Essential Roles of Metabolic Hormones on Gonadal Functions and Fertility of Livestock

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Abstract

Metabolic signals through the hypothalamo-hypophyseal-gonadal axis influence the reproductive functions. Metabolic hormones such as growth hormone, insulin, and insulin-like growth factor-1 (IGF-1) modulate the gonadal function by influencing gametogenesis and steroidogenesis. These growth factors promote the follicular cells mitosis, survival and maturation of the oocytes, ovulation process, and luteal cells function. The effect of these metabolic hormones on male fertility though have not been documented well, addition of IGF-1 as an additive in the semen extender improved semen quality. The metabolic hormones act through their receptors present in the gonads and gametes of various domestic animals. The optimal levels of metabolic hormones in the circulation that are sufficient for manipulating the gonadal function need to be arrived for each of the domestic species. Alteration of metabolic hormones through supplementation of macro- and micronutrients will optimize reproductive efficiency in dairy animals.

Keywords

Metabolic hormones · Growth hormone · Insulin · Insulin-like growth factor-1 · Livestock fertility

The productivity and reproductive capacities of the animals can be improved through modification in traditional methods of breeding, feeding, and management (Walsh et al. 2011). The reproductive axis is controlled by the "metabolic status sensor"

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A. Kumaresan, A. K. Srivastava (eds.), *Current Concepts in Bovine Reproduction*,
https://doi.org/10.1007/978-981-19-0116-4_5

rather than the "level of nutrition" (Blache et al. 2000). In this regard, the growth factors and metabolic hormones, that is, somatotrophin, insulin, and insulin-like growth factor-I (IGF-I), received considerable attention for improving fertility in domestic animals. Though hypothalamo-pituitary axis is an important site of action for these metabolic signals (Bagath et al. 2016), these factors also act directly on the gonads (Selvaraju et al. 2012a; Dupont et al. 2014). This chapter discusses the recent understanding of the metabolic signals regulating reproductive performance in domestic ruminants.

5.1 Metabolic Hormones and Reproduction

Insulin, the classical metabolic hormone secreted from the β cells of Islets of Langerhans, has been described for its key role in carbohydrate metabolism. Reproductive status, lactation, age, and nutritional status are the major determinants of endogenous insulin concentration in domestic animals. The binding sites for insulin, IGF-I, and GH have been demonstrated in ovary, oviduct, uterus, and embryo. These factors influence the intrafollicular growth (Gong et al. 1994), gametes function (Selvaraju et al. 2010), and embryo development (Xie et al. 2015). Studies directed toward the direct involvement of insulin on reproductive functions showed beneficial effect on gonadal function (Selvaraju et al. 2002, 2003; Baithalu et al. 2013).

5.2 Folliculogenesis

The ovary is one of the sites of action for metabolic hormones in several species. The development of small antral follicles is not strictly gonadotrophin dependent. It is suggested that factors, that is, IGF, FGF, and EGF families, directly influence follicular growth rate by enhancing granulosa cell proliferation. In these follicles, vascularization is poorly developed, suggesting that paracrine regulation might be of particular importance. The growth of small antral follicles under the influence of GH is probably by IGF-I of endocrine origin. The relative importance of different growth factors regulating the growth of small antral follicles has not been well established. The growth factors modulate survival, proliferation, and differentiation of follicular cells, acting in interaction with gonadotrophins (Monniaux et al. 1997) and might act in vivo by enhancing growth and terminal maturation of ovulatory follicles (Rao et al. 2011).

Insulin acts through either its classical receptors or IGF-I receptors or both depending upon the clinical circumstances. The insulin receptors have been demonstrated in the granulosa cells (McArdle et al. 1991). Though the presence of such receptors in the corpus luteum of bovine is unclear, the addition of insulin stimulated progesterone secretion from the buffalo luteal cells cultured in vitro (Baithalu et al. 2013). In a physiological concentration, insulin acts in synergy with FSH and LH through its receptor to stimulate granulosa cell mitosis in small follicles (Gong et al. 1993c; Vinodkumar et al. 2017). Insulin increases

intrafollicular IGF-I production, which is positively correlated with follicular development. In sheep, insulin recruits follicles as well as reduces atresia and thereby increases the number of ovulatory follicles (Matamoros et al. 1991). The peripheral concentrations of insulin and IGF-I were positively correlated with the number of gonadotrophin dependent follicles in sheep (Gong et al., 1996). In heifers, administration of long-acting bovine insulin at a concentration of 0.25 IU/kg body weight subcutaneously as a cotreatment with FSH increased the size of the ovulatory follicle (Simpson et al. 1994).

