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Review

The impact of adipose tissue-derived factors on the hypothalamic-pituitary-gonadal (HPG) axis

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ABSTRACT

Adipose tissue produces factors, including adipokines, cytokines and chemokines which, when released, systemically exert endocrine effects on multiple tissues thereby affecting their physiology. Adipokines also affect the hypothalamic-pituitary-gonadal (HPG) axis both centrally, at the hypothalamic-pituitary level, and peripherally acting on the gonads themselves. Among the adipokines, leptin, adiponectin, resistin, chemerin and the peptide kisspeptin have pleiotropic actions on the HPG axis affecting male and female fertility. Furthermore, adipokines and adipose tissue-produced factors readily affect the immune system resulting in inflammation, which in turn impact the HPG axis, thus evidencing a link between metabolic inflammation and fertility. In this review we provide an overview of the existing extensive bibliography on the crosstalk between adipose tissue-derived factors and the HPG axis, with particular focus on the impact of obesity and the metabolic syndrome on gonadal function and fertility.

Key words: Adipokines, Adipose tissue, Chemokines, Cytokines, Fertility, Gonads, Inflammation, Reproduction

INTRODUCTION

Adipose tissue

The Swiss naturalist, botanist, physician and classical linguist Conrad Gesner was the first, in 1551, to describe adipose tissue as a separate entity. He recognized two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). We now know that WAT stores excess energy and that, evolutionarily speaking, it first appeared in the teleost fish. On the other hand, the main function of BAT is energy expenditure as heat (non-shivering thermogenesis) and it first appeared later in the evolution as a characteristic of mammals. Up to the 90s, WAT was considered a simple depot of excess energy stored in the form of triglycerides and the only type of adipose tissue present in adults. It is however now known that adipose tissue is an extremely active endocrine and immune organ producing more than 100 hormones, the adipokines, and several immune effectors including cytokines and chemokines. In 1993, adipose tissue was shown to produce the cytokine tumor necrosis factor alpha (TNFa) and the following year, in 1994, the hormone leptin.

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It is today well established that adipose tissue is an important homeostatic organ regulating several vital physiological processes, including food intake and energy balance via its multiple effects on hunger and satiety centers, at the level of the hypothalamus, brain stem and cortex. Adipose tissue also affects adaptation to stress and the immune response. In the last few years the importance of adipose tissue for the hypothalamic-pituitary-gonadal (HPG) axis has emerged. More specifically, adipose tissue plays a crucial role in the onset of puberty, the seasonal regulation of sexual behavior and fertility and their adaptation to the availability of energy and the size of fat depots. The effects of adipose tissue on the HPG axis are mediated by adipokines, cytokines and chemokines. In this review, we provide an overview of the crosstalk between adipose tissue-derived factors and the HPG axis.

Obesity as a cause of chronic low-grade metabolic inflammation

Obesity is today a major medical problem in the developed and developing countries and is the underlying cause of several pathologic conditions. The most deleterious consequence of obesity is the development of chronic low-grade metabolic inflammation (CLGI), first within adipose tissue and subsequently systemically, which causes insulin resistance resulting in the development of diabetes mellitus and the metabolic syndrome.[1] The accumulation of adipose mass in the visceral part of the body (apple-type or android obesity) is associated with metabolic inflammation, while subcutaneous fat (pear-type or gynoid obesity) appears to be less detrimental to health.[2] It is believed that the initial cause of metabolic inflammation is adipocyte hyperplasia in WAT. Non-esterified fatty acids (NEFA) produced by these adipocytes induce local macrophages to produce high levels of TNFa which in turn induce adipocytes (in a paracrine manner) to produce more NEFA, pro-inflammatory cytokines, acute phase proteins and chemokines [such as the C-C motif chemokine ligand-2 (CCL2) or monocyte attractant protein-1 (MCP-1)] which attract more monocytes/macrophages within adipose tissue.[3,4] This self-intensifying crosstalk between WAT adipocytes and local macrophages results in the development of inflammation of visceral adipose tissue as well as systematic low-grade inflammation affecting multiple tissues, including the vascular endothelium and the gonads.

