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Review

Granulosa Cells: Central Regulators of Female Fertility

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Abstract: Background: Granulosa cells are somatic cells within the ovarian follicle. As the primary site of estradiol production, they are critical regulators of several aspects of female reproduction. This review aims to provide an overview of the physiology of mammalian granulosa cells and their importance for female fertility. Methods: the literature about the function and regulation of granulosa cells was reviewed. Results: a comprehensive summary and discussion of the role of granulosa cells on ovarian steroidogenesis and folliculogenesis, as well as factors that control granulosa cells function, are presented. Conclusion: The functions of granulosa cells are regulated by a plethora of intra- and extra-ovarian factors via autocrine, paracrine, and endocrine pathways, which creates a complex regulatory network. A comprehensive understanding of granulosa cells' physiology is vital for the development of innovative strategies to enhance reproductive outcomes in several species.

Keywords: ovary; estradiol; insulin-like growth factor; fibroblast growth factor; adipokines

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1. Introduction

Female fertility involves the biological processes of ovarian folliculogenesis, ovarian steroidogenesis, ovulation, fertilization, embryo development, and early pregnancy maintenance. The ovaries are critical regulators of these complex processes, and ovarian follicles are the basic functional units of the ovaries. Within ovarian follicles, granulosa cells (GC) communicate with the oocyte and surround theca cells (TC) to regulate ovarian function in autocrine and paracrine manners. Outside the follicles, the functions of GC are affected by a plethora of extra-ovarian factors in an endocrine manner to regulate female fertility. The aim of this review is to summarize the functions and regulation of mammalian GC in response to intra- and extra-ovarian factors. An emphasis will be given to the regulation of GC in ovarian antral follicles of mammals.

2. Ovarian Steroidogenesis

A major function of GC is to synthesize and regulate the production of sex steroids by the ovaries. Estradiol, the main steroid produced by GC, is a critical regulator of reproduction. Estradiol promotes female sexual behavior [1,2], development of female secondary sex characteristics [3], ovulation [4], and uterus preparation for embryo implantation [5,6]. Also, estradiol exerts important functions inside and outside the ovaries to regulate GC function during ovarian folliculogenesis, including through exerting control over the release of gonadotropins by the anterior pituitary [7,8] and through direct binding to GC to induce proliferation and maturation [9–11]. In GC, estradiol acts primarily via the receptor Erβ, which has different isoforms, to determine cellular function during ovarian folliculogenesis [11].

Steroidogenic tissues, including the ovaries, require cholesterol as a precursor for the production of steroids [12]. Steroidogenic cells obtain cholesterol from plasma lipoproteins or via de novo cholesterol biosynthesis from acetate [13]. Ovarian follicular cells utilize both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) for cholesterol uptake via the LDL receptor (LDLR) and the scavenger receptor class B member I (SR-BI), respectively, and these receptors are under hormonal regulation in the ovary [14–16].

Indeed, several in vitro studies have shown that GC of humans, cattle, pigs, and murine species can synthesize progesterone in response to the addition of both HDL and LDL in the medium [13,15,17–21]. Nevertheless, differences exist between species in the preference for HDL or LDL for cholesterol uptake by GC: bovine GC primarily utilizes cholesterol derived from LDL uptake to synthesize progesterone, whereas murine and porcine GC primarily use cholesterol delivered by HDL [13,15,18,19,22]; in humans, LDL is the main circulating lipoprotein, but follicular fluid of preovulatory follicles contains primarily HDL and human GC efficiently utilizes both lipoproteins for cholesterol uptake and progesterone production [17].

The first step of steroidogenesis is the conversion of cholesterol into pregnenolone, which is catalyzed by the cholesterol side-chain cleavage enzymes (P450scc), encoded by the gene *CYP11A1*, in the mitochondria [12]. Thus, cholesterol must be transported from the outer membrane to the inner membrane of mitochondria. A well-established regulator of this transport is the steroidogenic acute regulatory protein (StAR) enzyme and this is a rate-limiting step in steroidogenesis [23–25]. Other proteins have been recognized to transfer cholesterol into the mitochondria of steroidogenic cells, including StarD4, which belongs to a subfamily of StAR-related lipid transfer proteins [26,27].

