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REVIEW

New aspect on the regulation of in vitro oocyte maturation: role of the obesity, neuropeptides and adipokines

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Abstract

Oocyte quality determinants and nuclear and cytoplasmic maturation establish essential processes for fertilization and further development of the conceptus. Moreover, female fertility is strongly dependent on the metabolic status of the organism. Numerous sources indicate that obesity impairs ovarian function including oocyte physiology by inhibiting nuclear maturation, stimulating lipotoxicity and inflammation, enabling cumulus cells apoptosis, promoting reactive oxygen species formation and ultimately imposing pathogenic effects on mitochondria leading to infertility. Whereas, the number of overweight and obese individuals has reached alarming levels over the past decades, what is more, by 2030, the prevalence of overweight and obesity might reach 65.3% in adults in China and 78% in the USA. Thus, relationships between reproduction and metabolism are being intensively studied to prevent obesity-induced infertility. The metabolic markers of oocyte condition and function are adipokines and neuropeptides, which regulate food intake, lipid and glucose metabolism, insulin resistance and impart significant influences on reproduction. Thus, in this review, we focus on interrelationships between obesity, oocyte maturation and the role of selected neuropeptides and adipokines including leptin, adiponectin, kisspeptin, nesfatin-1, phoenixin, visfatin, chemerin and vaspin.

Keywords Oocyte maturation · Obesity · Adipokines · Neuropeptides

Introduction

Due to the increasing incidence of infertility caused by female and male factors, a rising number of couples are deciding to undergo assisted reproduction. Thus, improvements and advances in this procedure, both clinical and laboratory, have introduced cumulative delivery rate as a measure of the overall efficacy of in vitro fertilization (IVF), a procedure which gradually improved since its inception [1]. However, not all patients can undergo the ovulation stimulation procedure, that is part of IVF, therefore, the solution is in vitro oocyte maturation. Nevertheless, this

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procedure is still insufficient in humans and some domestic animals like pigs and need improvements [2, 3]. In addition to infertility, obesity is a common problem nowadays, 40% of adults worldwide are overweight or obese [4]. Obesity is not only linked to cancer, hypertension and cardiovascular diseases [5], but also negatively affects reproduction leading to infertility by acting upon the hypothalamus-pituitary-ovarian (HPO) axis function [4]. Besides, obesity is also a risk factor for proper oocyte maturation; oocytes collected from obese females showed low quality in both human and animal models [6–10]. For example, decreased oocyte size, oolemma diameter and zona pellucida thickness were noted in the oocytes collected from obese women [11]. It is a well-known fact that oocyte nuclear maturation and meiosis resumption, chromatin condensation and cytoplasm maturation are entirely dependent on proper oocyte metabolism, which is disrupted in obesity [12]. Thus factors linking oocyte maturation with obesity, fat storage or metabolism are being intensively studied nowadays and the goal of this study is to prevent obesity-induced infertility by understanding its mechanism on the oocyte level. Briefly, literature data clearly shows that white adipose tissue acts as an endocrine gland that produces biologically active adipokines, the secretion of which is dependent on fat content, and which have a pleiotropic function in the body including regulation of reproduction [13]. Also, in mammals and even fishes neuropeptidergic signalling is essential for the regulation of reproduction and energy metabolism [14, 15]. Thus, in this review, we described the link between oocyte maturation, obesity and adipokines/neuropeptides. This data may help, in the near future, to restore fertility in obese women, and will improve the in vitro oocyte maturation procedure itself.

Clinical aspects and future perspectives

It is crucial to improve our knowledge regarding how factors influence oocyte maturation depending on the metabolic conditions of the organism and to understand the molecular mechanisms of their direct actions to preserve and/or improve fertility. Particularly taking in mind the problem of the increasing number of obesity cases, and the fact that obesity consistently leads to infertility due to its direct effects on an oocytes condition [16]. Within the past few decades, success rates following IVF treatment have improved significantly, and the introduction of ovarian stimulation has played a vital clinical role [1]. However, there is still insufficient use of in vitro maturation of oocytes as a method to obtain viable offspring in humans and domestic animals [2, 3]. In vitro maturation of oocytes is a good alternative for patients at risk of ovarian hyperstimulation syndrome (i.e. in people with polycystic ovarian syndrome (PCOS)), or those seeking urgent fertility preservation, when controlled ovarian stimulation is not feasible and after recovery from cancer [2]. Additionally, this method reduces gonadotropin stimulation as well as the treatment time and costs [2]. Nevertheless, the overall quality of oocytes derived from the current in vitro maturation protocols is low [17]. Thus, a comprehensive understanding of the distinct mechanisms of oocyte maturation is crucial for obtaining more viable oocytes through in vitro methods. The available data regarding the actions of adipokines and neuropeptides will provide new, extremely valuable information on the molecular control of female oocyte functions to improve oocyte maturation in the context of obesity or to provide new molecular targets for pharmacological intervention. In the long term, this knowledge will contribute to the advancement of more effective methods of modifying in vitro oocyte maturation and maintaining energy homeostasis in human and farm animals.

Obesity

Worldwide, the number of individuals who are overweight and affected by obesity has increased alarmingly over the past decades. Moreover, by 2030, the prevalence of overweight and obesity in the adult population might reach up to 65.3% in China, and by 2035, up to 78% in the USA [18, 19]. Obesity occurs when too much energy in the form of fat is stored in the body. According to the World Health Organization (WHO 1997), obesity is defined as a body mass index (BMI) greater than 30 kg/m^2. A BMI higher than 25 kg/m^2 describes being overweight. Obesity is caused mainly by an excess intake of foods high in calories, reduced exercise and a sedentary lifestyle creating an imbalance in overall health. Nevertheless, the aetiology of this disease is complex and involves physiological, genetic, environmental, social, psychological, economic and even political factors [20]. For example, endocrine disruptors—industrially produced substances that occur in multiple sources like preservatives, flame oxidants and fertilisers—can affect the endocrine function and may also contribute to the development of obesity [21].