The magnitude of metabolic inflammation is best assessed in the fasting state, with acute phase inflammatory proteins and pro-inflammatory cytokines being the most frequently used. High-sensitivity C-reactive protein (hs-CRP) is the golden standard. Other acute phase proteins that can also be measured in assessing metabolic inflammation include haptoglobin, serum amyloid A (SAA) and fibrinogen. The cytokines measured include the interleukins IL-1, IL-1Ra, IL-6, IL-8, IL-18, IL-10 and TNFa. In addition, measurement can be made of adhesion and remodelling molecules of extracellular matrix, chemokines [(MCP-1, 3, 4, angiopoietin, metallothionein, macrophage inflammatory protein 1 (MIP1)], ICAM, VCAM, macrophage inhibitory factor (MIF) and soluble receptor factors of TNF (TNF receptor (sTNFR)-1. These factors, being present in the circulation, have a direct impact on the HPG axis. Nevertheless, there is limited information on their value as markers capable of revealing associations between metabolic inflammation and fertility.

EFFECTS OF METABOLIC INFLAMMATION ON THE HPG AXIS

Obesity provokes an inflammatory response within visceral adipose tissue which develops into a state of systemic CLGI. Indeed, in obesity the phenotype of adipocytes changes to a pro-inflammatory phenotype that causes the production of cytokines and chemokines which attract monocytes and neutrophils from the circulation, thus spreading the inflammation to adjacent resident stromal cells. This inflammatory response of visceral adipose tissue is characterized by local inflammation, which results in deregulation of adipokine production and subsequent changes of their levels in the systemic circulation. The inflammatory response is also associated first with insulin resistance and finally with hyperglycemia. Such systemic changes of the pro-inflammatory mediators and the adipokines as well as the ensuing hyperglycemia cause multiple effects on tissues including that of the HPG axis.

The hypothalamus is readily affected by the circulating cytokines and adipokines. Systemic inflammation has been shown to delay puberty in girls with prepubertal onset of inflammatory bowel disease[5] and in

animal models of inflammatory diseases.[6] This effect has been partly attributed to decreased levels of leptin. It has in fact been demonstrated that leptin-deficient mice (ob/ob) are infertile because they are incapable of producing gonadotropin-releasing hormone (GnRH) from the hypothalamus, this affecting the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary with a subsequent adverse effect on the release of estradiol from the ovaries.[7,8] Though leptin administration can reverse this effect,[7] inflammatory cytokines intervene aggravating the suppression of LH production.[9] Similarly, systemic inflammatory disease affects male fertility and patients with rheumatoid arthritis,[10] who consequently display reduced testosterone levels. These findings suggest that both adipokines and inflammatory factors exert an impact on the HPG axis and on fertility. In humans, the data are fairly consistent regarding the finding that obesity, via metabolic inflammation, results in reduced fertility in women[11] and men.[12] Inflammation-induced leptin resistance has been proposed as being a potential mechanism[13] linking obesity with HPG axis defects and subfertility. Indeed, male hormone levels diminish as the body mass index (BMI) increases,[14] an association affected by leptin both in male and female subjects.[15,16] Subfertility has been directly associated with CLGI and low testosterone levels.[17] In a cross-sectional study, CLGI, as demonstrated by elevated levels of the pro-inflammatory cytokine TNFa and the chemokines MIP1a and MIP1b, was associated with low testosterone and subfertility regardless of BMI. This finding suggested a direct link between inflammation and the HPG axis. The latter association was much stronger when BMI was also taken into account.[17] A direct link between TNFa and the HPG axis has been established in animal models where TNFa exerted a transcriptional suppression of FSH-induced LH receptor[18] and direct effects on LH secretion.[19] Similarly, adipokines also exert a direct effect on components of the HPG axis. For example, adiponectin induces FSH production from pituitary cells and insulin-induced LH.[20] Likewise, leptin induces LH secretion,[21] clearly pointing to the presence of direct crosstalk between adipokines and HPG function. Changes in inflammatory markers and gonadal sex steroids are causally linked.[22,23] It is now well-documented that obesity-induced metabolic inflammation affects the health of the HPG axis, which therefore suggests a potential strategy for its therapy, interventions to reduce metabolic inflammation having in fact been shown to improve fertility.[24]