Pregnenolone will be converted into progesterone by the action of the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which has been located in the endoplasmic reticulum, as well in the mitochondria, of steroidogenic cells [12,28,29]. Progesterone serves as a precursor to androgens, which, in turn, serve as substrates for estrogen synthesis. Progesterone will be converted to androgens by the enzyme cytochrome P450 17α-hydroxylase/17,20-lyase, encoded by the gene *CYP17A1*, and this enzyme is expressed by TC, but not GC [30–32]. Androgens are then converted into estradiol by the enzyme aromatase, which is encoded by the gene *CYP19A1* and is located exclusively in GC in the ovary [31,32]. Therefore, the communication between TC and GC is essential for the synthesis of estradiol [28,31,33].

It is important to note that GC express the genes that encode StAR and all steroidogenic enzymes for the production of steroids in vitro [18,28,34], and the expression of genes that encode P450scc, 3β-HSD, and aromatase will change according to the stage of the reproductive cycle in vivo, but the expression of StAR has been detected only in TC and not in GC in vivo [35–37]. Furthermore, research in ruminants shows that the expression of steroidogenic genes in ovarian follicular cells is regulated by the nutritional and metabolic status of the female [38,39]. This shows that the gene expression of steroidogenic enzymes depends on the status of GC during ovarian folliculogenesis, and this will be further discussed in this review.

3. Ovarian Folliculogenesis

Ovarian folliculogenesis is a highly regulated process in which the female gamete (oocyte) matures within the follicle surrounded by somatic cells, ultimately developing into a fertilizable egg. The first follicles formed in the ovary are called primordial follicles, and these consist of an immature oocyte arrested at the diplotene stage of meiosis I and surrounded by a single layer of flattened pre-GC [40,41]. After their formation, the majority of primordial follicles will remain dormant for months or years, and only a small number are recruited to keep growing through the process of ovarian folliculogenesis [42,43]. Primordial follicles remain dormant via the action of inhibitors of oocyte maturation, and their activation to keep developing is under the influence of a balance between inhibiting and activating factors [40,44,45]. Follicular activation results in the transition of follicles from the primordial stage to the primary stage. At this time, the oocyte begins to enlarge and is surrounded by a single layer of cuboidal GC [40,46]. The first pool of primordial oocytes will be activated to keep developing during the fetal life of some mammalian species, such as ruminants and humans, whereas this process will start during the early neonatal period in rodents, and pools of primordial follicles will be continuously activated throughout the entire reproductive life of the female [9,47,48].

GC are critical regulators of ovarian folliculogenesis. The exchange of growth factors between the oocyte and the surrounding somatic cells via exchange of growth factors is crucial for follicular development throughout the primordial, primary, secondary, and tertiary (antral) stages [40,46,49–52]. The development of preantral follicles, namely primary and secondary follicles, is characterized by the growth of oocytes, proliferation of GC, and development of TC [40,53]. It has been established that the development of preantral follicles occurs independently of the actions of the gonadotropins derived from the pituitary, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are critically important for the development of antral follicles [51]. Nevertheless, preantral follicles do respond to FSH, which stimulates follicular development [51,54,55].

During the female reproductive cycle, pools of antral follicles will grow, develop, and one or a small group will ultimately ovulate, whereas the great majority will degenerate during the process of follicular atresia [56]. The cyclic follicular development encompasses the processes of recruitment, selection, dominance, and ovulation or atresia, and this occurs in follicular waves during the reproductive cycle in ruminants and horses [36,47,57–60]. Recent observations show evidence that ovarian follicular development also occurs in waves during the menstrual cycle of women [61]. The effects of gonadotropins on GC are determinants for the control of the development of antral follicles. The term recruitment may refer to the process whereby a cohort of dormant primordial follicles are recruited to grow and develop (initial recruitment) or can refer to the process where a group of small antral follicles is rescued from atresia in response to subtle increases in circulating FSH and begins to grow during each reproductive cycle or follicular wave [43,62,63]. Selection refers to when one or more growing antral follicles, depending on the species, will be selected to continue to grow and become the dominant follicle, which will acquire functional characteristics that will allow it (or them) to ovulate [36,47,53,62]. The antral follicles that are not selected for dominance are called subordinate follicles and will undergo atresia like the majority of follicles in all stages of folliculogenesis [47].

