Factors affecting the fate of the canine corpus luteum: Potential contributors to pregnancy and non-pregnancy

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Abstract: The fate of the canine corpus luteum (CL) differs from that of other domestic species: beyond the extended luteal regression observed in both pregnant and non-pregnant cycles, active luteolysis is observed only in pregnant dogs. Luteal regression in the absence of pregnancy lacks a luteolytic trigger. The CL lifespan during pregnancy is around 60 days, as long as that of the cyclic CL. Although they are already available in the first half of diestrus, LH and especially prolactin (PRL) play a decisive luteotropic role from approximately day 25 post-ovulation onwards. Nevertheless, many locally-produced factors are orchestrated to ensure a fully functional CL, which in the bitch produces progesterone (P4), 17b-estradiol, and other local regulators. Recently, insulin has been described as another luteotropic factor in this species, able to increase glucose uptake in luteal cells and contribute to steroid biosynthesis. The locally-produced PGE2 is also a potent luteotropic factor in the first half of diestrus, promoting STAR expression, as are also proliferating, vasoactive- and immunomodulatory factors. These, in turn, all contribute to the formation and maintenance of the canine CL. Meanwhile PGF2a, produced by the utero-placental compartment, participates actively in triggering pre-partum luteolysis. Cytokines play different roles, either contributing as luteotropic or as acute inflammation molecules. So far, the one clinically most efficient mechanism of interrupting a pregnancy in the dog is to block P4 receptors, using an antigestagen (e.g., aglepristone) in the second half of diestrus. To enhance the chances of pregnancy, however, several luteotropic factors could be used.

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ABSTRACT

The fate of the canine corpus luteum (CL) differs from that of other domestic species: beyond the extended luteal regression observed in both pregnant and non-pregnant cycles, active luteolysis is observed only in pregnant dogs. Luteal regression in the absence of pregnancy lacks a luteolytic trigger. The CL lifespan during pregnancy is around 60 days, as long as that of the cyclic CL. Although they are already available in the first half of diestrus, LH and especially prolactin (PRL) play a decisive luteotropic role from approximately day 25 post-ovulation onwards. Nevertheless, many locally-produced factors are orchestrated to ensure a fully functional CL, which in the bitch produces progesterone (P4), 17b-estradiol, and other local regulators. Recently, insulin has been described as another luteotropic factor in this species, able to increase glucose uptake in luteal cells and contribute to steroid biosynthesis. The locally-produced PGE2 is also a potent luteotropic factor in the first half of diestrus, promoting STAR expression, as are also proliferating, vasoactive- and immunomodulatory factors. These, in turn, all contribute to the formation and maintenance of the canine CL. Meanwhile PGF2a, produced by the utero-placental compartment, participates actively in triggering pre-partum luteolysis. Cytokines play different roles, either contributing as luteotropic or as acute inflammation molecules. So far, the one clinically most efficient mechanism of interrupting a pregnancy in the dog is to block P4 receptors, using an anti-gestagen (e.g., aglepristone) in the second half of diestrus. To enhance the chances of pregnancy, however, several luteotropic factors could be used.

1. Introduction

The dog is unique among domestic species with regard to the evolution of reproduction. Cyclic diestrus lasts at least 60 days [1,2], i.e., as long as pregnancy or longer, and the corpus luteum (CL) plays the central role in regulating the estrous cycle and pregnancy. Since the dog placenta is unable to produce steroid hormones [3,4], crucial for successful pregnancy, and the canine CL is the only source of progesterone (P4) and 17b-estradiol (E2) during diestrus [5], the CL should be among the main foci of research in the dog when the aim is to manipulate pregnancy.

Hormones control the CL lifespan, either in an endocrine or paracrine/autocrine way [5–8]. Locally produced growth factors, cytokines and prostaglandins (PGs), modulate CL function, creating a balance leading to luteal regression in non-pregnant dogs or luteolysis in pregnancy (reviewed in Ref. [9]). In pregnant dogs, the trophoblast is the feto-maternal compartment most responsible for PGF2a production [10], which actively participates in pre-partum luteolysis. Aglepristone is a P4 receptor (PGR) blocker, which can be safely used to terminate pregnancy in dogs by evoking pre-term parturition/abortion [11]. Alternative methods are desirable, especially ones related to manipulating cyclicity and avoiding pregnancy. Neutering is a surgical approach, broadly used for control of street dog populations, but is considered very invasive, as well as expensive when applied on a mass scale [12]. On a smaller scale, but still very important for understanding canine pregnancy physiology, pregnancy failures are often observed due to luteal insufficiency [13], which raises the need to develop tools to improve that particular situation.

