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The effect of nutrition and metabolic status on the development of follicles, oocytes and embryos in ruminants

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The impact of nutrition and energy reserves on the fertility of ruminants has been extensively described. However, the metabolic factors and the molecular mechanisms involved in the interactions between nutrition and ovarian function are still poorly understood. These factors could be hormonal (either reproductive and/or metabolic) and/or dietary and metabolic (glucose, amino acids and fatty acids). In this review, we briefly summarize the impact of those nutrients (fatty acids, glucose and amino acids) and metabolic hormones (insulin/IGF-I, growth hormone, T3/4, ghrelin, apelin and the adipokines (leptin, adiponectin and resistin)) implicated in the development of ovarian follicles, oocytes and embryos in ruminants. We then discuss the current hypotheses on the mechanisms of action of these factors on ovarian function. We particularly describe the role of some energy sensors including adenosine monophosphate-activated kinase and peroxisome proliferator-activated receptors in the ovarian cells.

Keywords: nutrients, metabolic hormones, ovary, mechanism of action, ruminant

Implications

In pursuit of sustainable and economically viable livestock production systems that meet consumer demands, farmers are under increasing pressure to maintain or increase fertility of their herds. Nutritional management both before and after calving has a great impact on fertility. Nutrition influences ovarian follicle development in ruminants possibly through changes in metabolic hormones and also through direct effects of nutrients on the ovary. These interactions can be manipulated to improve reproductive performance. Here, we summarize the impact of nutrients and metabolic hormones implicated in the development of ovarian follicles, oocytes and embryos in ruminants.

Introduction

In ruminants as in other mammals, alterations of energy and protein metabolism related to variations in the diet can influence reproductive functions at different levels of the gonadotropic axis. For example, in dairy cows, *postpartum* energy balance affects the number of follicles, their rate of growth and development, and the size of the ovulatory follicle (Lucy *et al.*, 1991a; Boland *et al.*, 2001). In this species, negative energy balance (NEB) can also attenuate LH pulse frequency (Butler, 2003). However, there is evidence that indicates that nutritional effects on the recruitment and growth of follicles are mediated mainly by direct metabolic signals to the ovary that vary with metabolic status (Lucy, 2003; Webb *et al.*, 2004). In sheep, an increase in the energy content of the diet for a few days before reproduction during the late luteal phase improves the ovulation rate (Downing and Scaramuzzi, 1991). Many inter-related factors are involved in the nutritional effects on fertility in ruminants. These factors are the nutrients themselves (fatty acids, glucose and amino acids) and the hormonal signals from various peripheral tissues (insulin (pancreas), IGF-I (liver), growth hormone (GH) (pituitary), thyroid hormones (T3/4) and adipokines (adipose tissue) such as leptin, adiponectin and resistin)). In the present study, we will describe the effects of these factors on the ovary (follicles and oocytes) and embryos in ruminants.

Effect of fatty acids

In this part of the review, we will detail the effects of non-esterified fatty acids (NEFAs) and also the effects of dietary supplementation with fat on ovarian function.

NEFAs

In cattle, NEB is an important risk factor for delayed *postpartum* cyclicity (Beam and Butler, 1999). Follicles emerging

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before an NEB nadir have reduced growth and produce less oestradiol, and therefore require more time and a larger size to achieve a secretion rate of oestradiol capable of triggering the LH surge and ovulation (Beam and Butler, 1999). It has been suggested that the harmful effects of NEB on ovarian function are exerted through decreased LH-pulsatility and reduced circulating concentrations of IGF-I, insulin and glucose (Beam and Butler, 1999). However, metabolic alterations associated with NEB may also affect ovarian function by acting directly on the ovary. Increased lipolysis of body fat also occurs during periods of NEB, causing an elevation in the blood concentrations of NEFAs (Rukkwamsuk *et al.*, 2000). For example, during periods of NEB, total serum concentrations of palmitic (C16:0), stearic (C18:0) and oleic (C18:1) acids are increased (Rukkwamsuk *et al.*, 2000). Although there was no significant uptake of NEFAs by the bovine ovary in one study (Rabiee *et al.*, 1997), others have reported that in cattle increased concentrations of NEFAs in blood were reflected in the ovarian follicular microenvironment (Leroy *et al.*, 2004 and 2005). Thus, on balance, NEFAs may affect follicular growth and fertility by acting directly on the different ovarian cells, including the oocyte within the growing follicle, and may also affect the development of the fertilized oocyte, morula and early blastocyst.

Several reports show that elevated concentrations of plasma NEFAs and in the range of concentrations frequently observed in the follicular fluid of the dominant follicle in dairy cows were associated with reduced *in vitro* developmental competence of the oocyte (Jorritsma *et al.*, 2004, Leroy *et al.*, 2005, Aardema *et al.*, 2011) and compromised the viability of the bovine granulosa cells (Vanholder *et al.*, 2005), but with a positive effect on the production of oestradiol by granulosa cells (Vanholder *et al.*, 2005). A recent study has shown that exposure of the maturing oocytes to elevated concentrations of NEFAs has a negative impact on fertility not only through a reduction in the developmental capacity of the oocyte but also through compromised quality, viability and metabolic capacity of the early embryos (Van Hoeck *et al.*, 2011). The same laboratory suggests that these negative effects of NEFAs on the embryo could be a consequence of modified energy metabolism and particularly, mitochondrial β-oxidation of fatty acids in the oocyte (Van Hoeck *et al.*, 2013). A recent study has shown that bovine cumulus cells are able to protect maturing oocytes from potential harmful effects of increased local concentrations of fatty acids by intracellular storage of lipids (Aardema *et al.*, 2013).

In conclusion, the current state of knowledge suggests that nutritional states that result in high-circulating concentrations of NEFAs can, and often do, compromise development of the dominant follicle and also that of the early embryo, and thus diets or metabolic states that favour high concentrations of NEFAs should be avoided during the cycle of conception and the early postconception period.

Supplementation with dietary fat

Several reviews have reported that dietary supplementation with fat influences reproduction in cows through effects on follicle growth and steroid production, oocyte maturation and embryo development (Mattos *et al.*, 2000; Wathes *et al.*, 2007; Santos *et al.*, 2008; Thatcher *et al.*, 2011). The precise composition of the lipid supplement is crucial to these effects. For example, concerning the polyunsaturated fatty acids (PUFAs), the ratio of n-6 to n-3 may play an important role in reproduction in sheep and cattle (for review, Gulliver *et al.*, 2012).