ADIPOKINES AND THE HPG AXIS

Effects of leptin on the central component of the HPG axis

Leptin was isolated and identified as a product of adipose tissue in 1994.[25] The ob gene, which codes for its sequence, is exclusively expressed in adipocytes. It was thanks to the fact that leptin redefined adipose tissue as an endocrine organ that a complete change came about in our understanding of energy homeostasis. Leptin is expressed in the human pituitary localized to gonadotrophs and thyreoidotrophs in the pars distalis and tuberalis, as well as in somatotrophs in the pars distalis.[26] Leptin exerts multiple effects throughout the body via its receptor LepR, a product of the db gene, which has several splicing isoforms (a-f), the long isoform b appearing to mediate most of its effects. Leptin is a potent anorexigenic hormone, decreasing appetite through its effects on hypothalamic nuclei, inhibiting orexigenic factors neuropeptide Y (NPY) and agouti-related peptide (AgRP) and enhancing the actions of the anorexigenic peptides alpha-MSH/pro-opiomelanocortin (POMC) and cocaine- and amphetamine-related transcript (CART). It also increases energy expenditure. Leptin activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) complex which readily affects cytokine and chemokine transcription as well as sex hormone expression. Paradoxically, circulating leptin levels are high in the obese and closely correlate with fat mass/BMI because of the gradual development of resistance to leptin.

One of the major biological effects of leptin is its stimulation of the HPG axis. Of note, it has been demonstrated that leptin administration stimulates the HPG axis in genetically obese ob/ob mice, i.e. mice lacking endogenous leptin. These animals are infertile but, following the administration of leptin, become fertile. Furthermore, food-restricted animals have low levels of leptin because of its lower production by lean adipose tissue. These animals exhibit hypogonadotrophic hypogonadism which is reversed only by the administration of leptin, i.e. leptin

reverses the diet-induced inhibition of gonadotropin secretion. In fact, severely fasted animals, displaying low endogenous leptin, if given i.v. leptin respond by exhibiting an acute induction of their LH production. This effect of leptin takes place at the hypothalamic level where leptin induces the production of GnRH resulting in high LH levels.

Leptin stimulates the expression of hypothalamic GnRH and the neuronal activity of GnRH neurons.[27,28] However, the stimulatory effect of leptin on GnRH neurons, located in the preoptic hypothalamic area, does not appear to be a direct one. Indeed, leptin treatment does not induce its receptor substrate, pSTAT3, in GnRH neurons, while in immuno-cytochemistry studies no colocalization of GnRH and pSTAT3 within the same neurons is observed. Furthermore, the administration of leptin induces pSTAT3 in another area of the anterioventral/periventricular hypothalamic nucleus, while it has additionally been shown that GnRH neurons do not express leptin receptors. It now appears that an intermediate type of neurons, possessing leptin receptors, convey the adipose tissue/leptin message to GnRH-producing neurons.[28]