Regardless of the approach, and before discussing this question, we shall review the major general and local players controlling the CL lifespan in cyclic and pregnant dogs (summarized in Table 1), and then identify possible target mechanisms to increase the chances of pregnancy in the dog or of avoiding it.

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Table 1
Luteotropic factors and those involved in luteolysis or regression of the pregnancy and cyclic canine corpus luteum.

Luteotropic Factors	Pregnancy CL				Cyclic CL			
	Pre-implantation	Post-implantation	Mid gestation	Pre-Partum luteolysis	Formation	Maintenance	Early regression	Late regression
LH LH receptor	1.7 ng/mL increase	1.7 ng/mL until	1.7 ng/mL mid gestation	2.3 ng/mL =	1.5 ng/mL ↑	1.5 ng/mL ↑	1.5 ng/mL ↓	1.7 ng/mL =
Prolactin-PRL PRL receptor	constant constant	increase expression	until until	50 ng/mL ↓	2–4 ng/mL ↑	= gradually decreasing	=	9 ng/mL ↓
Insulin GLUT4	* *	* *	* *	* *	3.8 uU/mL ↑	2 uU/mL ↓	5 uU/mL =	1.7 uU/mL ↑
GLUT1	*	*	*	*	↑	↓	=	=
Progesterone	variably high, similar to non-pregnant			<2–3 ng/mL	Variably high, similar to pregnant >1 ng/mL levels <1 ng/ml indicate onset of anestrus			
PGR	constant	constant	↑	↑	higher	lower/ constant	lower/constant	higher
17b-estradiol ERa	21–42 pg/mL *	21–42 pg/mL *	21–42 pg/mL *	<12 pg/mL *	12–20 pg/mL constant	20–35 pg/mL constant	30–40 pg/mL constant	20-12 pg/mL ↓
ERb PGE2	* *	* *	* *	* *	constant constant	expression constant	throughout	diestrus
PTGS2	↑	↓	=	=	↑	↑	↓	↓
PTGES	↑	↓	=	=	↑	↑	↓	↓
PGT	↑	↑	↓	=	↑	↑	↓	↓
EP2	constant	expression	until	↑	↑	=	↓	=
EP4	constant	constant	↑	↓	constant	expression	throughout	diestrus
IL-6	*	*	*	*	↑	=	=	↓
IL-10	*	*	*	*	↑	*	*	*
VEGFA	↑	=	↓	=	↑	=	↓	=
VEGFR1	↑	=	↓	=	↑	=	↓	↑
VEGFR2	constant	expression	throughout	diestrus	↑	=	↑	↓
FGF2	*	*	*	*	↓	↑	↓	↓
Endothelin 1	constant	expression	throughout	diestrus	↑	=	↓	=
ETB	↑	=	↓	=	↑	=	↓	=
ECE1	constant	expression	until	↓	↑	=	↓	=
IGF1	↑	↓	↓	↓	↑	=	↓	=
IGFR1	constant	expression	until	↑	constant	expression	throughout	diestrus

Factors involved with		**Pregnancy CL**				**Cyclic CL**		
luteolysis or regression	**Pre-implantation**	**Post-implantation**	**Mid gestation**	**Pre-Partum luteolysis**	**Formation**	**Maintenance**	**Early regression**	**Late regression**
PGFM PTGFR PGFS	200 pg/mL constant low	700 pg/mL expression ↑	1000 pg/mL throughout =	7900 pg/mL diestrus =	900 pg/mL Stable low	500 pg/mL expression or	= throughout no	200 pg/mL diestrus detection
IL-1b	*	*	*	↑	constant	expression	throughout	diestrus
IL-8	*	*	*	↑	*	*	*	*
IL-12a	*	*	*	↑	constant	expression	throughout	diestrus
CCL3	*	*	*	↑	*	*	*	*

Table 1 (*continued*)

Luteotropic Factors	Pregnancy CL				Cyclic CL			
	Pre-implantation	Post-implantation	Mid gestation	Pre-Partum luteolysis	Formation	Maintenance	Early regression	Late regression
CCL13	*	*	*	↑	*	*	*	*
MHCII	*	*	*	↑	*	*	*	*
NF-kB (RELA)	*	*	*	*	constant	constant	↑	↓
TNFa	↑	↓	=	=	↑	↓	=	=
TNFR1	↑	↓	=	=	↑	↓	=	=
TNFR2	↑	↓	=	=	↑	↓	=	=
Endothelin 2	↑	↓	=	↑	↑	↑	↓	=
Endothelin 3	constant	expression	until	↑	constant	constant	↑	=
ETA	constant	expression	until	↑	constant	expression	throughout	diestrus

