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Physiology of follicle development in cattle

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Abstract

In cattle, follicles develop in cohorts, the later stages of which are characterised by a wave-like pattern. A dominant follicle in the cohort continues developing while other subordinate follicles regress. Follicle development is regulated by the interaction of endocrine (mainly FSH and LH) and intrafollicular (mainly TGF-β family members) factors, and by numerous intracellular molecular pathways (e.g. involving signal transduction and apoptosis).

Introduction

In cattle, growth of ovarian antral follicles from about 300µm to 5 mm in diameter takes more that than 30 days. Subsequent follicle growth to 15 or 20 mm in diameter is rapid and occurs in a wave-like pattern over the next 4 to 6 days. Early antral growth (to about 5 mm in diameter) is considered to be gonadotrophin independent but subsequent growth is principally regulated by the gonadotrophins, particularly by follicle-stimulating hormone (FSH). Numerous local factors also regulate follicle growth of which the TGFβ family members (including inhibins, activin and follistatin) and IGFs are the most important. Recent efforts to understand follicle development now also include studies of the intracellular molecular factors that regulate the proliferation or regression of follicle cells.

Follicle waves

In a number of species, follicle growth is characterised by a follicle waves pattern; with two or three waves occurring during the normal course of oestrous cycles in cattle ([3]). A follicle wave is characterised by the synchronous emergence of a group or cohort of follicles; as the wave progresses one of the members of the cohort is selected to become the dominant follicle whilst the remainder of the group undergo atresia (subordinate follicles). The day of follicle emergence is considered the first day of the follicular wave when a growing cohort of follicles can be first detected using ultrasonography at about 5 mm in diameter (this is also often described as follicle recruitment). Selection is the process that results in the decrease in the number of growing follicles to the species specific number of follicles that ovulate (usually one in cattle) and ends when the dominant follicle has been selected from the subordinate follicle as seen by a difference in follicle size ([3]). This divergence in growth rate is referred to as deviation ([7]) and is coincident with decreasing plasma FSH concentrations and the acquisition of luteinising hormone (LH) responsiveness by the dominant follicle ([12]). Whilst all dominant follicles are capable of ovulating, their ability to ovulate is dictated by the hormonal environment. Progesterone prevents ovulation of dominant follicles that mature during the luteal phase through its negative feedback regulation of LH. Dominant follicles that develop under these conditions regress like subordinate follicles. Once progesterone concentration decrease, the follicular phase ensues and LH pulsatility increases and, under the influence of oestradiol, a gonadotrophin surge leads to the ovulation of the dominant follicle.

LH, FSH and follicle waves

Antral follicles between about 4 and 9 mm in diameter are dependent upon FSH for growth and each follicle wave is preceded by a transient rise in FSH concentrations. The first transient rise in FSH occurs within one and two days of ovulation, immediately following the gonadotrophin surge when LH and oestradiol concentrations are low, and is associated with the emergence of a new cohort or wave of follicular development ([1, 12]). As FSH concentrations begin to decline on Day two to four of the cycle one follicle is selected to continue to grow and become the dominant follicle. Two or three transient FSH rises occur during the oestrous cycle of cattle and each is associated with the emergence of a cohort of follicles ([1]).

Oestradiol is produced by granulosa cells of ovarian follicles as a result of aromatisation of androgens produced in theca cells. Dominant follicles have higher intrafollicular oestradiol concentrations than subordinate follicles. This enhanced oestradiol production is one of the defining features of a dominant follicle. Oestradiol produced from the developing dominant follicle is involved in the negative feedback regulation of FSH. Important autocrine and/or paracrine changes within the dominant follicle confer its ability to survive the decline in FSH concentrations and result in the development of LH receptors on granulosa cells and continuing oestradiol production. It is now well demonstrated that this switch from FSH to LH dependency occurs and that LH then controls the fate of the dominant follicle (high LH during the follicular phase leads to ovulation but sustained low LH during the luteal phase leads to regression and atresia).

Inhibins, activins and follistatin

Differential response to the same FSH environment may be fundamental to dominant follicle selection and subordinate follicle regression. Numerous peptide growth factors, including members of the transforming growth factor-β (TGF-β) superfamily and the IGF system are involved in follicular development. The TGF-β superfamily of extracellular signalling molecules comprises over 30 structurally related but functionally diverse proteins that include two inhibins (A and B), three activins (A, B and AB) and follistatin ([11]).

