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Effect of dose of estradiol-17β on prominence of an induced 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) pulse and relationship of prominence to progesterone, LH, and luteal blood flow in heifers

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Abstract

Various doses of estradiol-17β (E_2) were used in heifers to induce a pulse of 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ (PGFM). The effect of E_2 concentration on the prominence of PGFM pulses and the relationship between prominence and intrapulse concentration of progesterone (P_4), LH, and luteal blood flow were studied. A single dose of 0 (vehicle), 0.01, 0.05, or 0.1 mg of E_2 was given (n = six/group) 14 d after ovulation. Blood samples were collected, and luteal blood flow was evaluated hourly for 10 h after the treatment. The 0.05-mg dose increased and the 0.1-mg dose further increased the prominence of the induced PGFM pulse, compared with the 0.0-mg dose and the 0.01-mg dose. The PGFM pulses were subdivided into three different prominence categories (<50, 50 to 150, and >150 pg/mL at the peak). In the 50 to 150 category, P_4 concentration increased ($P < 0.05$) between −2 h and 0 h (0 h = peak of PGFM pulse). In the >150 category, P_4 decreased ($P < 0.05$) between −1 h and 0 h, LH increased ($P < 0.05$) at 1 h, and luteal blood flow apparently decreased ($P < 0.05$) at 2 h of the PGFM pulse. The novel results supported the following hypotheses: (1) an increase in E_2 concentration increases the prominence of a PGFM pulse, and (2) greater prominence of a PGFM pulse is associated with a greater transient intrapulse depression of P_4 at the peak of the PGFM pulse. In addition, the extent of the effect of prostaglandin $F_{2\alpha}$ on the increase in LH and changes in blood flow within the hours of a PGFM pulse was related positively to the prominence of the PGFM pulse.

Keywords: Estradiol; Heifers; LH; Luteolysis; PGFM pulses; Progesterone

1. Introduction

In heifers, secretion of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) from the uterus induces luteolysis [1,2], and the onset of luteolysis begins 15, 16, or 17 d after ovulation [3]. Because of rapid metabolism in the lungs and short half-life of $PGF_{2\alpha}$ [4], the concentrations of the $PGF_{2\alpha}$ metabolite 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) often are used to represent the secretion of $PGF_{2\alpha}$. The half-life of PGFM is about 8 min, compared with <1 min for $PGF_{2\alpha}$ [4]. A sampling interval of 1 h has been recommended for detection of PGFM pulses in cattle [5,6]. Each pulse of PGFM is several hours in duration [7], and sequential pulses of $PGF_{2\alpha}$, as determined by PGFM concentrations, are needed to induce complete luteolysis in cattle [8], horses [9], and sheep [10].

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The regulation of $PGF_{2\alpha}$ secretion and subsequent timing of luteolysis in cattle involves expression of receptors for estradiol (E_2), progesterone (P_4), and oxytocin in the endometrium [11,12]. The concentration and day of exposure of uterus to E_2, P_4, and oxytocin are involved in the stimulation of $PGF_{2\alpha}$ production [13–15]. Exposure of the uterus to P_4 for 10 to 14 d after ovulation is required for an increase in the capacity of the endometrium for $PGF_{2\alpha}$ secretion [11]. The E_2 from developing ovarian follicles has been proposed to have a pivotal role in the induction of luteolysis in heifers [15–17] and sheep [18]. In this regard, luteolysis is delayed after destruction of ovarian follicles by electrocautery in sheep [19] and x-ray irradiation [16,20] or aspiration of follicle contents in heifers [15].

The PGFM pulses during luteolysis are more prominent than during preluteolysis [3,7] and are temporally associated with a greater concentration of E_2 during early luteolysis than during preluteolysis [21]. A pharmacologic dose (1 or 3 mg) of E_2 given intramuscularly or intravenously induces $PGF_{2\alpha}$ secretion within 6 to 8 h [14,22]. A treatment of 0.1 mg of E_2 [23,24] given 14 d after ovulation stimulates a prominent pulse of PGFM. A single treatment of 0.1 mg of E_2 results in a concentration of E_2 [23] similar to reported [25] concentrations in the preovulatory E_2 surge in heifers. Although the dose was considered physiological with reference to the preovulatory surge, the resulting concentration was greater than the concentration at the onset of luteolysis in cattle [26–28]. Thus, the effect of treatment with a physiological dose of E_2 on stimulation of $PGF_{2\alpha}$ production is not known.

During the last PGFM pulse of the preluteolytic period, P_4 decreases concomitantly with the increase in the ascending portion of the PGFM pulse. The P_4 suppression at the PGFM peak is followed by an increase or rebound in P_4 to a concentration that is similar to the concentration before the pulse [3,28]. A P_4 rebound also occurs after the peak of an E_2-induced PGFM pulse [23,24] and 1 or 2 h after the beginning of infusion of $PGF_{2\alpha}$ to simulate a spontaneous PGFM pulse [29,30]. The negative effect of $PGF_{2\alpha}$ on P_4 concentration is balanced against a positive effect of LH pulses during the end of the preluteolytic period and early in luteolysis, based on temporal relationships [21,31]. The LH increase during an LH pulse contributes to the increase in P_4 during a P_4 fluctuation [32,33], including the P_4 rebound that occurs after the P_4 suppression at the peak of a PGFM pulse [21].

During spontaneous luteolysis, the percentage area of the corpus luteum (CL) with color-Doppler signals of blood flow increases during the ascending portion of a PGFM pulse, reaches maximum at the peak of the pulse, and decreases after 2 h [2]. The luteal blood flow also increases in heifers concomitantly with the P_4 rebound after the peak of an E_2-induced PGFM pulse during the preluteolytic period [24] and during infusion of $PGF_{2\alpha}$ to simulate a PGFM pulse [29].

The purpose of the present experiment was to evaluate the following hypotheses: (1) an increase in E_2 concentration increases the prominence of a PGFM pulse, and (2) greater prominence of a PGFM pulse is associated with a greater transient intrapulse depression of P_4 at the peak of the PGFM pulse. In addition, the relationships between prominence of the PGFM pulse and the intrapulse changes in LH and luteal blood flow were studied.

2. Material and methods

2.1. Animals

Twenty-four dairy heifers (Holsteins) aged 18 to 24 mo and weighing 530 ± 18 kg (range: 490 to 580 kg) were used during June and July in the northern temperate zone. Heifers were selected with docile temperament and no apparent abnormalities of the reproductive tract, as determined by ultrasound examinations [34]. If the heifer presented more than one CL or the single CL was considered undersized (<3 cm^2) on 13 d after ovulation, the heifer was not used. The day of ovulation was determined by daily transrectal ultrasound examinations [34]. The heifers were kept under natural light in an open shelter and outdoor paddock and were maintained by *ad libitum* access to a mixture of alfalfa and grass hay, water, and trace-mineralized salt. Heifers remained healthy and in good body condition throughout the experiment. Animals were handled in accordance with the US Department of Agriculture Guide for Care and Use of Agricultural Animals in Research (Institutional Animal Care and Use Committee No. A-07-3400-A01250).

2.2. Follicle ablations

Ultrasound-guided transvaginal ablation of ovarian follicles was performed 13 d after ovulation to remove the follicle source of the circulating E_2, with the expectation that follicle ablation would favor an increase in the synchrony of PGFM pulses after an E_2 treatment; synchrony was not obtained when an E_2 treatment was given without previous follicle ablation [23,24]. Follicle ablation was performed as described [35]. Briefly, a