Pre-implantation – days 10–12 of gestation (o.g.); Post-implantation – days 18–25o.g.; Mid-gestation – days 30–45o.g.; Pre-partum luteolysis – days 58–61o.g.; Formation – day 10 post ovulation (p.o.); Maintenance – days 20 and 30 p.o.; Early regression – day 40 p.o.; late regression – day 60 p.o.; LH – luteinizing hormone; GLUT4/GLUT1 – facilitative glucose transporters 4 and 1; PGR – nuclear progesterone receptor; ERa/ERb – estrogen receptors a and b; PTGS2 – prostaglandin synthase 2; PTGES – prostaglandin E synthase; PGT – prostaglandin transporter; EP2/EP4 – prostaglandin receptors 2 and 4; IL – interleukin; VEGFA – vascular endothelial growth factor A; VEGFR1 and 2 – VEGFA receptors 1 and 2; FGF2 – basic fibroblast growth factor; ETB and ETA – endothelin receptors B and A; ECE1 – endothelin converting enzyme 1; IGF1 – insulin like growth factor 1; IGFR1 – receptor 1 for IGF; PGFM – metabolite of PGF2a; PTGFR – receptor for PGF2a; PGFS – prostaglandin F synthase; CCL 3 and 13 – Chemokine C–C Motif ligand 3 and 13; MHC II – major histocompatibility complex class II; NF-kB (RELA) – transcription factor, subunit p65, responsible for activation of NF-kB; TNFa – tumor necrosis factor a; TNFR1 and 2 – receptors 1 and 2 for TNFa. Increased (↑), decreased (↓) or equal (=) expression in relation to previous stage. * - no information available.

2. Classical endocrine regulators of luteal function

2.1. Prolactin and luteinising hormone

Luteinizing hormone (LH) triggers a marked preovulatory luteinization of canine follicular granulosa and theca interna cells. Independent of pregnancy, the canine CL may last as long as pregnancy (approximately 60 days) or longer, and is able to respond to LH and PRL, particularly in the second half of diestrus [14,15], when concentrations of both gonadotropins increase in peripheral blood [6,7]. Accordingly, immunoneutralization of LH during the second half of diestrus in non-pregnant dogs and during pregnancy was associated with a transient decline in serum P4 concentrations, but was not able to abbreviate the CL lifespan [16]. However, LH was reported to increase circulating PRL levels in canine pregnancy, placing LH in an indirect luteotropic role [7]. In the cyclic CL, LH receptors (LHR) were assessed at the mRNA level, showing an increase from day 5 up to days 15 and 25 post-ovulation (p.o.), and a decrease thereafter at day 35 p.o., with no significant changes until day 65 p.o. Interestingly, in the same study, LHR mRNA in the pregnancy CL increased from pre-implantation to mid-gestation and remained so until pre-partum luteolysis [17].

In non-pregnant dogs, plasma PRL concentrations fluctuate constantly around 2–4 ng/mL during diestrus and rise slightly to 9 ng/mL on day 60 p.o. However, PRL increases continuously in pregnant dogs towards the end of gestation, achieving 50 ng/mL close to parturition [15]. PRL receptors (PRLR) are expressed in cyclic and gestational canine CLs: during the estrous cycle the expression of PRLR increases from day 5–15, and decreases gradually towards day 65 p.o. Similarly, in pregnancy, PRLR expression is high in the developing CL and decreases gradually during luteal regression until mid-gestation (approximately day 35–40), and is strongly suppressed at pre-partum luteolysis [17]. Moreover, in isolated canine early luteal cells (approximately 3 weeks p.o.) prostaglandin E2 (PGE2) strongly stimulated PRLR expression [18]. In the same report, functional withdrawal of prostaglandin activity during the early luteal phase, associated with decreased intraluteal PGE2 synthesis, significantly diminished *in vitro* PRLR expression [18]. This apparent functional loop implies an indirect involvement of PGE2 in regulating sensitivity of the canine CL to circulating PRL.