Inhibins exert an FSH-suppressive action on the pituitary and are dimeric glycoproteins consisting of α and β sub-units produced in multiple molecular weight forms ranging from 29 – >160 kDa ([9]). Follicular fluid concentrations of inhibin A are positively related to antral follicle size. Conversely, inhibin B concentrations decrease with increasing follicle size. However, levels of inhibin B are very much lower than inhibin A, questioning the physiological relevance of inhibin B in cattle ([11]). All dimeric inhibin forms suppress FSH synthesis and release ([9]). Inhibins have a local role within follicles to suppress oestradiol production and to antagonise activin actions and thus inhibit follicular growth and differentiation.

Activin, a homodimer of the inhibin β sub-unit, opposes the actions of inhibins at both pituitary and ovarian level as they both compete for the type II activin receptor. However, activin activity is regulated by levels of follistatin. Follistatin neutralises activin function in the pituitary and ovary. Follicle growth is associated with an increase in activin-A concentrations in the largest follicle, with either a reciprocal decrease or no change ([2, 11]) in follistatin. Transient increases in activin-A at follicle deviation were associated with the beginning of increases in intrafollicular IGF-I and oestradiol ([7]). Activin enhances inhibin synthesis from granulosa cells. Activin is postulated to play a key role in inducing responsiveness of the follicle to FSH through the induction of FSH receptors and is involved in the promotion and maintenance of the folliculogenic state of the follicle. The induction of FSH receptors in undifferentiated follicles, which are defined as gonadotrophin independent, may be one method of recruiting/selecting follicles from the primordial pool, thus proposing a regulatory role for activin in the recruitment and development of follicles.

Follistatin is a single chained, glycosylated, cystine rich polypeptide and a product of granulosa cells. Follistatin neutralises the actions of activin in the pituitary and the ovary, it also displays inhibin-like activity albeit to a lesser degree, by suppressing FSH cell content of cultures pituitary cells ([11]).

IGF System

The bovine ovarian IGF system comprises IGF-I and IGF-II, the IGF-type I receptor, four different insulin-like growth factor binding proteins (IGFBPs) and most recently protease(s) against the IGFBPs ([13]). Free IGFs stimulate granulosa cell proliferation, steroidogenesis and inhibin and activin synthesis in an FSH dependant manner ([8]). Interestingly, intrafollicular IGF concentrations remain unchanged during follicle growth but follicular growth is associated with alterations in intrafollicular IGFBP concentrations. The IGFBPs bind to IGFs preventing interaction with the IGF receptor. Follicle oestrogen activity is negatively correlated with intrafolicular amounts of the lower molecular weight IGFBPs (IGFBP-2, -4 and –5). Reduced amounts of IGFBPs leads to higher levels of bioactive IGFs and may be considered essential for dominant follicle selection enabling the dominant follicle to survive declining and nadir FSH concentrations without undergoing apoptosis. Intrafollicular amounts of IGFBPs are regulated at the level of gene expression, and their binding to IGF is also controlled via proteolytic cleavage by IGFBP proteases in follicular fluid. Elevated levels of IGFBP proteases have been detected in surviving dominant compared to regressing subordinate follicles ([6]).

Subcellular (molecular) regulation of follicle development

The demise of cells within follicles is mediated via apoptosis (programmed cell death). Apoptosis is the final mechanism in a series of pathways that removes unwanted cells from the body. These pathways are regulated by numerous factors both inside and outside cells (e.g. growth factors, gonadotrophins, etc in follicle cells). The bovine genome codes for 30 to 40 thousand genes and the pattern of gene expression in ovarian cells that controls these pathways and follicle development is now being examined. These genes code for many factors including cytokines, receptors, signal transduction molecules, transcription and growth factors, enzymes, cell cycle regulators, cellular components and factors involved in apoptosis. It is the interaction of these molecules that decides cell survival, proliferation or death. A number of recent studies have started to examine this multitude of pathways that will give us a better understanding of the molecular regulation of follicle development ([4, 5, 10, 14]).

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Résumé
Chez les bovins, les follicules se développent en groupe et vers la fin du processus sous la forme de vagues folliculaires. Un follicule dominant d'un groupe poursuit son développement pendant que les autres follicules de plus faible dimension régressent. Le développement folliculaire est contrôlé par l'interaction endocrinienne (principalement la FSH et la LH), par des facteurs intrafolliculaires (principalement par les membres de la famille TGF-β), et, par des mécanismes moléculaires (e.g. implication de signaux de transduction et d'apoptose).

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