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Control of follicular growth and development

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Summary. During folliculogenesis a group of growing preantral follicles becomes responsive and dependent upon gonadotrophins, especially FSH, for their continued growth and differentiation. However, most of these follicles undergo atresia. The mechanisms that result in survival of a specific number of ovulatory (dominant) follicles appear to depend upon: (a) responsiveness of preantral follicles to gonadotrophins, (b) inhibitory and stimulatory factors from a dominant follicle, and (c) an exquisitely sensitive long-loop feedback system between the dominant follicle and pituitary gland.

Introduction

Folliculogenesis is spectacular not only because a primordial follicle may increase in diameter 400- to 600-fold before ovulation but because the growth of 500 to 1000 primordial follicles each oestrous cycle usually results in development of only a few ovulatory follicles. The fact that during the lifespan of an animal 99·9% of the primordial follicles fail to ovulate illustrates not only that development of an ovulatory follicle is an extremely rare biological event but also that the process of folliculogenesis is complex.

Goodman & Hodgen (1983) suggest the use of the following terms for describing folliculogenesis: *recruitment*—a gonadotrophin-dependent event during which a group of follicles gain the ability to respond to gonadotrophins and require gonadotrophins for continued growth; *selection*—a process whereby only a few of the 'recruited' follicles are 'selected' to escape atresia and survive to ovulate; and *dominance*—the mechanism that an ovulatory (or dominant) follicle(s) uses to escape atresia. The phenomenon of dominance is central to understanding folliculogenesis since it suggests that some follicles survive in a milieu suppressive to growth of other follicles, or that some follicles prevent growth of other follicles (Goodman & Hodgen, 1983).

This review will focus on the characteristics of development of dominant follicles during oestrous cycles, the mechanism of action of gonadotrophins during folliculogenesis, the potential intragonadal regulators of follicular growth and function, and the possible role of intragonadal regulators on recruitment and selection of the dominant follicle.

Endocrine and receptor changes that characterize the development of dominant follicles

The change in concentration of oestradiol in each ovarian vein during an oestrous cycle is the best endocrine marker for depicting the selection and dominance processes. These processes are associated with a unique follicular hierarchy, symmetrical and asymmetrical ovarian production of oestradiol, and marked changes in binding of human chorionic gonadotrophin (hCG) to follicles,

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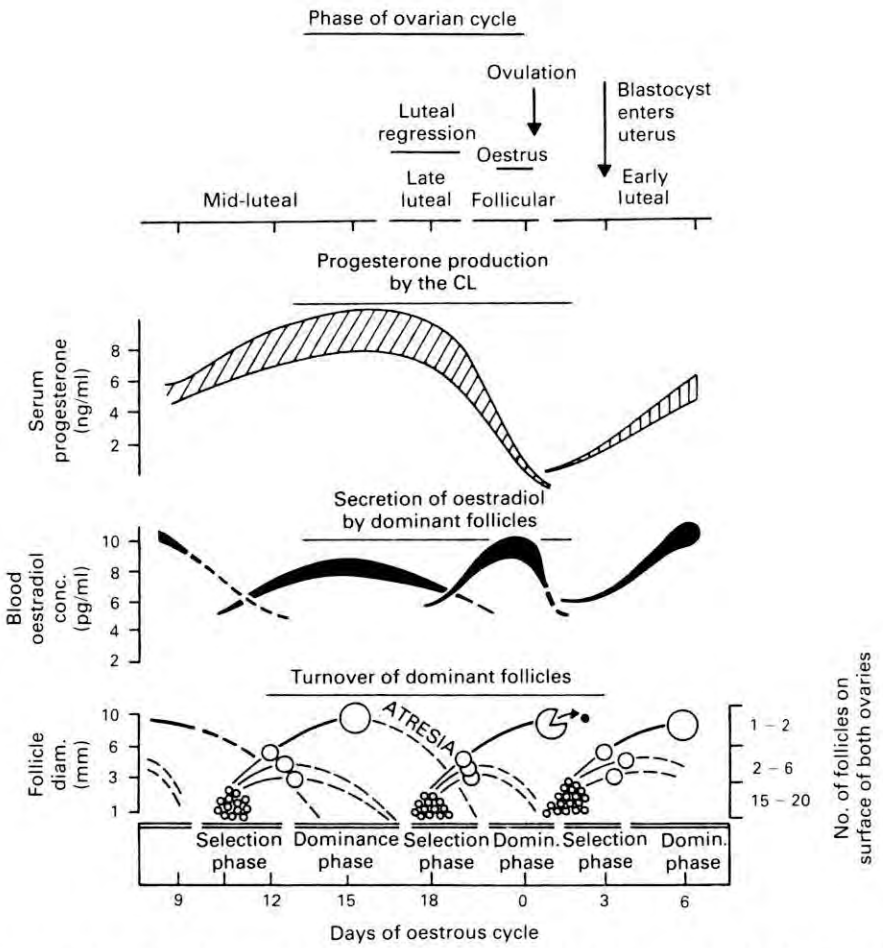

Fig. 1. Cycles of development of dominant follicles during the oestrous cycle of a cow. (After Ireland & Roche, 1987.)

especially in primates and cattle (Goodman & Hodgen, 1983; Ireland & Roche, 1987). In single-ovulating species, symmetrical ovarian production of oestradiol indicates that the selection process for a dominant follicle is on-going, whereas asymmetrical production of oestradiol indicates that selection is complete and dominance is underway. Endocrine markers for recruitment are ill-defined, although considerable evidence (discussed later) indicates that changes in FSH concentrations in blood may be the stimulus for recruitment (Ireland & Roche, 1987).

Cattle have at least 3 cycles of development of dominant follicles during an oestrous cycle (Fig. 1; Ireland & Roche, 1987). Unlike primates (Goodman & Hodgen, 1983), cattle have dominant non-ovulatory follicles that develop during the early- and mid-luteal phase (Matton *et al.*, 1981; Ireland & Roche, 1983a). These follicles are responsible for the increases in concentration of oestradiol in blood that occur several days after ovulation (Glencross *et al.*, 1973) and again after mid-cycle (Hansel & Echternkamp, 1972). Although these changes in concentrations of oestradiol are difficult to detect in the peripheral circulation, analysis of utero-ovarian venous blood samples established that symmetrical and asymmetrical production of oestradiol from each ovary occur not only during the follicular phase but also during the luteal phase of the oestrous cycle of cattle (Ireland *et al.*, 1985; Fogwell *et al.*, 1985). Coinciding with each cycle of development of a dominant

follicle is a marked increase in the ability of the dominant follicle to bind hCG specifically (Ireland & Roche, 1982, 1983a, b). Each cycle of development of the dominant follicle occurs in remarkably different hormonal environments (Fig. 1; Rahe *et al.*, 1980), suggesting that peri-ovulatory changes in gonadotrophins are not necessary for development of a dominant follicle.

Sheep, like cattle, have several periods during an oestrous cycle when concentrations of oestradiol increase in blood (Baird *et al.*, 1976). This supports the idea that cycles of development of dominant follicles occur in sheep (Smeaton & Robertson, 1971).

Physiological events such as luteolysis, movement of the blastocyst into the uterus, and oestrus and the preovulatory gonadotrophin surge, correspond with a different cycle of development of a dominant follicle in cattle (Fig. 1). Since oestradiol, produced primarily from a dominant follicle rather than other follicles, can influence each of these physiological events (Ireland & Roche, 1987), dominant follicles not only function to provide oocytes for fertilization but may have an important role in regulating a cascade of physiological events necessary for successful reproduction.

Gonadotrophins are required for development of dominant follicles, synthesis and secretion of oestradiol from these follicles and ovulation. However, the mechanisms that result in the cyclic appearance of ovulatory and non-ovulatory dominant follicles and secretion of oestradiol from these follicles in remarkably different hormonal environments during an oestrous cycle (Fig. 1) are unknown. In addition, the mechanisms that result in selection of only a few dominant follicles out of the hundreds of follicles that are recruited to grow each oestrous cycle are unknown.