Nevertheless, during the first half of the diestrus phase, i.e., from the day of ovulation until approximately day 24–28, the canine CL is independent of the potential luteotropic action of hypophyseal hormones [19] and hypophysectomy triggers only a transient decline in concentrations of plasma P4. After day 24 p.o., hypophyseal ablation and/or blockade of PRLR leads to luteolysis in the non-pregnant dog, further highlighting the role of PRL in regulating the CL lifespan [19,20]. Additionally, as a pleiotropic hormone, plasma PRL is able to modulate glucose homeostasis and insulin secretion, as shown in rats [21]. However, in humans, high doses of PRL (hyperprolactinemia) can cause insulin resistance and act as a diabetogenic hormone [22].

2.2. Progesterone and 17b-estradiol

In cows, E2 acts as an endocrine modulator of the cyclic CL lifespan [23]. It is produced by the recruited growing ovarian follicles during the follicular waves [24]. The system of ovarian venules and veins carries E2 into the main blood circulation, which then distributes E2 throughout the target organs, including the ovary containing the CL. Possible paracrine and autocrine effects of E2 on the bovine cyclic CL may not be excluded, since ovarian arterio-venous anastomoses exist [25,26], and the CL itself has been reported to produce E2 [27]. Together with PGF2a (prostaglandin F2 alpha), E2 can be considered a luteolytic factor in cows [28]. In pregnant cows, however, ovarian E2 production is maintained at low levels, and the main organ producing estrogens is the placenta [29], which is able to increase the amount of free and conjugated estrogens (from less than 1 to around 10 ng/mL) starting at 20 days prior to parturition [29]. Other luteolytic factors, induced by PGF2a,

apoptotic and immune factors, also contribute to luteolysis of the bovine pregnancy CL. In the rabbit, E2 is considered the main luteotropic factor, acting through its receptors to maintain the cyclic CL lifespan [30]. The cyclic rat CL is also considered to be sensitive to E2 as a luteotropic factor [31], as is the porcine CL [32,33]. Indeed, in the latter species, E2 seems to play a protective role by increasing LHR expression and P4 production in the cyclic pig CL, delaying the onset of PGF2a induced luteolysis [32]. In the human cyclic CL, a luteotropic role has been attributed to E2 [34], but there is some dispute about its involvement in luteolysis, mediating apoptotic events [35].

The role of P4 in modulating CL function is rather autocrine and/or paracrine, as is the role of E2 for the canine CL. We will discuss these aspects below, under "Paracrine and Autocrine regulators".

3. Non-classical endocrine regulators of CL function

Insulin plasma concentrations fluctuated during diestrus in non-pregnant dogs used for most of the experiments we conducted in this context [36]. Concentrations of 3.8 μU/ml were found on day 10 p.o., decreasing to around 2 μU/mL on days 20 and 30 p.o, increasing again up to 5 μU/mL on day 40 p.o. and decreasing again after they reached 50 p.o. ($p < 0.05$).

Recently, it was shown that insulin is able to increase glucose uptake by canine luteal cells through phosphorylated AKT-dependent glucose transporter 4 (GLUT4) translocation [8], as insulin does in classical insulin-sensitive tissues like skeletal muscle and adipose tissue [37–40]. GLUT4 is the only facilitative glucose transporter able to respond to insulin stimulus in white and brown adipose tissue, as well as in skeletal and cardiac muscles [37]. It also responds to exercise, increasing glucose uptake [41]. Postprandially and during exercise, more than 50% of cellular GLUT4 content is translocated into the plasma membrane, and the amount of glucose taken up correlates with this GLUT4 shift in cellular localization as well as with the physiological state of the tissue or cells [42]. Other tissues such as the uterus, placenta and CL, in humans, rodents and domestic animals, have been reported to express GLUT4 protein and SLC2A4, its encoding mRNA [8,43–46]. Both protein and mRNA can be differentially modulated during CL development and regression [8,44], placental age [46] and endometrial phases [43,45]. Nevertheless, to the best of our knowledge, glucose uptake under insulin stimulus has only been described for cyclic canine luteal cells [8], even though other above-mentioned studies attributed a role to GLUT4 in the functionality of endometrial and placental tissues on the basis of its expression.

In addition to contributing to glucose uptake by translocating GLUT4 from the intracellular compartment to the plasma membrane, insulin signaling is also able to increase SLC2A4 transcription and its translation to GLUT4, as shown in rat muscle cells [47] and canine luteal cells [8]. These results characterize insulin as playing a role in modulating canine CL function.

4. Paracrine and autocrine regulators of luteal function

4.1. Steroid hormones

Steroid hormones, especially E2 and P4, play the paramount role in controlling CL function, not only in the dog [5] but also in cows [27], humans [48], and pigs [49], among others. Since 2001, it has been known that E2 and P4 receptors are present in the canine CL and their expression is modulated during diestrus [5,50] and pregnancy [51–53]. Non-surgical termination of unwanted dog pregnancies can be achieved by aglepristone, a P4 receptor (PGR) blocker [10,54–56].

