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Bhuvana Plakkot
Department of Veterinary Physiology, Kerala Veterinary and Animal Sciences University, College of Veterinary and Animal Sciences, Mannuthy, Kerala, India

Shiji Sheeja Saju
Department of Veterinary Physiology, Kerala Veterinary and Animal Sciences University, College of Veterinary and Animal Sciences, Mannuthy, Kerala, India

Raji Kanakkaparambil
Department of Veterinary Physiology, Kerala Veterinary and Animal Sciences University, College of Veterinary and Animal Sciences, Mannuthy, Kerala, India

Correspondence
Bhuvana Plakkot
Department of Veterinary Physiology, Kerala Veterinary and Animal Sciences University, College of Veterinary and Animal Sciences, Mannuthy, Kerala, India

A review article on gonadotropins and their significant contribution in ovarian follicle development

Bhuvana Plakkot, Shiji Sheeja Saju and Raji Kanakkaparambil

Abstract
In all mammals, release of gonadotropins is a pulsatile process which appears to be the result of periodic secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus into the pituitary portal circulation. Follicle-stimulating hormone (FSH) and Leutinizing hormone (LH) are gonadotropins discharged by the pituitary gland that coordinate antral folliculogenesis and ovulation in female ovaries. Wave-like ovarian follicular growth pattern is observed in cattle, sheep, goat, horse and human. In the follicular phase of estrus cycle, several antral follicles undergo atretic degeneration, while only very few progresses towards ovulation. Every follicular wave includes recruitment, selection and dominance phases. The recruitment and selection processes govern the number of ovulatory follicles in these species with FSH and eventually LH playing prime roles. Through the postive and negative feedback mechanisms with the hypothalamo-pituitary axis, these hormones provide the basic process that regulates follicular recruitment, selection and dominance. Along with the adjustment of threshold levels of these hormones, differentiation between monovulatory and polyovulatory species is defined and thereby these hormones play a major role in prolificacy.

Keywords: Follicle-stimulating hormone, follicular wave, luteinizing hormone, ovulatory follicles, prolificacy

1. Introduction
The Follicle-stimulating hormone (FSH) and Leutinizing hormone (LH), also termed as the Gonadotropins, are the main regulators of follicular development and steroid hormone synthesis in the ovary. They are synthesised and secreted by the pituitary gland, under the stimulation of Gonadotropin releasing hormone (GnRH) secretion from the hypothalamus, and coordinates antral folliculogenesis and ovulation. The effect of GnRH is decided by its pulse frequency whereby, fast frequencies initiates LH release and slow frequencies initiates FSH release (Nicol *et al.* 2008) [1]. Being heterodimeric glycoprotein hormones, they consist of an α-subunit which is common to both FSH and LH, and unique β-subunits that confer biological activity and specificity to these hormones (Pierce and Parsons, 1981; Gharib *et al.*, 1990) [2, 3].
Coordination of follicle maturation with sexual behaviour and preparation for pregnancy occurs because of positive and negative feedback loops in the hypothalamic-pituitary-gonadal axis. The transforming growth factor-β superfamily members such as activins, inhibins, bone morphogenetic proteins (BMP) affects FSH release independently, rather than LH (Nicol *et al.*, 2008) [1]. Growth factors produced by ovaries such as activin, inhibin and follistatin modulate FSH secretion and local regulation of follicle development. Activin increases FSH synthesis and secretion whereas, inhibin and follistatin reduces it. Activin in pre-antral follicles causes elevation of granulosa cell number, FSH receptors and aromatase expression that in turn causes increased estradiol production (Macklon *et al.*, 2006) [4]. LH-induced androgen synthesis in theca cells are stimulated by inhibins (Roche, 1996) [5].
The follicles respond to gonadotropins in the presence of both these hormones and their receptors. Gonadotropin receptors include the follicle-stimulating hormone receptor (FSHR) and luteinizing hormone receptor (LHR) that binds to follicle - stimulating hormone (FSH) and luteinizing hormone (LH), respectively. Folliculogenesis includes regulation of the expression of these receptors and their connection with specific signal transduction pathways.
FSH acts solely on granulosa cells of the ovarian follicles by binding to specific membrane receptors (FSHRs) (Richards, 1980) [6]. This in turn stimulates granulosa cell proliferation and differentiation. FSH is chiefly responsible for the development of ovarian follicles, recruitment of the dominant follicles and LHR induction in granulosa cell.