Mechanism of action of gonadotrophins during folliculogenesis

Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the primary protein hormones involved in folliculogenesis (Hisaw, 1947). Gonadotrophins enhance steroidogenic enzyme activity in granulosa and theca cells after interaction of the gonadotrophins with their receptor sites and activation of cAMP-dependent processes. This results in an increased synthesis and accumulation of steroids especially oestradiol in the general circulation and in the follicular fluid of antral follicles. Since oestradiol is the key hormone for promoting folliculogenesis (Richards, 1980) and for triggering physiological events necessary for reproduction (Fig. 1), the dominant follicle(s) must possess an enhanced capacity over other follicles to synthesize and release this steroid. This enhanced capacity to produce oestradiol involves the action of both FSH and LH on theca and granulosa cells. The mechanism of action of FSH and LH on granulosa and theca cells has been exceptionally well-reviewed by Richards (1980), Hsueh *et al.* (1984) and Erickson *et al.* (1985). Much of our current understanding of the mechanisms of action of FSH and LH on folliculogenesis is derived from studies using immature and/or hypophysectomized rats and primary cultures of granulosa and theca-interstitial cells from rats and domestic species. The following is a brief summary of the results of these studies as they relate to folliculogenesis.

Receptors

Granulosa and theca cells contain a plethora of receptor sites for numerous hormonal and non-hormonal factors (Fig. 2), indicating that many factors other than gonadotrophins influence folliculogenesis. Many of these receptor sites are up-regulated or down-regulated ($\pm$) by FSH and LH, which supports the concept that gonadotrophins are the primary stimulators of folliculogenesis (Hisaw, 1947). Granulosa cells in preantral follicles possess FSH receptors and do not gain LH receptors until a follicle forms an antrum. Beginning at the preantral stage of development, theca cells contain LH receptors, but never gain FSH receptors (Richards, 1980). Follicles are, therefore, capable of responding to both FSH and LH at a very early stage of development. During folliculogenesis, FSH induces appearance of its own receptor and then LH receptor in granulosa cells. Regulation of the thecal LH receptor is unclear. FSH is also required for maintenance of gonadotrophin receptors throughout folliculogenesis (Richards, 1980).

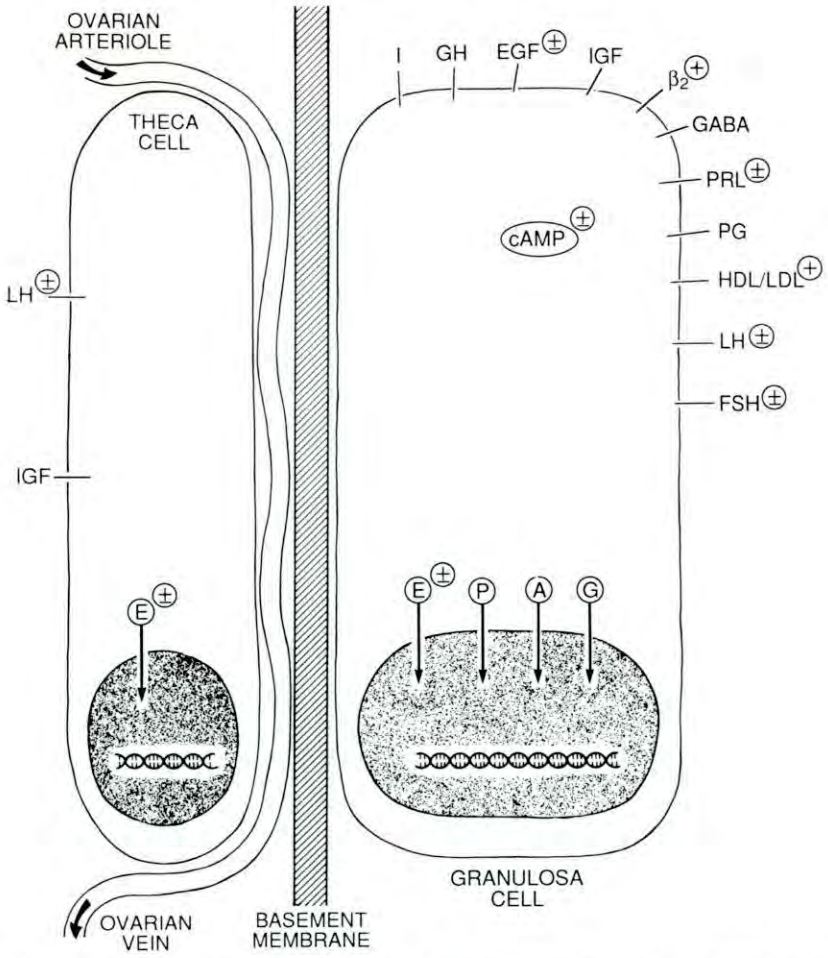

Fig. 2. Receptor sites that are present on granulosa or theca cells. I = insulin, GH = growth hormone, EGF = epidermal growth factor, IGF = insulin-like growth factor, β_2 = β_2-adrenergic hormones, GABA = gamma amino butyric acid, PRL = prolactin, PG = prostaglandin, HDL/LDL = high and low density lipoproteins, LH = luteinizing hormone, FSH = follicle-stimulating hormone, cAMP = cyclic adenosine monophosphate, P = progesterone, A = androstenedione, G = glucocorticoids. ± indicates that gonadotrophins can up- or down-regulate the receptor site. (Modified from Hsueh *et al.*, 1984.)

Response systems

Gonadotrophins bind to their receptor sites and activate the adenylate cyclase–cAMP response system. This results in activation of protein kinases and phosphorylation of various proteins that may be involved in folliculogenesis (Fig. 3). Adenylate cyclase is comprised of a regulatory subunit which interacts with the hormone–receptor complex. This subunit, called the G or N protein, is activated by guanine nucleotides and magnesium. Adenylate cyclase also contains a catalytic subunit which metabolizes ATP into cAMP when it is bound to the N subunit (Birnbaumer & Kirchick, 1983). Sustained high concentrations of gonadotrophins and slow rates of dissociation of gonadotrophins from their receptors result in abrogation of the receptor–adenylate cyclase–cAMP response system. This results in a temporary or permanent desensitization of the adenylate cyclase

in follicular cells to further gonadotrophin stimulation (Birnbaumer & Kirchick, 1983). During folliculogenesis, changes in episodic patterns of secretion of gonadotrophins, such as during a preovulatory gonadotrophin surge, may not only promote luteinization of granulosa cells and ovulation but also result in the demise of some populations of follicles (permanent desensitization) and enhance growth of others.

FSH increases the proposed regulatory subunit for protein kinase (R_{11}, Richards & Rolfes, 1979), the mRNA for this protein (Hedin *et al.*, 1986) and phosphorylation of several granulosa cell proteins (Richards *et al.*, 1983). The specificity of action of gonadotrophins therefore resides in the specific proteins which are phosphorylated in the granulosa and theca cells. It is not known whether proteins that are phosphorylated in response to gonadotrophin action are involved in induction of receptors, activation of enzymes for steroidogenesis, control of the luteinization process or other facets of folliculogenesis.