During antral follicular growth, GC proliferate under the control of intra- and extra-factors, including estradiol and FSH [9,28,64]. GC proliferation is especially important for initial follicular growth, but the growth of larger follicles during the later stages of folliculogenesis seems to depend more on antrum development [65]. As follicles keep growing and developing, GC and TC will undergo molecular and functional changes to determine the fate of antral follicles. This process of differentiation involves an enhancement of the steroidogenic capacity of follicular cells that occurs as follicles are selected to dominate and approach the preovulatory stage [66]. To enhance their steroidogenic capacity, GC of dominant and preovulatory follicles will increase the mRNA expression of the FSH receptor and the steroidogenic enzymes involved in the production of progesterone and estradiol [36,53,67]. Additionally, TC of the dominant follicles will increase their synthesis of androgens through an increase in the LH receptor and *CYP17A1* mRNA expression [37,53,68]. Furthermore, under the synergistic stimulus of FSH and increased estradiol, GC differentiation in dominant and preovulatory follicles involves the acquisition of LH receptors to induce terminal GC differentiation, stop cellular proliferation, and prepare follicles for ovulation [11,28,36,53,69–72].

Another important function of GC during ovarian folliculogenesis is the control of follicular degeneration. Several studies have reported that GC death via apoptosis is the main underlying mechanism of follicular atresia [73–76]. An important factor for induction of GC apoptosis is the deprivation of hormones that promote GC survival, including estradiol, insulin-like growth factors (IGFs), and FSH [77]. Additionally, a death-ligand receptor system is known to activate GC apoptosis [77,78].

4. Factors That Regulate Function of Granulosa Cells

The role of extra- and intra-ovarian factors on function of GC during ovarian folliculogenesis will be further discussed in this review. These include the IGFs system, fibroblast growth factors (FGFs), adipokines, and factors derived from the gastrointestinal

system. A plethora of other factors are known to regulate GC function and have been the focus of previous reviews, including the bone morphogenetic protein system [79], the angiotensin system [80], prohibitin [81], endothelins [82], insulin [83], anti-Müllerian hormone (AMH) [84], and several others.

4.1. The Insulin-like Growth Factor System

Insulin-like growth factor 1 (IGF1) and insulin-like growth factor 2 (IGF2) are single-chain polypeptides with a similar molecular structure to insulin that were first identified in the plasma of humans in the 1970s [85,86]. These growth factors are mainly produced by the liver and released in the circulation to stimulate endocrine actions in target cells, but they are also locally produced in tissues to exert a paracrine or autocrine action. For IGFs to elicit their actions, they bind to IGF receptor type 1 (IGF1R) and insulin receptors in various tissues (for reviews, see [87,88]. Current evidence shows that another receptor for IGFs, IGF receptor type 2 (IGFR2), also called cation-independent mannose-6-phosphate receptor, serves to prevent the action of IGF2 by degrading it upon activation and, therefore, controlling its availability rather than eliciting its action [89]. The affinity of IGF1R is greater for IGF1 than for IGF2, whereas the IGF2R has a higher affinity for IGF2 than for IGF1 [87,90,91]. The IGF1R receptor is a glycoprotein that possesses two extracellular α-subunits linked via disulfide bonds and two transmembranal β-subunits with tyrosine-kinase activity [90,92,93]. The binding of the ligand to the extracellular subunits of IGF1R in target cells results in intracellular signal transduction through several mechanisms, including kinase signaling, G protein signaling, and β-arrestin signaling [94].

The effects of IGFs in the ovaries are critically important and have been extensively studied (for previous reviews, see [66,83,95,96]. It has long been established that IGFs are synthesized by ovarian follicular cells of preantral and antral follicles to elicit autocrine and paracrine actions. In antral follicles, specifically, *IGF1* mRNA is present in both ovine GC and TC, but it is predominantly expressed in GC of other mammalian species, including bovine, porcine, and murine [97–105]. Also, in these species, *IGF2* mRNA is predominantly detected in TC [98,100,103,105]. In the antral follicles of humans, differences in expression of IGFs exist according to the stage of folliculogenesis: *IGF1* and *IGF2* mRNA expression is restricted to TC in small follicles while no *IGF1* mRNA has been detected in human TC or GC and *IGF2* mRNA has been detected exclusively in human GC [106]. It is important to note that *IGF2* has a greater mRNA expression than *IGF1* in the bovine ovary [107], and thus, IGF2 is considered the main intrafollicular IGF ligand, eliciting autocrine and paracrine effects, while most of the IGF1 comes from the liver to perform endocrine actions in this species [108]. In terms of expression of the type 1 receptor, *IGF1R* mRNA has been detected in both the GC and TC of ruminants [100,107] while being mainly detected in the GC of mice [109] and humans [106,110].