LH stimulates androgen synthesis within the ovarian theca cells, further leading to ovulation and luteinisation (Marshall and Kelch, 1986) [7]. Paracrine signalling activated by FSH and LH maintains growth and oestrogen secretion until a LH surge is discharged by the pituitary gland to induce ovulation. The LH surge triggers a series of reactions leading to the recommencement of meiosis in oocytes, an increase in the number of cumulus cells, follicle rupture and the corpus luteum formation (luteinisation) (Edson *et al*., 2009) [8].

2. Synthesis and secretion of gonadotropins

The hypothalamic neurons synthesize and secrete gonadotropin-releasing hormone (GnRH) which is a decapeptide hormone. The GnRH secretion is positively controlled by the neurotransmitters such as the catecholamines, epinephrine and norepinephrine, and negatively by the endogenous opioids such as β-endorphin. The GnRH in turn binds to its receptors present on the gonadotropes (gonadotropin secreting cells) in the pituitary and stimulates the synthesis and secretion of LH and FSH. Around 7-14% of cells in the anterior pituitary gland are gonadotropes. The same gonadotrope cell secretes both FSH and LH (Nakane, 1970) [9].

FSH is mostly secreted via the constitutive pathway in which the rate of synthesis is almost equal to the rate of release. Basal levels of LH are also released through the constitutive pathway; however, majority of LH is generally packaged in granules and stored in secretory vesicles for regulated release of hormone, which is called secretory pathway. LH has been observed to be associated secretogranin II (a secretory protein) as electron dense granules in the secretory vesicles (Anouar and Duval, 1992; Vallet *et al*., 1995; Crawford and McNeilly, 2002) [10, 11, 12]. Granules are then released from the gonadotropes by exocytosis upon appropriate signal(s), mainly under the influence of GnRH, during the preovulatory surge. Therefore, differential packaging of LH and FSH into separate granules is important for their varying release during the reproductive cycles. In every cycle this is the method in which process of synthesis, storage and release of gonadotropes occurs (McNeilly *et al*., 2003) [13].

The plasma half-life of FSH is 2 to 4 hours whereas; LH has a shorter half-life of 30 to 90 minutes. Observations from various studies show that the higher sialic acid content in FSH is responsible for its longer half-life in circulation compared to LH (Chappel *et al*., 1983) [14].

3. Functions of gonadotropins in the female

FSH plays major roles in selection of the dominant Graafian follicle, development of its follicular cavity (the antrum) and for the expression of LH receptors on granulosa cells. Lack of the hormone results in follicular death by apoptosis or follicular atresia. FSH, along with the midcycle LH surge, is entailed for ovulation to occur. Further luteinisation (formation of corpus luteum) is stimulated by LH.

The theca interna compartment when stimulated by luteinizing hormone (LH) synthesizes androgen. FSH stimulates aromatase activity in the granulosa cells and converts androgen to estradiol (Fortune, 1994) [15]. FSH also stimulates the synthesis of the steroid hormone progesterone by the granulosa cells and LH is necessary for the maintenance of progesterone production by the corpus luteum. Therefore, synergistic action of LH and FSH is essential to regulate the production of steroids by the ovary.

4. Gonadotropin receptors

Gonadotropin receptors are follicle-stimulating hormone receptor (FSHR) and a luteinizing hormone receptor (LHR). These are members of the rhodopsin/β2 adrenergic receptor subfamily of seven G-protein- coupled transmembrane receptors.

Primordial follicles were observed to be devoid of FSHR expression. However, in the secondary follicle, along with the theca cells appearance, FSHR was observed to exist on the surface of the granulosa cells (Yamoto *et al*., 1992) [16]. The FSHR expression increased from the preantral to the antral stage of follicular growth. Thus, the antral follicles begin to respond to FSH. Further, induction of LHR expression in the granulosa cells occurs under the influence of FSH stimulation. At the secondary follicle stage, LHR expression was observed in theca cells (Yung *et al*., 2014) [17]. However, LHR expression in the granulosa cells at this stage was ambiguous before FSH stimulation.

Once the induction of LHR expression by FSH occurs, multiple local factors coordinately improves its expression and prepares follicles for the LH surge, followed by ovulation. Acquisition of sufficient number of LH receptors is the highest priority for the progression of the follicles towards ovulation. A constant increase in LHR expression is observed until the LH surge. Immediately after the LH surge, a sharp decline in LHR expression in the preovulatory follicles was observed (Nakamura *et al.*, 1991) [18]. LHR upregulation followed this downregulation and it peaked in the mid-luteal phase.