Low leptin levels have been associated with sexual immaturity,[29,30] while it has been documented that the administration of leptin to female adolescents with endogenous leptin deficiency and hypogonadotropin hypogonadism triggers the onset of menarche.[31] The role of leptin in menarche is crucial. Thus, for instance, a 9-month increase in nutrient intake in young female athletes and ballet dancers resulted in an increase of leptin levels through the increase of body fat mass and the re-establishment of regular menstrual cycles.[32] The association of weight gain with the restoration of menses and improved fertility has also been noted in athletes with short- or long-term amenorrhea.[33] It is of particular interest that maternal malnutrition additionally appears to affect the fertility of female offspring, leading to premature reproductive senescence.[34] During the menstrual cycle leptin levels vary, the highest appearing in the luteal phase and the lowest during the early follicular phase.[35] Leptin levels positively correlate with FSH and LH. In fact, it has been suggested that leptin in combination with FSH may prove to be a sensitive biomarker for the prediction of sperm retrieval in men with non-obstructive azoospermia.[36] (Table 1)

Enter kisspeptin

Among the intermediate neurons, which possess leptin receptors and transmit adipose tissue/leptin messages to the GnRH-producing neurons, are the kisspeptin neurons. The kisspeptin gene was first isolated in Hershey, PA (USA), the location of Hershey's chocolate factory and because of this it was named after one of its chocolates. The kisspeptin gene was first identified as a human metastasis suppressor gene of melanomas and breast carcinomas and was given the name metastin. The 54-amino-acid product of the kisspeptin gene is the natural ligand for the GPR54 receptor, an orphan G protein-coupled receptor first identified in rats.

The kisspeptin gene is expressed in the central nervous system and in several extracranial sites. In the central nervous system, the kisspeptin gene is expressed in the hypothalamus (in the anteroventral periventricular and the arcuate nucleus) and the hippocampal dentate gyrus. In extracranial tissues, it is expressed in the vascular endothelium, in the cortex of the adrenal gland (where it stimulates aldosterone production) and in the islet cells of the pancreas (where it stimulates insulin production) and a multitude of other metabolic factors.[37] Crucially, kisspeptin and its receptor are present in the hypothalamic arcuate nucleus, located at the base of the hypothalamus outside the blood brain barrier and thus easily accessible to circulating hormones, where they furnish a vital link between peripheral metabolic signals. Most of the arcuate nucleus neurons express kisspeptin and the kisspeptin receptor gene.[38] Kisspeptin neurons send afferent projections to the NPY/AgRP (orexigenic) and the POMC/CART (anorexigenic) neurons.[39,40]

Effect of energy balance on hypothalamic kisspeptin

The importance of kisspeptin is that it forms a critical link between energy homeostasis and reproduction.[41-44] Kisspeptin levels are suppressed by food restriction, as for instance a 72 h fast, which may explain the disruption of the reproductive axis during a negative energy balance. Kisspeptin has no effect of its own on energy balance. Indeed, kisspeptin knockout (KO) and KISS receptor KO mice are viable but infertile, with minor changes of body weight, as compared to the wild-type (WT).[45] In addition, kisspeptin