As observed in primary cell culture studies, both IGFs 1 and 2 are mitogens of GC of several mammalian species, including humans, cattle, pigs, and rats [101,111–117]. Additionally, based on primary cell culture studies, IGFs are recognized to promote GC differentiation by amplifying the stimulatory effects of FSH on the production of estradiol and progesterone by GC of several species, including bovine, porcine, murine, and human [101,117–120]. Furthermore, IGF1 stimulates the acquisition of the LH receptor induced by FSH and mRNA expression of steroidogenic enzymes, including StAR and aromatase, in GC in vitro [117,118,121,122]. The effects of IGFs on stimulation of GC proliferation and differentiation are dependent on the expression of IGFR1 in these cells [109,117,123].

Insulin-like binding proteins (IGBPs) represent an important component of control of IGFs actions. To date, six IGBPs (IGFBP-1 to IGFBP-6) have been identified, and they are known to bind to IGFs in order to transport them through circulation and regulate their bioavailability and function, as previously reviewed [124,125]. Although no differences in total IGF intrafollicular concentrations between dominant and subordinate follicles have been detected in cattle [126], the bioavailability of IGFs in follicular fluid changes

during ovarian folliculogenesis in cattle, horses, sheep, pigs, and humans due to changes in levels of IGFBPs [66,95,96,127–131]. Thus, IGFBPs are considered important intra-ovarian factors to regulate the fate of follicles during folliculogenesis. As IGFs actions on GC are considered important for the selection of dominant follicles, changes in IGFBPs levels are required for the selection of dominant follicles in several species, including ruminants, horses, and pigs [66,95,96,102,127,132]. Interestingly, the pregnancy-associated plasma protein-A (PAPP-A) was identified in cattle as a protease that reduces IGFBPs in the follicles selected for dominance [66,95], and recent studies suggest that PAPP-A is derived from GC and is a marker of follicle selection and dominance in several mammalian species, including bovine, ovine, murine, and human [96,133,134].

4.2. Fibroblast Growth Factors

FGFs were initially reported to induce proliferation of fibroblasts [135,136], but the effects of these polypeptides go way beyond what the name implies and it is now well-established that not all FGFs affect fibroblasts [137,138]. FGFs have been detected in many tissues, eliciting various effects on development and metabolism, with some members acting exclusively during embryogenesis and others affecting both embryonic and adult tissues [139].

Several FGFs are synthesized by the different compartments of ovarian follicles. Among twenty two known FGFs, eleven have been detected within the ovaries of mammals, including FGF1 [140], FGF2 [141], FGF7 [142], FGF8 [143], FGF9 [144–146], FGF10 [147], FGF16 [148], FGF17 [149], FGF18 [150], FGF21 [151], and FGF22 [147]. In bovine antral follicles, FGF1, FGF2, FGF7, FGF18, and FGF22 are primarily produced by TC [140–142,147,150,152]; FGF8 is produced by oocytes, GC, and TC [143]; FGF9 is produced in greater concentrations by GC than TC [153]; FGF10 is produced by oocytes and TC [152]; FGF16 is produced by the oocyte [148]; and FGF17 is detected mainly in oocytes, but also in GC [149]. FGF21 is detected in porcine GC and TC [151].

