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Insulin-Like Growth Factor in animal reproduction

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Abstract. The development of female gametes production (gametogenesis) occurs in an interesting way, as its process depends of many combined factors. This review will approach these morpho function mechanisms of the ovary and the folliculogenesis, correlating the function of Insulin-Like Growth Factors (IGFs), which will influence in the production of steroids hormones, in the maintenance follicular maturation, and still elucidate how the diet assists better in these phases. Besides that, with the new researches in animal reproduction, it is important emphasize the role and assists of Insulin-Like Growth Factors during this physiologic process, showing all its potential for a more efficient follicular dynamics in any species.

Keywords: IGFs, physiology, and bioavailability

Fator de crescimento ligado à insulina na reprodução animal

Resumo. O desenvolvimento da produção de gametas femininos (gametogênese) ocorre de forma interessante, pois seu processo depende de diversos fatores combinados. Esta revisão abordará esses mecanismos morfofuncionais do ovário e a foliculogênese, correlacionando a função dos fatores de crescimento ligados à Insulina (IGFs) que irão influenciar na produção de hormônios esteroides, na manutenção da maturação folicular, e ainda elucidar como a dieta alimentar auxilia melhor nessas fases. Além disso, com as novas pesquisas em reprodução animal, é importante enfatizar o papel e auxiliar os Fatores de Crescimento Insulínicos durante este processo fisiológico, mostrando todo o seu potencial para uma dinâmica folicular mais eficiente em qualquer espécie.

Palavras chave: IGFs, fisiologia e biodisponibilidade

Factor de crecimiento ligado a la insulina en la reproducción animal

Resumen. El desarrollo de la producción de gametos femeninos (gametogénesis) ocurre de una manera interesante, ya que su proceso depende de varios factores combinados. Esta revisión abordará estos mecanismos morfofuncionales del ovario y la foliculogénesis, correlacionando la función de los factores de crecimiento ligados a la insulina (IGF) que influirán en la producción de hormonas esteroides, el mantenimiento de la maduración folicular y también aclarará cómo la dieta ayuda a mejorar dichas etapas. Además, con nuevas investigaciones en reproducción animal, es importante enfatizar el papel y ayudar a los factores de crecimiento de la insulina durante este proceso fisiológico, mostrando todo su potencial para una dinámica folicular más eficiente en cualquier especie.

Palabra clave: IGF, fisiología y biodisponibilidad

Introduction

Insulin-like Growth Factor 1 or IGF-1 is a peptide which has one exclusive receptor (IGFR-1) and six binding proteins (IGFBP-1, -2, -3, -4, -5 and -6) ([Luz et al., 2015](#)), which has as function to inhibit

or to promote the action of IGF. This peptide participates in regulation of follicular development, steroidogenesis and stimulating granulosa cells differentiation and proliferation. It is also one of the substances related with folliculogenesis regulation and have a high potential for *in vitro* follicular culture. In *in vitro* follicular culture, it must have attention for the enrichment of media with adequate nutrients for avoid follicular atresia and promote follicular development, like occurs in *in vivo* folliculogenesis, through interaction of endocrine, paracrine and autocrine factors. *In vitro* studies growing increasingly in animal reproduction, in especial for elucidation of IGF action, since it shows positive results in follicular maturation and spermatoc penetration ([Oberlender et al., 2013](#)). Besides that, *in vivo* studies shown that food restriction directly influences physiology of reproduction, there are evidences that energy restriction directly effects the negative post-partum energy balance in heifers modifying IGFs, insulin and growth hormone concentrations ([Walsh et al., 2012](#)).

The objective of this review is to present the functions of IGF in follicular recruitment and dominance, its action in conjunction with gonadotropic hormones and growth hormone, compare its effect concerning free insulin in the body, and demonstrate the differences of concentrations at different diets.

IGF system

As said, IGF system is composed by several important items like receptors, binding proteins, but mainly protein kinases, which mediated the bioavailability of IGFs actions ([Ginther et al., 2004a](#); [Nandi & Poretsky, 2013](#)). However, this mechanism varies a little among species and during different follicular states. IGF-1, also known as somatomedin C, is a single chain polypeptide of several families produced predominantly in the liver ([Luz et al., 2015](#)). It has endocrine function stimulating follicular development in preantral and antral phases, and it is considered one of regulation substances of folliculogenesis, therefore, can shows potential for *in vitro* follicle culture ([Magalhães-Padilha et al., 2012](#)).