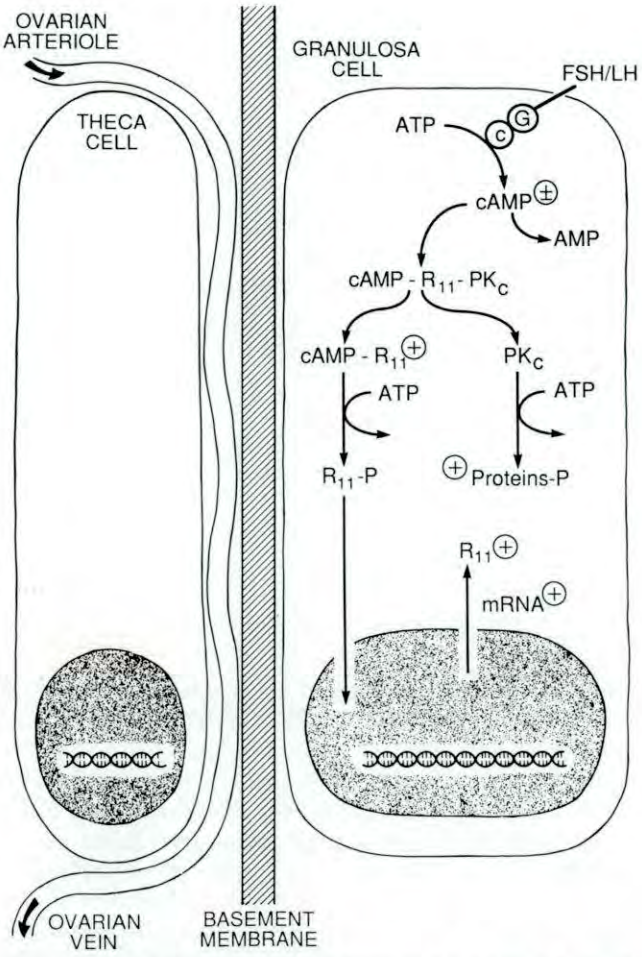

Fig. 3. Diagram representing the proposed mechanism of action for gonadotrophins. G = guanine and magnesium activated regulatory subunit of adenylate cyclase, C = catalytic subunit of adenylate cyclase, cAMP = 3′5′ cyclic adenosine monophosphate, AMP = 5′-adenosine monophosphate, R_{11} = regulatory subunit of protein kinase, PK_c = catalytic subunit of protein kinase, cAMP-R_{11} = phosphorylated R_{11}, Proteins-P = phosphorylated proteins. ± indicates regulation by LH or FSH.

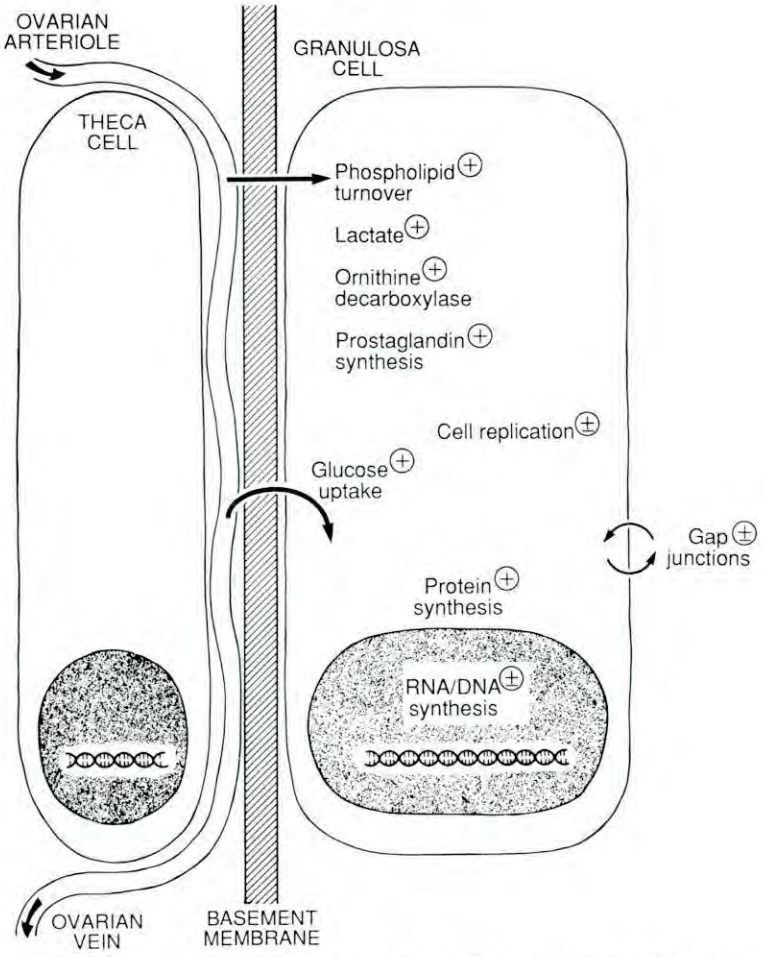

Fig. 4. Some of the major functions of the granulosa cell that are positively (+) or negatively (−) regulated by gonadotrophins. (Modified from Hsueh *et al.*, 1984.)

Several neurotransmitters, peptides and growth factors that have a role in folliculogenesis not only activate the cAMP response system but also activate phosphoinositide metabolism after binding to membrane receptors. Phosphoinositide metabolites, at least in other cell types, are involved in release of arachidonic acid for prostaglandin synthesis, activation of protein kinase C, calcium mobilization, and activation of guanylate cyclase for cGMP production. Oncogenes which are proposed to regulate all aspects of cellular growth are also linked to the phosphoinositide-response system (Berridge, 1984). Although it is unknown whether activation of the phosphoinositide-response system explains many of the well-known actions of gonadotrophins during folliculogenesis (Fig. 4), incubation of pig granulosa cells with LH, but not FSH or cAMP, results in accumulation of inositol phosphates in the medium (Dimino & Snitzer, 1986).

Steroidogenesis

The undifferentiated thecal cell is incapable of synthesizing androgens although it contains LH receptor (Erickson *et al.*, 1985). During folliculogenesis, the theca cell responds to LH primarily by

activation of the side-chain cleavage enzymes and the 17α-hydroxyprogesterone and 17–20-desmolase enzyme systems (Erickson *et al.*, 1985), allowing the theca cell to synthesize androgens. During folliculogenesis a granulosa cell, which does not produce androgens, is incapable of producing oestradiol until the theca cell differentiates into an androgen-producing cell (Fig. 5).

FSH and LH enhance the uptake of lipoproteins, liberation of cholesterol from lipoproteins, mobilization of cholesterol, conversion of cholesterol into pregnenolone through activation of the mitochondrial side-chain cleavage enzyme system and conversion of pregnenolone to progesterone through activation of the 3β-hydroxysteroid dehydrogenase enzyme system in granulosa cells.

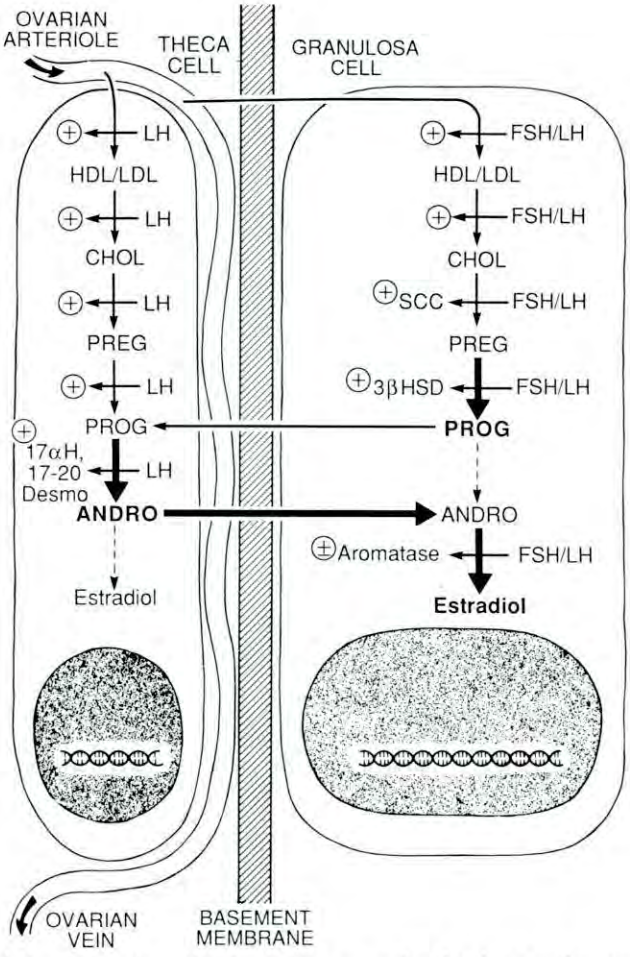

Fig. 5. Proposed steroidogenic pathways and enzymes for the theca and granulosa cell (modified from Erickson *et al.*, 1985; Hsueh *et al.*, 1984; Leung & Armstrong, 1980). Degree of darkness of arrows between steroids represent primary steroid synthesized. Arrows pointing to enzymes indicate whether enzyme activity is stimulated (+) or inhibited (−) by FSH or LH. Arrows from one cell to the other represent diffusion of steroid either from cell to cell or through the capillary network surrounding a follicle. Arrows from arteriole represent uptake. HDL/LDL = high or low density lipoproteins, CHOL = cholesterol, PREG = pregnenolone, PROG = progesterone, ANDRO = androgens, SCC = mitochondrial side-chain cleavage enzymes, 3βHSD = 3β-hydroxysteroid dehydrogenase, 17αH, 17–20 DESMO = 17α-hydroxylase and 17–20-desmolase.

