Available online 21 December 2013

Keywords:
Domestic dog (Canis familiaris)
Corpus luteum function
Pregnant
Non-pregnant

ABSTRACT

Canine reproductive physiology exhibits several unusual features. Among the most interesting of these are the lack of an acute luteolytic mechanism, coinciding with the apparent luteal independency of a uterine luteolysin in absence of pregnancy, contrasting with the acute prepartum luteolysis observed in pregnant animals. These features indicate the existence of mechanisms different from those in other species for regulating the extended luteal regression observed in non-pregnant dogs, and the actively regulated termination of luteal function observed prepartum as a prerequisite for parturition. Nevertheless, the supply of progesterone (P4) depends on corpora lutea (CL) as its primary source in both conditions, resulting in P4 levels that are similar in pregnant and non-pregnant bitches during almost the entire luteal life span prior to the prepartum luteolysis. Consequently, the duration of the prolonged luteal phase in non-pregnant bitches frequently exceeds that of pregnant ones, which is a peculiarity when compared with other domestic animal species. Both LH and prolactin (PRL) are endocrine luteotrophic factors in the dog, the latter being the predominant one. In spite of increased availability of these hormones, luteal regression/luteolysis still takes place. Recently, possible mechanisms regulating the expression and function of PRL receptor have been implicated in the local, i.e., intraluteal regulation of PRL bioavailability and thus its steroidogenic potential. Similar mechanisms may relate to the luteal LH receptor. Most recently, evidence has been provided for an autocrine/paracrine role of prostaglandin E2 (PGE2) as a luteotrophic factor in the canine CL acting at the level of steroidogenic acute regulatory (STAR)-protein mediated supply of steroidogenic substrate, without having a significant impact on the enzymatic activity of the respective steroidogenic enzymes, 3β-hydroxysteroid-dehydrogenase (3βHSD, HSD3B2) and cytochrome P450 side-chain cleavage enzyme (P450scc, CYP11A1). Together with the strongly time-dependent expression of prostaglandin transporter, luteal prostaglandins seem to be involved more in the process of luteal formation than in termination of CL function in the dog. The possible

☆ The material described in this review article was presented as an invited lecture at Ludwig Fraenkel Symposium "Endocrine Control of Corpus Luteum Function" in Wrocław, Poland (5–6 September, 2013).

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http://dx.doi.org/10.1016/j.repbio.2013.11.004

roles of other factors such as vasoactive compounds, growth factors or cytokines have not been extensively studied but should not be neglected.

1. Introduction

As the primary source of progesterone (P4) during pregnancy and the non-pregnant cycle, corpora lutea seem to be key organs regulating the reproductive cycle in dogs. Hence, not surprisingly, the physiological mechanisms regulating CL function have been subjected to increased scientific interest. However, even though expression and/or function of several, mostly luteotrophic, factors have been characterized, overall understanding of canine CL physiology remains poor, especially during its regression. Dogs are highly important in veterinary medicine, have a substantial role as laboratory animals and are also among the most important pets. Taking all of this into account, efforts need to be made to better understand canine reproductive physiology, especially that concerning CL function.

In addition to the lately debate (e.g., [1–6]), here an overview of our current knowledge concerning the endocrine, paracrine and autocrine control of the CL in non-pregnant and pregnant dogs, together with some new, unpublished data recently generated in our laboratory, e.g., concerning the expression of 15-hydroxy prostaglandin dehydrogenase (HPGD) and the LH receptor (LHR), is presented.

2. Luteal life span and patterns of steroid secretion

Among domestic animal species, the domestic dog (*Canis lupus familiaris*) is the only one classified as a predominantly non-seasonal, monoestrus breeder. The sexual cycle is characterized by a long luteal phase (diestrus) and an obligatory sexual quiescence phase between sexually active periods (anestrus), the length of which may depend on the breed [7]. Unlike in livestock, in which cyclicity depends on periodic production and secretion of luteolytic prostaglandin F2α (PGF2α) by the uterus, at least in non-pregnant dogs the luteal function is independent of a uterine luteolysin, because ovarian cyclicity is maintained following hysterectomy [8]. Consequently, also pointing towards inherent control mechanisms, the physiological luteal lifespan is similar in pregnant and non-pregnant bitches.

2.1. *Progesterone*

Following preovulatory luteinization, peripheral progesterone (P4) reaches levels of about 5 ng/ml at the time of ovulation [9]. After ovulation, strongly increasing luteal steroidogenic capacity results in the highest circulating P4 levels 15–25 days, or even up to 30 days after ovulation [8]. Then, a progressive P4 decrease marks the onset of luteal regression, which lasts in non-pregnant dogs as long as 1–3 months, until peripheral P4 levels falling below 1 ng/ml, by definition, indicate the onset of anestrus [9]. The P4 secretion pattern, which is up to that time-point similar in the non-pregnant and pregnant bitch, starts to differ at approximately day 60 of the luteal lifespan, when the circulating P4 concentration falls precipitously in the pregnant animal as a prerequisite for parturition (prepartum luteolysis), therefore rapidly reaching baseline levels.

While individual serum P4 levels vary strongly, the mean values can measurably differ between pregnant and non-pregnant bitches during the entire course of diestrus displaying values that are numerically but not statistically lower in the non-pregnant animals. In one study by Steinetz et al. [10], the mean P4 concentrations in pseudopregnant bitches were only 56% of the concentrations in pregnant females. Nevertheless, mostly due to the above-mentioned high individual variations, measurement of serum P4 is precluded as a means to distinguish between pregnant and non-pregnant dogs.

2.2. *Estrogens*

Because the canine placenta is devoid of steroidogenic activity [11,12], circulating estrogens appear to originate in corpora lutea (CL). This notion has been supported by studying the time-dependent expression of aromatase in canine luteal samples throughout diestrus [1,12]. There is, however, no pregnancy-associated increase in estradiol-17β (E2) production, and similar E2 secretion patterns are observed in both pregnancy and diestrus of non-pregnant dogs until the prepartum drop is observed, as for P4 [11,13]. This prepartum drop in E2 further implicates CL as the major source of estrogens in the dog.

Both E2 and P4 exert autocrine and/or paracrine, presumably luteotrophic, effects on the canine CL, since their respective receptors, i.e., P4 receptor (PGR) and estrogen receptors-alpha and -beta (ERα and ERβ), are expressed locally. This concept is further supported by the observation that interfering with P4 action at the level of PGR, e.g., by application of an antigestagen, results in preterm luteolysis [14,15]. It is possible that, indirectly, estrogens could act by priming PGR and prolactin receptor (PRLR) expression.

2.3. *Cortisol*

The elevated levels of cortisol measured in maternal blood peripartum appear to have erratic nature and seem to be not mandatory for normal parturition [16]. It has also been related to maternal stress [11,16]. On the other hand, as suggested by Concannon and collaborators [16], it is possible that cortisol circulating in maternal blood prepartum merely reflects much larger increases at the feto-placental and uterine levels.