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Two-way coupling between FSH and the dominant follicle in heifers

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ABSTRACT

Follicular Wave 1 and 2 and the associated FSH Surge 1 and 2 were used to designate the first two waves and surges of the interovulatory interval in two experiments in heifers. In experiment 1, a group with early (group E, N = 9) and late (group L, N = 5) development of the dominant follicle of Wave 1 were used as natural models to study FSH/follicle coupling. The day of wave emergence and the day of deviation in diameters between the two largest follicles were not different between groups. Emergence of Wave 2 and maximal FSH concentration in Surge 2 was approximately 1 day later ($P < 0.03$) in group L. Diameter of the dominant follicle of wave 1 (13.8 ± 0.3 mm vs. 12.0 ± 0.3 mm) and FSH concentrations in Surge 2 (0.29 ± 0.02 ng/mL vs. 0.21 ± 0.03 ng/mL) were first greater ($P < 0.05$) in group E than in group L at 4 and 5 days, respectively, after wave emergence. In experiment 2, treatment with estradiol (N = 8) when the dominant follicle of Wave 1 was ≥11 mm (Hour 0) resulted in a decrease ($P < 0.02$) in FSH and slower ($P < 0.05$) growth rate of the follicle between Hours 0 and 4. Results supported the following hypotheses: (1) the FSH surge that stimulates emergence of a follicular wave is associated with final growth of the dominant follicle of the previous anovulatory wave; and (2) suppression of FSH Surge 2 when the dominant follicle of Wave 1 is ≥11 mm is associated with a decrease in diameter. It is concluded for the first time that two-way FSH/follicle coupling in heifers continues during final growth of the dominant follicle of Wave 1 and that Surge 2 is the FSH source.

1. Introduction

Either two or three follicular waves develop during the estrous cycle or interovulatory interval (IOI) in cattle [1–3]. The first wave of the IOI (Wave 1) is the most extensively studied and has the most consistent characteristics of the follicles and associated hormone concentrations [4]. Usually one follicle in each wave becomes dominant and reaches ovulatory capacity at 10 mm [5]. A separate FSH surge stimulates the emergence of each follicular wave, and the surge is distinctive even when based on daily blood sampling [6,7]. The FSH surges that stimulate Wave 1, 2, and 3 are designated Surge 1, 2, and 3, respectively. Emergence of Wave 1 with 4 or 5 mm follicles and maximum concentration in FSH Surge 1 occur just before or on the day of ovulation. Deviation in diameter between the two largest follicles of a wave occurs when the largest follicle is approximately 8.5 mm or 2.5 days after follicle emergence at 4 or 5 mm [8]. Deviation is characterized by continuation in the rate of growth of the developing dominant follicle and the beginning of a decrease in the rate of growth of the remaining or subordinate follicles [4,8].

A close two-way functional coupling between FSH and the follicles is an integral component of FSH/follicle relationships from emergence to deviation [9]. The decline in FSH beginning at follicle emergence represents a function of the multiple growing follicles; follicles acquire the ability to suppress FSH during their growth from 3 mm to 5 mm [10]. The initial FSH suppression is attributed to inhibin [4,8]. By the time deviation occurs, estradiol contributes to the continuing FSH decline [4,11]. Estradiol increases in the follicular fluid of the largest follicle and in the systemic circulation at approximately the expected time of deviation

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[12–14]. The decrease in FSH is imposed by the follicles, but the follicles continue to require the decreasing FSH, indicated by a decrease in diameter of the three largest follicles within 8 hours during estradiol-imposed reduction of FSH to less than the concentrations at the middle of the FSH decline [9]. The FSH/follicle relationship changes from multiple- to single-follicle coupling at the beginning of deviation. The coupling from the single follicle to FSH has been demonstrated by an FSH increase within 4 or 5 hours after ablating the largest follicle at the expected beginning of deviation [9,11]. Coupling in the opposite direction (from FSH to the single follicle) has been demonstrated by an interference with growth of the largest follicle within 6 hours after estradiol treatment to depress FSH concentrations to less than the concentrations at the expected beginning of deviation [9,11,15]. The more developed largest follicle not only withstands but also requires the low FSH concentrations associated with deviation. In contrast, the smaller follicles are not further inhibited when FSH is experimentally reduced to less than the concentrations in control samples at the expected beginning of deviation [9]. Apparently, a developmental change occurs in the largest follicle by the beginning of deviation so that it is responsive to a concentration of FSH that is inadequate for the smaller follicles, thereby initiating deviation.