Table 1. Adipokines with an impact on the HPG axis

Name	Expression cells/ tissues	Regulation by:	Target cells or tissues	Function	Population studies	KO mice, mutations	References
Adipokines							
Leptin	Adipocytes, gonadotrophs, thyreoidotrophs, somatotrophs	Circadian rhythm during menstrual cycle	Hypothalamus, pitutary, ovaries	↑GnRH, pSTAT3, LH, FSH, estradiol *Outcomes:* Sexual maturation, puberty, seasonal regulation of sexual behavior		ob/ob KO mice: *Characteristic:* Low kisspeptin transcript in the hypothalamus	7, 8, 21, 25, 27-33, 35, 36, 68, 102
		Energy homeostasis, adipose cell mass and number	Hypothalamus, brain stem, cortex	↓NPY, AgRP and ↑a-MSH/ POMC, CART *Outcomes:* Decreased appetite			103
Adiponectin	Adipocytes, pituitary, theca cells, cumulus cells, oocytes, Leydig cells, spermatozoa, epididymis	Estrous cycle, GnRH, LH, FSH	Pituitary	↑FSH, progesterone, insulin-induced LH, IGF-1-induced progesterone and E2		AdipoR1 or adipoR2 knockdown in human granulosa KGN cells affect survival and production of sex steroids	20, 26, 55, 57, 60-63, 68, 73, 75, 76, 102
		Energy homeostasis, adipose cell mass and number	Immune cells	↑M2 macrophages, ↑monocyte apoptosis, ↓NFkB signaling *Outcomes:* Local and systemic anti-inflammatory effects and protection of Leydig cells			55, 58, 100, 102
			Pancreas	↑Survival pancreatic β-cells *Outcomes:* Insulin-sensitizing effects			56
			Arcuate nucleus, adipose tissue	↑Fat oxidation, ↓local inflammatory response *Outcomes:* Energy balance			58
Visfatin	Adipocytes, human primary granulosa cells, human granulosa KGN cell line, human cumulus cells, oocytes	Obesity, type 2 diabetes, cardiovascular disease	Immune cells	↑TNFa, IL-6, IL-1β *Outcomes:* Monocyte chemotactic activity			78, 81
			Ovaries	↑Leydig cell steroidogenesis *Outcomes:* Ovarian function	↑Visfatin, ↑LH (women with PCOS)		79, 101
Resistin	Adipocytes, porcine ovaries	Gonadotrophins, gonadal steroids, IGF1	Ovaries	↓ Steroids *Outcomes:* Ovarian steroidogenesis	↑Adiponectin to resistin ratio, ↑FSH, ↑LH, ↓free androgen index (women with PCOS)		82, 84, 94, 102

administration centrally has no effect on food intake, body weight and hypothalamic expression of NPY, AgRP, POMC or CART.[46] Furthermore, exogenous kisspeptin has no effect on food intake.[47] However, kisspeptin suppresses NPY/AgRP neurons, and thus appetite, indirectly via synaptic mechanisms,[48] while central administration of kisspeptin increases meal intervals and reduces nocturnal food intake in mice. Also of interest, kisspeptin receptor KO animals eat larger quantities of food. The fact that the kisspeptin gene is also expressed in adipose tissue accounts for the existence of a significant correlation between kisspeptin expression and BMI in visceral adipose tissue but not in subcutaneous tissue obtained from the same individuals. The expression of the kisspeptin gene in adipose tissue is regulated by sex hormones and food intake.[37,49]

Kisspeptin as an intermediary between leptin and GnRH neurons

A growing number of published reports document a direct effect of kisspeptin neurons on GnRH neurons and, moreover, indicate that the effect of leptin on GnRH neurons is mediated by kisspeptin. In the hypothalamus, the kisspeptin neurons in anteroventral periventricular nuclei send projections to the medial preoptic area where the GnRH cell bodies are located. Kisspeptin immunoreactive fibers are in fact present in both the medial preoptic nucleus and medial preoptic areas. In addition, GnRH neurons express the kisspeptin receptor GPR54, while leptin receptors are present in kisspeptin neurons in the hypothalamus. Male ob/ob mice (no leptin) exhibit low kisspeptin transcript in the hypothalamus compared to WT littermates. Exogenous leptin increases the expression of the kisspeptin gene in male ob/ob mice. Meanwhile, in guinea pigs, leptin induces depolarization of kisspeptin neurons. Kisspeptin injected into the lateral ventricle of mice elicits rapid and robust LH/FSH secretion, with similar observations having been reported in rats, sheep, monkeys and humans. Kisspeptin stimulates LH/FSH release via a direct stimulatory effect on GnRH neurons. However, kisspeptin has no direct effect on pituitary gonadotrophs but only via the GnRH. The importance of kisspeptin for GnRH neurons has been documented in KO animals. Thus, inactivating mutations of its receptor, GPR54, cause hypogonadotrophic hypogonadism in humans,[50] while in mice, targeted deletion of GPR54 results in severe hypogonadism, this showing that kisspeptin-GPR54 signaling is essential for LH/FSH production (Table 2).