Although a granulosa cell responds to LH by increasing the production of progesterone and oestradiol, FSH priming is required for this steroidogenic effect (Hsueh *et al.*, 1984).

In some species, such as pigs, the theca cell possesses an active aromatase enzyme system (Evans *et al.*, 1981) which diminishes the role of FSH in oestradiol production, at least during some stages of folliculogenesis. However, in most species, granulosa rather than theca cells possess the major aromatase activity (Leung & Armstrong, 1980).

Ability of the theca cell to produce androgens precedes acquisition of the aromatase system by granulosa cells in cattle (McNatty *et al.*, 1984). Moreover, on each day of the cycle in cows, 20–60 antral follicles may produce androgens, whereas only 1–3 antral follicles are able to metabolize androgens into oestrogens. This clearly illustrates that acquisition of the aromatase system, which is regulated by FSH (Leung & Armstrong, 1980), is a key maturation step during folliculogenesis for initiation of the dominance process.

Many factors, which could inhibit synthesis of oestradiol, such as FSH and LH binding inhibitors and follicular regulatory protein, are present in follicular fluid (Table 1). It is unknown whether dominant follicles use these factors to inhibit development of other follicles or are spared from the inhibitory effects of such factors. The activity of the steroidogenic enzymes and, in turn, oestradiol synthesis by a dominant follicle may not only be controlled by inhibitory proteins but by a complex interaction of ovarian steroids with steroidogenic enzymes (Leung & Armstrong, 1980). For example, androgens enhance aromatase activity whereas oestrogens inhibit androgen production. It is possible that ovarian steroids mediate their effects on steroidogenesis through synthesis of various intragonadal regulators of steroidogenic enzyme activity.

Modulators of gonadotrophin action

Various steroids and proteins enhance FSH action. For example, oestradiol, androgens, progesterone, LH, insulin, platelet-derived growth factor, insulin-like growth factors (Hsueh *et al.*, 1984) and transforming growth factor beta (Dodson & Schomberg, 1986) all enhance various aspects of FSH action, including induction of FSH or LH receptors and progesterone or oestradiol synthesis. In contrast, pharmacological doses of LH or FSH, glucocorticoids, fibroblastic growth factor, epidermal growth factor, calcium inhibitors (Hsueh *et al.*, 1984), transforming growth factor beta (Knecht & Feng, 1986), and follicular regulatory protein (diZerega *et al.*, 1984) all inhibit FSH action. The mechanisms of action of these modulators of FSH action are unknown.

Oestradiol is the best studied amplifier of FSH action. For example, in laboratory species, oestradiol markedly enhances the ability of FSH to increase its receptor in granulosa cells (Richards, 1980). Indeed, synthesis of oestradiol is required for FSH to promote folliculogenesis (Tonetta & Ireland, 1984; Tonetta *et al.*, 1985). Since oestradiol does not increase the FSH receptor (Richards *et al.*, 1976), the catalytic subunit of protein kinase (Richards *et al.*, 1984), the regulatory subunit of protein kinase (Ratoosh & Richards, 1985), and only slightly increases adenylate cyclase activity (Jonassen *et al.*, 1982), its action remains a mystery. Nevertheless, oestradiol has a well-known role in protein synthesis in many tissues, and so oestradiol-induced granulosa or theca cell proteins may be involved in enhancement of FSH action. It awaits to be determined whether these oestradiol-induced proteins include some of the various factors known to enhance FSH action.

Potential intragonadal regulators of follicular growth and function

The role of most of the various intragonadal hormonal and non-hormonal and putative regulatory factors (Table 1) in folliculogenesis is unknown. The intriguing possibility exists, however, that many of these factors operate in an endocrine, paracrine and autocrine fashion to regulate development of dominant follicles.

Follicular fluid contains numerous factors that are potential intragonadal modulators of folliculogenesis. In addition to ovarian steroids, follicular fluid contains non-gonadal protein hormones such as LH, FSH (McNatty *et al.*, 1975), insulin (Rein & Schomberg, 1982), prolactin (Meloni *et al.*, 1986) and prorenin (Glorioso *et al.*, 1986). Granulosa cells synthesize many hormonal and non-hormonal products other than steroids, including relaxin (Bryant-Greenwood *et al.*, 1980), oxytocin (Sheldrick & Flint, 1984), inhibin (Ling *et al.*, 1985), activin (Ling *et al.*, 1986) or follicle-stimulating hormone releasing protein (Vale *et al.*, 1986), proteoglycans (Yanagishita *et al.*, 1981), prostacyclins (Ranta *et al.*, 1986), plasminogen activator (Beers, 1975), anti-Müllerian hormone (Josso, 1986) and fibronectin (Skinner *et al.*, 1985). Inhibin and activin or FSH releasing protein, which directly regulate FSH secretion and modulate FSH-induced oestradiol synthesis, stand alone as the only protein hormones in follicular fluid to have their amino acid sequences determined following purification of preparations of follicular fluid (Ling *et al.*, 1985, 1986; Vale *et al.*, 1986; Ying *et al.*, 1986b). Hypoxanthine and adenosine have been isolated from follicular fluid (Downs *et al.*, 1985) and shown to possess the ability to inhibit oocyte maturation *in vitro*. Whether these purines represent the elusive oocyte maturation inhibitor (OMI) or a mediator of OMI activity remains to be determined.

An abundance of factors of unknown molecular identities also exists in follicular fluid and may be involved in regulating granulosa and theca cell function (Hammond, 1981; Sairam & Atkinson, 1984; see Table 1). The most recent potential intragonadal regulator of follicular function was discovered by Aten *et al.* (1986) in rat, human, sheep and cow ovaries. This factor, which is absent from follicular fluid, inhibits binding of radioactive GnRH to rat ovarian membranes. GnRH modulates gonadotrophin action in rats but not in other species, and high-affinity receptors for GnRH are found in rat ovaries but not ovaries of other species (Hsueh & Jones, 1981). The newly discovered ovarian factor is not GnRH since, unlike GnRH, it is heat-sensitive, its activity elutes differently than GnRH during HPLC, and it does not possess GnRH immuno-reactivity. Whether this ovarian factor has anti-gonadal properties in humans and domestic species awaits determination.

Recruitment and selection of the dominant follicle

In theory, the cyclic appearance of the ovulatory quota of dominant follicles throughout an oestrous cycle (Fig. 1) may involve the interaction of gonadotrophins with various intragonadal factors. Intragonadal factors would modulate the action of gonadotrophins such that only a few follicles are selected to become dominant.

