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Regulation and Function of Gonadotropins Throughout the Bovine Oestrous Cycle

Mark A. Crowe and Michael P. Mullen

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<http://dx.doi.org/10.5772/53870>

1. Introduction

Gonadotropins are protein hormones secreted by the pituitary gland and include luteinizing hormone (LH) and follicle stimulating hormone (FSH). Both LH and FSH govern the estrous cycle i.e. the cyclical pattern of ovarian activity that facilitates the transition of female animals between periods of reproductive non-receptivity to receptivity enabling mating and subsequent pregnancy. The onset of estrous cycles occurs at the time of puberty. In heifers puberty occurs at 6–12 months of age, generally at a weight of 200–250 kg. The normal duration of an estrous cycle in cattle is 18–24 days. The cycle consists of two discrete phases: the luteal phase (14–18 days) and the follicular phase (4–6 days). The luteal phase is the period following ovulation when the corpus luteum (CL) is formed (often further designated as met-estrus and diestrus), while the follicular phase is the period following the demise of the corpus luteum (luteolysis) until ovulation (often further designated as pro-oestrus and oestrus). During the follicular phase, final maturation and ovulation of the ovulatory follicle occurs, the oocyte is released into the oviduct allowing the potential for fertilization.

2. Gonadotropin regulation of follicle growth during the estrous cycle

Cattle are polyestrous animals and display estrous behavior approximately every 21 days. The estrous cycle is regulated by the hormones of the hypothalamus (gonadotropin-releasing hormone; GnRH), the anterior pituitary (follicle-stimulating hormone; FSH and luteinizing hormone; LH), the ovaries (progesterone; P₄, estradiol; E₂ and inhibins) and the uterus (prostaglandin F_{2α}; PGF). These hormones function through a system of positive and negative feedback to govern the estrous cycle of cattle [1]. GnRH was first isolated from the hypothalamus of pigs and is a decapeptide [2, 3]. Its control of the estrous cycle is mediated via its actions on the anterior pituitary which regulates the secretion of the gonadotrophs, LH and FSH [4].

The pulsatile secretion of basal levels of GnRH from the tonic center of the hypothalamus and the pre-ovulatory surge of GnRH from the surge center of the hypothalamus prevents the desensitisation of the GnRH receptor on the gonadotroph cells of the anterior pituitary. After transportation of GnRH from the hypothalamus to the pituitary gland via the hypophyseal portal blood system [5], GnRH binds to its G-protein coupled receptor on the cell surface of the gonadotroph cells [6]. This binding releases intracellular calcium which activates intermediaries in the mitogen activated protein kinases (MAPK) signaling pathway culminating in the release of FSH and LH from storage compartments in the cytoplasm [7]. FSH is only stored in secretory granules in the cytoplasm for short periods of time, whereas LH is stored for longer periods during the estrous cycle [8]. During the follicular phase of the estrous cycle there is a hormonal environment of basal progesterone due to the regression of the corpus luteum (CL). The increased E2 concentrations, derived from the rapid proliferation of the pre-ovulatory dominant follicle (DF), concomitant with the decrease in circulating concentrations of progesterone, induces a surge in GnRH and allows the display of behavioral estrus during which heifers/cows are sexually receptive and will stand to be mounted [9]. This pre-ovulatory GnRH surge induces a coincidental LH and FSH surge [10]. Only when serum progesterone concentrations are basal and LH pulse frequency increases to one per hour for 2–3 days does the DF ovulate [1]. Ovulation occurs 10–14 h after estrus and is followed by the luteal phase of the estrous cycle. The beginning of the luteal phase is also known as met-estrus and typically lasts 3–4 days. It is characterised by the formation of the CL from the collapsed ovulated follicle (corpus haemorrhagicum). Following ovulation, progesterone concentrations begin to increase due to the formation of the CL in which the granulosa and theca cells of the ovulated DF luteinize and produce progesterone in readiness for the establishment and maintenance of pregnancy and/or resumption of the estrous cycle [11]. During the di-estrous phase, progesterone concentrations remain elevated and recurrent waves of follicle development continue to be initiated by release of FSH from the anterior pituitary. However, these DFs that grow during the luteal phase of the estrous cycle do not ovulate, due to inadequate LH pulse frequency.

The progesterone dominant luteal phase of the estrous cycle, through negative feedback, only allows the secretion of greater amplitude but less frequent LH pulses (one pulse per 3 to 4 hours) that are inadequate for ovulation of the DF [12]. Finally, during the pro-estrous period, progesterone concentrations decrease when the CL regresses in response to PGF secretion from the uterus [13].