To elicit their intracellular actions in target cells, FGFs must bind to high-affinity single-chain transmembrane tyrosine kinase receptors (FGFRs), which have different ligand-specificities and are encoded by four different genes in vertebrates, namely *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4* [154,155]. The diversity of these receptors is further increased by the occurrence of alternative mRNA splicing of the sequence of the immunoglobulin domain III of the genes *FGFR1*, *FGFR2*, and *FGFR3*, resulting in isoforms IIIb and IIIc [138,139,154,156]. The localization of FGFRs in the different compartments of ovarian follicles is important for the FGFs to control ovarian physiology [140,149,152]. According to the ligand-binding specificity of FGFs synthesized in the ovary, FGF1 and FGF2 bind with high specificity to both FGFR1c and FGFR3c, and the latter also binds FGF8, FGF9, FGF16, FGF17, and FGF18 with high specificity [139,155]. Additionally, FGFR2b binds to FGF10 with high specificity, FGFR2c is the second preferred receptor for FGF9 and FGF16, and FGFR4 is the second preferred receptor for FGF8, FGF17, and FGF18 [139,155]. The mRNA expression of FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3c, and FGFR4 has been detected in GC of cattle, although the expression of FGFR4 is very low or absent according to different studies [140,147,149,152,157].

The synthesis of FGFs and their receptors by ovarian follicular cells varies according to the size of follicles and the stage of ovarian folliculogenesis in cattle. In terms of FGFs, *FGF2* mRNA expression is greater in TC of dominant follicles than that of subordinate follicles, *FGF7* and *FGF10* mRNA expression is greater in TC of future subordinate than that of future dominant follicles, and *FGF9* mRNA expression is greater in GC of subordinate than that of dominant follicles [140,141,146,147]. In terms of receptors present in bovine GC, mRNA relative abundance of *FGFR1b* and *FGFR2b* mRNA expression is greater in dominant than in subordinate follicles, while *FGFR1c* and *FGFR2c* are greater in subordinate than in dominant follicles [140,143,157]. In terms of FGFR3c, a positive association has been established between estradiol concentrations in follicular fluid and *FGFR3c* mRNA expression in bovine GC of ovaries obtained from slaughterhouse [143], but when *FGFR3c* mRNA was analyzed

in bovine GC from ovaries obtained following estrous synchronization, no differences were detected between subordinate and dominant follicles [157].

FGFs regulate ovarian physiology through autocrine, paracrine, and endocrine actions (for reviews, see [158,159]). Their actions were first reported in the ovary in 1977, when FGF1 was found to stimulate proliferation of bovine GC [160]. Since then, at least five FGFs have been shown to stimulate bovine or porcine ovarian follicle cell proliferation, namely FGF1, FGF2, FGF7, FGF9, and FGF21 [145,151,161–165].

FGFs also regulate mammalian GC steroidogenesis and differentiation, and this may differ according to the species and stage of follicular development depending on the FGF. FGF1 does not affect progesterone production by bovine GC, but it does inhibit progesterone production by porcine GC [166,167]. FGF2 suppresses FSH- or FSH plus IGF1-induced estradiol production by murine and bovine GC [168–171], but it enhances FSH-induced progesterone production and LH-induced production of both estradiol and progesterone by rat GC [168,169]. FGF7 inhibits FSH-stimulated estradiol production and aromatase activity by bovine and rat GC and suppresses hCG-stimulated progesterone production by bovine and human GC [142,172]. FGF8 suppresses FSH-induced estradiol production by rat GC [173]. FGF9 increases FSH- or FSH plus IGF1 stimulated estradiol production in murine and porcine GC but suppresses FSH plus IGF1-stimulated estradiol and progesterone production in bovine and porcine GC [145,171,174]. FGF10 suppresses FSH-stimulated estradiol production while FGF17 and FGF18 decrease FSH-stimulated estradiol and progesterone secretion by bovine GC [149,150,152]. A summary of the actions of FGFs on bovine GC steroidogenesis is presented in Table 1.

Table 1. Effects of fibroblast growth factors on steroidogenesis of bovine granulosa cells.