Recruitment

Hypophysectomy, or short-term suppressions of FSH in blood, clearly inhibits development of preantral and antral follicles (Nakano *et al.*, 1975; Carter *et al.*, 1961). FSH alone restores antral follicle development (Richards, 1980). Since preantral follicles possess FSH receptors (Hsueh *et al.*, 1984), gonadotrophin responsiveness (recruitment) may be developed during this stage of folliculogenesis. Once this occurs, the preantral follicle is thereafter dependent on FSH support for continued development into a dominant follicle (Richards, 1980). In laboratory species, the pro-oestrous and oestrous rises in FSH during one cycle regulate the recruitment of follicles for ovulation in the next cycle (Hirshfield & Midgley, 1978; Chappel & Selker, 1979). These data illustrate that FSH has a major role in the recruitment process. Similar studies were attempted in sheep but failed to alter the ovulation quota. However, unlike the study of Chappel & Selker (1979) in laboratory species, the post-ovulatory increase in FSH was only partly obliterated in sheep (Bindon & Piper, 1984).

Table 1. Putative ovarian factors and their biological actions

Factor	Tissue source	Species	Physical characteristics	Biological action	Reference
Angiogenic factor	Non-luteal ovaries, theca	Pig	Heat-labile, protease-sensitive	Blood vessel growth	Makris *et al.* (1984)
Renin-like activity	Follicular fluid	Human	Samples liberate radioimmunoassayable angiotensin	Blood vessel formation	Fernandez *et al.* (1985)
Luteinization inhibitor	Follicular fluid	Pig, cattle	M_r 100 000	Blocks LH-induced cAMP and progesterone production by granulosa cells in culture	Hammond (1981)
Gonadotrophin surge inhibiting factor	Follicular fluid	Pig	Heat-labile	Blocks preovulatory gonadotrophin surge	Littman & Hodgen (1984)
FSH binding inhibitor	Follicular fluid, serum	Cattle, pig, human	$M_r < 5000$, 10–11 amino acid peptide, protease-sensitive, putrescine (?)	Blocks binding of ^{125}I-labelled FSH to bovine granulosa cells or testes	Sluss & Reichert (1984) Darga & Reichert (1979) Sato *et al.* (1982) Sanzo & Reichert (1982)
LH binding inhibitors	Follicular fluid, serum	Human, pig, sheep	M_r 20 000	Blocks binding of ^{125}I-labelled LH to testes or luteal cells	Sanzo & Reichert (1982) Kumari *et al.* (1984)

Oocyte maturation inhibitor	Follicular fluid, granulosa cells	Human, pig, cattle	M_r < 2000, heat stable, may be hypoxanthine or adenosine	Inhibits in-vitro maturation of cumulus-enclosed oocytes of various species	Tsafriri *et al.* (1976) Hillensjo *et al.* (1980) Downs *et al.* (1985) Miller & Behrman (1986)
Follicular regulatory protein	Follicular fluid, serum	Pig, cattle, human	M_r 12 500–16 000, heat and trypsin sensitive	Inhibits aromatase activity by rat and porcine granulosa cells in culture, also inhibits progesterone synthesis	diZerega *et al.* (1984)
Transforming growth factor, beta-like activity	Follicular fluid	Pig	Similar to inhibin (?)	Actions unknown, TGF_B alters FSH-induced increases in LH receptor and epidermal growth factor in granulosa cells and promotes FSH release from pituitary cells in culture	Dodson & Schomberg (1986) Knecht & Feng (1986) Ying *et al.* (1986a ,b)
Gonadocrinin	Follicular fluid, ovary	Pig, cattle	M_r 1000–10 000, heat and trypsin sensitive	Stimulates release of LH and FSH from rat pituitary cells in culture	Ying *et al.* (1981)
GnRH-like ovarian hormone	Ovary	Human, cattle, sheep	M_r 1000–10 000, heat and protease sensitive, not GnRH	Inhibits binding of ^{125}I-labelled GnRH to rat ovarian luteal homogenates	Aten *et al.* (1986)
Insulin-like growth factors	Follicular fluid, granulosa cells	Pig	Immunoassay and radioreceptor assay activity	Stimulate granulosa cell replication, enhance FSH action	Adashi *et al.* (1985) Hammond *et al.* (1985) Hsu & Hammond (1986)

Selection and dominance

Selection may be a three-part process involving the ability of preantral follicles to respond to gonadotrophins, elaboration of inhibitory factors from a dominant follicle and feedback between dominant follicles and the pituitary gland.

Atresia is observed in preantral follicles of all species. Selection of the ovulatory quota of follicles may therefore begin at the preantral stage of folliculogenesis. Initiation of follicular growth from the non-growing pool of avascular follicles is probably asynchronous (Lintern-Moore & Moore, 1979). Therefore, all growing follicles may not be at the same stage of development during recruitment. One reason that growing preantral follicles do not continue to grow, although each in theory receives a similar gonadotrophin stimulus during recruitment, may be the result of a gradient of subtle differences in number of granulosa or theca cells and/or amount of gonadotrophin receptor per follicle. The number of follicles responding to gonadotrophins would then depend upon the strength of the recruitment stimulus (i.e. amount of gonadotrophins) and the inherent ability of each follicle to respond. Direct evidence for these assumptions does not exist for any species.

A popular theory is also held that dominant follicles elaborate various hormonal and non-hormonal factors (Table 1) that control selection by modulating the gonadotrophin-induced recruitment process. For example, gonadotrophin-induced follicular growth is more effective in promoting multiple follicle growth before establishment of follicular dominance in primates (diZerega & Hodgen, 1980). Furthermore, factors from a dominant follicle or corresponding ovarian vein inhibit steroidogenesis (Table 1) by granulosa cells, supporting the idea that a dominant follicle may inhibit growth of other follicles but not itself. A strong possibility also exists that during folliculogenesis antral follicles receive unequal amounts of gonadotrophin because of differences in vasculature (Zeleznik *et al.*, 1981). This could also result in the selective growth of a dominant follicle.

A feedback system between a dominant follicle and the pituitary gland and the ability of a dominant follicle to survive in an hormonal milieu suppressive to growth of other follicles may explain, in part, the selection process. In cattle, a dominant follicle possesses markedly greater inhibin bioactivity and oestradiol content than do other follicles (Padmanabhan *et al.*, 1984). Follicular fluid, which contains inhibin, and oestradiol both depress secretion of FSH (Zeleznik, 1981; Kesner & Convey, 1982; Ireland *et al.*, 1983). FSH enhances oestradiol and inhibin production in cultures of granulosa cells (Hsueh *et al.*, 1984). Thus, a classical long-loop negative feedback system may exist between inhibin and oestradiol from the dominant follicle and FSH from the pituitary gland. Results of several studies support this concept. After removal of a single ovary in most species, the remaining ovary compensates for the loss of the other and maintains the original ovulatory quota. In sheep, removal of one ovary results in only a 20–30% increase in FSH lasting 6–7 h (Findlay & Cumming, 1977). This transient increase in FSH is sufficient to enhance growth of more follicles and/or prevent atresia of existing follicles resulting in a normal ovulation quota. Compensatory follicular growth is blocked if the rise in FSH is suppressed after removal of an ovary (Welschen *et al.*, 1979). Further evidence for the sensitivity of the dominant follicle–pituitary feedback system is best shown in the studies of Zeleznik (1981), Zeleznik *et al.* (1985), Dierschke *et al.* (1985), Pathiraja *et al.* (1984) and Webb & Gauld (1987). Physiological doses of oestradiol given during the follicular phase result in short-term suppression in concentrations of FSH in blood and atresia of the existing dominant follicle. Moreover, infusion of oestradiol antibodies enhances concentrations of LH and FSH and results in development of multiple dominant follicles in primates and sheep. Finally, several studies in sheep suggest that an association exists between FSH and inhibin which may affect ovulation rate. For example, prolific breeds of sheep, especially the Booroola Merino, have higher concentrations of FSH in blood and lower ovarian values of inhibin bioactivity than do less prolific breeds of sheep. Immunization of sheep against follicular fluid, which contains inhibin and other potential regulatory factors, enhances ovulation rates (Bindon &

Piper, 1984). In summary, modulation of many factors involved in the selection process, especially in sheep, results in enhanced rates of ovulation (Driancourt, 1987).