Effects on the follicle development. In the dairy cow, a diet enriched with long-chain fatty acids increases the number of medium follicles (6 to 9 mm) and the diameter of the preovulatory follicle (Lucy *et al.*, 1991b). These positive effects of long-chain fatty acids on the size of the dominant follicle have been confirmed in several studies (Mattos *et al.*, 2000; Robinson *et al.*, 2002; Ambrose *et al.*, 2006; Bilby *et al.*, 2006). In addition, different effects were observed on the follicular growth between monounsaturated fatty acids (MUFA) and polyunsaturated (PUFA) fatty acids: PUFAs promoted follicular growth to a greater extent than did MUFAs (Bilby *et al.*, 2006).

Several studies have suggested that supplementation of cattle with PUFAs increased the plasma concentrations of steroid by stimulating ovarian production of steroid hormones through various mechanisms, including increased availability of lipoprotein–cholesterol (Hawkins *et al.*, 1995; Lammoglia *et al.*, 1996), modulation of prostaglandin synthesis (Knickerbocker *et al.*, 1986), and the direct stimulation of ovarian steroidogenesis (Staples *et al.*, 1998). In another study on cows, it was shown that diets enriched in n-6 PUFAs increased the secretion of progesterone by the granulosa cells (Wehrman *et al.*, 1991). Although progesterone production appears *in vivo* to be lower with n-3 and higher with n-6, the exact mechanism through which n-3 and n-6 modulate progesterone and oestradiol is unclear (for review, Gulliver *et al.*, 2012). In dairy cows, diets enriched with fatty acids (both MUFAs and PUFAs) significantly increased the concentration of cholesterol in plasma, follicular fluid and the corpus luteum (Staples *et al.*, 1998). It is well known that cholesterol is the precursor for the synthesis of progesterone by the ovarian cells. Thus, higher fertility in cattle fed diets enriched with PUFAs may be associated with increased circulating concentrations of progesterone in the luteal phases, both before and after artificial insemination. Prostaglandins are important regulators of parturition, and in ruminants they are responsible for the regression of the corpus luteum, leading to a new oestrous cycle. In cows, oestradiol had stimulatory effects on uterine secretion of prostaglandin F2α (PGF2α) (Knickerbocker *et al.*, 1986), and consequently may increase the sensitivity of the corpus luteum to PGF2α, which would promote regression of the corpus luteum. Thus, decreased plasma concentrations of oestradiol could prevent premature regression of the corpus luteum and therefore early embryonic mortality. Furthermore, the type of PUFA will also affect the synthesis of PGF2α. Indeed, dietary PUFA intake inhibits PGF2α production in bovine endometrial explants, with a more pronounced effect

following n-6 rather than n-3 supplementation (for review, Wathes *et al.*, 2007).

Effects on the cumulus–oocyte complex (COC) and the embryo. Compared with rodents, the oocytes and embryos of farm animals including cattle contain relatively high levels of intracellular lipids, with triglycerides being the major component. For example, the mouse oocyte contains 4 ng of triglyceride, whereas the cow oocyte contains 63 ng, and the sheep oocyte contains 89 ng (McEvoy *et al.*, 2000; Sturmey *et al.*, 2009). Fatty acids are an endogenous source of energy during oocyte maturation; several lines of evidence support the idea of fatty-acid oxidation as a source of essential ATP for oocyte maturation and for early development of the embryo. For example, the triglyceride content of the bovine oocytes decreased during *in vitro* maturation (IVM), as well as after fertilization (Ferguson and Leese, 1999). In addition, lipase activity was increased in the bovine oocytes following IVM (Cetica *et al.*, 2002). In the oocytes from mice, inhibition of β-oxidation during the IVM of oocytes prevented the AMP-activated, protein kinase-mediated resumption of meiosis in the mouse (Downs *et al.*, 2009), and in cattle it impaired the developmental competence of oocytes (Dunning *et al.*, 2010). Furthermore, Paczkowski *et al.* (2013) have shown that the oxidation of fatty acids is essential for nuclear maturation of the oocytes in mice, cattle and pigs (Paczkowski *et al.*, 2013).

Dietary fatty acids altered the composition of fatty acids in the cumulus cells, granulosa cells and oocytes that may also have consequences on oocyte quality (Kim *et al.*, 2001). For example, in ewes, the number and quality of oocytes was increased when animals were fed a diet enriched in PUFAs (saponified fish oil) 74.3% *v.* 57%; (Zeron *et al.*, 2002). Moreover, in these animals, there was an increase in the proportion of long-chain fatty acids in the plasma and cumulus cells (Zeron *et al.*, 2002). In dairy cows, another study has shown that a diet enriched in a mixture of saturated and unsaturated fats affected oocyte development and maturation (Fouladi-Nashta *et al.*, 2007). The two fatty acids linoleic acid (LA) and linolenic acid (ALA) are both found in the plasma and follicular fluid of cows (Childs *et al.*, 2008), and it has been reported that supplementation of bovine oocytes with ALA during IVM resulted in an increased maturation rate, a higher yield of blastocysts and the production of better-quality blastocysts (Marei *et al.*, 2009). Opposing results have been observed for supplementation with LA by the same group (Marei *et al.*, 2009). Indeed, they reported that treatment of bovine COCs with physiological concentrations of LA affected the molecular mechanisms that control nuclear maturation of oocytes, leading to a decreased proportion of oocytes reaching the MII stage after 24 h in culture, and the inhibition of subsequent early embryo development (Marei *et al.*, 2010). Further studies from this group revealed that LA induced alterations in the distribution of mitochondria and their activity, associated with increased concentrations of reactive oxygen species (Marei *et al.*, 2012).

Thus, the current state of knowledge suggests that PUFAs could promote the growth of follicle and could increase granulosa cell steroidogenesis in cattle. However, the ratio of n-6 to n-3 in ruminant diets is particularly important in determining the relative availability of the precursors for eicosanoid formation. The effects of PUFA on the oocyte and embryo development are unclear and need more investigations.

Effect of glucose

The published evidence suggests that the adverse effects of systemic treatment with insulin on reproductive function do not occur if the circulating concentrations of glucose are maintained at physiological levels (Downing *et al.*, 1999), and concentrations of glucose that are either above or below the normal physiological range can have deleterious effects on fertility. For example, one study (Downie and Gelman, 1976) suggested that low-circulating glucose may be responsible for infertility in cows, and in another study pregnancy rate was higher in cows with high-circulating concentrations of glucose compared with cows with low-circulating concentrations of glucose; however, there was a trend for pregnancy rate to decline in cows with very high concentrations of circulating glucose (Pehrson *et al.*, 1992). Finally, Selvaraju *et al.* (2002) reported that insulin and glucose concentrations were higher in cows that subsequently became pregnant than in non-pregnant animals (Selvaraju *et al.*, 2002). All of this evidence suggests that fertility of cows is strongly influenced by the insulin glucose system.