Obesity negatively influences fertility through its direct effects on the function of the HPO axis. Women with obesity are three times more likely to experience infertility than women with a normal BMI [22]. In one study, women with a BMI > 30 kg/m^2 showed a 2.7-fold increased risk of infertility and a 25–37% increased risk of miscarriages [16]. Women with obesity showed a decreased amplitude of luteinizing hormone (LH), increased insulin levels and enhanced insulin resistance (IR) [23], which promotes the synthesis of androgens. These androgens can be aromatized into estrogens, which create negative feedback to the hypothalamus and pituitary, and consequently lead to menstrual abnormalities and ovulatory dysfunctions linked with the development of PCOS, which causes to anovulation

and infertility [24]. In turn, the increase of androgens due to PCOS stimulates lipolysis and impairs adipocyte differentiation, insulin signalling and the generation of adipokines [25]. Moreover, the resulting decreased fertility characterized by lower implantation, higher miscarriages and higher pregnancy complication rates are mainly related to endocrine and metabolic disorders. These disorders also may be linked to disrupted steroid metabolism and adipokines secretion [22], which directly regulates follicular growth, ovulation, corpus luteum function and early embryo development. Obesity also causes considerable changes in uterine receptivity and markers of decidualisation and implantation, leading to endometrial dysfunction [26]. Finally, maternal obesity leads to fetal overgrowth and a higher frequency of large-for-gestational-age infants [27]. Considering its harmful effect, the mechanisms by which obesity affects female fertility have been intensively studied on many levels, including the germ cell level, to prevent the development of infertility.

Neuropeptides and adipokines as a marker of metabolic conditions

There is a close relationship between obesity and the plasma levels of neuropeptides and adipokines, which indicates the role of these proteins in obesity development and regulation of obesity-related disorders like inflammation, insulin resistance (IR) and diabetes [28]. These proteins are expressed in numerous tissues and have pleiotropic functions in the body, but they are especially involved in the regulation of energy metabolism. It indicates that adipokines and neuropeptides act as a link between fattening and whole-organism physiology including also reproduction, which is directly and negatively influenced by obesity [29]. Briefly, neuropeptides and their receptors are mainly expressed in the brain (where they ten regulate food intake and gonadotropins secretion [29]), while adipokines and their receptors are mainly expressed in adipose tissue (where regulates adipose tissue differentiation [28]); however, these molecules are also present in peripheral tissues including the muscles, heart, stomach, intestine, liver, kidney, spleen, endocrine tissues (e.g. pancreas), thymus and reproductive tract (e.g. hypothalamus, pituitary, ovary, testis, uterus and placenta) of multiple species, thus adipokines and neuropeptides act on endocrine, paracrine and autocrine functions that collectively help to regulate reproduction [29].

The levels of neuropeptides and adipokines are strictly correlated with body weight and energy metabolism. For example, obese mice had reduced expression of the kisspeptin (a neuropeptide that induces sexual maturation, and also functions to inhibit food intake) gene. When considering the significant number of kisspeptin neurons normally found in the average hypothalamus, this also indicates that obesity can affect reproduction on the central, hypothalamus level by affecting kisspeptin synthesis [30]. Similarly, male mice fed a high-fat diet showed lower nesfatin-1 in the serum, the neuropeptide, which has a negative effect on food intake, indicating that neuropeptide levels are a good predictor of fattening in both sexes [31]. On the other hand, in humans PNX (neuropeptide with ability to induce adipogenesis) serum levels correlated with BMI and increased as body weight increased [32]. Exercise-induced weight loss has been connected to decreased circulating visfatin levels (an adipokine with positive effect on insulin secretion) [33], which indicates that these proteins respond in real time to the fat content in the body. Also, insulin-enhanced anti-inflammatory adiponectin level in human adipose tissue [34] and anorexic leptin mRNA expression in rat adipocytes [35, 36], also directly link these hormones to IR and diabetes that accompany obesity. Obesity is often linked to chronic inflammation: proinflammatory cytokines can upregulate anti-inflammatory chemerin serum levels in humans [37, 38]. In mice and humans, adipogenic vaspin mRNA expression in visceral adipose tissue and serum concentration was increased with IR, obesity and elevated leptin levels, and decreased with weight loss [39]. Therefore, the level of adipokines and neuropeptides in the blood is a good predictor of all metabolic disorders occurring during obesity and leading to poor body condition, including the disorders related to fertility. Taking into account that the levels of some neuropeptides/adipokines are increased and the levels of others are decreased in obesity, their actions should be considered together since such synthesis and interactions may be crucial to ensuring homeostasis of the entire body. For example, any lack of specific hormones related to a physical activity causes an increased level of other hormones to produce a similar physiological effect.

These molecules are not only influenced by the metabolic status of the organism, but also are directly linked to its regulation. Studies in mice have shown that injection of kisspeptin-10 [40], nesfatin-1 [41] and leptin [42] reduced the amount of food consumed, which indicates that they can also regulate body weight via the neuronal pathway by influencing the hunger and satiety centers. Research on the murine preadipocytes 3T3-L1 cell line revealed that PNX-14 directly enhanced adipogenesis [43]. Moreover, adipokines also directly influence the causes and metabolic conditions accompanying obesity. For example in skeletal muscles of humans and mice, adiponectin promoted insulin sensitivity and fatty acid oxidation [44, 45] and acted as an anti-inflammatory factor [46]. Moreover, visfatin exerted a crucial role in the stimulation of insulin secretion in pancreatic islets in the response to glucose in mice [47]. Chemerin decreased recruitment of neutrophils and macrophages to inflammatory sites by peritoneal macrophages in mice [48, 49],

similar to vaspin in 3T3-L1 cells [50], which also resulted in adipogenesis progression and lipid accumulation [51]. These data indicated that adipokines and neuropeptides are directly related to obesity and at the same time can have both a positive and negative impact on the progression of obesity and its accompanying diseases/conditions. Further research using high-throughput methods such as transcriptome, proteome or metabolome analysis is necessary to understand the relationships between function of adipose tissue hormones in the anti-obesity response, taking into account that they are not only involved in food intake, but also insulin resistance and inflammation regulation that accompany obesity.