In ruminants, IGF-I stimulates both proliferation and differentiation of granulosa cells in vitro. Depending on species and stage of follicle growth, IGF-I may be synthesized and secreted from the granulosa (Khalid et al. 2000) and thecal cells (Voutilainen et al. 1996). But studies indicate that the intrafollicular IGF-I is derived mostly from the circulating pool (Gong et al. 1993b; Perks et al. 1995). IGF-I receptors are present in the granulosa and thecal cells, and IGF-I acts on the granulosa cells in an autocrine and paracrine manner. It enhances the granulosa cell proliferation, aromatase activity, and progesterone biosynthesis (Gong et al. 1994; Rao et al. 2011). IGF-1 also plays an important role in the selection of preovulatory follicles by amplifying the actions of FSH/LH (Monget et al. 1993).

In the sheep, IGF-I primarily stimulates the proliferation of granulosa cells from small (1–3 mm diameter) but not from large (>5 mm in diameter) follicles. In contrast, IGF-I stimulates the secretion of progesterone by granulosa cells from large but not small follicles. Thus, IGF-I stimulates either proliferation or differentiation of granulosa cells, depending on the stage of development of follicles (Gong et al., 1996; Monniaux et al. 1997). In lactating cows, due to metabolic stress, decreased IGF-1 concentration and reduced expression of pregnancy-associated plasma protein-A (PAPP-A) in the granulose cells in the dominant follicle were reported as compared to nonlactating animals (Sanchez et al. 2014). Exposure of oocytes to a high concentration of IGF-I for a short duration increased inner cell mass proliferation during in vitro blastocyst formation in bovine (Velazquez et al. 2012).

The growth factors may also play an important regulatory role in antral follicular developmental processes. The only competent mature follicles in a wave will be able to develop in the presence of decreasing serum concentration of FSH. The IGF family is likely to be important in the selection of dominant follicles (Rao et al. 2011). The IGF-I and estradiol potentiate the action of FSH on granulosa cells differentiation. The increase in bioavailable IGF in large antral follicles during terminal follicular development (Gong and Webb 1996) and high responsiveness of granulosa cells to FSH during final follicular growth results from intrafollicular synthesis.

In vitro supplementation of LH, IGF-1, and EGF increased the expression level of vascular endothelial growth factor in luteal cell and granulosa cells culture of the preovulatory follicle. These growth factors play an important role in stimulating luteal and preovulatory follicular angiogenesis in buffalo corpus luteum (Chouhan et al. 2015) and follicles (Babitha et al. 2014), respectively.

From the recent findings, it is evident that growth factors are likely determinant for the development of small follicles before they become gonadotrophin dependent, but whether they play an essential role in the development of gonadotrophin-dependent follicles remains to be determined.

5.3 Gonadotrophins Secretion

Insulin and glucose metabolism are involved intimately with pituitary-ovarian function in ruminants (Downing et al. 1995a, 1995b). Insulin could affect GnRH or LH secretion by affecting the level of glucose or amino acid metabolism (McCann and Hansel 1986; Downing et al. 1995a, b). This hormone may alter the activity of the follicular cells either alone or in synergy with gonadotrophins (Gong et al. 1994).

A study from sheep revealed that insulin infusion during the luteal phase of the estrous cycle delayed preovulatory decline in FSH concentration by 8 h, and this could be due to an indirect effect associated with reduced secretion of estradiol and inhibin during the follicular phase (Downing and Scaramuzzi 1997). In sows, insulin treatment increased FSH concentration only during the first 24 h after injection (Cox et al. 1987). Contrarily, administration of insulin @ 40 IU two times a day and 0.4 IU/kg body weight could not produce any detectable changes in the FSH secretion in cattle (Harrison and Randel 1986) and pigs (Matamoros et al. 1991), respectively.