Downing *et al.* (1999) stated that there is a synergism between insulin and glucose at the ovarian level, and it is likely that the effects of short-term nutrition on ovulation rate in ewes may be mediated by direct ovarian actions of insulin and glucose (Downing *et al.*, 1999). Mammals primarily rely on intracellular oxidation of glucose and fatty acids to provide the energy necessary to support most physiological processes. Although peripheral tissues may utilize both glucose and fatty acids, the ovary uses glucose as its principal source of energy (Rabiee *et al.*, 1999; Scaramuzzi *et al.*, 2010). Glucose is available for cellular oxidation and energy production by entering the cells passively when its circulating concentrations are high and also actively at low concentrations, with the latter implying a role for insulin (Wade and Schneider, 1992). It seems that the effect of glucose on fertility is primarily related to its properties as a metabolic fuel.

Within the follicle, glucose can be metabolized by four different pathways: (i) by glycolysis to produce ATP and pyruvate or lactate; (ii) by the pentose phosphate pathway to provide precursors for the synthesis of purine nucleotides and NADPH for various biosynthetic pathways including antioxidant defence; (iii) by the hexosamine biosynthetic pathway to provide substrates for the glycosylation of proteins and the synthesis of the hyaluronic acid required for cumulus expansion; and (iv) by the polyol pathway producing sorbitol and fructose whose roles in follicular function remains largely unknown (for a review see Collado-Fernandez *et al.* (2012)). In cattle, the role of these four pathways for the utilization of glucose during the growth and development of follicles and

their oocytes is not clearly known. Nowadays, it is believed that the follicle has well-developed systems to sense glucose and nutritional status (Webb *et al*., 2004; Garnsworthy *et al*., 2008; Scaramuzzi *et al*., 2010). Different glucose transporters, including the GLUT family, are expressed in the oocyte, the somatic cells of the follicle and in the early embryo, and the expression of some of them is controlled by steroids and insulin (Purcell and Moley, 2009). This system allows the follicle to regulate its growth and development, mainly by altering FSH-induced effects on the synthesis of oestradiol by the granulosa cells, in accordance with the availability of glucose (Webb *et al*., 2004; Scaramuzzi *et al*., 2010).

The role of glucose is essential in determining the quality of the oocyte (Sutton-McDowall *et al*., 2010) because it is its main energy source. In sheep, glucogenic treatments improve oocyte quality, evaluated by the kinetics of their *in vitro* development and by the production of blastocysts (Berlinguer *et al*., 2012). However, even if glucose is the preferred energy substrate for the cumulus cells (Sutton-McDowall *et al*., 2010), the oocytes of most mammalian species consume little glucose, with pyruvate being the usual energy substrate (Eppig, 1976; Rieger and Loskutoff, 1994). In general, oocytes take up pyruvate efficiently and have a lower capacity for glucose transport, as well as limited expression and activity of some glycolytic enzymes (reviewed by Purcell and Moley, 2009; Sutton-McDowall *et al*., 2010). Thus, oocytes rely on the uptake of CC-derived oxidizable substrates, principally pyruvate for the synthesis of ATP. However, ATP and glucose can also be directly transferred to oocytes from GC/CC through gap junctions (Wang *et al*., 2012).

Effect of amino acids

In contrast with fatty acids and glucose, there are few studies reporting the effects of amino acids on ovarian functions in ruminants. Downing *et al.* (1995) intravenously infused a mixture of branched-chain amino acids in sheep and observed an increased ovulation rate, whereas Garnsworthy *et al.* (2008) reported that diets with a high content of leucine increased plasma concentrations of insulin in dairy cows, but did not alter their follicular dynamics (Garnsworthy *et al*., 2008). In dairy heifers, an association was observed between the total concentration of free amino acids in the plasma and oocyte cleavage, suggesting that dietary amino acids could mediate the oocyte quality (Rooke *et al*., 2009); however, Sinclair, *et al.* (2000) also showed that in heifers excessive levels of protein in the diet negatively affected the subsequent development of oocytes *in vitro* (Sinclair *et al*., 2000)

In comparison with carbohydrate metabolism, and despite their important roles, there is little information about amino-acid uptake and metabolism by follicles and oocytes, especially during the earlier stages of folliculogenesis in cattle. Studies measuring amino acids in follicular fluid and the reproductive tract in mice have provided valuable information on the availability of substrates, reporting significantly higher levels of some amino acids in the follicular fluid compared with the reproductive tract (Harris *et al*., 2005). In cattle, LH has been shown to increase glutamine oxidative metabolism by oocytes and COCs (Zuelke and Brackett, 1993). Furthermore, the addition of glutamine to bovine IVM media promoted the nuclear maturation of oocytes (Bilodeau-Goeseels, 2006), although supplementation of defined IVM media with non-essential and essential amino acids increased the levels of maternal mRNA in the oocytes and enhanced embryo development (Watson *et al*., 2000). Finally, Hemmings *et al.* (2012) quantified the amino-acid profiles (i.e. rates of depletion and accumulation) of bovine oocytes at MII, following IVM (Hemmings *et al*., 2012). Glutamine, arginine and asparagine were all depleted at the highest rates, whereas alanine and glycine accumulated in the media (Hemmings *et al*., 2012). Similar to studies carried out on embryos, oocytes with a higher potential for development after IVF and those of lesser potential had different amino-acid profiles (Hemmings *et al*., 2012). Overall, the quality of oocytes and embryos was related to amino-acid turnover; those with the highest turnover of amino acids had the poorest quality. For example, oocytes that failed to cleave depleted more glutamine, released more alanine and had a greater depletion of total amino acids compared with oocytes that cleaved (Hemmings *et al*., 2012). Furthermore, these data were used to predict fertilization and cleavage potential (Hemmings *et al*., 2012). These studies provide further evidence of the importance of amino-acid metabolism to the developmental competence of oocytes.

Nutrient sensors

Metabolic hormones

The effects of acute changes in the dietary intake on ovarian activity have been correlated with changes in the circulating concentrations of metabolic hormones, including insulin, IGF-I, GH, the thyroid hormones, triiodothyronine (T3), and thyroxine (T4), ghrelin, apelin and the adipokines (leptin, adiponectin, resistin), and there is an extensive literature describing the effects of diet on the circulating concentrations of these metabolic hormones. Here, we have focused more on the action of the metabolic hormones on ovarian functions in ruminants.

Insulin (pancreas) and IGF-I (liver). Insulin and IGF-I are produced by the pancreas and liver, respectively, and are often proposed as signalling molecules linking metabolism to fertility (Diskin *et al*., 2003). They interact with the reproductive axis at the level of the central nervous system as well as in the follicle itself. Here, we only described some effects of insulin and IGF-I on the ruminant ovary.

