Proceedings of the 8th International Symposium on Canine and Feline Reproduction
ISCFR

June 22-25, 2016
Paris, France

In a joint meeting with the XIX EVSSAR Congress

Reprinted in IVIS with the permission of the ISCFR Organizers
The crafty and cunning canine CL: understanding its development and regulation.

Mariusz P. Kowalewski, Sophie Zatta, Aykut Gram.

Institute of Veterinary Anatomy, University of Zurich, Zurich, Switzerland

kowalewskipl@yahoo.de

Being the only major source of circulating steroids in the dog (Canis familiaris), corpora lutea (CL) play central roles in facilitating canine fecundity. They exhibit similar functional activities during pregnancy and in non-pregnant cycles and generate similar progesterone (P4) concentrations under both conditions. Luteal development is prostaglandin (PG)-driven. Thus, blocking luteal COX2 (PTGS2) expression results in decreased PGE2-synthase (PTGES) and STAR protein expression, and consequently in lowered P4 concentrations. Additionally, luteal PRL-receptor (PRLR) expression is affected\(^1,2\). Luteal maintenance appears, in turn, PRL-governed\(^1\). However, major differences concern the cessation of canine luteal function, indicating different regulatory mechanisms. Thus, whereas in non-pregnant cycles slowly progressing luteal regression takes place in the absence of endogenous luteolysin, in pregnant bitches the luteal phase is terminated by the prepartum luteolysis, as indicated by a steep drop in circulating P4. The latter, i.e., prepartum luteolysis, is associated with an increased release of utero-placental PGF2\(\alpha\). The trophoblast appears to be the major source of the luteolytic PGF2\(\alpha\)\(^3\). Its function in providing PGs appears to be regulated via cell-to-cell communication with maternally-derived stromal cells expressing P4 receptor (PGR). The local involvement of oxytocin in this process is strongly implied. The utero-placental increase of cortisol-receptive glucocorticoid receptor, however, does not seem to be critical for induction of the luteolytic cascade. Interestingly, luteal vascular functionality, but not its angiogenic or vasculogenic properties, seems to play a role in active luteolysis, and not during luteal regression. Nevertheless, the underlying regulatory downstream mechanisms involved in the cessation of luteal function in dogs remain largely unclear. Therefore, next-generation sequencing (RNA-Seq) was performed on mRNA isolated from CL collected from the late luteal phase (day 65 after ovulation) and compared with transcriptomes expressed in CL during prepartum luteolysis. The main functional terms determined higher represented during luteal regression related to ECM-remodelling, proliferation, regulation of transcription and positive response to steroidogenic activity. This strongly contrasted with the more highly represented terms related to activation of the immune system, acute-phase-reaction, negative regulation of angiogenesis and steroidogenesis, degradation of mitochondria and apoptosis found during prepartum luteolysis. Among the overrepresented genes were: e.g., IL1B, CXCL8, CCL3, CCR7 and SAA. Interestingly, the immune response was more strongly activated during natural luteolysis compared with samples derived from dogs in which pre-term luteolysis was induced at mid-gestation with an antigestagen. In the latter situation, inhibition of transcription and gene expression prevailed, as well as inhibition of proliferation and morphological remodelling processes. Consequently, the luteolysis observed in pregnant dogs prior to parturition appears to be an acute immune process driven by utero-placental PGF2\(\alpha\), contrasting with the slow process of morphological and functional remodeling during corpus albicans formation in pseudopregnant bitches without involvement of the immune system. The effects of antigestagen appear to be more strongly related to withdrawal of the luteotropic function of P4 than to the PGF2\(\alpha\)-driven inflammatory reaction during normal parturition. Research supported by The Swiss National Science Foundation (SNSF); research grant number 31003A_160251. [1] Kowalewski MP. Luteal regression vs. prepartum luteolysis: regulatory mechanisms governing canine corpus luteum function. Reprod Biol. 2014 Apr;14(2):89-102.; [2] Kowalewski MP, Ihle S, Siemieniuch MJ, Gram A, Boos A, Zdutczyk S, Fingerhut J, Hoffmann B, Schuler G, Jurczak A, Domoslawska A, Janowski T. Formation of the early canine CL and the role of prostaglandin E2 (PGE2) in regulation of its function: an in vivo approach. Theriogenology. 2015 Apr 1;83(6):1038-47.;[3] Kowalewski MP, Beceriklisoys HB, Pfarrer C, Aslan S, Kindahl H, Küçükaslan I, Hoffmann B. Canine placenta: a source of prepartal prostaglandins during normal and antiprogestin-induced parturition. Reproduction. 2010 Mar;139(3):655-64.