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Time related changes in luteal prostaglandin synthesis and steroidogenic capacity during pregnancy, normal and antiprogestin induced luteolysis in the bitch

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ABSTRACT

In nonpregnant and pregnant dogs the corpora lutea (CL) are the only source of progesterone (P4) which shows an almost identical secretion pattern until the rapid decrease of P4 prior to parturition. For the nonpregnant dog clear evidence has been obtained that physiological luteal regression is devoid of a functional role of the PGF2α-system and seems to depend on the provision of StAR. Yet in pregnant dogs the rapid prepartal luteal regression, coinciding with an increase of PGF2α, may be indicative for different regulatory mechanisms. To assess this situation and by applying semi-quantitative Real Time (Taq Man) RT-PCR, expression patterns were determined for the following factors in CL of pregnant and prepartal dogs and of mid-pregnant dogs treated with the antiprogestin Aglepristone: cyclooxygenase 2 (Cox2), prostaglandin E2 synthase (PGES), prostaglandin F2α synthase (PGFS), its receptors (EP2, EP4 an FP), the steroidogenic acute regulatory protein (StAR), 3β-hydroxysteroid-dehydrogenase (3βHSD) and the progesterone receptor (PR). Peripheral plasma P4 concentrations were determined by RIA. CL were collected via ovariohysterectomy from pregnant bitches ($n = 3–5$) on days 8–12 (Group 1, pre-implantation

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period), days 18–25 (Group 2, post-implantation period), days 35–40 (Group 3, mid-gestation period) and during the prepartal progesterone decline (Group 4). Additionally, CL were obtained from groups of 5 mid-pregnant dogs (days 40–45) 24 h, respectively 72 h after the second treatment with Aglepristone. Expression of Cox2 and PGES was highest during the pre-implantation period, that of PGFS and FP during the post-implantation period. EP4 and EP2 revealed a constant expression pattern throughout pregnancy with a prepartal upregulation of EP2. 3βHSD and StAR decreased significantly from the pre-implatation period to prepartal luteolysis, it was matched by the course of P4 concentrations. Expression of the PR was higher during mid-gestation and prepartal luteolysis than in the two preceding periods. After application of Aglepristone the overall mRNA-expression resembled the situation during prepartal luteolysis except for EP2, which remained unchanged.
These data suggest that – as in the nonpregnant bitch – also in the pregnant bitch luteal production of prostaglandins is associated with luteal support rather than luteolysis. On the other hand induction of luteolysis by the PR blocker Aglepristone points to a role of luteal P4 as an autocrine factor in a positive loop feedback system controlling the availability of P4, StAR and 3βHSD.

1. Introduction

In pregnant and nonpregnant bitches the corpora lutea (CL) are the only sources of progesterone (P4) (Concannon et al., 1989), with the course of P4-concentrations in peripheral blood being virtually identical shortly until parturition, when it declines around day 60 of pregnancy to basal levels preceding the onset of fetal expulsions (Concannon et al., 1978). In nonpregnant dogs P4-levels continue to decrease gradually and reach anoestrus levels <1 ng/ml between days 60 and 90 (Feldman and Nelson, 1987). During the first 20–30 days after ovulation the newly formed CL are independent of gonadotropic support (Concannon et al., 1987); thereafter in the second half of dioestrus or gestation, removal of pituitary gland support results in luteolysis as LH and in particular prolactin have become essential luteotropic factors (Concannon, 1980; Okkens et al., 1990). Availability of prolactin and LH increases during this period, commencing with the decline of P4 (Gräf, 1978; Hoffmann and Schneider, 1993). Hence luteal regression occurs in spite of an increased gonadotropic support (Hoffmann et al., 1996).

In the nonpregnant bitch luteal function is independent of a luteolysin of uterine origin since normal ovarian function was observed after hysterectomy (Hoffmann et al., 1992). In pregnant bitches, however, the immediate prepartal P4 decrease coincides with an increase of PGF2α (Concannon et al., 1988; Nohr et al., 1993) of unknown origin suggesting a functional role in relation to parturition, also because luteal life-span can be terminated by exogenous application of PGF2α, though relatively high dosages or repeated treatments are necessary and strong side effects can occur (Romagnoli et al., 1991; Concannon and Hansel, 1977).

As observed in other species among the many factors involved in the control of luteal function prostaglandins seem to be of particular importance. Thus in ruminants and the pig onset of cyclic luteolysis is triggered by a well timed release of PGF2α from the endometrium, while luteal PGF2α, which is expressed in many species (reviewed by Wiltbank and Ottobre, 2003), seems to contribute to structural luteolysis (Diaz et al., 2002; Hayashi et al., 2003). Small amounts of uterine PGF2α acting via induction of luteal Cox2 stimulate the intraluteal production of PGF2α (Diaz et al., 2002). On the other side, PGE2 has shown to be a very potent luteotropic factor in several species. It stimulates luteal P4 secretion via a cAMP-mediated pathway as was shown for cattle, rabbits and humans (Kotwica et al., 2003; Marsh and LeMaire, 1974; Boiti et al., 2001). Its luteotrophic efficiency has been shown to be comparable to that of LH (Weems et al., 1997).