Finally, neuropeptides and adipokines have been linked to the regulation of reproduction via the HPO axis by influencing gonadotropins secretion and ovarian function, including steroidogenesis, folliculogenesis, the proliferation of ovarian cells and oocyte maturation. Kisspeptin-54 has been shown to activate gonadotropin-releasing hormone (GnRH) neurons directly by stimulating gonadotropins secretion in mice [52, 53], thus its decreased level in obesity [30] may be linked to hormonal disturbances that are noted in obesity-related infertility. Nesfatin-1 decreased GnRH secretion in fish [54] and significantly increased LH and follicle-stimulating hormone (FSH) levels in female rats [55]. PNX-20 stimulated GnRH secretion in mice [56] and gonadotropin secretion in male rats [57]. Adipokines also directly regulate hypothalamic function, mainly GnRH secretion. Briefly, leptin significantly induced *GnRH* mRNA expression in humans [58], thus an elevated adipokine in obesity [30] may have a beneficiary effect on hypothalamus pulsatory activity during obesity as it may compensate the lack of kisspeptin, while adiponectin acted in an opposite manner in the murine GT1-7 cell line [59]. Adipokines can also directly influence LH and FSH secretion from the pituitary. For example, leptin increased LH and FSH secretion in rats [60], providing confirmation of its action described in the hypothalamus [53], and adiponectin stimulated LH secretion in pigs [61], similar to visfatin [62] and chemerin [63] in the follicular phase of the porcine oestrous cycle, and has indicated the positive role of adipokines in ovulation induction. Finally, in the ovary, there is found kisspeptin overexpression enhanced proliferation and inhibited apoptosis of human KGN cells, a granulosa cell (Gc) line [64], similar to nesfatin-1 in porcine Gc [65]. Recent studies have also shown the important function of PNX-14 in the porcine ovary; it increased Gc proliferation [66] and progesterone (P_4) secretion by luteal cells [67]. Adiponectin increased the secretion of P_4 and 17β-oestradiol (E_2), which is necessary for ovarian follicle growth before ovulation, in the presence of FSH in porcine ovary [68], similar to visfatin in human Gc [69] and vaspin in porcine [70] and human [71] ovarian cells, all of which indicated that the lack of this protein may leads to disruption in folliculogenesis and ovulation. Leptin inhibited steroidogenesis in human Gc and theca cells (Tc; [72, 73]) and decreased the number of ovulated oocytes [74]. Chemerin inhibited P_4 and E_2 secretion in human Gc [75] and promoted the proliferation and migration of ovarian cancer cells in human cell lines [76], which indicated a negative action of this protein in ovarian function and related oocyte maturation. In porcine luteal cells, vaspin regulatory actions involve activation of 78-kDa glucose-regulated protein (GRP78) and mitogen-activated kinase (MAPK), leading to prostaglandin E synthesis and positive regulation of angiogenesis [77]. Based on these findings, adipokines and neuropeptides have a direct impact on the regulation of reproductive function in various species. Interestingly, there is no linear relationship between the level of adipokines and neuropeptides in obesity, their impact on food intake and adipogenesis, and their role in reproduction. We cannot consider these substances as beneficial or harmful in both aspects. However, there is a relationship in the regulation of obesity and the level of neuropeptides itself, e.g. the level of kisspeptin is lower in obesity [30] and kisspeptin itself reduces food intake [40], which indicates that the lack of kisspeptin will worsen obesity. Similarly, the level of PNX is higher in obesity [32] and this additionally stimulates adipogenesis [43], at the same time both kisspeptin [52] and PNX [56] stimulate GnRH secretion and accelerate sexual maturation. Therefore, it seems that the only sensible solution is to test these hormones for reproductive functions, always using control and obese animals to learn their role in both conditions, however, this is a gap in current knowledge that needs to be filled. As mentioned above, due to their different, often opposite effects on reproduction, it would be worthwhile to test their common action, or at least the action of opposing adipokines/neuropeptides under different metabolic conditions.

Obesity and oocyte maturation

One of the most important processes for future fertilisation and propagation of a species is oocyte maturation. However, oocytes collected from obese females showed low quality as described in humans and mice [6–10], as well as domestic animals including mares [78] and pigs [79]. For instance, oocytes from obese women were significantly smaller including oocyte and oolema diameter and zona pellucida thickness compared with those oocytes from women of normal weight [11]. It is well known that the three steps for oocyte maturation: oocyte nuclear maturation and meiosis resumption, chromatin condensation and cytoplasm maturation are all necessary to maintain proper fertility. These steps are entirely dependent on oocyte metabolism and linked to proper lipid storage and mitochondrial function in parallel with the proper function and metabolism of cumulus cells

(CCs) [12]. Appropriate oocyte metabolism provides energy for meiotic progression, balancing intracellular redox and osmotic potential, and provides building blocks for oocyte growth. Indeed, the accumulation of lipids in oocyte and surrounding CCs culminated in lipotoxicity (harmful effect caused by the accumulation of excess lipids in non-adipose tissues, which disrupts normal cellular function) and inflammation, CCs apoptosis, endoplasmic reticulum (ER) stress (occurs when the ER a cell organelle responsible for protein folding and processing, becomes overwhelmed or dysfunctional, leading to the accumulation of misfolded or unfolded proteins leading to cell damage or death)and reactive oxygen species (ROS) formation in cumulus-oocyte complex (COCs), and dysfunction of oocyte mitochondria [80], leading to infertility. Besides, proinflammatory signalling was overstimulated in the ovaries of obese mice; consequently, there was a depletion of fully grown preovulatory follicles [81]. Similarly, oocytes collected from obese human individuals were characterized by increased expression of proinflammatory and oxidative stress-related transcripts but had lower levels of fat metabolism genes [82]. When focusing on oocyte nuclear maturation and chromatin condensation, studies have shown that 39.45% of oocytes from obese mice completed germinal vesicle breakdown (GVBD) compared with 89.46% in control subjects [83]; moreover, polar body extrusion was inhibited in oocytes from obese mice [83–85]. There were more abnormally arranged spindles and a higher percentage of non-aligned chromosomes in obese mouse groups [86–88]. Luzzo et al. [88] reported high rates of meiotic aneuploidy characterised by disorganised spindles and chromosomes improperly aligned on the metaphase plate in obese mice.