3. Gonadotropin regulation of final maturation of the pre-ovulatory follicle and ovulation

The growth, development and maturation of ovarian follicles are fundamental processes for high reproductive efficiency in farm animals. A fixed number of primordial follicles are established during fetal development with ovarian follicle growth taking a period of 3–4 months and categorized into gonadotropin independent and gonadotropin dependent stages [14]. Gonadotropin dependent follicle growth in cattle occurs in waves with 2–3 waves per estrous cycle [15, 16 Fig.1].

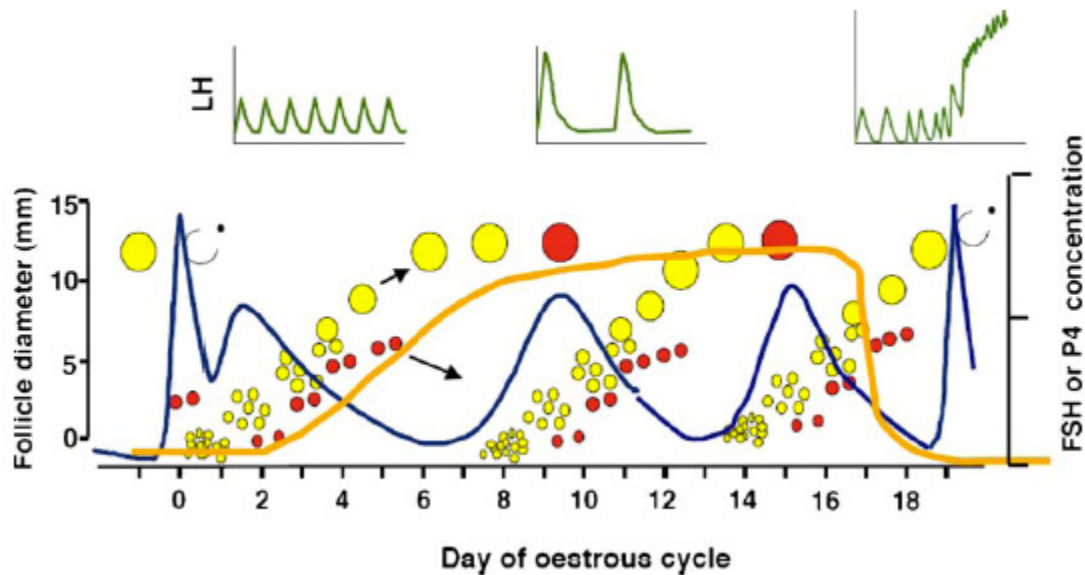


Figure 1. Schematic depiction of the pattern of secretion of follicle-stimulating hormone (FSH; blue line), luteinizing hormone (LH; green lines), and progesterone (P4; orange line); and the pattern of growth of ovarian follicles during the estrous cycle in cattle. Each wave of follicular growth is preceded by a transient rise in FSH concentrations. Healthy growing follicles are shaded in yellow, atretic follicles are shaded red. A surge in LH and FSH concentrations occurs at the onset of estrus and induces ovulation. The pattern of secretion of LH pulses during an 8-h window early in the luteal phase (greater frequency, lesser amplitude), the mid-luteal phase (lesser frequency, lesser amplitude) and the follicular phase (high frequency, building to the surge) is indicated in the inserts in the top panel. Taken from [17].

Each wave of growth involves emergence, selection and dominance followed by either atresia or ovulation of the DF. As mentioned above both FSH and LH have a prominent role in ovarian follicle development. Given that follicles are involved in the positive and negative feedback mechanisms of the hypothalamic–pituitary–gonadal (HPG) axis (estradiol and inhibins), these hormones have a governing role in the regulation of the estrous cycle of cattle. The beginning of gonadotropin dependent follicle development is typified by the emergence of a follicle cohort typically consisting of 5–20 follicles ≥ 5 mm and is correlated with a transient increase in FSH concentrations [10, 18]. This marks the beginning of dependency of follicle growth on FSH [19] with FSH receptors (FSH-R) localized within the granulosa cells of the follicles by Day 3 of the follicle wave [20, 21]. This enables FSH to perform its required down stream signalling effects including promoting cellular growth and proliferation [22, 23]. These transient increases in FSH concentrations also leads to an increase in aromatase enzyme activity (P450arom; CYP19), in the granulosa cells of ovarian follicles, which converts androgen to estrogen [24]. As the DF is selected from the cohort of follicles, the diameter increases and it is recognized as the largest healthy follicle in the cohort [25]. This increase in size leads to an increase in follicular fluid estradiol and inhibin concentrations [24]. Dominance occurs when the DF reaches 9 mm in diameter, and it actively suppresses FSH, thus preventing further follicle wave emergence until the DF either undergoes atresia or ovulated. The increase in estradiol concentrations in concert with inhibin are the key endocrine signals that suppress FSH concentrations from the anterior