The canine CL is the only source of steroid hormones during pregnancy and non-pregnant diestrus, since the placenta is unable to synthetize them [3,4]. In order to achieve its function, P4 has to bind to nuclear or membrane receptors. After binding to nuclear receptors, the P4-receptor complex connects to the promoter region of target genes, and it may recruit additional transcription binding factors to initiate or repress transcriptional activity (see review by Ref. [57]). In canine luteal tissue of pregnant and non-pregnant dogs, PGR is expressed in a time-dependent manner, apparently exhibiting an inverse relationship to circulating P4 levels [5,50,53]. Interestingly, PGR is expressed in both luteal and non-luteal cells. Progesterone plasma levels vary strongly individually and reach maximum values between days 15–30 p.o [1,9,58]. (values of 25–35 ng/mL, sometimes over 80 ng/mL can be recorded). In the second half of the luteal phase, steroidogenesis slowly declines until sudden luteolysis occurs before parturition; in non-pregnant dogs, progressive and protracted CL regression occurs secondary to fatty degeneration of luteal tissue and in the absence of a luteolytic signal.

Basal P4 levels of <0.1 ng/mL determine the beginning of anestrus [2]. The presence of PGR in different populations of cells within the canine CL implies a broad local regulation of physiological processes. It has been postulated that P4 is able to induce proliferation of endothelial and stromal cells, suppress immune cell function [52] and act in a positive feedback over the luteal cells, in an autocrine manner triggering its own production [53]. The first half of diestrus, when luteal P4 production achieves full capacity, displays a plethora of luteotropic factors, including the glucose transporter 1 (GLUT1), whose expression is triggered by P4 itself through its own receptor, as shown in murine and human endometrial cells [59], favoring glucose uptake to supply the needs of the developing, fully secretory CL. GLUT1 was assessed in cyclic canine CL in the context of hypoxia-regulated genes, and showed a high correlation with P4 production in the first half of diestrus [58]. Knockout studies in mice shed light upon PGR functions in the ovary, resulting in an anovulatory phenotype [60]. However, one should be careful in extrapolating mouse data to canine CL function, because blocking PGR functionality in the dog does not affect ovulation [61].

In our most recent, as yet unpublished study, the expression of membrane progesterone receptors (MPGRs) was examined in pregnant and cyclic canine CL. Overall, diestrus and pregnancy stages influenced the expression of MPGRs, although expression patterns differed among PGRMC (P4 membrane receptor component) 1, 2, PAQR (class II progestin and adipoQ receptor) 5, 7 and 8. The combination of data already gathered on PGR functionality and new data on MPGRs may bring new insights into P4 action in the canine CL during its maturation, maintenance and regression.

Regarding estrogen actions, two main nuclear receptors have been described, ERa and ERb, encoded by ESR1 and ESR2 genes, respectively. ERs are broadly distributed throughout the body [62], pointing towards dependency of the organism upon estrogens for achieving homeostasis. ERa and ERb are not always present in the same organs, but if they are, the ratio of ERa to ERb also plays a role in the response to estrogens, in a tissue-dependent manner [63]. Moreover, when expressed together, ERa and ERb heterodimerize [64]. More recent data indicate that, whereas homofusion of either ERa or ERb evokes signals similar to the parent ER, heterodimers emulate the transduction effects of ERa, affirming the latter as the dominant partner in the ERa/ERb dimer [65].

In the canine cyclic CL, both ERa and ERb are expressed [5,50], and predominantly found in steroidogenic cells, while being less represented in non-steroidogenic cells. The mRNA and protein expression levels of ERa appear to diverge [5,50]. The ERa protein was found consistently distributed in luteal and non-luteal cells during diestrus, but in luteal cells a gradual increase from day 35