IGF-2, called somatomedin A is also a peptide growth factor with high degree of structural homology with pro insulin, and has gene expression in theca cells ([Luz et al., 2015](#)). It is considered the main intraovarian IGF ([Magalhães-Padilha et al., 2012](#)). Furthermore, it is believed that it has the same biology potential as somatomedin C, since both induce steroidogenesis and mitosis of granulosa cells ([Spicer & Aad, 2007](#)).

For insulin like growth factor receptors, there are two types that measure actions of both, IGFs and insulin itself. The IGFR-1 binds to IGF-1 (more affinity) and -2 (mimics the IGF-1 action), and still have a bigger relation with insulin. Already IGF-2 binds to both IGFs, with less affinity, and do not has connection with insulin ([Magalhães et al., 2012](#); [Spicer, 2004](#)), then the binding of IGF-2 with its receptor occurs by degradation of the receptor binding of the complex ([Hawkes & Kar, 2004](#)). It is also known that IGF-2 has its expression regulated in both, granulosa and theca cells ([Echternkamp et al., 2012](#)). Finally, it is described by [Spicer & Aad \(2007\)](#) that the IGFR-1 helps IGF-2 to increase production and differentiation of granulosa cells, whereas the IGFR-2 is associated with aid the reduction of granulosa cells responses to IGF-2.

IGFBPs are present in bovine follicular fluid and have as main role regulation of IGF bioavailability, acting by inhibition and improvement of the action of two types of growth factor in target cells ([Fortune et al., 2001](#); [Magalhães-Padilha et al., 2012](#)). Separately, IGFBPs-2 and -4 have your gene expression occurring in granulosa and theca cells, respectively, and are present in greater quantity in subordinate follicles than in dominants follicles. However, all of them change their concentration during follicle development and atresia ([Canty et al., 2006](#)).

In addition, there is a proteolytic enzyme present in bovine follicular fluid, in greater quantity in dominant follicles, responsible for IGFBPs degradation, mainly IGFBP-4 and -5 ([Fortune et al., 2004](#)). That enzyme is known as PAPP-A (Pregnancy-Associated Plasma Protein A), a protein kinase that promotes a break of the binder, decreasing the amount of binding proteins, consequently raising free IGFs concentration, which increases production of estradiol when associated with FSH ([Buratini Júnior, 2007](#); [Luz et al., 2015](#)).

Beyond growth factors, hormones also act together directly or/and indirectly for control folliculogenesis mechanisms. Among them, growth hormone (GH) is an important metabolic regulator of several stages of follicular development process, in special in initial antral phase, and as a stimulant

for the release of the IGF-1 ([Magalhães et al., 2012](#)). GH is a hormone that also acts on hypothalamic-pituitary axis by positive feedback mechanism with GnRH, which can through somatomedins, control LH and FSH secretion and action ([Frandsen et al., 2011](#)). It has active participation in folliculogenesis and oocyte development, besides stimulating blastocysts production when associated to insulin, thus increasing production and embryo survival ([Barbosa et al., 2017](#)). GH receptors are found in high quantities in granulosa cells from preantral and antral follicles, in oocytes, and seen in liver ([Chase Junior et al., 1998](#)). In ovary, GH stimulates steroidogenesis directly or indirectly, being the second throughout the potentiation of the action of LH, which will improve luteinization of target cell, and increase its expression and production in same cells through IGF-1 ([Barbosa et al., 2017](#)).

Communication between growth hormone and IGF-1 started by the binding of GH to its receptor on cell surface ([Barbosa et al., 2017](#)), and IGF-1 will acts like primary regulator of GH by negative feedback mechanism ([Chase Junior et al., 1998](#)). Therefore, in situations where the animal is in malnutrition state, the liver will become insensitive to GH, reducing its liver receptors. With GH receptors decrease, there will be no stimulus for release IGF-1, and consequently increase GH serum in circulation ([Chase Junior et al., 1998](#)).