Poorer oocyte quality in the context of obesity is linked to impaired energy metabolism and mitochondrial activity. In a pig model, high palmitic acid levels were strictly linked to obesity and led to mitochondrial dysfunction, denoted by high ROS and low adenosine triphosphate (ATP) levels in oocytes [79]. Oxidative stress–induced mitochondrial damage leads to a compensatory response of increased mitochondrial biogenesis and fission [12]. For example, there were more mtDNA copies in germinal vehicle (GV) oocytes from obese mice, as confirmed by increased expression of the mitochondrial biogenesis and fission markers peroxisome proliferator-activated receptor-gamma coactivator and dynamin-related protein [83]. Similarly, the expression of mitochondrial transcription factor A and nuclear respiratory factor 1 (nuclear genes that encode mtDNA transcription factors) were elevated in metaphase II (M2) [89], while the mitochondrial membrane potential was lower in both GV and M2 oocyte [80, 90]. Interestingly, in mice, Ou et al. [91] showed increased mitochondrial membrane potential in GV oocytes and decreased membrane potential in M2 oocytes during IR, which often accompanied obesity. All these data clearly confirm that mitochondrial activity is highly disrupted in oocytes from obese individuals.

Biochemical analyses have also provided interesting results regarding microtubule assembly and chromosome movement during meiosis requires ATP [92]. Obesity is linked to increased androgen levels, which reduce the citrate content, glucose-6-phosphate dehydrogenase activity and lipid levels [93], leading to abnormal Krebs cycle and pentose phosphate pathway metabolism. As literature data shows glucose levels were elevated in obese mice [94], while mitochondrial dysfunction was closely linked to elevated glucose [95–97]. Consequently, oocytes from obese mice were more oxidised and generated more ROS, while ER stress was described to decrease CCs expansion and led to poor pre-implantation development rates [98, 99]. In a culture of obese mouse oocytes, treatment with the ER stress inhibitor salubrinal reversed the reduced oocyte quality by increasing the levels of mitochondrial replication factors—mitochondrial transcription factor A and dynamin-related protein—as well as mtDNA level [92]. To summarise, obesity negatively influences oocyte maturation by affecting both nuclear and cytoplasmic maturation thus it is necessary to find the molecular target linking obesity with fertility to restore reproductive efficiency in individuals with obesity (Fig. 1).

In the following chapters, we focus on describing the expression and role of adipokines and neuropeptides in in vitro oocyte maturation because these molecules are marker proteins of obesity and metabolic status. Briefly, the level of neuropeptides and adipokines changes with the amount of adipose tissue, and they themselves influence the regulation of metabolism including the influence on processes that negatively affect oocyte function during obesity such as lipids accumulation, ROS formation and ER stress in different tissue especially in the reproductive tract [28, 29]. However, the number of studies comparing the level or role of neuropeptides and adipokines in obese and normal-weight oocytes is very limited, but if such data exists, it is discussed in the following chapters.

Role of select neuropeptides on oocyte maturation

Expression of kisspeptin in the oocyte and its effect on oocyte maturation

Previous literature data indicated that kisspeptin is an inductor of reproduction; its main action is linked with stimulation of GnRH secretion and sexual maturation [52], but kisspeptin also is able to act directly on the ovary and stimulate Gc growth [99]. Kisspeptin mRNA and protein expression has been reported in pig [100], rat [101], mouse [102], dog

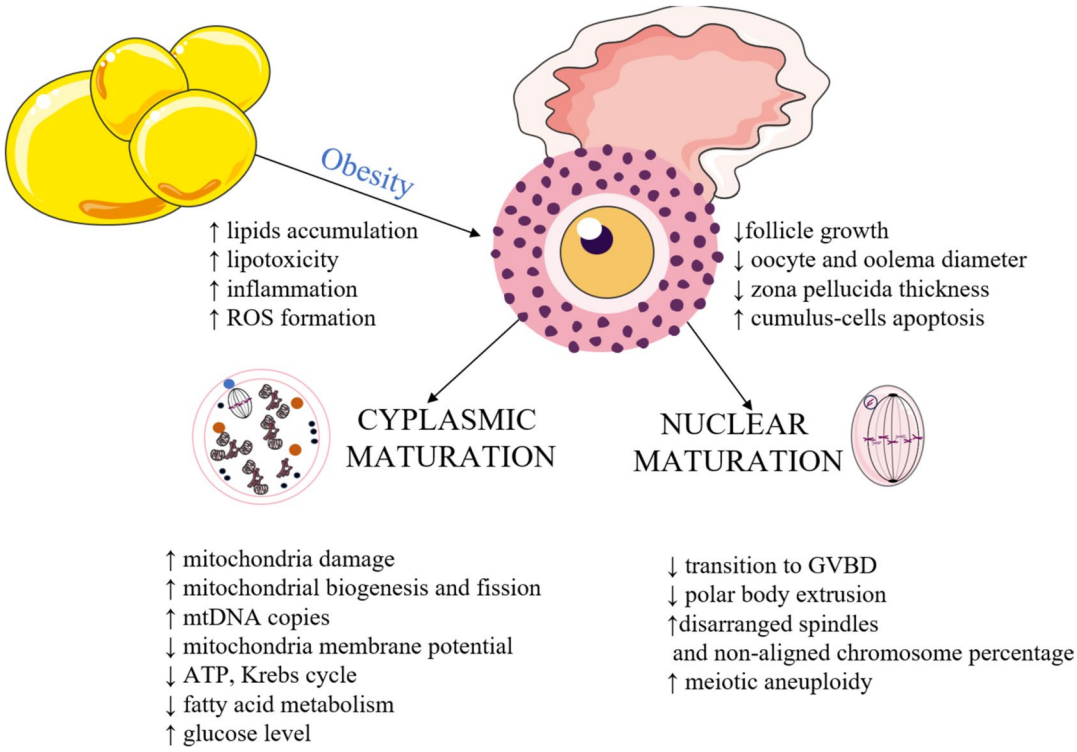

Fig. 1 Effect of obesity on oocyte maturation. ROS, reactive oxygen species; GVBD, germinal vesicle breakdown; ↑, stimulation; ↓, inhibition

[103], cat [104] oocytes and in human CCs [105, 106]. Expression of the kisspeptin receptor KiSS1-derived peptide receptor (GPR54) has been reported in dog oocytes [103]; in mouse [102] and pig [100] COCs; and in humans CCs [105]. In a recent study, the mRNA expression of kisspeptin and its receptor did not differ at different stages of nuclear and cytoplasmic maturation of human oocytes during standard in vitro maturation [107]. However, in a porcine model, during 44 h of oocyte maturation, kisspeptin expression began after 22–26 h, while the receptor showed similar expression throughout the entire process [100] (Fig. 2). The differences between pigs and women in the expression of kisspeptin may depend on the lipid content in oocytes, which are more abundant in pigs [108] and may influence kisspeptin expression by secretion of multiple substances, but this requires further research.