5. Mechanism of action of LH and FSH

FSH and LH binds to their specific G-protein coupled receptors (FSHR and LHR respectively) followed by a rapid stimulation of adenylate cyclase activity. This results in increased levels of cyclic adenosine monophosphate (cAMP) which then interact with the regulatory subunit of protein kinase A, resulting in enhancement of enzymatic activity (Channing and Kammerman, 1974; Richards, 1994; Richards *et al*., 1998) [19, 20, 21]. Activated protein kinase A adds phosphates to other enzymes and changes conformation and modulates their catalytic activity. This causes the activation of transcription factors that regulate gene activity. Eventually, stimulation of steroid genesis occurs. The nature of the steroid produced is controlled by the factors like cell type and species. In differentiated follicles (dominant follicles), LH receptors are present in theca cells whereas, granulosa cells contain both FSH and LH receptors (Hsueh *et al*., 1984) [22].

Androgen is synthesised by the theca cells under the influence of LH (Fortune and Armstrong, 1977; Liu *et al*., 2015) [23,24] and further this androgen crosses the basement membrane, gets converted into estrogen within the granulosa cells under the influence of FSH (Dorrington *et al*., 1975) [25]. The enzyme aromatases present within the granulosa cells convert androgen to estrogen. The granulosa cells also have enzymes that are required for biosynthesis of progesterone. The theca cells contain negligible aromatase activity (Liu and Hsueh, 1986) [26]. The two-cell–two-gonadotropin theory states that the luteinizing hormone stimulates thecal cells to synthesize androgens, and follicle-stimulating hormone stimulates granulosa cells to synthesize estrogens from androgens by the aromatase enzyme activity (Fortune, 1994) [15].

6. Phases of ovarian follicle development

According to Campbell (2009) [27], there are two different

developmental phases for the follicle which is separated by a prolonged intermediate phase. The gonadotropin-independent phase is from initiation of primordial follicle to the late preantral phase in which follicle development appears to be governed by expression of a range of local factors. The phase in which follicles responds to the actions of gonadotrophins but do not need them for normal growth and development is termed as intermediate gonadotropin-responsive phase. The phase from the small antral to large antral follicles is the gonadotropin-dependent phase, as critical threshold concentrations of LH and FSH are highly essential for the follicles of this size to occur.

6.1 Gonadotropin-responsive phase

This phase functionally begins around the beginning of the multi-laminar tertiary stage of the follicles (Picton *et al.*, 2003) [28], which is also around the stage of development in which expression of LH receptor (LHR) mRNA is observed for the first time. This is also when the theca interna starts forming around the granulosa cells (McNatty *et al*., 2000) [29]. This phase is steroidogenic in nature as there will be production of progesterone, androgens and oestradiol in small but significant quantities (Webb *et al.,* 2003) [30]. Along with that, high levels of mRNA and protein for inhibin/activin subunits are expressed by these follicles.

The end of this phase is denoted by the peak of the granulosa cells mitotic index within small antral follicles, along with a characteristic elevation in the rate of follicular atresia and elevation of steroidogenic enzymes and endocrine factors because of the beginning of somatic cells differentiation (McNatty *et al.*, 1999) [31].

6.2 Gonadotropin-dependent phase

The final stages of folliculogenesis lie primarily under the control of FSH and LH, along with the varied expression of both somatic cell and oocyte derived growth factors that modulate the action of gonadotrophins at major stages of follicle development (Webb *et al.*, 2003) [30].

Stimulation of follicle growth and differentiation occurs chiefly under the influence of FSH, however, LH also plays an important role in normal folliculogenesis and oocyte maturation. In a normal cycle, in most of the species, the elevation in pulsatile secretion of LH influences the final maturation and development of antral follicles, and their oocytes, to ovulation (Hillier, 2001) [32]. In addition, LH also influences pituitary FSH release by controlling the level of ovarian oestradiol secretion and inhibin-A secretion whereby, it can indirectly effect on the development of FSH-responsive follicles (Campbell *et al.*, 2007) [33].

7. Wave - like ovarian follicle growth pattern

The wave-like development pattern of antral follicles during the oestrous cycle in cow, sheep, goat, horse, as well as during the human menstrual cycle was developed after the initiation of ultrasound-based research (Evans *et al*., 1994) [34]. The emergence of the first growth wave is considered to be the day of ovulation (Day-0), followed by the second way on day 9-10 in a two-wave cycle whereas, in a three-wave cycle the second wave occurs on day 8-9 and the third on day 15-16 (Mapletoft *et al*., 2002) [35]. Whereby, it clearly defines that growth waves develop during the follicular as well as the luteal phase of the oestrous cycle.