pituitary gland via negative feedback reducing FSH to basal concentrations [10, 26, 27]. The selected DF becomes increasingly responsive to LH [27] and continues growth in the face of decreasing FSH concentrations. Irrespective of the stage of the estrous cycle during which follicles develop, the switch from FSH [18] to LH dependency [28] is propagated through the presence of LH receptors (LH-R) on the granulosa cells [29]. LH-R are localised to the theca and granulosa cells of healthy follicles, at different stages of follicle development [20]. As the follicle grows, the theca cell LH-R increases and LH-R is acquired by the granulosa cells of the follicle undergoing selection to become the DF [29-31]. Moreover, evidence suggests transient increases in circulating LH concentrations that occur at or around the time of follicle selection [32], allows the DF to continue E2 production and grow in the face of declining FSH concentrations [33]. During the early luteal phase lesser amplitude and greater frequency (20–30 pulses/24 h) LH pulses occur, in the mid-luteal period LH pulses are of greater amplitude and lesser frequency (6–8 pulses/24 h) both of which are of insufficient amplitude and frequency for final maturation and subsequent ovulation of the DF [12]. Thus, the DFs produced during the luteal phase of the estrous cycle undergo atresia, E2 and inhibin production decreases, and removes this negative feedback block to the hypothalamus/pituitary, FSH secretion can increase and a new follicle wave emerges. The production of high concentrations of estradiol is a defining characteristic of the DF [33, 34] and prior to visible differences in follicle diameter; the putative DF has greater follicular fluid concentrations of estradiol compared with other follicles in its cohort [10, 35, 36]. The synthesis of estradiol is dependent on the production of androgens in the theca cells and subsequent aromatisation of these androgens to estrogens in the granulosa cells known as the two cell/two gonadotropin model [37]. Production of estradiol from growing follicles is dependent on sufficient LH pulse frequency [38, 39]. The binding of LH to its receptors in the theca cells drives the conversion of cholesterol to testosterone through a series of catalytic reactions [40]. Testosterone, once produced in the theca cells, diffuses out into the granulosa cells where it is converted to estrogens by the aromatase enzyme [40]. Estradiol not only has a local effect on follicle development, but it also has a systemic role via a positive feedback mechanism to the hypothalamus and pituitary gland. During the follicular phase of the estrous cycle, when progesterone concentrations are basal, this large concentration of estradiol produced by the pre-ovulatory DF induces a GnRH surge from the hypothalamus. The resulting LH surge is of sufficient amplitude and frequency to stimulate final maturation and ovulation of the DF [10]. The increased estradiol concentrations also induces expression of estrous behaviour, required for successful mating [41]. Other intra-ovarian produced factors play a role in regulating the estrous cycle either indirectly by altering the synthesis of estradiol or via direct negative feedback mechanisms to the hypothalamus and the anterior pituitary gland. The insulin like growth factor (IGF) super-family consisting of its two ligands IGF-I and IGF-II [42-44], two receptors IGFR-I and IGFR-II [45], and its numerous binding proteins and proteases (IGFBP 1-6, pregnancy-associated plasma protein-A: PAPP-A) are responsible for the bioavailability of IGF-1 in the ovarian follicle. The bioavailability of IGF-I contributes to the growth, proliferation and steroidogenic capacity of the future DF [36, 46, 47], indirectly affecting the estradiol induced negative feedback mechanism to the hypothalamus and pituitary. This in addition to early

acquisition of LH receptors by the granulosa cell layer of the follicle undergoing selection are considered to be the main mechanisms facilitating the process of follicle selection [48]. The transforming growth factor beta (TGF) super-family contains over 30 structurally related proteins including ligands (TGF, anti-mullerian hormone, inhibins, activins, and bone morphogenetic proteins (BMP's), receptors (TGFRI and II, activin receptor-like kinases; ALK's, accessory receptors (TGF-RIII) and downstream signaling molecules (similar to mothers against decapentaplegic; SMADS). The ligand members of this super-family were first identified in follicular fluid through their modulation of secreted FSH [49]. Activin can increase the production of estradiol in follicular fluid [50] whereas follistatin impedes activins' positive steroidogenic effects, both of which can alter the estradiol feedback mechanism to the hypothalamus and pituitary [51]. Inhibins which have been detected in granulosa cells in cattle play a role in the suppression of FSH secreted in the anterior pituitary also regulating the oestrous cycle [52].