In another study, kisspeptin-10 at 1 and 10 nM directly affected standard oocyte maturation by stimulating the intracellular release of calcium (Ca^{2+}) and activation of MAPK in rats [109]. In sheep, 5, 10 and 15 ug/mL kisspeptin stimulated standard oocyte maturation through the expansion of CCs and extrusion of the first polar body [110]. In pigs, kisspeptin at dose 10^{-6} M stimulated standard nuclear maturation of oocytes by increasing the expression of the maturation marker genes growth differentiation factor 9 and bone morphogenetic protein 15 [100]. In a fish model, stimulation with human kisspeptin and a combination of human and fish kisspeptin increased the percentage of mature oocytes [111]. Lack of kisspeptin signalling also impairs oocyte maturation, as shown in in vivo mouse models [112]. Additionally, GPR54 knockout mice showed a premature lack of ovulation, which progressed with age and could be reversed by gonadotropin stimulation [112]. Besides, an in vivo study showed that kisspeptin-54 injection promoted oocyte maturation in humans [113]. These data clearly confirm the important role of kisspeptin in oocyte maturation: it is species and dose-independent. Hence, kisspeptin may represent a potential drug target to restore fertility in women especially in obesity in which the kisspeptin level is lowered [78] and requires supplementation not only to decrease food intake [40] but also to improve reproduction (Table 1).

Expression of nesfatin-1 in the oocyte and its effect on oocyte maturation

The presence of nucleobindin-2 (*NUCB2*) mRNA, the precursor of nesfatin-1, and nesfatin-1 protein expression were observed in mouse ovary, Tc, Gc and oocytes [114], and in rat oocytes [115]. Interestingly, Cao et al. [116] reported nesfatin-1 protein in porcine COCs and decreased *NUCB2* mRNA with the transition from small to large follicles for both COCs and Gc. Gonzalez et al. [117] described nesfatin-1 protein expression in CCs of zebrafish (Fig. 2).

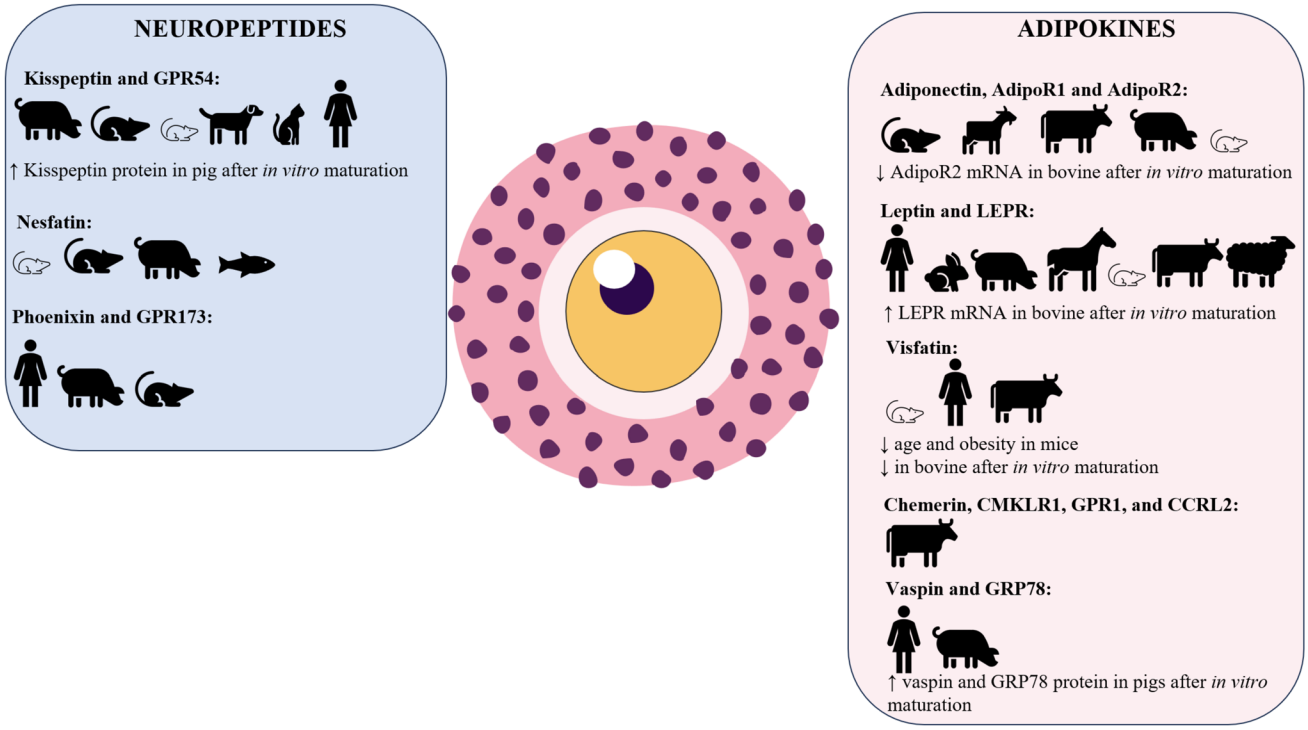

Fig. 2 Expression of neuropeptides and adipokines in cumulus-oocyte complexes. Rodent hollow shape, mice; rodent full shape, rat