Insulin has been reported to increase LH production in cultured pituitary cells (Adashi et al. 1981). In ewes, administration of insulin during the midluteal phase or follicular phase did not affect characteristic preovulatory LH surges (Beam and Holcombe 1992), indicating that mechanisms controlling the frequency of LH pulses in ruminants may not be sensitive to serum insulin concentration. In contrast, LH pulse frequency (4.3 ± 0.4 vs. 1.8 ± 0.3 pulses/day) and mean LH concentration (0.48 ± 0.04 vs. 0.32 ± 0.03 ng/ml) were significantly reduced by insulin infusion during midcycle and $PGF_2\alpha$ given at the end of infusion (Downing and Scaramuzzi 1997).

5.4 Steroidogenesis

Insulin and IGF-I either alone or in combination with gonadotrophins have been found to have a profound effect on steroidogenesis of cultured bovine granulosa and luteal cells (Gong et al. 1993b; Baithalu et al. 2013). The addition of insulin and IGF-I to the granulosa cell culture medium on cattle and pigs stimulated estradiol secretion (Gong et al. 1994; Gutierrez et al. 1997) in a dose-dependent manner. Similarly, the administration of insulin increased the concentration of estradiol levels in the follicular fluid in heifers (Simpson et al. 1994) and ovulation rate in sheep (Downing and Scaramuzzi 1997). The reduced protein and mRNA expression of insulin receptor and alpha p85 of PI3K alter insulin signaling pathway (Hein et al. 2015) that could affect normal follicular steroidogenesis. The level of IGF-I was less

in follicular fluid of cystic cows, suggesting that the animals with cystic ovary had an altered regulation of the IGF system in the bovine ovary (Rodríguez et al. 2015).

The IGF-I and/or insulin may have a direct effect on the follicles and corpus luteum, resulting in the increased peripheral concentration of progesterone (Lucy et al. 1993). Insulin increases aromatase activity (Dorrington et al. 1987) and progesterone production in the porcine granulosa (May and Schomberg 1981) and bovine luteal (Sauerwein et al. 1992) cells culture. The higher release of progesterone by insulin was observed during the late (15–18d) luteal phase cell culture (Sauerwein et al. 1992). Administration of insulin for 4 days in sheep during the follicular phase decreases serum progesterone levels during the treatment period, suggesting the influence of insulin on corpus luteum regression or steroidogenesis (Beam and Holcombe 1992). In heifers, progesterone concentration (ng/ml) in the follicular fluid has been reported lower (71 ± 24 vs. 178 ± 19) in insulin-treated than control cows (Simpson et al. 1994).

The type-I IGF receptors are present in the corpus luteum. IGF-I enhances FSH-stimulated estrogen and progesterone production in granulosa cells of bovine (Gong et al. 1994) and ovine (Monniaux and Pisselet 1992). In theca cells, IGF-I synergizes with LH, increases LH receptors that augment androgen biosynthesis (Nahum et al. 1995). In granulosa cells, IGF-I increases FSH-mediated estrogen synthesis (Adashi et al. 1985) and after luteinization in synergy with LH stimulates progesterone synthesis. In the corpus luteum, the IGF-I-binding site increases during the luteal phase and attains maximum toward the end of the luteal phase.

The effect of IGF-I and insulin on luteal secretion changes with the stage of the cycle. Though insulin and IGF-I could effectively stimulate progesterone secretion from the late luteal stages, the total release of progesterone is limited to IGF-I stimulation alone (Sauerwein et al. 1992). The rise in plasma IGF-I at estrus is regulated by follicular estrogen. The follicular estradiol at estrus increases uterine IGF-I synthesis, which acts in an endocrine manner via type-I IGF receptor to affect late follicular or early luteal development (Perks et al. 1995).

5.5 Oocyte Maturation and Embryo Quality

Insulin plays an important role in oocyte maturation. Insulin induces bovine cumulus cell expansion and has a positive effect on embryo development in vitro (Zhang et al. 1991). Similarly, IGF-I is also an important mediator of follicular development, oocyte maturation, and subsequent embryo development. Follicles containing mature oocytes that failed to fertilize in vitro had a lower concentration of IGF-I (Jimena et al. 1992). IGF-I has been found to mediate and amplify estradiol action, which is essential for oocyte maturation.