4. Estrous behavior

A recent review of the literature [53] reported mean inter-ovulatory intervals of 22.9 and 22.0 days for lactating dairy cows and heifers, respectively. Standing to be mounted by a bull or herd mate is the primary and most definitive sign of oestrus in cattle. Estrogen, specifically, estradiol, is the primary signal to the brain that induces expression of estrus, but only in the absence of progesterone [54]. It appears that stressors which elevate blood concentrations of cortisol are capable of delaying or blocking the pre-ovulatory LH surge and affecting the expression of estrus without altering pro-oestrous concentrations of blood oestradiol (see review by [55]). In a recent review, Diskin [56] calculated that for dairy cows the average duration of standing estrus was 8.1 h with 9.1 standing events or mounts recorded during standing estrus. There is evidence [57] that the duration of standing estrus decreases as milk production increases (14.7 and 2.8 h in cows yielding 25 or 55 kg milk, respectively). For heifers it would appear that the duration of standing estrus is somewhat longer, 12–14 h [56]. For beef cows, kept indoors, the average duration of standing estrus has been reported to be less than 8.5 h [56]. Both the duration of standing estrus and intensity of estrous expression are affected by a range of environmental factors including under foot surface type, size of the sexually active group and the presence of a bull [56]. Breaks or quiescent interludes in standing activity have also been observed in 30% of dairy cows at [58] while breaks with an average duration of 2.6 h in 67% of beef heifers have been recorded [59]. There is no evidence from dairy cows [60], beef cows or heifers [56] that either the onset of standing estrus or end of estrus follows any distinct diurnal pattern.

5. Gonadotropin regulation of Corpus luteum function

The CL originates from the cells of the ovulatory follicle. LH, the major luteotropic hormone in cattle [61], is responsible for stimulating luteinization of the theca and granulosa cells of the pre-ovulatory follicle into luteal cells [62]. The function of the CL is to produce sufficient concentrations of progesterone throughout the luteal phase of the estrous cycle to maintain

pregnancy (if a conceptus is present) and during pregnancy, to decrease gonadotropin secretion and prevent behavioral oestrus occurring. Progesterone is required for the maintenance of pregnancy with many studies reporting a positive association between progesterone concentrations and the probability of embryo survival [63-66]. The proposed mechanisms by which progesterone affects embryo survival are indirect, not acting on the embryo itself but via effects on the uterine endometrium [67, 68]. Available evidence in both cattle and sheep, has identified that sustained increased concentrations of progesterone during the luteal phase of the estrous cycle alters the expression pattern of genes in the uterus [69-73] which in turn alters the composition of the uterine histotroph i.e. availability of enzymes, carrier proteins, hormones and nutrients to the developing embryo prior to implantation [68]. Moreover, alterations in systemic progesterone during the early luteal phase have been shown to have significant effects on conceptus elongation [67, 71, 74]. During the mid-luteal phase, these sustained high concentrations of circulating progesterone down regulate the nuclear progesterone receptor in the luminal epithelium of the endometrium [75]. This is a critical switch in allowing the synchronous increase or decrease in genes of the endometrium that are required to initiate uterine receptivity – regardless of the pregnancy status of the animal [76]. If, by Day 16 of the estrous cycle, the maternal recognition of pregnancy signal (interferon tau) has not been detected in sufficient quantities, luteolysis of the CL occurs. PGF is secreted by the uterus in the bovine [77] and is the major luteolytic hormone in ruminants [78-80]. Oxytocin receptors in the uterus binds oxytocin which propagates the episodic secretion of PGF from the uterus. PGF then mediates the luteolytic mechanism via countercurrent exchange between the uterine vein and the ovarian artery (Fig. 2), inducing regression of the CL. This reduces circulating progesterone concentrations, estradiol concentrations increase and GnRH in the hypothalamus is stimulated as the animal enters the follicular phase of the estrous cycle.

6. Conclusions

The estrous cycle in cattle is typically 18–24 days in duration, with estrous behavior expressed for a 2–24-h period during the late follicular phase. During normal estrous cycles there are typically two to three and occasionally four waves of follicular growth each involving a period of emergence, selection and dominance followed by either atresia or ovulation of the DF. The gonadotropin hormones FSH and LH are the main regulators of folliculogenesis and steroidogenesis with LH being the major luteotrophic hormone. LH pulse frequency is the major determinant affecting the ultimate fate of a selected DF. Pulsatile PGF of uterine origin is the main hormonal signal that induces luteolysis of the CL and the switch from the luteal to the follicular phase of the estrous cycle.

Author details

Mark A. Crowe* and Michael P. Mullen

School of Veterinary Medicine, University College Dublin, Ireland

* Corresponding Author

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