Table 1 Effect of neuropeptides on oocytes maturation. MAPK, mitogen-activated kinase; CCs, cumulus cells; GDF9, growth and differentiation factor 9; BMP15, bone morphogenesis factor 15; GVBD, germinal vesicle breakdown; M2, metaphase 2; ROS, reactive oxygen species; JAK/STAT3, Janus kinase; PRKAA1, AMP activated kinase; ↑, stimulation; ↓, inhibition

Species	Dose	Effect
Kisspeptin		
Rat	1 nM and 10 nM	↑ intracellular release of Ca^{2+} via MAPK [109]
Sheep	5, 10 and 15 ug/mL	↑ CCs expansion, extrusion of the first polar body [110]
Pig	10^{-6} M	↑ maturation markers GDF9 and BMP15 level [100]
Mice	knockout	↓ oocyte maturation [112]
Human	1.6 nmol/kg, 3.2 nmol/kg, 6.4 nmol/kg or 12.8 nmol/kg	↑ M2 oocytes [113]
Nesfatin-1		
Pig	1, 10 and 100 ng/mL	↑ nuclear and cytoplasmic maturation [116]
Zebrafis h	40 and 50 ng/mL	↓ GVBD oocytes [54]
Zebrafish	10 ng/mL	↓ GVBD oocytes [117]
Phoenixin		
Zebrafish	10 and 100 ng/mL	↑ GVBD oocyte and vitellogenin mRNA level [119]
Mice	-	↑ number of ovulated oocytes with a higher level of maturation [118]

The studies conducted by Cao et al. [116] showed that nesfatin-1 at doses 1, 10 and 100 ng/mL increased porcine nuclear and cytoplasmic maturation. In contrast, Rajeswari et al. [54] reported that nesfatin-1-like peptide (NLP) delayed oocyte maturation in zebrafish, denoted by a decrease in the percentage of GVBD oocytes. Additionally, 10 ng/mL nesfatin-1 decreased the number of GVBD oocytes in zebrafish [117]. These data clearly indicate the species-dependent action of nesfatin-1 on oocyte maturation and its similarities with NLP. To check this species-dependent phenomenon, it would be worth knowing the level of nesfatin-1 and other interfering metabolomic hormones in fish in various metabolic states (Table 1).

Expression of PNX in the oocyte and its effect on oocyte maturation

PNX and its receptor G protein-coupled receptor 173 (GPR173) gene and protein expression has been noted in human (PNX-20; [118]) and porcine (PNX-14) oocytes and CCs [66]. Additionally, PNX-20 expression has been described in the rat ovary, including oocytes [120] (Fig. 2).

There is not a lot of data about the action of PNX on oocyte maturation. In zebrafish oocytes, 10 and 100 ng/mL PNX-20 increased the percentage of GVBD oocytes, oocyte maturation and vitellogenin mRNA expression [119]. Besides, PNX-20 significantly increased the follicular area in a mouse ovarian tissue culture model, leading to an increased number of ovulated oocytes with a higher level of maturation [118]. These data indicate the positive role of PNX on oocyte maturation but require further examination, especially considering that there is no data about the action of PNX-14, which is also expressed in COCs. This data and positive effect of PNX on GnRH secretion [56], as well as its elevation in increased adiposity [32] suggest a direct compensatory effect of PNX on reproduction in obesity (Table 1).

Role of select adipokines on oocyte maturation

Expression of adiponectin in the oocyte and its effect on oocyte maturation

The gene and protein expression of adiponectin and its receptors adiponectin receptor 1 and 2 (AdipoR1 and AdipoR2) have been confirmed in rat [68], goat [120] and cow [121, 122] oocytes. On the other hand, in mouse oocytes, only *AdipoR1* and *AdipoR2* gene expression was noted [123], while in pigs, ADIPOR1 and ADIPOR2 protein expression was described in CCs and oocytes from small and large follicles, with higher expression in small follicles [124], however, the presence of receptors indicates that exogenous adiponectin can exert its effects. Additionally, Maillard et al. [122] noted that *ADIPOR2* gene expression was lower in bovine oocytes and CCs that had been standard in vitro matured for 24 h compared with immature oocytes and CCs (Fig. 2).

In a pig model, 30 µg/mL adiponectin increased the number of prophase I of meiosis (M1) or M2 oocytes during standard in vitro maturation obtained from large follicles through MAPK pathway activation [124]. In goats, the administration of 5 or 10 µg/mL adiponectin was associated with a reduction in the proportion of oocytes blocked at the GV and GVBD stages and increased the number of M1 and M2 oocytes; this effect was also mediated through the MAPK pathway during standard in vitro maturation [120, 125]. In the context of mouse oocytes, Richards et al. [123] identified positive correlations between AdipoR1 expression and the occurrence of M2 oocytes. Moreover, synergistic treatment with 20 µg/mL adiponectin and FSH enhanced the conversion of oocytes to the M2 stage in standard in vitro oocyte maturation procedure. Conversely, Maillard et al. [122] observed the opposite effect: 10 µg/mL adiponectin inhibited the progression of bovine oocytes to the M2 stage during standard in vitro maturation. Taken together, these data indicate that adiponectin promotes in vitro oocyte maturation across almost all studied species except cows, which may indicate that this adipokine has a species-dependent action. Moreover, the reduction in adiponectin levels observed in obesity [34] may be the result of the poorer quality of oocytes observed in obese people [6], given adiponectin positive effect on their maturation (Table 2).

Expression of leptin in the oocyte and its effect on oocyte maturation

Leptin and leptin receptor (LEPR) gene and protein expression have been described in oocytes collected from women [126], rabbits [127], pigs [128] and horses [129, 130]. In mouse oocytes, only leptin protein has been detected [131–133], but *Lepr* mRNA expression has been described [134, 135]. Furthermore, in bovine oocytes, van Tol et al. [136] noted leptin and *LEPR* mRNA expression, while Panda et al. [137] confirmed *LEPR* mRNA expression in COCs. Additionally, *LEPR* mRNA expression was upregulated in bovine COCs during maturation [136]. Macedo et al. [138] described the protein abundance of leptin and LEPR in sheep oocytes. Such a broad description of the presence of leptin in oocytes of various species indicates that it is a key and conserved hormone necessary for its maturation (Fig. 2).