Fibroblast Growth Factor	Main Source Within Ovarian Follicles	Effects on Steroidogenesis of Granulosa Cells	References
FGF2	Theca cells	FGF2 suppresses FSH- and FSH plus IGF1-induced estradiol production	[141,170,171]
FGF7	Theca cells	FGF7 suppresses FSH-induced estradiol and progesterone synthesis	[142,149]
FGF9	Granulosa cells	FGF9 suppresses FSH plus IGF1-induced estradiol and progesterone synthesis and mRNA expression of *CYP19A1* and *FSHR*	[145,153,171]
FGF10	Theca cells and oocytes	FGF10 suppresses FSH-induced estradiol synthesis	[152]
FGF18	Theca cells	FGF18 suppresses FSH-induced estradiol and progesterone synthesis and mRNA expression of *CYP19A1*, *CYP11A1*, *FSHR*, *STAR*, *HSD3B1*, and *HSD17B1*	[150]

Based on observations of effects of FGFs and the RNA expression of their receptors in GC, it is clear that some of these intra-ovarian factors modulate the fate of follicles during ovarian folliculogenesis, at least in cattle. As previously mentioned, several FGFs decrease FSH- or FSH plus IGF1-induced estradiol secretion by GC in vitro, including FGFs 9, 10, 17, and 18 and, thus, suppress an important characteristic of the dominant follicle. The observation that the mRNA abundance of *FGF9* and *FGFR2c* is greater in GC of subordinate follicles further supports the hypothesis that this polypeptide is important to

stimulate GC proliferation during early folliculogenesis but serves as an anti-differentiation factor in GC of subordinate follicles in an autocrine manner [145,146,171]. Moreover, theca-derived FGF18 is considered a pro-atretic factor that induces the apoptosis of bovine GC [150,175]. Among other factors, it seems that IGF1, a pro-differentiation factor of GC [117,118], is important to keep levels of FGF9 and FGF18 low in bovine GC during GC differentiation [145,175].

4.3. Adipokines

Adipose tissue is a multifunctional organ that serves as a major energy reservoir and is involved in a wide range of physiological processes [176,177]. The adipose tissue secretes adipokines, which regulate several biological processes, including reproduction through endocrine actions [176,178–181]. To date, several adipokines are known to affect female fertility, as previously reviewed [178,180–183]. As circulating levels of adipokines change according to the nutritional and energetic status of female mammals [183–187], adipokines represent an important link between energy metabolism and female fertility, although further research is still required to fully unveil how energy metabolism affects ovarian function.

The effects of adipokines on ovarian function have been receiving attention of researchers, as the effects of novel adipokines keep being characterized. To date, several adipokines have been recognized to elicit actions in GC of mammals. Additionally, adipokines or their precursors, as well as their receptors, are synthesized by ovarian follicular cells (Table 2). Furthermore, mRNA expression of some adipokines and receptors change according to the stage of the reproductive cycle (Table 2). Discrepancies exist in reports of mRNA and protein expression of adipokines and their receptors in GC. Some of this variation between studies may be explained by possible differences in the stage of folliculogenesis when samples were collected, especially in cattle, because most follicular cells came from ovaries obtained at slaughterhouse without control of the estrous cycle. Further investigation is still necessary to fully unveil the impact of locally synthesized adipokines as autocrine and paracrine regulators of ovarian function.

Table 2. Expression of adipokines and their receptors in ovarian follicular cells.

Adipokine	Expression of Ligand or Receptor	Species	Reference
Adiponectin	*AdipoR2* mRNA is predominantly present in theca cells but also in granulosa cells and is greater in theca cells of larger follicles with no differences in expression in granulosa cells according to size of follicles.	Bovine	[188]
	AdipoR1 and *AdipoR2* mRNA is greater in granulosa cells of dominant than subordinate follicles.	Bovine	[189]
	mRNA expression of adiponectin is greater in granulosa cells of large follicles and in theca cells of small follicles, while *adipoR1* and *adipoR2* mRNA is expressed in granulosa and theca cells of large follicles.	Bovine	[190]
	Adiponectin and receptors adipoR1 and adipoR2 mRNA and protein expression are predominantly expressed in theca cells, but also in granulosa cells.	Murine	[191]
	AdipoR1 and AdipoR2 mRNA and protein are expressed in granulosa cells, but AdipoR2 expression is greater.	Human	[191]
	AdipoR1 and *AdipoR2* mRNA is expressed both in granulosa and theca cells.	Human	[192]