and elevated expression on day 65 were observed [5]. In contrast, the transcripts levels were elevated from day 5 to day 25, and decreased gradually towards day 65 p.o [5]. The expression of ERb and ERS2, however, was not greatly affected by the stage of diestrus [5]. However, in another recently published study, the transcript levels of both ESR1 and ESR2 were also investigated in the CL of non-pregnant dogs, both showing time-dependent effects and increased expression towards day 30 p.o [66]. Interestingly, despite high individual variations in that study, their expression was not affected by functional withdrawal of prostaglandins [66]. Nevertheless, taking into consideration the expression and distribution patterns of the respective proteins, ERa and ERb, cumulatively the available data imply that the ratio of ERa to ERb may change with increasing ERa expression towards the end of diestrus [5,50]. Additionally, estrogen sulphotransferase 1 (SULT1), an enzyme responsible for conjugation and inactivation of estrogens, was found to be increased during luteal regression of the cyclic canine CL on day 65 p.o. compared to pre-partum luteolysis in pregnancy CLs of the same age, which was interpreted as a sign of a functional withdrawal of estrogens [52]. Notably, SULT1 was among the genes commonly upregulated in luteolytic dogs, both during natural luteolysis and in mid-pregnant dogs in which luteolysis/abortion was induced by an antigestagen [52]. The latter finding implies a role of PGR in mediating the local availability of estrogens, making estradiol unavailable for its otherwise expressed receptors.

As described for rat Sertoli cells [67], the functions of 17b-estradiol, if transferred to the CL, could be related to proliferative as well as anti-proliferative processes, and this would indeed depend on the ERa/ERb ratio as already described for human breast cancer cells [68]. Moreover, the description of membrane-bound estrogen receptors in the hamster ovary, the ESR36 [69], a splice variant of the ESR1 gene involved in non-genomic signaling of estrogens, leads us to assume that E2 action in follicles is broader than originally presumed. Although currently there are no data addressing the presence of membrane-bound estrogen receptors in CLs, their contribution to the regulation of luteal function warrants further investigation.

Additionally, nuclear ERs have been related to metabolic disorders. Insulin resistance increases in muscle cells treated with ERb agonist, whereas ERa shows a protective effect for insulin resistance and obesity [70,71]. Often driven by the estrous cycle and pregnancy, hormone fluctuations may lead to impairment of glucose metabolism and insulin resistance in humans, and ERs have been implicated in this process [72]. When we consider that insulin plays a luteotropic role in the canine CL [8], fluctuations of ERs in the tissue could also have an effect on insulin-driven GLUT4 glucose uptake.

And last, but not least, the priming action of E2 in the canine CL for the expression of PRL and, reciprocally, for PGR [17], attributes another critical autocrine and paracrine role to E2.

4.2. Prostaglandins

Prostaglandin F 2a (PGF2a) is the most-studied PG in domestic animals, and its main function is termination of the luteal phase in non-pregnant females to allow resumption of cyclicity. In ruminants, PGF2a originates in the uterus and acts on the CL by a counter-current mechanism involving the uterine vein and the ovarian artery. In the non-pregnant dog, PGF2a does not seem to play a physiological role in CL regression [9,73]. Expression of the PGF2a-synthase (PGFS) enzyme is very low or absent in both pregnant and non-pregnant canine CL [74,75]. Nevertheless, due to its constitutive expression of the respective receptor, PTGFR [53,74], the canine CL remains responsive to exogenously administered PGF2a [76–78]. However, as reported, e.g., for early pregnant bitches, serious dose-dependent adverse side effects, mainly related to emesis and induction of defecation, are to be expected [77]. In contrast to non-pregnant dogs which lack endogenous PGF2a secretion by the uterus, the utero-placental unit of pregnant bitches secretes PGF2a that leads to pre-partum luteolysis [9,10,79]. It originates predominantly from the microsomal compartment of fetal trophoblast cells in the placenta, and triggers contractility of the myometrium and apoptosis of luteal cells [10,75].

As for PGE2, it seems to be the most important prostaglandin controlling early CL function in dogs. It acts as a luteotropic factor directly involved in CL formation and P4 production [73], as well as indirectly by increasing blood flow and enhancement of PRL receptor [66,80]. The whole machinery necessary for PGE2 synthesis and action in the dog is present in both pregnant and non-pregnant CLs. It starts with a massive expression of cyclooxygenase 2 (PTGS2) and the converting enzyme PGE2 synthase (PTGES) when P4 plasma levels are rising [81], associated with the expression of the PG transporter (PGT). The expression of HPGD, an enzyme responsible for PGs degradation, is negatively correlated with PTGES and PGT. Moreover, when PTGS2 is blocked *in vivo* following the use of the selective COX2 blocker firocoxib, an inhibition of STAR and HSD3B accompanied by reduced P4 concentrations is observed [82,83]. In a follow-up study, also including the RNAseq approach on CL tissues from non-pregnant dogs treated with firocoxib from day 5–30 p.o., Tavares Pereira and collaborators [66,84] documented the expression of genes related to immune system, vascularization and general global luteal transcriptomic changes. Genes belonging to the angiopoietin family (ANGPT) were down-regulated, whereas endothelin 1 and some pro-inflammatory cytokines, e.g., IL1b, IL6 and IL12a, were increased. The up-regulation of the above-mentioned cytokines by a COX2 inhibitor points to a possible immunosuppressive effect of PGs in the canine cyclic CL [66,84]. The findings regarding the ANGPTs and their receptors indicate a destabilization of blood vessels when PGs are not available.