Components of the insulin and IGF systems in the ovary. The insulin system consists of insulin itself and the insulin receptor (IR), which mediates the action of insulin. The IR has a high degree of homology with the IGF-I receptor (IGF-IR), and IGF-IR and IR hybrid receptors have been reported (Dupont and LeRoith, 2001). The IGF system is composed of

several members, including IGF-I and IGF-II, two receptors (IGFR-1 and IGFR-2) and at least six binding proteins (insulin-like growth factor binding proteins: IGFBP-1, -2, -3, -4, -5 and -6) (Monget *et al.*, 2002). The essential components of both the insulin and IGF systems are all present in the follicle in ruminants (Table 1). The IGFBPs are present in biological fluids and act by inhibiting or potentiating the action of the two IGFs (IGF-I and IGF-II) in target cells (Monget *et al.*, 2002). The regulation of the bioavailability of IGF-I by IGFBPs is necessary for the co-ordinated development *in vitro*, of the bovine oocyte and follicle (Thomas *et al.*, 2007). The receptors for insulin and IGF-I belong to the same subfamily of receptor tyrosine kinases with two extracellular α-subunits and two trans-membrane β-subunits. They have structures that are highly homologous and they induce a number of similar intracellular signalling pathways (Dupont and LeRoith, 2001). Upon activation by ligand binding, both IR and IGF-1R, which contain endogenous tyrosine kinase activity, phosphorylate several intracellular substrates such as the insulin receptor substrate (IRS) proteins (IRS-1 through -6) and Shc, leading to the activation of at least two signalling pathways, PI3K/AKT and MAPK. In ruminants, IRs and IGF-1Rs are widely distributed throughout all ovarian compartments, including the follicles (Spicer *et al.*, 1994; Shimizu *et al.*, 2008) and luteal cells (Einspanier *et al.*, 1990). In bovine granulosa and theca cells, the expression of the mRNA for IR changes considerably during development from the preantral to the pre-ovulatory stage of folliculogenesis (Shimizu *et al.*, 2008). Similarly, the expression of IGF-1R in bovine granulosa and theca cells is increased during the final stages of follicular development and decreased at the onset of atresia (Armstrong *et al.*, 2000). Because IGF-I and/or insulin have an essential role in the final stage of follicle development, it has been suggested that abnormal concentrations of these metabolic hormones lead to follicular dysfunction, resulting in excessive atresia or the formation of follicular cysts (Braw-Tal *et al.*, 2009).

The effects of insulin on follicular function. Numerous studies have shown the importance of insulin as a signal mediating the effects of acute changes in nutrient intake on follicle dynamics in cattle (Webb *et al.*, 2004). The infusion of insulin into beef heifers increased the diameter of the dominant follicle (Simpson *et al.*, 1994). *In vitro* research has shown dose-dependent stimulatory effects of insulin on the proliferation and steroid synthesis of the bovine granulosa cells and theca cells; these effects can be exerted via their direct stimulatory actions on the follicle as well as by increased local responsiveness of the follicle to FSH and LH (Spicer *et al.*, 1994).

The effects of IGFs on follicular function. IGF-I is a hormone that modulates the maturation of the dominant follicle during the first follicular wave *postpartum* (Beam and Butler, 1998), and circulating IGF-I in ovulatory cows at the first follicular wave *postpartum* is higher than that in anovulatory cows, regardless of parity (Beam and Butler, 1998). As for insulin, *in vitro* research has shown dose-dependent stimulatory effects of IGF-I on the proliferation and steroid synthesis of bovine granulosa cells and theca cells; these effects can be exerted via their direct stimulatory actions on the follicle as well as by increased local responsiveness of the follicle to FSH and LH (Spicer and Echternkamp, 1995). In the bovine granulosa cells, IGF-I induced the upregulation of steroidogenic and apoptotic regulatory genes via the activation of phosphatidylinositol-dependent kinase/AKT (Mani *et al.*, 2010). The addition of IGF-I to the culture medium improved the *in vitro* development of caprine preantral follicles (Magalhaes-Padilha *et al.*, 2012).

The effects of insulin and IGF on the oocyte and embryo. Both IGF-1R and IR are also present in the bovine oocytes and embryos (Nuttinck *et al.*, 2004). Several studies have observed that COCs treated with IGF-I, alone or in combination with either epidermal growth factor or angiotensin II, showed increased cumulus expansion, improved rates of nuclear maturation and enhanced metabolism of pyruvate (Lorenzo *et al.*, 1994; Stefanello *et al.*, 2006). The intra-ovarian administration of IGF-I was able to improve the developmental capacity of oocytes from pre-pubertal cattle (Oropeza *et al.*, 2004). A short *in vivo* exposure of oocytes to a supra-physiological IGF-I microenvironment increased the *in vitro* proliferation of the inner cell mass cell during the transition from morula to blastocyst (Velazquez *et al.*, 2012). In bovine blastocysts, insulin acted as a survival factor, blocking apoptosis, whereas IGF-I stimulated the development of blastocyst and also total cell number (Byrne *et al.*, 2002).

Collectively, these data indicate that maintaining the concentrations of IGF-I and insulin within a normal physiological range is required for proper ovarian follicular function and embryo development.

GH (anterior pituitary gland). GH produced by the adenohypophysis exerts effects on almost every organ of the body, including the ovary, either directly after binding to specific GH receptors (GHR) or indirectly after binding to hepatic GHR, and stimulating the production of hepatic IGF-I (Webb *et al.*, 2004). Treatment of cattle with exogenous GH has significant effects on follicular development (Gong *et al.*, 1993) and the function of the corpus luteum (Lucy *et al.*, 1999). GH can selectively stimulate particular populations of follicles; for example, in heifers, it inhibited the development of the preovulatory follicle but stimulated the growth of the second-largest follicles (Lucy *et al.*, 1994). The possibility that GH can act at ovarian sites is suggested by the detection of GH-binding activity, GHR immunoreactivity and expression of the mRNA encoding GHR in the ovarian tissue in cows (Kolle *et al.*, 1998). GH receptors have been detected in the granulosa cells, thecal cells and luteal cells (Kolle *et al.*, 1998) (Table 1), and the abundance of the mRNA encoding GHR in the bovine ovary varied in a cell-specific way during the ovarian cycle (Kolle *et al.*, 1998). However, the involvement of GH in the physiological mechanisms underlying nutritional influence on ovarian function in the cattle can be attributed to the stimulatory action of GH

Table 1 *The expression of various metabolic factors in the ovary and embryo of ruminants*