Table 2. *Cont.*

Adipokine	Expression of Ligand or Receptor	Species	Reference
Apelin	mRNA and protein expression of apelin and receptor is greater in granulosa and theca cells of large follicles than in cells of small follicles.	Bovine	[193]
	mRNA and protein expression of apelin and its receptor is expressed in granulosa and increases according to follicular size.	Bovine	[194]
	mRNA expression of apelin was not detected in granulosa cells and apelin receptor mRNA was greater in granulosa cells of large estradiol-inactive (subordinate) follicles in comparison to small subordinate and dominant follicle	Bovine	[195]
	mRNA expression of apelin and its receptor in granulosa cells does not change according to follicular size and estradiol levels in follicular fluid.	Bovine	[196]
	mRNA and protein expression of apelin and its receptor is expressed in granulosa and theca cells.	Human	[197]
Asprosin	*FBN1* mRNA [1] expression is greater in theca cells than in granulosa cells, and it varies in theca cells but not granulosa cells, according to the size of the follicle. mRNA expression of the asprosin receptor (OR4M1) is greater in granulosa cells than theca cells and is greater in both cells of small follicles in comparison to large follicles.	Bovine	[198]
	FBN1 mRNA is greater in granulosa cells of medium subordinate follicles than dominant follicles and other sizes of subordinate follicles; *OR4M1* mRNA is greater in granulosa cells of small subordinate follicles than dominant follicles and other sizes of subordinate follicles.	Bovine	[199]
Chemerin	Chemerin mRNA and protein expression is greater in granulosa cells of small follicles than of large follicles, whereas there is no influence of follicular size in expression of chemerin receptors (CMKLR1, GPR1, and CCRL2).	Bovine	[200]
	mRNA and protein expression of chemerin and its receptor, CMKLR1, is greater in granulosa cells than in theca cells.	Human	[201]
	Chemerin mRNA abundance is expressed in granulosa cells.	Murine	[202]
Irisin	*FNDC5* [2] and irisin receptors (*ITGAV* and *ITGB1*) mRNA is expressed by granulosa cells.	Bovine	[203]
Leptin	Leptin protein expression is greater in granulosa cells of subordinate than of dominant follicles, whereas no differences exist in protein expression of leptin receptor (LEPR) in granulosa cells according to size of follicles.	Bovine	[189]
	mRNA and protein expression of leptin and its receptor is detected in granulosa cells of preovulatory follicles.	Human	[204]
	mRNA and protein expression of leptin is greater in theca cells than in granulosa cells.	Murine	[205]
Resistin	Resistin mRNA is detected in granulosa cells.	Bovine	[206]
	Resistin mRNA and protein is detected in granulosa cells.	Human	[207,208]
	Resistin mRNA is not detected in granulosa cells.	Murine	[206]

Table 2. *Cont.*

Adipokine	Expression of Ligand or Receptor	Species	Reference
Omentin	INTL1 [3] mRNA is detected in granulosa–lutein cells.	Human	[209]
	INTL1 protein expression was observed in granulosa and theca cells. Omentin gene and protein expression in follicles changed throughout the estrous cycle.	Porcine	[210]
Visfatin	Visfatin mRNA and protein is expressed by granulosa cells.	Human	[211]

[1] Asprosin is a product of the cleavage of profibrilin 1, encoded by the gene *FBN1*. [2] Irisin is the product of the cleavage of precursor encoded by gene *FNDC5* [3]. Omentin is also described as intelectin1 (*INTL1*).

Several adipokines are known to regulate GC steroidogenesis, and these effects depend on species and interaction with other hormones. In bovine GC, the adipokines asprosin, resistin, visfatin, apelin, gremlin, leptin, adiponectin, chemerin, and irisin alter estradiol synthesis in vitro (Figure 1) [193,200,203,206,212–218]. In human GC, leptin decreased LH-induced estradiol synthesis, resistin suppressed FSH- and IGF1-stimulated estradiol production, and chemerin suppressed estradiol synthesis stimulated by IGF1, whereas visfatin and apelin enhanced estradiol synthesis stimulated by FSH and IGF1, respectively, in vitro [197,201,207,211,219,220]. In rat GC, leptin suppresses FSH plus IGF1-stimulated estradiol production while adiponectin and resistin enhance IGF1-stimulated estradiol production, but resistin suppresses estradiol synthesis in basal conditions [191,206,221].