4.3. Cytokines

Cytokines have been brought into focus in the regulation of CL function only in recent decades, when several immune cells, e.g., lymphocytes, macrophages, plasmocytes and dendritic cells, have been reported to secrete their cytokine products in the CL of cattle and other species, affecting its function (see review by Ref. [85]). Additionally, recently, specific subsets of miRNA have been implicated in cytokine-mediated regulation of cyclic and pregnancy CLs in cattle [86]. In the canine CL, the expression of cytokines was reported for the first time in the studies of Hoffmann and collaborators [50,87,88]. Although the presence of $CD4^+$ and $CD8^+$ immune cells was identified within the canine CL, at that time only a few cytokines, e.g., interleukin- (IL) 8, 10 and 12, TNFa and TGFB1 were differentially regulated throughout diestrus and, thus, implicated in the regulation of CL function [88]. Using qPCR and RNA sequencing, it has recently been shown that expression of other cytokines is also modulated according to the phase of diestrus in the canine cyclic and pregnant CL [8,66,84]. Whereas pro-inflammatory cytokines such as IL-1b and IL-12a do not exhibit time-dependent expression in the first half of the cyclic CL lifespan, IL-10 and IL-6 show up-regulation on days 10 and 20 p.o., respectively [8,66]. When luteal tissue samples from non-pregnant dogs in late diestrus were compared with luteal samples from dogs undergoing pre-partum luteolysis using next-generation RNA sequencing, 1595 differentially expressed genes (DEG) were detected [52]. Gene expression in prepartum luteolysis pointed towards an acute immune and inflammatory response, represented by massively increased expression of IL-1b, chemokine (C–C motif) ligand 3 (CCL3), major histocompatibility complex class II (MHCII) and chemokine (C–C motif) ligand 13 (CCL13). In contrast, the transcriptome of CL

samples from non-pregnant dogs provided evidence for luteal regression to be characterized as a prolonged, degenerative process without involvement of significant immune response. In another study [89], TNFA and its two receptors were detected during the whole of diestrus in both pregnant and non-pregnant CLs. In the cyclic canine CL, the expression patterns of TNFA, TNFR1 and TNFR2 were the same as in the CL of pregnancy, decreasing from day 5 until day 35 p.o and remaining low until day >65 p.o.

4.4. Growth factors

Several families of growth factors have been reported as present in the canine CL, as described below. Some of their functions in the CL encompass capillary bed formation and maintenance, cell proliferation and migration and steroidogenesis. The CL is a temporary endocrine gland, the formation of which relies on angiogenesis, and regression/luteolysis upon withdrawal of its vascular bed. It depends on a finely-tuned synchronization among different vascular-related growth factors. VEGFA and its receptors (VEGFR1/FLT1 and 2/KDR) have been localized to luteal and endothelial cells throughout diestrus [90] and their expression changed according to the luteal phase. The highest mRNA expression of VEGFA and its two receptors was on day 20 p.o., although VEGFR2 showed another peak of expression on day 40 p.o [58]. It is known that when VEGFA binds to VEGFR2, a positive proliferation response occurs, whereas the binding to VEGFR1 leads to a sequestration of the available VEGFA, impairing the binding to VEGFR2 [91]. Moreover, VEGFA and FGF2 have been shown to increase steroidogenesis through increased expression of STAR in the bovine CL [92], a fact that led us to speculate if this could also be true for the canine CL, since the highest expression of STAR occurs concomitantly with P4 secretion. FGF2 mRNA was also assessed in the canine cyclic CL and it showed fluctuations during diestrus, increasing from day 10 to day 30 p.o. (maximum expression) and declining towards day 70 p.o [58]. In the canine CL of pregnancy, VEGFA and its two receptors were also studied [93] at specific time points. Similarly, as in pregnant dogs, the highest VEGF and VEGFR1 expression was observed in early until fully mature CLs, compared with later luteal stages, corresponding to the time of increasing P4 secretion [93]. The expression of VEGFR2 did not vary strongly throughout pregnancy. The stable expression of VEGFR2 may indicate the need for VEGFA signaling also when the pregnant canine CL starts its remodeling towards pre-partum luteolysis.