The peripheral concentration of metabolic hormones has been positively correlated with the number of transferable embryos in cattle (Gong et al. 1993a, 1996). Elevated IGF-I levels in oviductal secretion have been observed at the time of embryo passage in cyclic cows (Herrler et al. 1992). The oviductal cells and preimplantation buffalo embryo possess IGF-I and insulin receptors (Daliri et al.

1999). Supplementation of culture media with insulin and IGF-I stimulates early embryonic development (Totey et al. 1996). Further, IGF-I reduced the deleterious effect of heat shock by slightly improving in vitro oocytes nuclear maturation and cleavage rates following in vitro fertilization in bovines (Meiyu et al. 2014). This embryonic development is supported by both autocrine and paracrine actions of insulin and IGF-I. A beneficial effect of insulin was observed on folliculogenesis and steroidogenesis in superovulated goats (Selvaraju et al. 2003). IGF-1 treatment improves the oocyte developmental competence by regulating the PI3K/Akt and apoptosis signaling (Javvaji et al. 2020).

5.6 Estrous Response

The onset of estrus was not affected in ewes treated with insulin after MAP sponge removal (Kirkwood et al. 1991). The estrous cycle length did not differ significantly in insulin-treated (during the luteal phase) ewes as compared to control (Beam and Holcombe 1992). Though earlier studies in pigs reported no effect of insulin on the weaning to estrous interval (Ramirez et al., 1997), later study reported a decrease in weaning to the estrus interval in pigs treated with insulin after weaning and opined that exogenous insulin creates a general anabolic signal that resulted in shortening the weaning to the estrous interval (Whitley et al. 1998).

5.7 Ovulation Rate and Superovulatory Response

The superovulatory response is positively correlated with the number of small follicles present in the ovaries at the beginning of FSH injection, and attempts were made to increase the number of small (2–5 mm diameter) antral follicles in cattle (Gong et al. 1993b) and goat through growth hormones and insulin (Selvaraju et al. 2002). Priming with rbGH in FSH-treated heifers increased ovulation rate and recovery of embryos. Treatment with rbGH stimulates follicular development and maturation through the increase in the peripheral concentration of insulin and IGF-I (Gong et al. 1993b). Further, increased follicular and peripheral IGF-I levels have been reported after insulin treatment in cattle (Simpson et al. 1994), ewes (Kirkwood et al. 1991) and sows (Cox et al. 1987).

Low fertilization rate and recovery of abnormal embryos continue to be the major limiting factors following superovulation and embryo collection in farm animals. This has been attributed to aberrations in oocyte maturation and asynchrony between maturational events between oocyte and follicle. Ovarian hyperstimulation and abnormal steroid levels are not only harmful to the egg quality but also to the uterine environment affecting the fertilization and embryo development. The circulating concentration of insulin and IGF-I has been associated with increased ovulation rate in cattle (Gong et al. 1993b) without alteration in serum LH profiles (Harrison and Randel 1986). Interaction of insulin and IGF-I with FSH might be physiologically important to increase ovulation rate due to the effect of these metabolic hormones in

decreasing follicular atresia (Cox et al. 1987). The rise in plasma insulin mobilizes more glucose supply to the follicles, which enhances ovulation rate without significant change in gonadotrophin concentration in ewes (Downing et al. 1995b). Insulin and glucose infusions inhibit the secretion of oestradiol in ewes. The suppressive effect of insulin was suggested to allow the selection of more than one ovulatory follicle leading to multiple ovulation (Downing et al. 1995b).

5.8 Metabolic Hormones on Improving Conception Rate

Reproductive wastage due to repeat breeding is a common reproductive problem in dairy cattle. The incidence of infertility in India ranges from 15 to 33.85 percent (Khan et al. 2016; Dutta et al. 2019), the majority of which is due to repeat breeding in cattle (Thakor and Patel 2013). The causes of repeat breeding have been attributed to genetic abnormalities, senility, nutritional deficiency, periestrus hormonal asynchrony, delayed ovulation, inadequate luteal function, and managemental factors (Maurer and Echternkamp 1982). These causes lead to either fertilization failure or early embryonic mortality. The repeat breeding condition due to fertilization failure/early embryonic mortality might originate from poor egg formation either during the early stages of follicle maturation and/or in the immediate preovulatory stages of follicular development. Repeat breeding animals had a significantly lower number of 1 to 3 mm size follicles. However, no difference was observed in 4 to 7 mm and $>$ 8 mm diameter of follicles, corpus luteum weight, and the number of corpora albicantia (Maurer and Echternkamp 1985). It was concluded that repeat breeding females possess a smaller population of antral follicles or an endocrine status insufficient for oogenesis. In the repeat breeding cows, the disturbances in endocrine profile at periestrus leading to poor egg quality (Kurykin et al. 2011).