If inhibin and oestradiol interact to regulate the number of dominant follicles, how then would a dominant follicle(s) survive in an hormonal milieu (especially low FSH) that is suppressive to growth of other follicles? Oestradiol, which markedly enhances FSH and LH action (Hisaw, 1947; Richards, 1980), is in remarkably greater concentrations in dominant follicles than in other co-existing follicles (Ireland & Roche, 1982, 1983a, b). Because of its greater oestradiol levels, a dominant follicle may survive in an oestradiol- or inhibin-induced FSH-deficient milieu. Other follicles with diminished levels of oestradiol undergo atresia.

Because the interaction of oestradiol and FSH alone could provide a model which explains selection and dominance, what role, if any, do intragonadal factors have on regulation of development of dominant follicles? Since most of these factors (Table 1) are inhibitory to follicular function, they may represent metabolic products secreted from each follicle (or a dominant follicle alone) that are necessary to cause atresia. These factors could also be degradative by-products of atresia. Clearly, the predominant ovarian event is atresia, and follicles may synthesize and secrete factors for stimulation of this process.

In summary, gonadotrophins, especially FSH, regulate the recruitment process. FSH, oestradiol, and perhaps inhibin, control, in part, the selection process. It is unknown whether a dominant follicle secretes factors, other than oestradiol, that participate in the dominance process. In conclusion, the concepts of recruitment and selection seem indisputable, whereas evidence for the dominance process remains equivocal.

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References

Adashi, E.Y., Resnick, C.E., D'ercole, A.J., Svoboda, M.E. & YanWyk, J.J. (1985) Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. *Endocr. Reviews* **6,** 400–420.

Aten, R.F., Ireland, J.J., Polan, M.L., Weems, C.W. & Behrman, H.R. (1986) GnRH-like ovarian hormone (GLOH) is present in several species which do not have GnRH receptors. *Endocrinology* **118** (Suppl.), 221, Abstr. 763.

Baird, D.T., Land, R.B., Scaramuzzi, R.J. & Wheeler, A.G. (1976) Endocrine changes associated with luteal regression in the ewe: The secretion of ovarian oestradiol, progesterone and androstenedione and uterine prostaglandin $F_{2\alpha}$ throughout the oestrous cycle. *J. Endocr.* **69,** 275–286.

Beers, W. (1975) Follicular plasminogen and plasminogen activator and effect of plasmin on ovarian follicle wall. *Cell* **6,** 379–386.

Berridge, M.J. (1984) Inositol trisphosphate and diacylglycerol as second messengers. *Biochem. J.* **220,** 345–360.

Bindon, B.M. & Piper, L.R. (1984) Endocrine basis of genetic differences in ovine prolificacy. *Proc. 10th Int. Congr. Anim. Reprod. & A.I., Urbana-Champaign* **IV,** pp. 17–26.

Birnbaumer, L. & Kirchick, H.J. (1983) Regulation of gonadotropic action: The molecular mechanisms of gonadotropin-induced activation of ovarian adenylyl cyclases. In *Factors Regulating Ovarian Function*, pp. 287–310. Eds G. S. Greenwald & P. F. Terranova. Raven Press, New York.

Bryant-Greenwood, G.D., Jeffrey, R., Ralph, M.M. & Seamark, R.F. (1980) Relaxin production by the porcine ovarian graafian follicle in vitro. *Biol. Reprod.* **23,** 792–800.

Carter, F., Woods, M.C. & Simpson, M.E. (1961) The role of the pituitary gonadotropins in induction of ovulation in the hypophysectomized rat. In *Control of Ovulation*, pp. 1–23. Ed C. A. Villee. Pergamon Press, New York.

Chappel, S.C. & Selker, F. (1979) Relation between the secretion of FSH during the periovulatory period and ovulation during the next cycle. *Biol. Reprod.* **21,** 347–352.

Darga, N.C. & Reichert, L.E., Jr (1979) Evidence for the presence of a low molecular weight follitropin binding inhibitor in bovine follicular fluid. *Adv. exp. Med. Biol.* **112,** 383–388.

Dierschke, D.J., Hutz, R.J. & Wolf, R.C. (1985) Induced follicular atresia in rhesus monkeys: strength-duration relationships of the estrogen stimulus. *Endocrinology* **117,** 1397–1403.

Dimino, M.J. & Snitzer, J. (1986) Luteinizing hormone (LH) causes rapid increases in accumulation of

inositol phosphates in granulosa from medium follicles of porcine ovaries. *Biol. Reprod.* **34,** Suppl. 1, 168, Abstr. 237.

diZerega, G.S. & Hodgen, G.D. (1980) The primate ovarian cycle: Suppression of human menopausal gonadotropin-induced follicular growth in the presence of the dominant follicle. *J. clin. Endocr. Metab.* **50,** 819–825.

diZerega, G.S., Campeau, J.D., Ujita, E.L., Schreiber, J.R., Battin, D.A., Montz, F.J. & Nakamura, R.M. (1984) Follicular regulatory proteins: Paracrine regulators of follicular steroidogenesis. In *Gonadal Proteins and Peptides and their Biological Significance*, pp. 215–228. Eds M. R. Sairam & L. E. Atkinson. World Scientific Publ. Co., Singapore.

Dodson, W.C. & Schomberg, D.W. (1986) Transforming growth factor beta enhances FSH-stimulated LH receptor induction in granulosa cells. *Endocrinology* **118** (Suppl.), 290, Abstr. 1037.

Downs, S.M., Coleman, D.L., Ward-Bailey, P.F. & Eppig, J.J. (1985) Hypoxanthine is the principal inhibitor of murine oocyte maturation in a low molecular weight fraction of porcine follicular fluid. *Proc. natn. Acad. Sci., U.S.A.* **82,** 454–458.

Driancourt, M.A. (1987) Follicular dynamics and intraovarian control of follicular development in the ewe. In *Follicular Growth and Ovulation Rate in Farm Animals* (in press). Eds J. Roche & D. O'Callaghan. Martinus Nijhoff, The Hague.

Erickson, G.F., Magoffin, D.A., Dyer, C.A. & Hofeditz, C. (1985) The ovarian androgen producing cells: A review of structure/function relationships. *Endocr. Reviews* **6,** 371–399.

Evans, G., Dobias, M., King, G.J. & Armstrong, D.T. (1981) Estrogen, androgen and progesterone biosynthesis by theca and granulosa of preovulatory follicles in the pig. *Biol. Reprod.* **25,** 673–682.

Fernandez, L.A., Tarlatzis, B.C., Rzasa, P.J., Caride, J., Laufer, N., Negro-Vilar, A.F., DeCherney, A.H. & Naftolin, F. (1985) Renin-like activity in ovarian follicular fluid. *Fert. Steril.* **44,** 219–223.

Findlay, J.K. & Cumming, I.A. (1977) The effect of unilateral ovariectomy on plasma gonadotropin levels, estrus and ovulation rate in sheep. *Biol. Reprod.* **17,** 178–183.

Fogwell, R.L., Cowley, J.L., Wortman, J.A., Ames, N.K. & Ireland, J.J. (1985) Luteal function in cows following destruction of ovarian follicles at midcycle. *Theriogenology* **23,** 389–398.

Glencross, R.G., Munro, I.B., Senior, B.D. & Pope, G.S. (1973) Concentrations of oestradiol-17β, oestrone and progesterone in jugular venous plasma of cows during the estrous cycle and in early pregnancy. *Acta endocr., Copenh.* **73,** 374–384.

Glorioso, N., Atlas, S.A., Laragh, J.H., Jewelewicz, R. & Sealey, J.E. (1986) High concentrations of prorenin in human ovarian follicular fluid. *Endocrinology* **118** (Suppl.), 222, Abstr. 765.

Goodman, A.L. & Hodgen, G.D. (1983) The ovarian triad of the primate menstrual cycle. *Recent Prog. Horm. Res.* **39,** 1–73.