Kisspeptin as a mediator of gonadal sex steroid feedback

Kisspeptin neurons act as the main mechanism relaying gonadal sex steroid feedback to GnRH. Kisspeptin mediates the positive and negative effects of gonadal steroids on GnRH neurons. Indeed, most kisspeptin neurons in the anteroventral periventricular nucleus express gonadal steroid receptors. Thus, in females high levels of estrogens and progesterone stimulate kisspeptin neurons of the anteroventral periventricular nucleus to induce the preovulatory surge of GnRH/LH. RT-PCR analysis reveals that the total hypothalamic content of the kisspeptin transcript increases following gonadectomy and decreases after sex steroid replacement. Furthermore, administration of estradiol in ovariectomized mice induces the expression of kisspeptin. Kisspeptin neurons also receive circadian signals from the supra-chiasmatic nucleus. When estradiol levels and the circadian signals are both high, kisspeptin neurons become activated causing ovulation via GnRH.

Kisspeptin in puberty and seasonal breeding

Leptin stimulates GnRH production and plays the most important role in the initiation of puberty. Kisspeptin, being a potent inducer of GnRH, conveys the adipose tissue signal for the initiation of puberty.[51,52] Some mammals become fertile only during the annual breeding season which is controlled by the duration of daylight. During the short winter days, these animals have reduced hypothalamic concentrations of kisspeptin and thus their sexual activity is low. But in the long summer days, kisspeptin levels increase, stimulating the animals to breed. Administration of kisspeptin to animals during the winter months causes ovulation even in a non-breeding season.

Effects of adiponectin on the central component of the HPG axis

Adiponectin, also known as Acrp30,[53] is predominantly produced by adipocytes. It is the most abundantly circulating adipokine, its normal levels in the plasma being in the range of 1-50 mg/L. Cir-

Table 2. Products of adipocytes with an impact on HPG axis

Name	Expression cells/tissues	Regulation by:	Target cells or tissues	Function	Population studies	KO mice, mutations	References
Adipokine/Cytokine							
Chemerin	Adipocytes, granulosa cells, theca cells, corpus luteum, oocytes	TNFa, insulin, androgen	Ovaries	↓Antral follicle growth arrest and steroidogenesis, ↓FSH-induced aromatase expression and stereoidogenesis *Outcomes:* ↑Granulosa cell apoptosis	↑Chemerin (obesity, type 2 diabetes, metabolic syndrome, cardiovascular disease)		86, 90-93, 95, 96
			Immune cells	↑Chemoattraction of macrophages and dendritic cells, ↑macrophage adhesion *Outcomes:* Pro-inflammatory effect	↑Chemerin, ↑CRP, ↑TNFa, ↑IL-6, ↑leptin, ↑resistin (obesity)		87- 90
Cytokines							
IL-6	Adipocytes	Adipose tissue mass and number	Immune cells	↑Immune response *Outcomes:* Pro-inflammatory effect	↑IL-6, IL-8, MIF (women with poor ovarian response), ↑ IL-6 (obesity, metabolic inflammation)		102, 104
TNFa	Adipocytes, macrophages	NEFA	Ovaries	↓ FSH-induced LH receptor and LH secretion, ↓ testosterone *Outcomes:* Subfertility	↑ TNFa , IL-6, IL-8 (infertility), ↑ TNFa (obesity, metabolic inflammation)		17-19, 105
Chemokine							
IL-8	Adipocytes, macrophages		Immune cells, semen	↑Chemoattraction of macrophages *Outcomes:* Pro-inflammatory effect	↑IL-8 (prostatitis-like symptoms in males of infertile couples)		102, 106
Other molecules							
NEFA	Adipocytes	TNFa	Immune cells	↑TNFa in macrophages of adipose tissue *Outcomes:* Pro-inflammatory macrophages	↑ NEFA (obesity)		3
FFA	Adipocytes		Ovaries	↑ Granulosa cell apoptosis *Outcomes:* ↓Granulosa cell survival	↑ FFA in follicular fluid, poor morphology of the cumulus oocyte complex		66, 67
Kisspeptin	Adipose tissue, hypothalamic neurons	Sex hormones, food intake (in adipose tissue) Seasonal breeding, Leptin (in hypothalamus)	Hypothalamus	↑ GnRH *Outcomes:* Stimulates LH/ FSH release, ovulation		**Kisspeptin KO mice & Kisspeptin receptor KO mice** *Characteristic:* Infertile **Inactivating mutations of GPR54 receptor in humans:** *Characteristic:* Hypogonadotrophic hypogonadism	37, 41-45, 49, 51