GH in ruminants can act, when in FSH associating, in order to regulate IGF-1 secretion in dose-dependent manner and stimulate estrogens production ([Khalid et al., 2000](#)), and when associated to insulin, increase granulosa cells proliferation ([Langhout et al., 1991](#)). [Barbosa et al. \(2017\)](#) concluded that, as well as IGF-1, GH when used in in vitro production of embryos acts like anti-apoptotic factor, increasing the production of viable cells and improving the quality of the oocyte.

As another control mechanism, we have insulin, a polypeptide hormone, which captures glucose, and also act like mediator of follicular development mechanism, embryo development, oocyte maturation and steroidogenesis. In addition, it has a greater interaction with the IGFs ([Nandi & Poretsky, 2013](#)). According to [Serafim et al. \(2013\)](#), the effect of this hormone in follicle maturation and atresia is specie-specific, and it is dose-dependent. However, the effects on nutrition have been elucidated, due its relation with glucose ([Scaramuzzi et al., 2011](#)).

However, plasma concentrations affinity of insulin and IGF (particularly IGF-1) are mediated by IGFBP-1 of granulosa cells and liver, which will regulate free IGF-1 inversely proportional ([Nandi & Poretsky, 2013](#)). That is, when there is high nutrient intake, insulin concentration increase and IGFBP decrease, consequently IGF bioavailability it rises ([Chase Junior et al., 1998](#)). According to [Bilby et al. \(2004\)](#), when insulin is added to in vitro embryo culture media, is observed higher rate of cleavage and blastocyst production, higher mitotic activity, and lower apoptosis rate. In addition, hyperinsulinemia has positive effect in embryo quality, since it increases their production directly, with larger size and higher post-thaw hatch rate, as shown by [Bastos et al. \(2007\)](#).

Folliculogenesis

Folliculogenesis is the process by which primordial follicles can reach follicular pre-ovulatory stage, involving activation, growth and maturation stages ([Buratini Júnior, 2007](#)). This process is controlled by a complex interaction between endocrine, paracrine and autocrine factors (they are growth factors, peptides and hormones). What will happen with the follicle depends on the balance between stimulatory factors (responsible for follicular development and survival) and inhibitory factors (responsible for atresia) on ovary. Lastly, this process is divided into two phases: pre antral and antral phase ([Luz et al., 2015](#)).

Pre antral follicular development is the phase where occur the activation of primordial follicles making then primary follicles, after these primary follicles become secondary follicles. Regulation of this process is conducted by factors produced locally (intraovarian factors) ([McNatty et al., 1999](#)). Besides that, literature is slightly controversial about the real role of gonadotropins at this time (just responsible or little dependent). According to [Gutierrez et al. \(2000\)](#) and [Webb et al. \(2003\)](#), in this stage, FSH has a permissive role and non-regulatory of the follicle development. However, for [Wandji et al. \(1996\)](#), cattle pre antral follicles present FSH receptors, consequently regulating their development. There are evidences that FSH and LH can act in pre antral phase, promoting survival, activation and growth of early follicles ([Buratini Júnior, 2007](#)). However, primordial follicles do not have FSH receptors, therefore is possible that the hormone can act by regulation of expression of several growth factors essential for activation, and after that in follicular growth ([Gutierrez et al., 2000](#); [Webb et al.,](#)

2003). According [Webb et al. \(2003\)](#), IGF seems to help follicular growth in pre antral phase by endocrine action. These follicles present IGF-1 and binding proteins receptors (IGFBP-2 and -3). Besides that, [Gutierrez et al. \(2000\)](#) and [Fortune et al. \(2004\)](#) claim that IGFs stimulate correct development when insulin doses close to physiological are used.