	Follicle					
Metabolic hormone	Theca	Granulosa	Oocyte	Corpus luteum	Embryo	References
Insulin/IGF-I receptors	+	+	+	+	+	Armstrong *et al.* (2000), Shimizu *et al.* (2008)
GH receptor	+	+	nr (ruminants) + (human)	+	nr (ruminants) + (human)	Kolle *et al.*, (1998), de Prada and VandeVoort (2008)
Thyroid hormone receptor (TR)	nr	nr (ruminants) + (human and mouse)	nr (ruminants) + (human and mouse)	nr (ruminants) + (human and mouse)	nr	Zhang *et al.* (1997)
Ghrelin and GHS-R	+	+	+	+	+	Miller *et al.* (2005), Du *et al.*, (2009 and 2010)
Leptin and Ob-R	+	+	+	+	+	Spicer and Francisco (1997), Boelhauve *et al.* (2005), Dayi *et al.* (2005), Paula-Lopes *et al.* (2007)
Adiponectin, AdipoR1 and R2	+	+	+	+	+	Maillard *et al.* (2010), Tabandeh *et al.* (2010)
Resistin	+	+	+	+	nr	Maillard *et al.* (2011), Spicer *et al.* (2011)
Apelin and APJ	+	+	nr	+	nr	Shirasuna *et al.* (2008), Shimizu *et al.* (2009)
PPARγ	−/+	+	+	+	+	Lohrke *et al.* (1998), Mohan *et al.* (2002), Froment *et al.* (2003)
AMPK	+	+	+	+	+	Tosca *et al.* (2007a and 2007b), Pikiou *et al.* (2013)

GH = growth hormone; GHS-R = growth hormone secretagogue receptor; nr = not reported in the literature; PPAR = peroxisome proliferator-activated receptors.

on the hepatic synthesis of IGF-I, and a direct action of GH on the follicle remains to be demonstrated convincingly (Webb *et al.*, 2004).

T3 and T4 (thyroid gland). In cattle, greater nutrient intake after calving increased the concentrations of T4 in the plasma (Ciccioli *et al.*, 2003), similar to the response in non-lactating cows (Delavaud *et al.*, 2002). Follicular fluid from the bovine ovaries contains free fractions of thyroid hormones that suggests a possible role for these hormones in the regulation of follicular function. In super-ovulated Brahman cows, induced hypothyroidism improved weight gain and body score condition, increased ovarian response to FSH, and affected the ovulation, fertility and secretion of progesterone (Bernal *et al.*, 1999). In cows, the physiological status of the bovine antral follicles (i.e. dominant *v.* subordinate) may impinge on the accumulation of T4 in the follicular fluid (Ashkar *et al.*, 2010), and hormonally induced ovarian hyperstimulation increased the circulating levels of free T4 and the follicular fluid content of total T4 (Mutinati *et al.*, 2010). Furthermore, the thyroid hormones (T3 and T4) directly altered *in vitro* steroidogenesis in the bovine granulosa and theca cells (Spicer *et al.*, 2001). A recent study has shown that the supplementation of IVM media with T3 can have a beneficial effect on the kinetics of embryo development (Costa *et al.*, 2013). In the ovaries of human and mice, thyroid hormone receptors (TRα-1, TRα-2 and TRβ-2) are present in the oocytes, cumulus, granulosa and luteal cells (Zhang *et al.*, 1997) (Table 1). Thus, thyroid hormones may have direct stimulatory effects on the ovarian function and embryo development in cattle.

Ghrelin (stomach). Ghrelin is primarily secreted from the X/A-like cells of the oxyntic gland in the stomach. The X/A-like cells constitute a distinct population of endocrine cells in the oxyntic mucosa that make up ~20% of all endocrine cells in the oxyntic gland. Ghrelin is also present in several other tissues, including the reproductive tissues of sheep and cattle (Miller *et al.*, 2005; Deaver *et al.*, 2013). The functional ghrelin receptor, GH secretagogue receptor 1 A (GHS-R1A), belongs to a large family of rhodopsin-like, G-protein coupled, 7-transmembrane domain receptors (Howard *et al.*, 1996). Ghrelin is an acute regulator of feed intake; circulating ghrelin concentrations increase during fasting or NEB, and exogenous administration of ghrelin stimulates feed intake in rats and cattle (Bradford and Allen, 2008). In these species, Ghrelin also influences energy metabolism and increases metabolic efficiency. Thus, it appears that ghrelin is a key metabolic component involved in the physiological response to energy deprivation.

Ghrelin and its receptor are present in the ovary of the adult and foetal sheep (Miller *et al.*, 2005) (Table 1). In the sheep ovary, ghrelin and its mRNA are present throughout the oestrous cycle with the highest levels observed during the luteal phase (Du *et al.*, 2009). More precisely, detectable concentrations of ghrelin are found in the oocytes and thecal cells at all stages of follicular development, the granulosa cells of antral follicles and in all developmental stages of the

corpora lutea (Du *et al*., 2009) (Table 1). In the sheep, ghrelin promotes *in vitro* oocyte maturation via the ERK1/2 pathway (Bai *et al*., 2012) and *in vitro* formation of blastocysts (Wang *et al*., 2013). In the Holstein heifers, the expression of ghrelin was limited to the granulosa cells in the ovarian follicles, suggesting that the follicular distribution of ghrelin is species dependent (Deaver *et al*., 2013). In the dairy heifers, ghrelin and GHS-R1A and their mRNAs are also present in the ampulla and isthmus of the oviducts and the uterus (Deaver *et al*., 2013).

However, despite the presence of ghrelin and its receptor in various parts of the reproductive tract, its effects, if any, *in vivo* on fertility in ruminants are not known.

Adipokines (adipose tissue). The traditional view of the adipose tissue as a passive store of dormant triglycerides, which are mobilized during NEB, has been challenged by recent research that has shown that the adipose tissue also secretes a variety of hormones collectively known as the adipokines (Tersigni *et al*., 2011). Leptin, adiponectin and resistin are the three best studied adipokines in relation to ovarian function in ruminants. These hormones are significant mediators of energy metabolism and they have all been implicated as mediators of nutritional influences on reproduction (Tersigni *et al*., 2011).

Leptin. A positive association between nutrient intake and concentrations of leptin in the plasma has been reported in sheep (Delavaud *et al*., 2000) and cattle (Delavaud *et al*., 2000 and 2002). The effects of leptin can be divided into two main categories: the first is a central effect in the brain after binding to its long-form receptor (Ob Rb), and the second a peripheral effect (including the ovary). The Ob Rb is the primary mediator of the action of leptin because it is the only isoform that is capable, after ligand binding, of relaying full downstream signalling along the signal transduction pathways. There are at least six isoforms of Ob-R that are expressed in several organs including the ovary, where leptin can directly exert regulatory actions.