culating adiponectin is found in trimer, hexamer and high molecular weight (HMW) forms, the latter considered the metabolically bioactive form.[54] Two distinct receptors have been described and cloned for adiponectin, namely AdipoR1 (almost ubiquitously expressed and abundantly so in skeletal muscle, binds the globular form) and AdipoR2 (predominantly expressed in the liver and WAT, binds the full-length protein). Adiponectin exerts local and systemic anti-inflammatory effects by inhibiting the formation of the NF-κB complex and its translocation to the nucleus, thereby suppressing the expression of downstream pro-inflammatory genes and the secretion of pro-inflammatory cytokines (TNFa, IL-6) while also stimulating production of anti-inflammatory cytokines (IL-10, IL-1RA). It promotes polarization of macrophages towards the anti-inflammatory M2 phenotype and enhances monocyte apoptosis. Adiponectin also possesses anti-atherogenic properties.[55] Furthermore, adiponectin exhibits insulin-sensitizing effects, promotes survival and preserves pancreatic β-cells.[56] Adiponectin affects energy balance both at the arcuate nucleus level and by acting on adipose tissue, in a paracrine manner, by up-regulation of fat oxidation and by suppressing the local inflammatory response.[57,58] Unlike most adipokines, adiponectin production is down-regulated in obesity and related metabolic disorders and circulating levels are negatively correlated with BMI and visceral fat mass.[59]

Adiponectin exerts direct effects on the HPG axis at all levels. Adiponectin is expressed in the porcine pituitary, its levels varying depending on the phase of the estrous cycle, as well as on GnRH- and/or LH and FSH.[20] LH administration in vivo during the late follicular phase induces adiponectin in follicular fluids, decreases androgen levels and increases ovarian sensitivity to insulin.[60] The expression of adiponectin receptors is also identified in GH-, FSH-, LH- and TSH-producing cells in the pars distalis but not in the pars tuberalis. Moreover, AdipoR1 are detectable in lateral hypothalamic neurons and on the nucleus basalis.[26] In the gonads, they are present in the granulosa cells of the ovaries.[61] In the ovaries, the gonadotrophins LH and FSH can modify the expression levels of AdipoR2, but not AdipoR1, that eventually contribute to enhanced 3βHSD activity and increase progesterone secretion in human granulosa cells.[62] In vitro, AdipoR1 or AdipoR2 knockdown in human granulosa-like tumor cell line KGN cells affects both their survival as well as their production of sex steroids via the MAPK ERK1/2 pathway.[63]