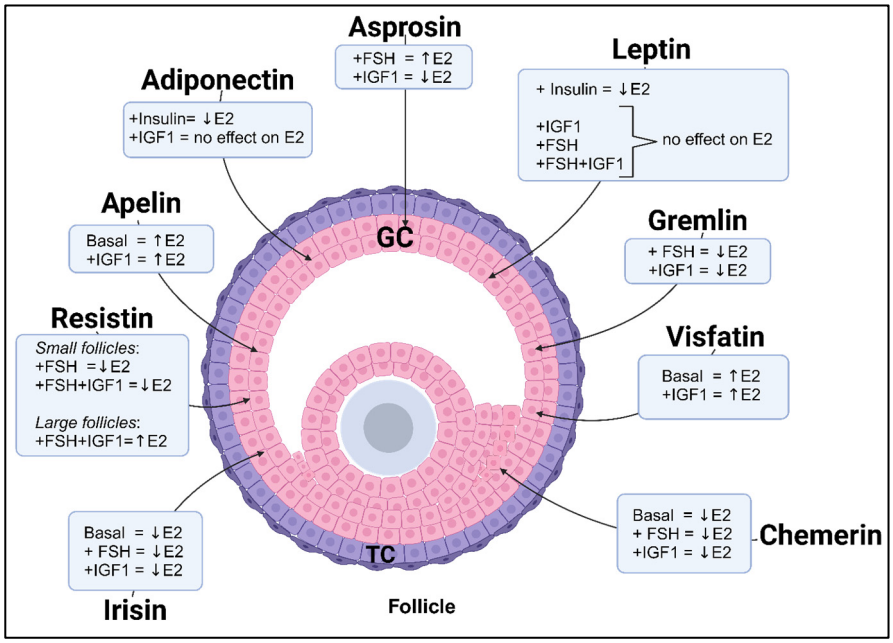

Figure 1. Effects of adipokines on bovine granulosa cells in vitro. The figure shows granulosa cells (GC) surrounding the oocyte and surrounded by theca cells (TC) within an ovarian follicle. A summary of effects of adipokines on bovine GC steroidogenesis in vitro is presented. E2 = estradiol; FSH = follicle-stimulating hormone; IGF-1 = insulin-like growth factor 1.

Due to their impact on GC functions, adipokines are likely to be important regulators of ovarian folliculogenesis. Adipokines that enhance in vitro estradiol synthesis in the presence of FSH or FSH plus IGF1, for example, may act as contributors to GC differentiation during dominance and the preovulatory stage, while adipokines that suppress estradiol production under the same conditions may be preventing this process. An example of adipokine that may act as an anti-differentiation factor in bovine GC is chemerin because it is a suppressor of estradiol synthesis, and its receptors are predominantly expressed in

small follicles [200]. Another example of adipokine that may be especially important to GC function during early folliculogenesis in cattle is asprosin; its receptor mRNA expression is greater in GC of subordinate than dominant follicles, it stimulates GC proliferation, and it enhances FSH-stimulated estradiol synthesis, whereas it suppresses IGF1-stimulated estradiol production by GC in vitro [199,218]. Still, the observation that the intrafollicular injection of asprosin increased the ovulatory rate of buffalo cows suggests that the actions of asprosin may be timely regulated, and further research is necessary to fully unveil its role in GC regulation and female fertility [222].

4.4. Factors Derived from Gastrointestinal Tract

Peptide hormones derived from the gastrointestinal tract are important regulators of energy metabolism (for reviews, see [223,224]). Recent studies have reported actions of these peptides on mammalian GC regulation. Ghrelin, a hormone known to be secreted by the stomach, has been reported to reduce estradiol and progesterone synthesis by human granulosa–lutein cells and estradiol synthesis by bovine GC in vitro [225,226]. Incretins, hormones derived from the intestine, have been shown to suppress FSH-stimulated progesterone, but not estradiol, in rat GC in vitro [227]. These findings highlight the importance of further research to elucidate how GC and other metabolic organs communicate to regulate female fertility in mammals.

5. Conclusions

GC orchestrate female fertility through autocrine, paracrine, and endocrine manners. The regulation of GC functions is crucial to determine the fate of ovarian follicles during folliculogenesis through the modulation of cell proliferation and the secretion of sex steroids. The specific role of several regulators of GC function requires further investigation for a complete understanding of how GC are affected by metabolism.

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