Antral follicular development phase is the growth of secondary follicles up to pre ovulatory stage. Antral follicles are recruited, in domestic species, and growth in follicular wave controlled by gonadotropins ([Buratini Júnior, 2007](#)). This moment is critically dependent of FSH and LH ([Fortune et al., 2001](#); [Ginther et al., 2003](#)), increasing estrogenic activity in granulosa and theca cells, resulting in increase on steroids synthesis, mainly estradiol. As in the previous phase, beyond gonadotropins, growth factors locally produced act in paracrine and endocrine way, helping in follicular development ([Fortune et al., 2004](#); [Ginther et al., 2003](#); [Webb et al., 2003](#)). According to [Adams et al. \(1992\)](#), [Fortune \(1994\)](#) and [Ginther et al. \(1996\)](#), increase in plasmatic concentration of FSH will stimulate follicular recruitment and follicular wave emergence. Later, among recruited follicles, one is selected and is now called dominant follicle, because acquires ovulatory capacity and takes remaining follicles to atresia by inhibin secretion and increase in estradiol synthesis. However, we knew that follicles are only FSH dependent until dominance occurs, after this, they will grow under LH influence only ([Buratini Júnior, 2007](#)). According to [Buratini Júnior \(2007\)](#), LH receptor gene expression in granulosa cells was detected only after dominant follicle selection.

Development of follicles until ovulation requires different mechanisms and specialized cells types, being they in certain time dependent of gonadotropins (endocrine control) and in other moment responsive to local factors. These factors are extremely important in selection of the dominant follicle, oocyte maturation and ovulation ([Rovani et al., 2018](#)). This development occurs in waves, in which only one follicle is selected and will grow, while the others subordinates follicles come into atresia.

After pre antral and antral follicular phase, ovulation will occur due an increase in estradiol concentrations, and a LH peak, this will cause the rupture of this follicle ([Evans & Fortune, 1997](#)). After that, there is the formation of corpus luteum from remaining cells of the ovulated follicle after LH peak ([Buratini Júnior, 2007](#)). This new cellular formation will produce progesterone. In addition, this progesterone production will cease when luteolysis occur ([Trevisol et al., 2013](#)). The fact of IGFs have relation with FSH amount to follicular growth and estradiol production ([Fortune et al., 2004](#)), it is understood that the IGF may have big importance in selection of dominant follicle. Total IGF concentrations have no difference in follicular fluid of dominant follicles in relation to subordinated follicles ([De la Sota et al., 1996](#)). However, concentration of free IGF-1 was higher in follicular fluid of largest follicle when compared with the second largest one on the same wave, even before observing differences in estradiol concentrations or follicle diameter ([Beg & Ginther, 2006](#)).

According to [Fortune et al. \(2004\)](#), reduced concentrations of IGFBP-4 in dominant follicle of cattle suggest an increased in proteolytic degradation of this protein by pregnancy-associated plasma protein A (PAPP-A). In addition, IGFBP-5 and -2 also suffered degradation, being the second one due inhibitory action of FSH that cannot recognized it.

Follicular deviation is the most important event in follicular selection; it is characterized by difference in growth rates between dominant and subordinate follicles in the end of selection phase on follicular wave. The end of this phase and beginning of the deviation occur when the future dominant follicle reaches a minimum diameter of approximately 8,5mm in heifers and 22,5mm in mares ([Ginther et al., 2004a](#)). It is also known that changes that happen from a subordinate to get dominant follicle are due to their capacity of develop greater sensitivity to LH ([Ginther et al., 2003](#)).

Deviation process has as systemic component, FSH circulation suppression due inhibin secretion (production stimulated by IGF-1 and LH) and estradiol (production stimulated only by LH, in mares) produced by development of dominant follicle ([Ginther, 2017](#)). According [Beg & Ginther \(2006\)](#), free IGF-1 present in follicular fluid increases during the development of the largest follicle, and decrease in second largest follicle during the moment of follicular selection. Besides that, estradiol concentration in follicular fluid also increases in dominant follicle in the beginning of deviation. To explanation that, [Rivera & Fortune \(2003\)](#) claim that in cows, the high concentration of free IGF-1 in the largest follicle at this time, it is related with high proteolytic degradation of IGFBP-4 and -5.