Hammond, J.M. (1981) Peptide regulators in the ovarian follicle. *Aust. J. biol. Sci.* **34,** 491–504.

Hammond, J.M., Lino, J., Baranao, S., Skaleris, D., Knight, A.B., Romanus, J.A. & Rechler, M. (1985) Production of insulin-like growth factors by ovarian granulosa cells. *Endocrinology* **117,** 2553–2555.

Hansel, W. & Echternkamp, S.E. (1972) Control of ovarian function in domestic animals. *Am. Zool.* **12,** 225–243.

Hedin, L., Ratoosh, S., Lifka, J., Durica, J., Jahnsen, T. & Richards, J.S. (1986) Hormonal regulation of mRNA for the regulatory subunit of type II cAMP-dependent protein kinase in ovarian granulosa cells. *Endocrinology* **118** (Suppl.), 221, Abstr. 761.

Hillensjo, T., Pomerantz, S.H., Schwartz-Kripner, A., Anderson, L.D. & Channing, C.P. (1980) Inhibition of cumulus cell progesterone secretion by low molecular weight fractions of porcine follicular fluid which also inhibit oocyte maturation. *Endocrinology* **106,** 584–591.

Hirshfield, A.N. & Midgley, A.R., Jr (1978) The role of FSH in the selection of large ovarian follicles in the rat. *Biol. Reprod.* **19,** 606–611.

Hisaw, F.L. (1947) Development of the graafian follicle and ovulation. *Physiol. Rev.* **27,** 95–119.

Hsu, C.J. & Hammond, J.M. (1986) Gonadotropins and estradiol regulate the production of insulin-like growth factor-I/Somatomedin C by porcine granulosa cells in culture. *Endocrinology* **118** (Suppl.), 290, Abstr. 761.

Hsueh, A.J. & Jones, P.B.C. (1981) Extrapituitary actions of gonadotropin-releasing hormone. *Endocr. Reviews* **2,** 437–461.

Hsueh, A.J., Adashi, E.Y., Jones, P.B.C. & Welsh, T.H., Jr (1984) Hormonal regulation of the differentiation of cultured ovarian granulosa cells. *Endocr. Reviews* **5,** 76–127.

Ireland, J.J. & Roche, J.F. (1982) Development of antral follicles in cattle after prostaglandin-induced luteolysis: changes in serum hormones, steroids in follicular fluid, and gonadotropin receptors. *Endocrinology* **111,** 2077–2086.

Ireland, J.J. & Roche, J.F. (1983a) Development of non-ovulatory antral follicles in heifers: changes in steroids in follicular fluid and receptors for gonadotropins. *Endocrinology* **112,** 150–156.

Ireland, J.J. & Roche, J.F. (1983b) Growth and differentiation of large antral follicles after spontaneous luteolysis in heifers: changes in concentration of hormones in follicular fluid and specific binding of gonadotropins to follicles. *J. Anim. Sci.* **57,** 157–167.

Ireland, J.J. & Roche, J.F. (1987) Hypothesis regarding development of dominant follicles during a bovine estrous cycle. In *Follicular Growth and Ovulation Rate in Farm Animals* (in press). Eds J. Roche & D. O'Callaghan. Martinus Nijhoff, The Hague.

Ireland, J.J., Curato, A. & Wilson, J. (1983) Effect of charcoal-treated bovine follicular fluid on secretion of LH and FSH in ovariectomized heifers. *J. Anim. Sci.* **57,** 1512–1515.

Ireland, J.J., Fogwell, R.L., Oxender, W.D., Ames, K. & Cowley, J.L. (1985) Production of estradiol by each ovary during the estrous cycle of cows. *J. Anim. Sci.* **59,** 764–771.

Jonassen, J.A., Bose, K. & Richards, J.S. (1982) Enhancement and desensitization of hormone responsive adenylate cyclase in granulosa cells of preantral and

antral ovarian follicles: effects of estradiol and follicle-stimulating hormone. *Endocrinology* **111**, 74–79.

Josso, N. (1986) Anti Müllerian hormone: new perspective for a sexist molecule. *Endocr. Revs* **7**, 421–433.

Kesner, J.S. & Convey, E.M. (1982) Interaction of estradiol and luteinizing hormone releasing hormone on follicle stimulating hormone release in cattle. *J. Anim. Sci.* **54**, 817–825.

Knecht, M. & Feng, P. (1986) Transforming growth factor-beta inhibits LH receptor formation and enhances EGF receptor formation induced by FSH in rat granulosa cells. *Endocrinology* **118** (Suppl.), 32, Abstr. 17.

Kumari, G.L., Kumar, N., Duraiswami, S. & Roy, S. (1984) Ovarian lutropin receptor binding inhibitor. In *Gonadal Proteins and Peptides and their Biological Significance*, pp. 161–175. Eds M. R. Sairam & L. E. Atkinson. World Scientific Publ. Co., Singapore.

Leung, P.C.K. & Armstrong, D.T. (1980) Interactions of steroids and gonadotropins in the control of steroidogenesis in the ovarian follicle. *Ann. Rev. Physiol.* **42**, 71–82.

Ling, N., Ying, S.Y., Ueno, N., Esch, F., Denoroy, L. & Guillemin, R. (1985) Isolation and partial characterization of a Mr 32 000 protein with inhibin activity from porcine follicular fluid. *Proc. natn. Acad. Sci. U.S.A.* **82**, 7217–7221.

Ling, N., Ying, S.Y., Ueno, N., Shimasaki, S., Esch, F., Hotta, M. & Guillemin, R. (1986) Pituitary FSH is released by a heterodimer of the B-subunits from the two forms of inhibin. *Nature, Lond.* **19**, 779–782.

Lintern-Moore, S. & Moore, G.P.M. (1979) The initiation of follicle and oocyte growth in the mouse ovary. *Biol. Reprod.* **20**, 773–778.

Littman, B.A. & Hodgen, G.D. (1984) Pharmacologic ovarian stimulation in monkeys: Blockade of the luteinizing hormone surge by a highly transient ovarian factor. In *Gonadal Proteins and Peptides and their Biological Significance*, pp. 111–125. Eds M. R. Sairam & L. E. Atkinson. World Scientific Publ. Co., Singapore.

Makris, A., Ryan, K.J., Yasumizu, T., Hill, C.L. & Zetter, B.R. (1984) The nonluteal porcine ovary as a source of angiogenic activity. *Endocrinology* **15**, 1672–1677.

Matton, P., Adelakoun, V., Couture, Y. & Dufour, J.J. (1981) Growth and replacement of the bovine ovarian follicles during the estrous cycle. *J. Anim. Sci.* **52**, 813–818.

McNatty, K.P., Hunter, W.M., McNeilly, A.S. & Sawers, P.S. (1975) Changes in the concentration of pituitary and steroid hormones in the follicular fluid of human graafian follicle throughout the menstrual cycle. *J. Endocr.* **64**, 555–571.

McNatty, K.P., Heath, D.A., Henderson, K.M., Lun, S., Hurst, P.R., Ellis, L.M., Montgomery, G.W., Morrison, L. & Thurley, D.C. (1984) Some aspects of thecal and granulosa cell function during follicular development in the bovine ovary. *J. Reprod. Fert.* **72**, 39–53.

Meloni, F., Ben-Rafael, Z., Fateh, M. & Flickinger, G.L. (1986) Molecular weight variants of prolactin in human follicular fluid. *Biol. Reprod.* **34** (Suppl. 1), 104, Abstr. 110.

Miller, J.G.O. & Behrman, H.R. (1986) Oocyte maturation is inhibited by adenosine in the presence of FSH. *Biol. Reprod.* **35**, 833–837.

Nakano, R., Mizuno, T., Katayama, K. & Toja, S. (1975) Growth of ovarian follicles in rats in the absence of gonadotrophins. *J. Reprod. Fert.* **45**, 545–548.