Leptin and its receptor are present in the follicle; the concentration of leptin in the follicular fluid is related to atresia in the small follicles (Dayi *et al*., 2005) (Table 1). In the ovarian follicles, the highest coexpression of the leptin/Ob-R system was observed in the theca and in the interstitial and granulosa cells of small follicles with E2 concentration <0.5 ng/ml (Sarkar *et al*., 2010). The actions of leptin on ovarian and follicular function appear to be inhibitory; it inhibits in a dose-dependent manner, insulin-induced production of progesterone and oestradiol by cultured granulosa cells from small and large bovine follicles (Spicer and Francisco, 1997). There is also evidence for this inhibitory effect of leptin *in vivo* on oestradiol in sheep during the follicular phase of the cycle (Kendall *et al*., 2004). Similarly, leptin inhibited the insulin-induced production of progesterone and androstenedione by the thecal cells *in vitro* (Spicer and Francisco, 1998). Leptin has also a weak inhibitory effect on gonadotropin- and/or IGF-I-induced steroidogenesis of the bovine thecal and granulosa cells (Spicer *et al*., 2000). In the bovine species, leptin and its receptor transcripts are present in the corpus luteum and their expression decrease during luteal regression (Sarkar *et al*., 2010). Leptin increased *in vitro* IGF-I-induced luteal progesterone production (Nicklin et al., 2007).

Leptin enhanced bovine oocyte maturation and improved the ability of the bovine oocyte to sustain embryonic development. Indeed, the addition of leptin to the IVM medium enhanced meiotic maturation and embryo development of calf oocytes, and improved the quality of embryos derived from these oocytes (Jia *et al*., 2012). van Tol *et al*. (2008) confirmed that leptin enhanced meiotic maturation of bovine oocytes (van Tol *et al*., 2008). Furthermore, they showed that this effect was cumulus cell-mediated (van Tol *et al*., 2008), whereas Paula-Lopes *et al*. (2007) observed that leptin enhanced both oocyte maturation and their developmental capacity by mechanisms that were both cumulus cell-independent and -dependent (Paula-Lopes *et al*., 2007). In contrast, Cordova *et al*. (2011) observed that the addition of leptin to the IVM medium used to mature oocytes from prepubertal cows did not increase the development potential of the oocytes (Cordova *et al*., 2011).

In conclusion, it seems that elevated circulating concentrations of leptin that are a result of hunger and poor nutrition are associated with a pattern of inhibition of the ovarian function but, paradoxically, with improved oocyte quality. However, the positive effects of leptin on oocyte quality were obtained *in vitro*, and the relationship between the circulating concentrations of leptin and oocyte quality *in vivo* are not known for ruminants. In mice, leptin is essential for normal preimplantation and/or implantation processes, but it is not required for pregnancy and parturition once implantation is established (Malik *et al*., 2001).

Adiponectin. Adiponectin is a protein produced mainly by the white adipose tissue. In humans, the level of expression of its mRNA varies depending on the location of the adipose tissue, and it is lower in the visceral adipose tissue than in the subcutaneous adipose tissue (for review, Kadowaki and Yamauchi (2005). The expression of adiponectin is higher in thin than in obese subjects (for review, Kadowaki and Yamauchi (2005). Adiponectin is involved in lipid and carbohydrate metabolism and seems to have an important role in the pathophysiology of obesity and type 2 diabetes (for review, Kadowaki and Yamauchi (2005). In healthy humans and cattle, the blood concentrations of adiponectin are of the order of 5 to 30 mg/l, which represents 0.01% of the total plasma proteins (for review, Kadowaki and Yamauchi (2005); Giesy *et al*. (2012). In humans and rodents, low concentrations of plasma adiponectin are predictive of insulin resistance and type 2 diabetes. In these species, dietary factors can modulate circulating adiponectin (Reis *et al*., 2010). In this latter review, it was concluded that diets rich in saturated fat reduced the concentration of adiponectin, whereas diets rich in PUFAs and supplementation with n-3 PUFAs increased both gene expression of adiponectin and its concentration in the circulation. However, an effect of dietary components on the

circulating concentration of adiponectin has not yet been reported in ruminants. In the plasma from humans, mice and cattle, adiponectin circulates in a variety of high molecular weight (HMW) dimeric and trimeric forms. In dairy cows during late pregnancy, adiponectin circulated almost exclusively as HMW complexes, and this pattern was unaffected by early lactation (Giesy *et al.*, 2012). Decreasing plasma concentrations of adiponectin with advancing lactation are in good agreement with decreased insulin sensitivity that also occurs with advancing lactation. These are the expected adaptive responses to the increased glucose requirements of the lactating mammary gland, which preferentially diverts glucose from the adipose tissue, skeletal muscle and other tissues to the mammary gland (Mielenz *et al.*, 2013). In humans and rodents, exogenous adiponectin improved insulin sensitivity by the activation to its receptors AdipoR1 and AdipoR2 (for review, Kadowaki and Yamauchi (2005); they are receptors with seven transmembrane domains and they have an inverted topology compared with normal G-protein-coupled receptors. Once activated, AdipoR binds an adapter protein (APPL), which in turn activates adenosine monophosphate-activated kinase (AMPK) (Kadowaki and Yamauchi, 2005). AMPK is a major component of the signalling pathway that regulates the metabolic effects of adiponectin (Kadowaki and Yamauchi, 2005).

Some evidence suggests that adiponectin could regulate ovarian function and affect the embryo at very early stages of pregnancy during the pre-implantation period (Palin *et al.*, 2012). In the bovine species, adiponectin and its receptors are present in different follicular cells (oocytes, theca, granulosa and cumulus cells) and luteal cells (Maillard *et al.*, 2010) (Table 1). Moreover, it has been shown that the physiological status of the ovary is related to the pattern of expression of adiponectin and its receptors in follicular and luteal cells from the bovine ovary (Tabandeh *et al.*, 2010). Indeed, the expression of adiponectin, AdipoR1 and AdipoR2 was higher in the theca and cumulus cells and the oocytes of dominant follicles compared with those of atretic follicles during both the follicular and luteal phases (Tabandeh *et al.*, 2012). In our laboratory, we have shown that adiponectin decreased insulin-induced steroidogenesis and increased IGF-I-induced proliferation of the bovine granulosa cells in culture possibly by a mechanism that involved the ERK1/2 MAPK pathway (Maillard *et al.*, 2010). Lagaly *et al.* (2008), have also observed an inhibitory effect of adiponectin on bovine steroidogenesis but only in the theca cells. Concerning the oocyte and embryo, we have shown that adiponectin did not modify either oocyte maturation or embryo development *in vitro* in bovine species.

The available data on the physiological role of adiponectin in the follicle suggest that it has no direct actions and that its action appears to be the modulation of ovarian actions of insulin and IGF-I. However, more research is required to confirm or refute these suggestions. The role of adiponectin *in vivo* in the early embryonic development of cattle remains to be investigated.