Supplementation of exogenous leptin at concentrations ranging from 1 to 100 ng/mL enhanced the percentage of rabbits' oocytes in the M2 stage through the Janus kinase and MAPK signalling pathways during standard in vitro oocyte maturation [139]. Using the same standard in vitro oocyte maturation in goats, 10 and 100 ng/mL leptin decreased the proportion of GV and GVBD oocytes, with no impact on the percentage of M1 oocytes stage, but showed an increase in M2 oocytes [140]. Craig et al. [128] noted that in pigs, 10 and 100 ng/mL leptin enhanced meiotic maturation by increasing the percentage of M2 oocytes and cytoplasmic maturation, as evidenced by elevated cyclin B1 protein expression during standard in vitro oocyte maturation. Similarly, Kun et al. [141] noted that 10 and 100 ng/mL leptin increased the percentage of porcine oocytes in the M2 stage in standard oocyte in vitro maturation. In horses, Consiglio et al. [129] reported that 100 ng/mL leptin enhanced meiotic maturation in expanded-cumulus oocytes during rescue

Table 2 Effect of adipokines on oocyte maturation. MAPK, mitogen-activated kinase; CCs, cumulus cells; GVBD, germinal vesicle breakdown; M2, metaphase 2; ↑, stimulation; ↓, inhibition

Species	Dose	Effect
Adiponectin		
Pig	30 µg/mL	↑ meiotic maturation, M2 oocytes via MAPK pathway [124]
Goats	5 and 10 µg/mL	↑ M2 oocytes via MAPK pathway [120, 125]
Bovine	10 µg/mL	↓ M2 oocytes [122]
Mice	20 µg/mL	↑ M2 oocytes [123]
Leptin		
Rabbit	1 to 100 ng/mL	↑ M2 via JAK2/STAT3 and MAPK signaling pathways [139]
Goats	10 and 100 ng/mL	↓ GV and GVBD oocytes, ↑ M2 oocytes [140]
Pigs	10 and 100 ng/mL	↑ M2 oocytes, cytoplasmic maturation, cyclin B1[128, 141]
Mare	100 ng/mL	↑ meiotic maturation [129]
Sheep	10, 50, 100 ng/mL	↑ M2 oocytes, glutathione level, mitochondrial activity [142]
Mice	100 ng/mL	↑ GVBD, first polar body extrusion, and the percentage of M2 oocytes via MAPK pathway [132, 133]
Buffalo	10 ng/mL	↑ M2 oocytes [137, 143]
Prepubertal bovine	1000 ng/mL	↑ TUNEL-positive cells [145]
Bovine	1–100 ng/mL	↑ M2 oocytes [146]
Bovine	1 and 10 ng/mL	↑ M2 oocytes, ↓ TUNEL-positive cells [147]
Visfatin		
Mice	5–500 ng/mL	↑ oocyte developmental competence [154]
Mice	Knockout	↑ ROS, ↓ membrane potential, ATP level [150]
Pigs	Knockout	↓ oocyte maturation, spindle formation, CCs expansion [155]
Chemerin		
Bovine	100, 200, 400 ng/mL	↓ oocytes maturation via CMKLR1 and MAPK pathway [156]
Vaspin		
Pig	1 ng/mL	↑ M2 oocytes, P4 level via MAPK and PRKAA1 pathway [158]

in vitro maturation. In sheep, 10, 50 and 100 ng/mL leptin increased the proportion of M2 oocytes in standard in vitro oocyte maturation [142]. At a dose of 25 ng/mL, there were enhanced antioxidant glutathione levels and mitochondrial activity in sheep oocytes during in vitro maturation, which was performed in oocytes derived from in vitro grown follicles [138]. In mice, 100 ng/mL leptin increased GVBD oocytes, first polar body extrusion and the percentage of M2 oocytes through the MAPK signalling pathway during standard in vitro maturation [133], and increased the percentage of GVBD oocytes [132]. In buffalo, 10 ng/mL leptin increased the percentage of M2 oocytes during standard in vitro oocyte maturation [137, 143]. Interestingly, oocytes from cows with higher circulating leptin levels exhibited more active mitochondria and a higher lipid content than those from cows with lower leptin levels [144]. Cordova et al. [145] found that leptin at 1000 ng/mL delivered during in vitro maturation of oocytes from prepubertal calves increased the number of TUNEL-positive cells and reduced B-cell lymphoma 2-associated X-protein and tumor protein p53 mRNA expression compared with the control subjects. The two aforementioned studies indicate the negative effect of leptin on oocyte condition during standard in vitro oocyte maturation. On the other hand, Jia et al. [146] observed that 1–100 ng/mL leptin enhanced the percentage of calf oocytes in the M2 stage in standard in vitro oocyte maturation procedure. Van Tol et al. [136] reported that 1000 ng/mL leptin did not affect nuclear maturation in cows during standard in vitro oocyte maturation procedure. Notably, Paula-Lopes et al. [147] found that 1 and 10 ng/mL leptin enhanced the proportion of bovine oocytes with extruded polar bodies, increased the percentage of M2 oocytes and reduced the proportion of TUNEL-positive CCs in standard in vitro oocyte maturation procedure. In summary, the above data indicate that in general, leptin stimulates oocyte maturation; however, the data from cows are inconsistent with data from other species. In addition, there is a need to consider differences between prepubertal and mature animals. Nevertheless, leptin is the best-described adipokine in the context of in vitro oocyte maturation. In addition to the compensatory role in obesity in the case of leptin, it is worth noting that it activates the same signalling pathways that are involved in the regulation of energy metabolism, such as MAPK kinase [140], or inflammation, such as Janus kinase [139], which

explains the close relationship of this adipokine with obesity and reproduction regulation (Table 2).