Padmanabhan, V., Convey, E.M., Roche, J.F. & Ireland, J.J. (1984) Changes in inhibin-like bioactivity in ovulatory and atretic follicles and utero-ovarian venous blood after prostaglandin-induced luteolysis in heifers. *Endocrinology* **115**, 1332–1340.

Pathiraja, N., Carr, W.R., Fordyce, M., Forster, J., Land, R.B. & Morris, B.A. (1984) Concentration of gonadotrophins in the plasma of sheep given gonadal steroid antisera to raise ovulation rate. *J. Reprod. Fert.* **72**, 93–100.

Rahe, C.H., Owens, R.E., Fleeger, J.L., Newton, J.H. & Harms, P.G. (1980) Pattern of plasma luteinizing hormone in the cyclic cow: dependence upon period of the cycle. *Endocrinology* **107**, 498–503.

Ranta, T., Huhtaniemi, I., Jalkanen, J., Ritvos, O. & Ylikorkala, O. (1986) Activation of protein kinase C stimulates human granulosa-luteal cell prostacyclin production. *Endocrinology* **118** (Suppl.), 67, Abstr. 147.

Ratoosh, S.L. & Richards, J.S. (1985) Regulation of the content and phosphorylation of R_{II} by adenosine 3′,5′-monophosphate, follicle-stimulating hormone, and estradiol in cultured granulosa cells. *Endocrinology* **117**, 917–927.

Rein, M.S. & Schomberg, D.W. (1982) Characterization of insulin receptors on porcine granulosa cells. *Biol. Reprod.* **26** (Suppl. 1), 113, Abstr.

Richards, J.S. (1980) Maturation of ovarian follicles: Actions and interactions of pituitary and ovarian hormones on follicular cell differentiation. *Physiol. Rev.* **60**, 51–89.

Richards, J.S. & Rolfes, A.I. (1979) Hormonal regulation of cyclic AMP binding to specific receptor proteins in rat ovarian follicles. *J. biol. Chem.* **255**, 5481–5489.

Richards, J.S., Haddox, M., Tash, J.S., Walter, U. & Lohmann, S. (1984) Adenosine 3′5′-monophosphate-dependent protein kinase and granulosa cell responsiveness to gonadotropins. *Endocrinology* **114**, 2190–2198.

Richards, J.S., Ireland, J.J., Rao, M.C., Bernath, G.A. & Midgley, A.R., Jr (1976) Ovarian follicular development in the rat: Hormone receptor regulation by estradiol, follicle stimulating hormone and luteinizing hormone. *Endocrinology* **99**, 1562–1570.

Richards, J.S., Sehgal, N. & Tash, J.S. (1983) Changes in content and cAMP-dependent phosphorylation of specific proteins in granulosa cells of preantral and preovulatory ovarian follicles and in corpora lutea. *J. biol. Chem.* **258**, 5227–5232.

Sairam, M.R. & Atkinson, L.E. (1984) The trail of gonadal proteins and peptides. In *Gonadal Proteins and Peptides and their Biological Significance*, pp. 3–6. Eds M. R. Sairam & L. E. Atkinson. World Scientific Publishing Co., Singapore.

Sanzo, M.A. & Reichert, L.E., Jr (1982) Gonadotropin receptor binding regulators in serum. *J. biol. Chem.* **257**, 6033–6040.

Sato, E., Ishibashi, T. & Iritani, A. (1982) Purification and action sites of a follicle stimulating hormone

inhibitor from bovine follicular fluid. *J. Anim. Sci.* **55,** 873–877.

Sheldrick, E.L. & Flint, A.P.F. (1984) Ovarian oxytocin. In *Gonadal Proteins and Peptides and their Biological Significance*, pp. 257–272. Eds M. R. Sairam & L. E. Atkinson. World Scientific Publ. Co., Singapore.

Skinner, M.K., McKeracher, H.L. & Dorrington, J.H. (1985) Fibronectin as a marker of granulosa cell cytodifferentiation. *Endocrinology* **117,** 886–892.

Sluss, P.M. & Reichert, L.E., Jr (1984) Porcine follicular fluid contains several low molecular weight inhibitors of follicle-stimulating hormone binding to receptor. *Biol. Reprod.* **30,** 1091–1104.

Smeaton, T.C. & Robertson, H.A. (1971) Studies on the growth and atresia of Graafian follicle in the ovary of the sheep. *J. Reprod. Fert.* **25,** 243–252.

Tonetta, S.A. & Ireland, J.J. (1984) Effect of cyanoketone on follicle-stimulating hormone (FSH) induction of receptors for FSH in granulosa cells of the rat. *Biol. Reprod.* **31,** 487–493.

Tonetta, S.A., Spicer, L.J. & Ireland, J.J. (1985) CI-628 inhibits follicle-stimulation hormone (FSH)-induced increases in FSH receptors of the rat ovary: requirement of estradiol for FSH action. *Endocrinology* **116,** 715–722.

Tsafriri, A., Pomerantz, S.H. & Channing, C.P. (1976) Inhibition of oocyte maturation by porcine follicular fluid: partial characterization of the inhibitor. *Biol. Reprod.* **14,** 511–516.

Vale, W., Rivier, J., Vaughan, J., McClintock, R., Corrigan, A., Woo, W., Karr, D. & Spiess, J. (1986) Purification and characterization of an FSH releasing protein from porcine follicular fluid. *Nature, Lond.* **19,** 776–779.

Webb, R. & Gauld, I.K. (1987) Endocrine control of follicular growth in the ewe. In *Follicular Growth and Ovulation Rate in Farm Animals* (in press). Eds J. Roche & D. O'Callaghan. Martinus Nijhoff, The Hague.

Welschen, R., Dullaart, J. & DeJong, F.H. (1979) Interrelationships between circulating levels of estradiol-17β, progesterone, FSH, and LH immediately after unilateral ovariectomy in the cycling rat. *Biol. Reprod.* **18,** 421–427.

Yanagishita, M., Hascall, V.C. & Rodbard, D. (1981) Biosynthesis of proteoglycans by rat granulosa cells cultured in vitro: modulation by gonadotropins, steroid hormones, prostaglandins, and a cyclic nucleotide. *Endocrinology* **109,** 1641–1649.

Ying, S.Y., Ling, N., Bohlen, P. & Guillemin, R. (1981) Gonadocrinins: peptides in ovarian follicular fluid stimulating the secretion of pituitary gonadotropins. *Endocrinology* **108,** 1206–1215.

Ying, S.Y., Becker, A., Baird, A., Ling, N., Ueno, N., Esch, F. & Guillemin, R. (1986a) Type beta transforming growth factor (TGF-B) is a potent stimulator of the basal secretion of follicle stimulating hormone (FSH) in a pituitary monolayer system. *Biochem. Biophys. Res. Commun.* **135,** 950–956.

Ying, S.Y., Becker, A., Ling, N., Ueno, N. & Guillemin, R. (1986b) Inhibin and beta type transforming growth factor (TGF_{β}) have opposite modulating effects on the follicle stimulating hormone (FSH)-induced aromatase activity of cultured rat granulosa cells. *Biochem. Biophys. Res. Commun.* **136,** 969–974.

Zeleznik, A.J. (1981) Premature elevation of systemic estradiol reduces serum levels of follicle-stimulating hormone and lengthens the follicular phase of the menstrual cycle in Rhesus monkeys. *Endocrinology* **109,** 352–355.

Zeleznik, A.J., Schuler, H.M. & Reichert, L.E., Jr (1981) Gonadotropin-binding sites in the Rhesus monkey ovary: role of the vasculature in the selective distribution of human chorionic gonadotropin to the preovulatory follicle. *Endocrinology* **109,** 356–361.

Zeleznik, A.J., Hutchison, J.S. & Schuler, H.M. (1985) Interference with the gonadotropin-suppressing actions of estradiol in Macaques overrides the selection of a single preovulatory follicle. *Endocrinology* **117,** 991–999.