The second dominant follicle (DF) ovulates in mono-ovulatory animals that elicit two-wave growth pattern, whereas the third dominant follicle ovulates in a three-wave pattern. However, dominant follicle from last but one follicular growth wave also ovulates in poly-ovulatory species like sheep and goats (double ovulations).

According to Webb *et al*. (1999) [36], each growth wave can be divided into a recruitment, selection and dominance phase. In the recruitment phase, gonadotrophin stimulates a group of rapidly growing follicles, specifically FSH being majorly responsible for the recruitment of a new group of antral follicles for the next growth wave. Whereas, selection is a phase in which one or more of the recruited follicles are selected for further development. Dominance is a process in which one or several dominant follicles undergo rapid development at the same time when, growth and development of other follicles are suppressed.

7.1 Role of gonadotropins in follicle recruitment, selection and dominance

Recruitment indicates a group of antral follicles that escapes apoptosis due to elevated levels of circulating FSH. As a consequence of dominant follicle regression during a growth wave, or ovulation at the end of an oestrous cycle, a transient elevation of circulating FSH occurs. The loss of dominant follicle causes reduction of hormones (such as estrogen and inhibin) synthesized by the follicle. As a result of elimination of negative feedback mechanism, it causes a temporary increase of FSH secretion by the pituitary gland. FSH is an element of survival for early antral follicles being the stage at which most follicles undergo atresia and perish under physiological conditions (Chun *et al*., 1996) [37]. As a result, FSH is majorly responsible for the recruitment of a new group of antral follicles for the next growth wave.

The recruited follicles in every follicular growth wave will undergo a selection process. In species such as cattle and horses (mono-ovulatory) normally a dominant follicle is developed from a single follicle, while the remaining follicles undergo regression (Ginther *et al*., 2000) [38]. The initiation of a follicular growth wave is dependent on a transient elevation of FSH that peaks and diminishes afterwards (Kulick *et al.*, 1999) [39]. Suppression of FSH release is mainly due to the negative feedback effect of estradiol and inhibin produced and secreted by the growing follicles, even when these follicles are still dependent on FSH for their uninterrupted growth. Thus, a multiple follicle-FSH-coupling occurs during selection phase.

All growing follicles have the ability to become a dominant follicle, however after differentiation, that occurs between the future dominant follicle and the remaining subordinate follicles (also termed as deviation), a dominant follicle is formed from the largest follicle, while the others regress (Beg and Ginther, 2006) [40]. As the dominant follicle becomes the primary inhibitor of FSH release, it causes atretic degeneration of the subordinate follicles. Still the dominant follicle continues to grow, even when FSH is at the basal level. The suppression of FSH secretion prevents the emergence of a new group of growing follicles (Ginther *et al*., 2000) [38] and it enables only future dominant follicle to survive.

Mihm and Austin (2002) [41] reported that the dominant follicle adequately utilises FSH and FSH-dependent growth factors to adjust itself to the endocrine and ovarian environment. Whereas, LH plays a major role during the dominance phase. Before the deviation begins, LH receptors starts arising in granulosa cells of the future dominant follicle. It is deduced that the dominant follicle goes through a change

in gonadotrophin dependency from FSH to LH (Mihm *et al*., 2006) [42], due to which the dominant follicle is able to thrive and mature in the environment wherein only low circulating levels of FSH is present. Nonetheless, basal FSH levels still continue to be crucial to the dominant follicle during the dominance phase.

A reduction in the intrafollicular ratio of estradiol: progesterone in the dominant follicle is a major change observed during the dominance phase (Mihm *et al*., 2006) [42], which is a preparation for ovulation.

Progesterone to a certain extent inhibits GnRH pulse frequency and considered as the primary effector of LH (McCartney *et al*., 2007) [43]. The threshold level of estradiol determines its feedback effect on gonadotropin release. Below the threshold concentration, estradiol promotes a negative feedback effect whereas, plasma concentration above the threshold exhibits a positive feedback effect (Wiltbank *et al*., 2002) [44]. Peripheral estradiol concentration elevation is such that it has a significant impact on the GnRH pulse frequency, resulting in elevated LH secretion. Along with the absence of a functional corpus luteum (CL), this will cause the LH surge to occur, which in turn stimulates ovulation and luteinisation.

