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Expression and functional implications of luteal angiopoietins in pregnant dogs
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The corpus luteum (CL) is a transient endocrine gland that is the sole source of circulating progesterone (P4) in domestic dogs during pregnancy and in non-pregnant cycles. Rapid vasculo- and angiogenesis are essential for its development and maintenance. Recent results from our group have shown upregulated expression of the VEGF system and endothelin receptor B, reflecting the high vascularization rate and increased blood supply during early luteal formation in both pregnant and non-pregnant dogs (1,2). In addition, by complementing the effects of VEGF, angiopoietin (ANG) -1 and -2, two functional antagonists acting through their receptors (TIE1 and TIE2), are involved in regulating vascular maturation and stability (ANG1), or inducing destabilization and proliferation of endothelium (ANG2). Yet, the proliferative and proangiogenic functions of ANG2 depend on the presence of VEGF, as endothelial cell death and vessel regression are observed in the absence of biologically available VEGF (3). However, expression of the ANG-system (i.e. ANG1, ANG2, TIE1 and TIE2) has not yet been investigated in canine CL. Therefore, here, its expression and localization was characterized in CL of pregnant dogs at selected stages of pregnancy: pre-implantation (days 8-12, n=5), post-implantation (days 18-25, n=5), mid-gestation (days 35-40, n=5), and during normal (n=3) and antigestagen-induced luteolysis/abortion (n=10) (Aglepristone, 10 mg/kg bw; 2x/24 h apart, samples taken 24 and 72h after the second treatment). In addition, canine lutein cells obtained from the early luteal phase (up to 21 days after ovulation) were incubated with luteotrophic factor PGE2 to determine its interactions with ANG-system expression. The luteal ANG1 and TIE1 mRNA levels were elevated at early luteal stages and decreased significantly towards prepartum luteolysis. ANG2 and TIE2 did not change significantly over time. Thus, the ratio of ANG2/ANG1 was significantly elevated during prepartum luteolysis coincident with lowered VEGF. The ANG-system remained unaffected in dogs, in which luteolysis/abortion was induced by antigestagen at mid-gestation (days 40-45). One of the most interesting findings of the in-vitro study was that PGE2 stimulated expression of ANG2 in early canine lutein cells, whereas the expression of ANG1 was strongly suppressed, and TIE 2 remained unaffected. No TIE1 expression was detectable in lutein cell cultures. At the cellular level, as shown by immunohistochemistry and in situ hybridization, all members of the ANG-system were detectable in the capillaries and endothelial cells. Weaker signals were targeted to the luteal cells. In conclusion, high concomitant expression of ANG1 with the VEGF system in early CL suggests its roles during vascular maturation and stabilization in CL. On the other hand, the increase in the ratio of ANG2/ANG1 in the absence of the VEGF system during luteolysis suggests its contribution to PGF2α-mediated vascular degeneration and disruption.

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