Expression of visfatin in the oocyte and its effect on oocyte maturation

Visfatin has been observed in mouse oocytes [148–150], where, in aged oocytes, both visfatin gene and protein expression decreased significantly, as confirmed by immunohistochemistry [150]. Furthermore, reduced visfatin expression was observed in oocytes from obese mice [151]. Besides, visfatin protein expression was noted in humans [69] and bovine oocytes [152], where visfatin decreased after standard in vitro oocyte maturation, which indicated that visfatin is more important in oocyte maturation than early embryogenesis and depend on maternal and no zygotic genome (Fig. 2).

Shen [153] reported a positive correlation between visfatin follicular fluid levels and the number of obtained oocytes. Moreover, 5–500 ng/mL visfatin dose-dependently enhanced oocyte developmental competence in mice during standard in vitro maturation. Additionally, in vivo administration of visfatin with gonadotropins during superovulation in older mice improved oocyte developmental competence [154]. Inhibiting visfatin enzyme activity in aged mouse oocytes with FK866, a pharmacological inhibitor, resulted in elevated ROS levels, reduced mitochondrial membrane potential and decreased ATP levels, suggesting a further impact on mitochondrial function [150]. The inhibition of visfatin activity by pharmacological blocker also reduced the oocyte maturation in pigs during standard in vitro maturation, having a negative effect on spindle formation and CCs expansion [155]. These data clearly indicate that visfatin is crucial for proper oocyte maturation and may act as protector adipokine due to its strong positive effect for the organism, especially oocyte, during obesity and aging (Table 2).

Expression of chemerin in the oocyte and its effect on oocyte maturation

There is not a lot of data about chemerin and oocyte maturation. The expression of chemerin and its three receptors (chemokine-like receptor 1 (CMKLR1), G protein-coupled receptor 1 (GPR1), and C–C motif chemokine receptor-like 2 (CCRL2) has been reported in the bovine ovary, including oocytes [156] (Fig. 2).

Increased chemerin in human follicular fluid may be associated with a reduced oocyte fertilisation and lower high-quality embryo rates [157]. Only one study had indicated a direct chemerin action on oocyte maturation. The researchers reported that 100, 200 and 400 ng/mL chemerin significantly reduced cholesterol synthesis, oocyte maturation and MAPK phosphorylation in cattle during standard in vitro oocyte maturation [156]. Given the limited amount of research, the role of chemerin in oocyte maturation requires further investigation. Of note, the initial clinical and in vitro data have indicated its negative function and the level of chemerin in the follicular fluid itself can serve as a simple diagnostic marker of oocyte developmental competence (Table 2).

Expression of vaspin in the oocyte and its effect on oocyte maturation

The mRNA and protein expression of vaspin and its receptor GRP78 have been described in pig COCs, while immunolocalisation of vaspin and its receptor have been observed in CCs and oocytes. Moreover, vaspin and GRP78 protein expression were increased in in vitro–matured oocytes during standard procedure [158]. Vaspin and GPR78 protein expression has also been described in human oocytes and CCs [71] (Fig. 2).

There is only one study about the direct effect of vaspin on oocyte maturation. In pigs, 1 ng/mL vaspin enhanced oocyte maturation in standard procedure, as evidenced by the presence of the first polar body and increased P_4 production by COCs through activation of the MAPK and AMP-activated kinase (AMPK) pathways [158]. Notably, vaspin and its receptor are also present in human oocytes and its function in the ovary is similar in pigs and women [77]. Studies using the pig model may also partly suggest the potential positive role of vaspin in the in vitro maturation of human oocytes [72]. Vaspin has a positive effect on the entire reproductive system including oocyte maturation; thus, like leptin, adiponectin or PNX, vaspin plays a protective role during obesity to prevent fertility (Table 2).

Conclusion

We highlighted the importance of adipokines such as leptin, adiponectin, chemerin, visfatin and vaspin, and neuropeptides including kisspeptin, nesfatin-1 and PNX in nuclear, but also in some cases, if included in original research, in cytoplasmic maturation of the oocytes and molecular mechanism of its actions. Firstly, in this publication, we have collected articles describing the expression of neuropeptides and adipokines in COCs. Data indicate that they are present in oocytes in humans and numerous farm animal species, as demonstrated by the example of leptin, which has been described in humans, rodents and farm animals such as pigs, horses, cows and sheep. According to the authors, adipokines such as vaspin are also present in COCs of many species and their description

only in humans and pigs results from their relatively new role in reproduction and requires further research using other species. Moreover, the presence of receptors for neuropeptides and adipokines in the structures of COCs indicates that they may have a direct function on their maturation, even if such studies as in the case of vaspin and human oocytes have not yet been performed. Similarly, changes in the levels of the described hormones and their receptors after oocyte in vitro maturation seem to confirm this hypothesis, as demonstrated for kisspeptin, adiponectin, leptin, visfatin and vaspin. Finally, there are scientific works indicating that the level of visfatin changes in the oocytes of obese mice [151], which confirms the hypothesis that adipokines and neuropeptides, the concentration of which depends on adiposity [28], are direct markers of obesity also in the oocyte. Unfortunately, the amount of work in this area is very limited and further comparative studies should be undertaken using oocytes from normal weight and obese individuals. Briefly, adipokines/neuropeptides effects on oocyte maturation depend on studied molecules, e.g. vaspin, adiponectin and kisspeptin stimulate while chemerin decreases in vitro oocyte maturation. Some of these molecules exert species-dependent effects: e.g. leptin stimulates oocyte maturation in all studied species [139–143] except cows [145], while nesfatin-1 has a stimulatory effect in cow [116] oocytes and an inhibitory effect in zebrafish oocytes [54]. Nevertheless, understanding the role of these metabolism-linked molecules on oocyte function and maturation is paramount for the identification of potential molecular targets for future pharmacological interventions to prevent and treat infertility in domestic animals and humans [1;4]. Therefore, according to the authors of this manuscript, comprehensive studies should be carried out on the role of adipokines and neuropeptides in in vitro oocyte maturation in various species, also using their combinations and modern high-throughput techniques such as transcriptomic, metabolomic and methylome analysis, in order to fully understand the relationship between obesity, adipokines/neuropeptides and reproduction, especially considering the often opposing role of these hormones in maintaining the body's energy homeostasis.

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Declarations

Competing interests The authors declare no competing interests.

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