Resistin. Resistin is a protein of 108 amino acids in humans and 114 amino acids in mice belonging to the family of 'resistin-like molecules' or 'FIZZ' (found in the inflammatory zone) (Schwartz and Lazar, 2011). It consists of two homodimers linked by disulphide bridges (Schwartz and Lazar, 2011). In mice, resistin is produced by adipocytes, whereas in humans it is produced by macrophages in the bone marrow and transported to adipocytes (Kaser *et al.*, 2003; Patel *et al.*, 2003). Very little information is currently available on the mode of action of resistin. No receptor has been clearly identified, and the signalling pathway used by resistin remains obscure. Recent tudies suggest that resistin could bind to a receptor tyrosine kinase known as receptor tyrosine kinase-like orphan receptor (ROR1) in murine pre-3T3-L1 adipocytes or to the receptor known as TLR4 (Toll-like receptor 4) in the mouse hypothalamus (cited in Reverchon *et al.*, 2013).

In cattle, resistin has not been extensively studied. It is produced by the adipose tissue and in greater amounts in lactating compared with non-lactating cattle (Komatsu *et al.*, 2003). Resistin is also present in the bovine ovaries (Table 1). Furthermore, human recombinant resistin decreases basal but not IGF-I-induced progesterone and oestradiol production by the bovine granulosa cells (Maillard *et al.*, 2011). Spicer *et al.* (2011), have also observed that resistin preferentially inhibited steroidogenesis in the granulosa cells from small follicles and inhibited proliferation of the granulosa cells from large follicles, suggesting that the ovarian response to resistin is altered during follicular development. The little data available suggest that resistin may be involved in the nutritional regulation of ovarian function and fertility in ruminants and on this basis is worthy of further investigation.

Other adipokines including chemerin and visfatin, known to regulate insulin sensitivity, have been sequenced and are present in the cattle ovaries. However, the physiological effects, if any, of these newer adipokines in ovarian function remains to be determined.

Apelin (stomach). Apelin is a peptide isolated from extracts of the bovine stomach (Tatemoto *et al.*, 1998). It has been identified as the endogenous ligand of the human orphan, APJ receptor (Tatemoto *et al.*, 1998). Apelin is derived from a larger precursor, preproapelin, the cDNA for which has been cloned in humans, cattle, rats and mice (Tatemoto *et al.*, 1998). Plasma apelin is upregulated in rodents and humans during obesity, there is a strong relationship between adipocyte-secreted apelin and insulin levels (Boucher *et al.*, 2005). In goats, feeding caused a slight increase in plasma apelin concentrations, and this increase was enhanced by water deprivation (Sato *et al.*, 2012).

In the bovine ovary, the apelin/APJ system is involved in mechanisms regulating angiogenesis during follicular maturation and luteal development (Schilffarth *et al.*, 2009). Apelin and APJ are expressed in the bovine granulosa cells, and progesterone increases the expression of APJ in these cells (Shimizu *et al.*, 2009) (Table 1). Theca cells also

have both apelin and APJ and their expression is increased by exogenous LH (Shimizu *et al.*, 2009). These latter authors suggest that the apelin/APJ system could play a role during follicle selection and dominance in cows. The apelin–APJ system is also present in the bovine corpus luteum (Shirasuna *et al.*, 2008) where it could be involved in the maturation of corpus luteum and the luteolytic cascade as a regulator of intra-luteal arterioles (Shirasuna *et al.*, 2008).

If similarly to the other gut hormones, such as ghrelin, apelin is nutritionally regulated, then it could be another potential regulator of nutritional influences on ovarian function in ruminants.

AMPK

Most of the metabolic hormones discussed above modulate the phosphorylation of AMPK (Tosca *et al.*, 2008). AMPK is a metabolic sensor of the energy state of a cell: it has a key role in the regulation of lipid, carbohydrate and protein metabolism in the peripheral and central tissues (Tosca *et al.*, 2008). It is a heterotrimeric serine/threonine kinase that is composed of a catalytic α subunit and two regulatory subunits β and γ subunits, each encoded by a different gene and for each of which, there are two or three isoforms (Hardie and Carling, 1997). These different isoforms allow the possible formation of 12 $\alpha\beta\gamma$ complexes. The balance of these complexes depends on the tissue (Hardie and Carling, 1997). The activity of AMPK is regulated allosterically by the binding of AMP or ATP onto the γ regulatory subunit by phosphorylation of the α subunit at threonine 172 by an AMPK kinase (either LKB1 (serine/threonine kinase 11) or CaMKKβ (calmodulin-dependent kinase kinase-β)) and its subsequent dephosphorylation by a phosphatase (protein phosphatase-1, protein phosphatase 2A or protein phosphatase 2C) (Hardie and Carling, 1997). The main mechanism for the activation of AMPK is a decrease in the intracellular ratio of ATP to AMP. AMPK can be activated by certain physiological conditions (exercise, stress) by the action of metabolic hormones (leptin, adiponectin, ghrelin) and by the pharmacological agents, 5-aminoimidazole-4-carboxamide-1-β-D-riboside (AICAR), metformin and the thiazolidinediones (Hardie and Carling, 1997). It regulates energy homeostasis maintaining a constant concentration of intracellular ATP by stimulating catabolic pathways and inhibiting anabolic pathways (Hardie and Carling, 1997). In the ovary, AMPK controls cellular proliferation and survival and also reproductive functions such as ovarian steroidogenesis and oocyte maturation (Dupont *et al.*, 2008).

In cattle, AMPK has been identified in different cell types of ovarian follicles (oocyte, cumulus cells, granulosa and theca) and in the corpus luteum (Tosca *et al.*, 2007a and 2007b; Gallet *et al.*, 2011) (Table 1). In cultured bovine granulosa cells, AMPK inhibited the secretion of progesterone and/or oestradiol in response to AICAR or metformin (Tosca *et al.*, 2007a). This decrease can be explained by the inhibition of the steroidogenic enzymes, 3β-hydroxysteroid-dehydrogenase (3βHSD) and P450scc (p450 side-chain cleavage) and of steroidogenic acute regulatory protein (StAR) and also by inhibition of the MAPK/ERK pathway (mitogen-activated protein kinase/extracellular-regulated kinase) (Tosca *et al.*, 2007a). In these cells, the activation of AMPK in response to metformin also reduced cell growth and protein synthesis, MAPK ERK1/2 signalling and P90RSK phosphorylation in response to IGF-I (Tosca *et al.*, 2010). *In vivo*, we showed that the infusion of glucose (Gallet *et al.*, 2011) or feeding lupins (Zouaidi, unpublished data) inhibited AMPK in sheep follicles, suggesting that good nutrition or glucose can block the inhibitory actions of AMPK in the follicle.