Early embryonic mortality in cattle has also been due to the inadequate functioning of corpus luteum. The delayed formation of corpus luteum with or without lowered secretion of progesterone during the luteal phase leads to luteal dysfunction. The possible causes of luteal dysfunction are abnormal folliculogenesis, inadequate or inappropriate timing of preovulatory LH surge, hormonal asynchrony at periestrus period, delayed ovulation, and lack of LH support during the luteal phase. The ability of a mature oocyte to fertilize and develop into competent embryo depends on the changes in its follicular microenvironment before ovulation. The higher progesterone and lower levels of LH at estrus could affect normal embryo development. An altered follicular milieu by the hormonal asynchrony during periestrus period also causes resumption of meiosis before the LH surge, leading to ovulation of an excessively aged oocyte.

Since metabolic hormones regulate growth, maturation, and ovulation of follicular and also luteal function, the modulation of metabolic hormones may regulate fertility in infertile animals. Though the half-life of insulin in ruminants is approximately 12 to 13 minutes (Trenkle 1972), modified insulin preparations with longer biological half-life are available and can be used to improve fertility in animals

(Selvaraju et al. 2002; 2012). The administration of long-acting insulin at concentrations of 1.0 IU/kg bodyweight for 3 days given at 6, 28, and 50 h after 60 mg MAP sponge removal did not affect the pregnancy rate (69 vs. 74%) and subsequent litter size (1.65 vs. 1.69) as compared to control in ewes (Kirkwood et al. 1991). In another study, in ewes, insulin administration at concentrations of 1.0 IU/kg body weight from day 12 of the estrous cycle to 24 h after estrus did not increase pregnancy rate (63 vs. 80%) and subsequent litter size (2.2 ± 0.3 vs. 1.9 ± 0.3) as compared to control (Beam and Holcombe 1992). Contrarily, sows receiving insulin injection 0.4 IU/kg body weight once daily for 4 consecutive days beginning on the day of weaning increases farrowing rate (92.3 vs 76.7%) as compared to control. It was opined that apart from the action of insulin on ovarian function, it also affects the establishment of pregnancy (Ramierz et al. 1997). However, with the same treatment schedule, no effect on pregnancy rate (85.7 ± 3.6 vs. 88.8 ± 3.2%) and embryo survival (53.0 ± 5.70 vs. 51.0 ± 5.40) over the control in sows were also reported (Whitley et al. 1998). The beneficial effect of insulin on fertility in repeat breeder cattle has been observed (Selvaraju et al., 2002b).

Ovarian steroids (estradiol and progesterone) and protein hormones especially GH influence insulin secretion (McCann and Reimers 1985). Basal insulin concentration was greater at estrus than at diestrus and nonlactating pregnant cows had lower serum insulin concentration than the nonlactating nonpregnant cows. However, progesterone increases the ability of the beta-cells to secrete insulin in response to intravenous administration of glucose in the rat (Ashby et al. 1978). Similar way, estradiol treatment produces hypoinsulinemia in cows (Laarveld et al. 1982). However, it has not been established how exogenous steroids affect insulin secretion. The level of milk yield was negatively associated with plasma insulin and IGF-I concentration. But the concentration of IGF-I in milk was not associated with fertility (Taylor et al. 2004). The growth hormone treatment stimulates follicular development, the advancement of puberty in heifers (Cooke et al. 2013), and the conception rate in cattle (Ribeiro et al. 2013), but not embryo production in buffalo (Ferraz et al. 2015).