Endothelins (ETs: ET1, ET2 and ET3) belong to another growth factor family involved in vascularization of the canine CL. They bind to two receptors, ETA and ETB, whose activation results in opposite actions: binding to ETA leads to vasoconstriction while binding to ETB to vasodilatation. ETs have also been shown to induce P4 secretion in cows [94]. Gram and collaborators [80] reported time-dependent expression of ETs, their receptors and their converting enzyme (ECE1) in canine cyclic and pregnant CLs. Cyclic CL development was associated with strong expression of ETB, ECE1 and ET2, which decreased towards the mid and late luteal phases. Pre-partum luteolysis was characterized by higher expression of ET2 and ET3 as well as of ETA. This difference of expression between canine pregnant and cyclic CL may be due to the response to PGF2a, derived from the utero-placental compartment, actively vasoconstricting blood vessels and contributing to a rapid termination of pregnant CL function [80].

The IGF1 and its receptor IGF1R belong to another family of growth factors, the insulin-like growth factors, which have been studied in the canine CL [95]. As already postulated for cows [96], IGF1 and its receptor have been proposed to act as paracrine and autocrine factors within cyclic and pregnant canine CLs, since they were co-localized in luteal and endothelial cells. Moreover, their mRNA expression pattern differed: in cyclic CL, IGF1 expression decreased on days 45 and 65 p.o. and IGFR1 remained unchanged, whereas in the pregnant CL there was a constant decrease from pre-implantation until pre-partum luteolysis and IGFR1 increased at pre-partum luteolysis [95], indicating a response to PGF2a, as previously shown in cows [97].

5. Perspectives

The more than 15,000-year successful partnership between dogs and humans [98] has placed the dog as a family member in many societies, launching the concept of a multi-species family, which nowadays is also shared by cats, with all the bonuses and onuses [99].

On the one hand, developed countries have achieved a high degree of dog welfare conditions, but the concern remains that some breeds, which developed based on their phenotype, are not able to reproduce. On the other hand, most countries still face problems of poor animal welfare conditions, including uncontrolled stray and feral populations of dogs and cats. So, ultimately, should we conduct research in order to increase or to avoid canine reproduction? The quest to find non-surgical methods to safely manipulate reproduction in dogs is of paramount importance.

Given the above analyses and understanding of luteotropic and luteolytic factors governing cyclic and pregnant canine CL lifespans, we can infer that more research is necessary to terminate an unwanted pregnancy at its beginning, i.e., to decrease P4 levels so that the CL is not able to achieve its full secretory capacity. Surgical procedures are available but not always desired, since they are invasive and permanent. Possible targets for that purpose, in the first half of diestrus, have to be identified among the upstream regulators of steroidogenesis and P4 receptors (PGRs), before PGR is activated and triggers the positive feedback loop of its own expression and P4 production. Candidates could be genes and proteins related to the first supply of energy to the CL, such as SLC2A1/GLUT1 and insulin receptor (INR), and related also to vasculogenesis, such as VEGFA and its receptors. Nevertheless, one should keep in mind that the blockade of these genes, which show a whole body distribution, has to be local. We could take advantage of already developed research in cancer, where the use of targeted gene therapy is a reality [100]. Additionally, if our aim is to prevent a pregnancy in canines, we could locally target as early as the luteinization process of granulosa cells [101], depleting their nutritional supply and/or inducing their apoptosis, then avoiding ovulation without the use of hormone-related treatments, which are very deleterious for bitches [102,103]. To corroborate our line of thought, a recent publication by Rhodes [104] addressed the necessity of sterilizing dogs and cats using non-hormone and non-surgical approaches that are as permanent as possible. It is our hope that this review could contribute to devise strategies for developing new molecular-based drugs.

On the contrary, if our aim is to promote pregnancy in dogs, which sometimes is not successful due to luteal insufficiency [13,105], this review discusses a plethora of luteotropic factors that could be targeted locally in the first half of pregnancy, which would be able to stimulate luteal P4 production, as for example, PGE2, transcription factors associated with PGR signaling, growth factors and IL-10, among others. The use of exogenous P4 for this purpose has been reported as well [106], but its efficacy cannot readily be determined.

Because the canine CL exhibits so many local factors regulating its function and lifespan, and because modern biotechnology offers diverse possibilities for manipulating them without affecting overall general health of the animals, we recommend investing in devising approaches to regulate the canine CL function at the local level.

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