In mammals, LH pulses prior to ovulation are significantly important for maturation of follicle and ovulation. Prostaglandin E series which are synthesised in response to the mid-cycle LH surge by the follicle are crucial for the rupture of the follicle and release of the oocyte into the periovarian space (Filion *et al*., 2001) [45]. Smith *et al*. (1994) [46] presumed that LH stimulates and prepares granulosa and theca cells for luteinisation. While the CL continues to be active, the first dominant follicle of the cycle generally emerges. Due to progesterone release from the corpus luteum, a negative feedback causes LH pulse frequency to lower in the mid-luteal phase and atresia of the LH dependent dominant follicle occurs. Whereas, due to luteolysis during the dominance phase of the second dominant follicle ovulation of this follicle occurs. Apart from that, if the CL continues to be active, progesterone release remains and the following LH suppression will cause regression of the second dominant follicle as well. Only the elevated LH pulse frequencies in the follicular phase will be beneficial for the survival of dominant follicle, promoting maturation and finally ovulation (Mihm and Austin, 2002) [41].

8. Role of gonadotropins in prolificacy

Prolificacy means average number of offspring in each litter. Prolificacy is mainly governed by ovulation rate, which is further determined by ovarian follicular development prior to ovulation. Elevated ovulation rate is linked to an augmented period of ovulatory follicle recruitment, both in sheep (Bartlewsky *et al*., 1999) [47] and goats (Ginther and Kot, 1994) [48]. After which, the dominant stage is attained by the selected follicles and it exhibits an inhibitory effect on development of the remaining follicles.

Compared to catte, goats have higher occurence of poly-ovulatory cycles, and this in turn introduced the concept of co-dominance, elaborating that every wave of ovarian follicle development has the presence of two large follicles (Rubianes and Menchaca, 2003) [49]. Webb *et al*. (2016) [50] reported that in a study conducted recently by Gong *et al*. (2016) (unpublished), to explain the physiological concentration of gonadotropins needed for the selection of dominant follicle, they derived that multiple ovulation could be established on continous infusion of FSH (physiological concentration) for an adequate time period, LH being at a basal level. Also, stimulation of growth of greater number of pre-ovulatory follicles was possible beginning with FSH exposure followed by LH pulses alone. However, LH pulses were observed not to have a chief impact on the pattern of development of follicle prior to ovulation. Whereas, complete synthesis of estradiol and the capability of pre-ovulatory follicles to acquire ovulatory competence were achieved under adequate pulsatile release of LH. They also concluded that selection of single dominant follicle involved crucial role of FSH exposure initially and the capability to shift the dependence from FSH to LH.

Abdennebi *et al*. (1999) [51] stated that in the initial stages of follicular phase, higher follicle gonadotropin responsiveness was observed in ewes with greater ovulation rate. Thus, a greater correlation was observed among plasma FSH concentration and rate of ovulation. These studies depicted that estrous cycle in prolific sheep showed higher FSH mRNA expression as well as greater pituitary response of FSH secretion. Montgomery *et al*. (1992) [52] reported that the negative feedback by estrogen and inhibin released from the individial follicles reduced in several high fecundity strains of sheep. This resulted in the selection of more preovulatory follicles. In another study, it was observed that such animals had a smaller sized preovulatory dominant follicle than strains with low fecundity (Baird and Campbell, 1998) [53].

9. Conclusion

Since the ultrasonographic research is increasing progressively, a wave-like follicular growth pattern during the estrus cycle has become evident. The follicles undergo a selection process after recruitment, during which the FSH dependent follicle will have to thrive in an environment of reduced FSH concentration. As a result, majority of them undergo gradual atretic degeneration, while only a single follicle continues to develop after deviation, especially in mono-ovulatory species. This is possible mainly because of the tranfer of gonadotropin dependency of the follicle to LH, rather than FSH. Based on many studies, it is infered that one of the main factors responsible for a differentiation between mono-ovulatory and poly-ovulatory species is follicle selection process. It was even proved that in the Chinese Erhualian pig being one of the highest prolific breeds of the world, FSH beta gene was chiefly responsible for the prolific character (Du *et al*., 2002; Zhao *et al*., 1998) [54,55]. Presumably that a slightly elevated concentration of FSH is released in polyovulatory species like pigs, which makes it possible for higher number of follicles per group to acquire ovulatory size and thus explains prolificacy. Studies directed at revealing the variation in expression of genes and level of hormones among highly prolific species like Booroola sheep, and low prolific breed or a normal population could demonstrate significant differences in this aspect (Hunter *et al*., 2004) [56].

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