Some studies have also established a link between AMPK and meiotic maturation of the oocyte (Downs and Chen, 2006). In cattle, similar to the pig, pharmacological activation of AMPK blocked nuclear maturation of the oocyte (at prophase of the first meiotic division or at the germinal vesicle stage (Bilodeau-Goeseels *et al.*, 2007; Tosca *et al.*, 2007b), whereas in mice AMPK improved the resumption of meiosis by accelerating rupture of the nuclear membrane (Bilodeau-Goeseels, 2011) or breakdown of the germinal vesicle (Downs and Chen, 2006). Although there are some differences among species, AMPK appears to be important for the breakdown of the germinal vesicle during nuclear maturation of the oocyte. Recently, Pikiou *et al.* (2013) suggested that activation of AMPK in response to metformin could decrease the ability of bovine oocytes to cleave following *in vitro* fertilization (Pikiou *et al.*, 2013). Although the role of AMPK in nuclear maturation could be to promote early embryonic development, it is unclear whether AMPK is involved in cytoplasmic maturation of oocytes. In cows, AMPK is also found in the corpus luteum. In cultured bovine luteal cells, the activation of AMPK regulated LH-induced progesterone secretion (Hou *et al.*, 2010).

Thus, AMPK could control ovarian steroidogenesis in the granulosa cells, oocyte maturation and embryo development, and it could also be involved in the function of the corpus luteum. An improved understanding of the role of AMPK during meiosis in the oocytes will facilitate the control of this process *in vitro*, resulting in increased developmental competence and increased efficiency of procedures for the *in vitro* embryo production.

Peroxisome proliferator-activated receptors (PPARs)

PPARs are nuclear transcription factors that are classified as members of the steroid hormone receptor superfamily. To date, three related PPAR isotypes have been described: PPARα, PPARβ/δ and PPARγ. The three isotypes share a high degree of homology but differ in tissue distribution and ligand specificity (Berger and Moller, 2002). The PPAR family (α, β/δ and γ) integrates energy regulation with lipid and glucose metabolism and affects insulin sensitivity (Kota *et al.*, 2005). Furthermore, PPARγ expression in the adipose tissue is nutritionally regulated (Vidal-Puig *et al.*, 1996).

There are a variety of natural and synthetic agents that activate PPARs. Among its natural ligands, there are long-chain fatty acids, especially PUFAs, including linoleic and arachidonic acids, and some derivatives including 15-deoxy-delta 12, 14-prostaglandin J2 (PGJ2), eicosapentaenoic acid and acid

9- and 13-hydroxyoctadecadienoic acid (Tontonoz *et al.*, 1995; Kliewer *et al.*, 1997). Prostaglandins activate all members of the PPAR family, with a preferential activation of PPARβ by PGJ2 (Forman *et al.*, 1997). Various synthetic ligands, such as industrial plasticizers (phthalates), nonsteroidal anti-inflammatory drugs, fibrates (a class of drugs used to treat hyperlipidemia), and thiazolidinediones, activate these receptors (Forman *et al.*, 1997). However, there is a ligand specificity for each form of PPAR. For example, fibrates (WY-14 643, clofibrate) show a strong affinity for PPARα, but at higher concentration they can also activate PPARγ. Thiazolidinediones (troglitazone, ciglitazone, pioglitazone and rosiglitazone) activate PPARγ.

The PPARs form and function as heterodimers with retinoid-X-receptor (RXR). Once the ligand binds (e.g. long-chain fatty acids, fibrates, thiazolidinediones) to the ligand-binding domain, it produces a covalent modification of the PPAR structure (Waku *et al.*, 2009) activating the nuclear receptor. The activated PPAR/RXR binds to a specific DNA sequence (PPAR research response element) in the promoter region of specific target genes inducing or repressing their expression.

The three PPAR isoforms have been detected in the ovary and PPARγ is the one most extensively studied in the ovarian tissue (Table 1). This is because, in addition to the high expression level of PPARγ in the follicle of various species (for review see Froment *et al.*, 2003; Dupont *et al.*, 2008), its synthetic ligands and widely used as drugs treat polycystic ovary syndrome, one of the commonest ovarian dysfunctions causing infertility in women. In ruminants, PPARγ was detected in the ovine and bovine ovary (Sundvold *et al.*, 1997; Lohrke *et al.*, 1998; Froment *et al.*, 2003). In the bovine species, transcripts for RXRα, RXRβ and PPARγ were detected at all stages of early pregnancy beginning from the unfertilized oocyte through to the hatched blastocyst (Mohan *et al.*, 2002) (Table 1). In cyclic ewes, the expression of PPARγ is mainly limited to the granulosa cells of antral follicles and corpora lutea (Froment *et al.*, 2003). In cows, the concentration of PPARγ in the corpus luteum increased after ovulation, and then decreased during regression of the corpus luteum (Lohrke *et al.*, 1998; Viergutz *et al.*, 2000). Furthermore, in mice, the conditional inactivation of PPARγ in the ovary leads to reduced fertility (Cui *et al.*, 2002). This decrease is not because of an alteration in ovarian folliculogenesis, but a drop in the number of embryos implanted and probably because of decreased progesterone secretion by the corpora lutea (Cui *et al.*, 2002). In bovine large lutein cells, PPARγ plays a role in the arrest of the cell cycle to maintain a differentiated state (Viergutz *et al.*, 2000). Furthermore, synthetic ligands of PPARγ increased progesterone secretion by bovine lutein cells (Lohrke *et al.*, 1998).

Thus, it seems that PPARγ is essential *in vivo* for the formation and maintenance of a functional corpus luteum capable of secretion of progesterone compatible with embryo implantation. One hypothesis is that PPARγ is involved in the beneficial effects of some PUFAs on the fertility of cattle.

Conclusions

In ruminants, fertility is a key parameter for the profitability of the farmers, and a positive nutritional status and good metabolic health are both associated with successful reproduction and help ensure high fertility. Some nutritional strategies could reduce the risk of metabolic disturbances and, consequently, not only improve herd health but also enhance fertility. The data presented in this review highlight the importance of specific nutrients (glucose, saturated and PUFAs, and certain amino acids) on ovarian function in ruminants. Nutrition influences ovarian follicular development in ruminants possibly through changes in metabolic hormones and also by the direct effects of particular nutrients on the ovary. Metabolic hormones that appear to have important established functions in these processes include insulin, leptin and the IGFs. Other metabolic hormones that may have important roles include GH, T3/4, ghrelin, apelin, and some novel adipokines produced by the adipose tissue, including adiponectin and resistin. The importance of these metabolic hormones is either debatable or unknown and they are interesting areas for future research. The adipokines, in particular, have emerged as potentially important regulatory factors in the fields of fertility and reproduction in human and possibly ruminants. These adipokines and their receptors are expressed in cattle ovary; however, further studies are necessary to determine whether their plasma concentrations are nutritionally regulated in ruminants. There is emerging evidence that dietary long-chain n-3 PUFAs can act as specific regulators of some reproductive processes. The molecular mechanisms of action of these PUFAs is still unknown in ruminants. However, PUFAs could mediate their action through the activation of PPARγ or/and AMPK by modulating plasma concentration of some adipokines such as adiponectin or resistin, as has been described in humans and rodents. AMPK appears to be a key signal regulating the amount of energy required for the growth of follicles, oocytes and embryos

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