According [Ginther et al. \(2004b\)](#), the hypothesis that IGF-1 is able to stimulate estradiol production in heifers and mares near to follicular deviation was proven in their studies. In these researches, intrafollicular injection of rh-IGF-1 (recombinant human) in subordinate follicles from cattle in the beginning of deviation, increased estradiol concentration in follicular fluid. However, the same injection had no effect on progesterone concentrations in the same species. In another study ([Ginther, 2017](#)), with mares, was noted that IGF-1 increased temporarily progesterone concentration, but had no difference in estradiol concentration. Therefore, their hypothesis is confirmed only in heifers and not in mares, reaffirming that there may be physiological differences between species ([Ginther et al., 1996, 2003; Ginther et al., 2004a; Ginther et al., 2004b](#)).

Based on experiments of [Spicer & Aad \(2007\)](#), IGF-2 presented directly effect and participation in some points: increased production of estradiol and progesterone by granulosa cells but had its effect suspended when antibodies against IGFR-1 were present; it was more active in follicular larger cells than smaller cells; increased DNA synthesis and numbers of viable cells; and had its mRNA binding expression of IGFR-2 increased in granulosa cells of small follicles and theca cells of larger follicles.

Intrafollicular mediators of nutritional influence (metabolites and nutrients) present directly effect on follicular function, which the most studied are leptin, glucose, insulin, growth hormone (GH), and IGF. Besides that, there are intrafollicular factors linked directly to the activation mechanism of follicular divergence, they are IGF system, steroids hormones, peptides (inhibin), and others.

Gonadotrophic hormones

Gonadotrophic hormones (FSH – Follicle Stimulating Hormone, and LH – Luteinizing Hormone) are already present in fetal animal life, and participate in many reproductive physiologic mechanisms such as sexual differentiation. Their production is GnRH dependent and their release are mediate by feedbacks to the hypothalamus by steroid hormones (estradiol and progesterone) and peptides (inhibin) ([Frandsen et al., 2011](#)).

Granulosa and theca cells of secondary follicles develop receptors for these hormones, making it responsible to them. Under LH action theca cells proliferate and produce androgens, and under FSH action the same cells proliferate and develop enzymes to convert androgens into estradiol ([Frandsen et al., 2011](#)).

On folliculogenesis, both hormones will influence estradiol synthesis and accumulation increase mainly, due esteroidogenic activity in granulosa and theca cells ([Magalhães et al., 2012](#)). FSH in high plasmatic concentrations is responsible for follicular recruitment and emergence of follicular wave ([Fortune et al., 2004](#)); while LH, besides participating in subsequent follicle grow, will increase its pulsatility and generate the hormonal peak, which will lead the dominant follicle to ovulation and assist in maturation oocyte boosting the resumption of meiosis ([Fortune et al., 2004; Ginther et al., 2003](#)). During folliculogenesis, in follicular selection phase, it is necessary that FSH induces production of IGFBP-4 degradation protease, which will act only in one follicle among many, causing increase of IGF bioavailability ([Oliveira et al., 2011](#)). The fact is that the expose time of follicle to FSH is critical for both: selection and dominance, although this last process also occurs depending of others factors action, such as esteroidogenesis and local action of IGF-1 ([Webb et al., 2003](#)). Thus, LH is also important for regulation of ovarian function, once it is causes follicle luteinization, preparing it for ovulation or atresia. However, recent studies have shown that its bigger action occurs in advanced follicles stage, which have cells with greater number of receptors for this hormone even before divergence, which will result in a better viability of the follicle ([Ginther et al., 2003](#)).

Estradiol

Estradiol is a primary estrogen biologically active produced by ovary from androgenic precursors. The estrogens, in general, perform various activities, such as development of secondary female sex characteristics, negative and positive feedback to control LH and FSH, and have anabolic protein effect in ruminants ([Hafez & Hafez, 2004](#)). In addition, still participates in formation of pre ovulatory wave of gonadotropins ([Zielak-Steciwko & Evans, 2016](#)).

It is known that estrogens concentrations like estradiol are high in blood of utero-ovarian vein, ipsilateral to ovarian with dominant follicle. This explains the fact that follicular growth is interrupted

when estradiol increase, since it will signal the inhibin to act to prevent the FSH action, leading the follicle to dominance ([Ginther et al., 1996](#)). Based on studies, it is understood that variations of estradiol concentrations will occur directly proportional to FSH, showing the interaction of these two hormones, mainly on follicular divergence stage of the wave ([Ginther et al., 2003](#)).

