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Is nitric oxide luteolytic or antiluteolytic?

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Abstract

Nitric oxide (NO) has been reported to be luteolytic based on treatment of cows in vivo with an inhibitor of nitric oxide synthase (NOS-produces NO), which delayed the decline in progesterone by two to three days [Jaroszewki J, Hansel, W. Intraluteal administration of a nitric oxide synthase blocker stimulates progesterone, oxytocin secretion and prolongs the life span of the bovine corpus luteum. Proc Soc Exptl Biol Med 2000;224:50–5; Skarzynski D, Jaroszewki J, Bah, M, et al. Administration of nitric oxide synthase inhibitor counteracts prostaglandin $F_{2\alpha}$-induced luteolysis in cattle. Biol Reprod 2003;68:1674–81]. The objective of this experiment was to determine the effect of a long acting NO donor or a NOS inhibitor infused chronically into the interstitial tissue of the ovarian vascular pedicle adjacent to the ovary with a corpus luteum on secretion of progesterone during the ovine estrous cycle. Ewes were treated either with Vehicle ($N = 5$); Diethylenetriamine (DETA-control for DETA-NONOate; $N = 5$); (*Z*)-1-[2-(2-aminoethyl)-*N*-(2-ammonioethyl) amino]diazen-1-ium-1,2-diolate (DETA-NONOate-long acting NO donor; $N = 6$); or L-nitro-arginine methyl ester (L-NAME-NOS inhibitor; $N = 6$) every 6 h from 24:00 h (0 h) on day 8 through 18:00 h on day 18 of the estrous cycle. Jugular venous blood was collected every 6 h for analysis for progesterone and corpora lutea were collected at 18:00 h on day 18 and weighed. Weights of corpora lutea were heavier ($P \leq 0.05$) in DETA-NONOate-treated ewes when compared to Vehicle, DETA, or L-NAME-treated ewes, which did not differ amongst each other ($P \geq 0.05$). Profiles of progesterone in jugular venous blood on days 8–18 differed ($P \leq 0.05$) in DETA-NONOate-treated ewes when compared to Vehicle, DETA,

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or L-NAME-treated ewes did not differ ($P \geq 0.05$) amongst each other. It is concluded that NO is not luteolytic during the ovine estrous cycle, but may instead be antiluteolytic and prevent luteolysis.

Keywords: Corpus luteum; Sheep; Progesterone; Nitric oxide; L-NAME; Estrous cycle

1. Introduction

Thirty to 40% of ovine, bovine, and porcine embryos are lost during the first trimester of pregnancy [3–13]. Further losses occur at later stages of pregnancy [14]. These losses may be due to deficiencies in progesterone secretion, since progesterone is required throughout gestation to maintain pregnancy in ewes [15,16]. Secretion of progesterone by the corpus luteum during the ovine or bovine estrous cycle is regulated by luteinizing hormone (LH) via cAMP [15–18], but not by the mid-pregnancy corpus luteum [15,16]. Progesterone secretion by the corpus luteum at mid-pregnancy in ewes and cows is stimulated by PGE_1 and/or PGE_2 [15,16]. Loss of progesterone secretion by the corpus luteum at the end of the estrous cycle is via uterine secretion of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), which is delivered locally from the uterine vein to the adjacent ovarian artery of the luteal-containing ovary [15,16]. Uterine secretion of $PGF_{2\alpha}$ begins around day 12 in ewes [15,16]. Although $PGF_{2\alpha}$ is a vasoconstrictor and could cause luteolysis through ischaemia of the corpus luteum, loss of luteal LH receptors and decreases in ovarian blood flow occur after the onset of luteolysis and cAMP and progesterone decline [17–20]. Endometrial LH receptors may also play a role in luteolysis through increases in uterine $PGF_{2\alpha}$ secretion [21–27]. Endometrial LH receptors increase during luteolysis and LH increases $PGF_{2\alpha}$ secretion late in the estrous cycle and may enhance the luteolytic process [26,27].

Nitric oxide (NO) has been reported to play a role in luteolysis, since L-nitro-arginine methyl ester (L-NAME), an NO synthase (NOS) inhibitor, delivered into the bovine corpus luteum in vivo delayed decreases in progesterone only two to three days [1,2]. Also, an NO donor decreased progesterone secretion by dissociated bovine luteal cells in vitro [28,29]. However, an NO donor inhibited $PGF_{2\alpha}$-induced luteolysis by rat luteal tissue in vitro and NO may be antiluteolytic rather than being luteolytic [30]. This could suggest that luteal tissue from different species respond differently to NO. However, NO donors and endothelin-1, also reported to be luteolytic [31], do not alter bovine luteal tissue slice progesterone or $PGF_{2\alpha}$ secretion in vitro, but instead increases PGE_2 secretion [32]. PGE_1 or PGE_2 in vitro or in vivo regardless of species are both luteotropic and antiluteolytic [15–18]. Bovine luteal tissue slices from the estrous cycle or pregnancy secrete PGE_2 and $PGF_{2\alpha}$, which increases linearly with time in culture and the PGE_2:$PGF_{2\alpha}$ ratio remains at least 1:1 [33] and progesterone secretion is not altered [34]. This linear secretion of PGE_2 and $PGF_{2\alpha}$ does not occur with ovine luteal tissue of the estrous cycle in vitro [35]. Therefore, the objective of this experiment was to determine whether an NO donor or NOS inhibitor infused chronically into the interstitial tissue of the ovarian vascular pedicle of the luteal-containing ovary affected ovine luteal progesterone secretion during the estrous cycle.