On the day after deviation, near the ending nadir of the FSH surge that stimulated emergence of the wave [11], the dominant follicle is approximately 10 mm and has acquired the capacity to ovulate [5]. The continued development is driven at least partly by LH (reviewed in Ginther [4], and Ginther et al. [8,16]). For example, follicles do not grow beyond 7 to 9 mm when LH is suppressed [17]. Although LH concentration is slight (<1 ng/mL), concentrations increase before deviation and decrease after deviation [11,18,19]. Specific studies are lacking on the role of FSH on the continued growth of the dominant follicle after dominance or ovulatory capacity is established. At the ending nadir of the FSH Surge 1 on the day after deviation, FSH begins to increase as the ascending portion of Surge 2. Thus, FSH concentrations increase after the follicle is approximately 10 mm, but apparently it has not been considered whether the increase in FSH in Surge 2 has a role in the continued development of the dominant follicle of Wave 1. Although not commented on, inspection of published follicle and FSH profiles in cattle [6,7] indicate that the final growth and regression of the dominant follicle of Wave 1 are temporally associated with the increase and decrease, respectively, in FSH during Surge 2. This observation provides rationale for specific hypotheses.

In experiment 1, two groups of heifers with different data profiles for the diameters of the dominant follicle of Wave 1 were used. Hypothesis 1 was that the FSH surge that stimulates the emergence of a follicular wave is associated with the final growth of the dominant anovulatory follicle of the previous wave. The temporal relationship between maximal diameter of the dominant follicle of Wave 1 and maximal FSH concentrations during Surge 2 and the circulatory concentrations of LH and estradiol during Wave 1 were also considered. In experiment 2, FSH concentration was reduced by a single treatment with a single dose of estradiol when the dominant follicle of Wave 1 was ≥11 mm. Hypothesis 2 was that suppression of FSH Surge 2 when the dominant follicle of Wave 1 is ≥11 mm is associated with a diameter decrease.

2. Materials and methods

2.1. Heifers

Holstein dairy heifers (*Bos taurus*) aged 18 to 24 months were used during June to August in the northern temperate zone. The heifers were kept in natural light in an open shelter and were provided *ad libitum* access to water, trace-mineralized salt, and primarily grass hay. The IOIs were natural in that they did not involve induced luteolysis, induced ovulation, or synchronization of estrus or ovulation before or during the IOI. The day of ovulation preceding the experiment was determined using transrectal ultrasonic imaging [20]. An IOI was not used if two ovulations occurred at the beginning or end of the IOI. Heifers were handled in accordance with the US Department of Agriculture Guide for Care and Use of Agricultural Animals in Research.

2.2. Experiment 1

Follicle data and blood samples were collected daily; previous studies have shown that the changing diameter of the dominant follicle and the changing concentrations in the FSH surge can be compared adequately from data obtained daily [6,7]. Ultrasonic examinations were done from ovulation to 13 days after ovulation to obtain most of the daily diameter changes of the dominant follicle of Wave 1, including diameters during the initial regressing phase and the complete FSH Surge 2. Follicles ≥6 mm in diameter were identified from day to day as described [20]. The emergence of Waves 1 and 2 was defined retrospectively as the day that the dominant follicle of the wave was 6 mm with an increase in diameter the next day. The day of emergence of Wave 1 was used as the reference point because data seemed less variable than for the ovulation reference point. This was indicated by the apparent reduction in standard error of the means and smoother follicle and hormone data profiles.

As a part of a previous study [21], heifers were divided according to the locations of the extant CL and preovulatory follicle in the contralateral or opposite ovaries (group E, N = 9) or in the ipsilateral or same ovary (group L, N = 5). The previous study demonstrated that the dominant follicle of Wave 1 emerged at 6 mm on the same day in each group, but the postdeviation diameter increase was earlier for group E and later for group L. In the current study, comparisons were made between groups for diameters of the dominant follicle of Wave 1, FSH concentrations for Surge 2, and LH and estradiol concentrations temporally associated with follicle deviation during Wave 1. In addition, FSH, LH, and estradiol for each group were normalized to the day of maximum diameter of the dominant follicle of Wave 1 and were studied from 4 days before to 5 days after the maximum diameter. This was done to consider the temporal relationships of the hormones during FSH Surge 2