About progesterone, estrogen in physiological doses in presence of low progesterone concentration stimulates the release of LH to trigger ovulation, while in environment with high concentration and high doses, estrogen block gonadotropins action, including LH, showing its importance for maintenance of follicular wave and corpus luteum regression ([Moraes et al., 2002](#)). In addition, it was observed that inhibin increases with emergence wave evolution, and it is by itself responsible for FSH suppression before deviation, and will act together with estradiol when divergence stage starts ([Ginther et al., 1996, 2003](#)).

According to [Ginther et al. \(2004b\)](#), IGF-1 plays positive role directly or indirectly stimulating androgen production, mainly androstenedione in dominant follicle in heifers, which reflects in greater estradiol concentration. It is known that IGF-1 has influence and directly effect in increased of progesterone production by granulosa cells remaining on ovulated follicle in cattle ([Ryan et al., 2008](#)). Besides that, IGF-1 has effect on anti-apoptotic pathways like MAPK and/or PI3K/Akt, and when activated participates in steroidogenesis, inducing essential enzyme production in this process, such as P450 cholesterol desmolase and aromatase ([Luz et al., 2015](#)).

Feeding (Restrictions and diets)

Nutrients ingested by animal's act in organism in many levels of the hypothalamic-pituitary-gonad axis, and this will directly and indirectly control hormones metabolism, especially those related to ovarian development functions and embryo production. Therefore, food management, both excess and scarcity, have influence in folliculogenesis ([Armstrong & Webb, 2003](#)).

Growing beef cattle and lactating cows require a balanced food to supply the demand of the body ([Prata, 2013](#)). One of the problems that could occur at this time is the negative energy balance, this can happen, when animals have an inability to consume energetic diet that will be enough for development, maintenance and lactation. Can also occur the acute dietary restriction. Both problems are associated with altered secretion of gonadotropins, reduction in follicle diameter and circulating estradiol concentration, and ovulatory failure ([Walsh et al., 2012](#)). [Walsh et al. \(2012\)](#) observed that physiologic reproductive changes occur when cattle are subjected to acute dietary restriction. In heifers, there is a decrease in IGF-1 and insulin concentration in circulation, and the same occur with estradiol and IGF-1 in follicular fluid. Also is observed a reduce in mRNA expression in granulosa cells by FSH action, and in contrast, increase in expression of the mRNA in theca cells by IGFBP-2 action.

As consequence of an induced dietary restriction, the catabolic environment can cause anovulation due of decreased in estradiol synthesis, because FSH responsiveness, IGF signalization in granulosa, and LH responsiveness in theca cells of dominant follicles ([Walsh et al., 2012](#)). Dietary restriction for long periods, interfere in GnRH and LH production and secretion, this can also induce cattle to periods of prolonged anestrus ([Prata, 2013](#)).

It is imperative to remember that IGF-1 regulates the bioavailability of GH by feedback mechanisms with their respectively receptors, cows subjected to food restriction during considerable time, shows a decrease in IGF-1 concentration due insensitivity and decreased of hepatic receptors of GH ([Chase Junior et al., 1998](#)).

Already animals that consume high energetic dietary shown increase in glucose, insulin and IGF-1 due IGFBPs regulatory mechanism. Besides that, they have a high hepatic metabolism, which consequently leads to a decrease in hormone concentrations in circulation, such as estradiol and progesterone, due a higher hepatic degradation ([Prata, 2013](#)).

Final considerations

It is understood IGF system as a family well divided of proinsulins and proteins, which has the function of assisting in some female physiological reproductive mechanisms, such as folliculogenesis. Your production/activation happen when organism needs them, they are produced in liver and will act on target cells, while their bioavailability is controlled by IGFBPs. Therefore, it is important to

understand the physiology of IGF system for better understanding of physiological factors of folliculogenesis and oogenesis, begin able to take the opportunity of them in organism, once that IGF-1 helps the follicle in the primordial phase, development, while IGF-2 makes batter the steroidogenesis in dominant follicle, promote spermatic broken, and helps the oocyte final maturation.

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