5.9 Effect of Metabolic Hormones and Male Fertility

Impaired male fertility is a major problem in animal breeding and may have a significant effect on the breeding population, because the ratio of males to females is extended particularly when AI is used. Glucose, amino acids, or nutrient-related metabolites, such as insulin, growth hormone, and the insulin-like growth factors, influence the hypothalamo-hypophyseal-gonadal axis for supporting gametogenesis and steroidogenesis. These nutritional effects could continue to affect pre- and post-fertilization events within the female reproductive tract. The biochemical mechanisms underlying sperm maturation and the development of motility and fertilizing ability remain largely undefined. The ability of spermatozoa to travel and fertilize the egg develops during their transit through the epididymis; this process is likely controlled by seminal plasma composition.

The presence of various growth factors, IGFs, EGF, and TGFβ and unidentified growth factors in seminal plasma plays a regulatory role in sperm physiology or reproductive tract maintenance (Patil et al. 2020). IGF-I has been proposed to have a direct or indirect role in spermatogenesis/steroidogenesis in the testis and its derangement may be involved in male infertility. Recently, considerable research has been carried out on the relationships between IGF-I and male reproductive traits in breeding animals. The spermatogonial stem cells development is influenced by the growth factors including IGF-1 (Binsila et al. 2020). IGF-I is a mitotic polypeptide that stimulates glucose uptake by various cells. Its effects on female reproductive functions have been extensively studied. However, there has been little research on relationships between IGF-I and male reproductive traits in breeding animals.

IGF-I in seminal plasma was shown to be primarily of testicular or epididymal origin. In several species, IGF-I and IGF-II are regulators of testicular and also be post-testicular regulators of reproductive function. Scrotal circumference and percentage of normal sperm cells are related to blood serum IGF-I concentration in yearling Angus bulls (Yilmaz et al. 2004). When the rams are supplemented with nonconventional protein rich source such as detoxified Karanjia cake in the diet at above a certain level affects the expression of IGF1 receptors in the testis and thus the semen production capacity (Dineshkumar et al. 2013).

IGF-I maintains sperm motility in vitro either through energy metabolism or its antioxidant effect (Henricks et al. 1998). The effects of IGF-I on capacitation have not yet been evaluated. Since the IGF-I cell surface receptor has the tyrosine kinase domain, and the tyrosine phosphorylation has a key role in capacitation/acrosome exocytosis, IGF-I could also potentially modulate the mature sperm cell function. It was also suggested that IGF-I may affect sperm motion characteristics that are typical of hyperactivated sperm (Henricks et al. 1998). These sperm-motion characteristics are important in penetration of the zona pellucida and transport through oviductal mucus. The IGF-I may influence the semen quality by acting as antioxidants and protecting sperm membrane quality (Selvaraju et al. 2009; Susilowati et al. 2015). A study from buffalo also suggests that addition of IGF-I in the semen extender improves the cryosurvivability of sperm (Selvaraju et al. 2016; Kumar et al. 2019).

Modulating IGF I concentration in seminal plasma of healthy breeding bulls by diet may improve their fertilization efficiency. The modulation of components of the IGF system in the testis in healthy breeding bulls increases their fertilization efficiency (Sauerwein et al. 2000), but a study from this lab revealed that the IGF-I improved sperm function and not in vitro fertility (Selvaraju et al. 2010). In mature rams, peripheral concentrations of IGF-I are affected by dietary composition mainly through changing energy levels either by carbohydrate rich grain source (Selvaraju et al. 2012a) or by oil rich in polyunsaturated fatty acids (Selvaraju et al. 2012b). Plant oils with predominantly polyunsaturated fatty acids have also been shown to increase serum and seminal plasma concentrations of IGF-I rams (Selvaraju et al., 2012). Since IGF-I is a testicular and post-testicular regulator of reproductive function, modulating the serum and seminal plasma IGF I level may improve semen quality and fertility.

Studies indicate that modulation of metabolic hormones levels in the testis may influence spermatogenesis and steroidogenesis and such regulation is highly important in the cattle industry to improve fertility. Through dietary energy, seminal plasma IGF-I levels can be modulated and the optimum level of seminal plasma IGF-I required for maintaining optimum semen quality needs to be established.

5.10 Conclusion

The metabolic hormones reflect the nutritional status and influence the reproductive function in males and females. These regulators are responsible for maintaining functional competence of gametes and fertility. Dietary modulation of the metabolic hormones may improve the reproductive efficiency in livestock.

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