Direct effects of obesity on the gonads

Adipose tissue and obesity can affect the gonads indirectly via effects on the central HPG axis, i.e. by affecting the GnRH hypothalamic neurons and/or the gonadotrophs of the pituitary or directly, on the gonads themselves, irrespective of the central nervous system effects. It should be noted here that the gonads have their own "sensor of energy reserves". This is the gonadal 5' AMP-activated protein kinase (AMPK) which senses caloric abundance, as in obesity, and caloric restriction. AMPK plays a crucial role in the regulation of gonadal steroidogenesis and the proliferation and survival of somatic gonadal cells, as well as in the maturation of oocytes and spermatozoa and that of a host of other steps in gonadal physiology.[64] In the ovaries, AMPK is present in granulosa and theca cells, oocytes and corpora lutea. In the testes, it is present in Sertoli, Leydig and germinal cells. AMPK activators inhibit the production of progesterone and estradiol by mammalian granulosa cells. Indeed, metformin, a potent insulin sensitizer, suppresses IGF1-induced cell proliferation and protein synthesis through AMP-activated protein kinase in cultured bovine granulosa cells.[65] It should be borne in mind that metformin is now the first-line treatment for obesity-induced polycystic ovaries. High levels of saturated free fatty acids, such as palmitic acid and stearic acid, suppress granulosa cell survival due to increased apoptosis, as evidenced by DNA ladder formation and annexin V-EGFP/propidium iodide staining.[66] Furthermore, women with elevated free fatty levels in their follicular fluid have poor morphology of the cumulus oocyte complex.[67]

As mentioned above, the adipokines are hormones produced by adipose cells. Their rate of production depends on energy homeostasis and adipose cell mass and number. In addition to the effects of adipokines on GnRH neurons in the hypothalamus and on the gonadotrophs of the anterior pituitary, they also affect, in a direct manner, both female and male gonads. It should be noted however that while the adipokines directly affect the gonads, existing data suggest that

their gonadal effects do not fully explain the observed reproductive dysfunction in obesity, i.e. their impact on reproduction depend on both central and peripheral effects.[68]

Obesity affects several aspects of ovarian physiology including folliculogenesis, ovulation, oocytes and the production of ovarian steroids.[69] Indeed, diet-induced adiposity may cause ovarian dysfunction ranging from simple menstrual irregularities to the polycystic ovarian syndrome. Thus, ovaries taken from obese mice exhibit accelerated apoptosis of ovarian cell follicles. Similarly, oocytes isolated from obese mice are smaller in size and fewer in number compared to those of lean controls.[70] Furthermore, in diet-induced obesity models, mitochondria in mouse oocytes and zygotes appear to be malfunctioning possibly as a result of oxidative stress.[71] Again, the mouse model of diet-induced obesity has shown their ovaries to display lipid accumulation and lipo-toxicity of the oocytes and an acceleration of the apoptosis of granulosa and cumulus cells.[72] In other words, it appears that lipid accumulation, endoplasmatic reticulum (ER) stress, mitochondrial dysfunction and apoptosis are markedly increased in the ovaries of obese mice, resulting in anovulatory cycles and decreased fertilization.[72]

Direct effects of adiponectin on the female gonad

The mammalian ovaries and particularly the follicles express the AdipoR1 and AdipoR2 receptors; accordingly, treating pig granulosa cells with adiponectin induces changes characteristic of the periovulatory period. Moreover, additive effects are observed between adiponectin and insulin in inducing several granulosa cell gene expressions, thus suggesting that adiponectin actions on the ovary may be mediated via its insulin-sensitizing effects.[73] In addition, adiponectin and its receptor genes are also expressed in theca cells, cumulus cells and oocytes of the dominant follicles compared to atretic follicles during the follicular and luteal phases. A positive correlation is observed between the adiponectin transcript in the ovarian cells of the dominant follicle and follicular fluid E2 levels, indicating an association between adiponectin and follicular dominance and oocyte competence.[74] Adiponectin increases the production of progesterone in human ovaries,[62] though it does not alter estrogen production.[61,75] Treatment of human granulosa cells with adiponectin in vitro increases insulin-like growth factor I (IGF-1)-induced progesterone and E2 secretion but not IGF-1-induced proliferation.[76]

Direct effects of visfatin on the female gonad

Visfatin directly affects ovarian function. Visfatin, which was originally described as an adipokine with an insulinomimetic and insulin secretagogue effect,[77] possesses monocyte chemotactic activity by inducing TNFa, IL-6 and IL-1β production via stimulation of the p38MAPK and ERK pathways. Visfatin levels are increased in obesity, type 2 diabetes and cardiovascular disease and are positively correlated with levels of IL-6 and CRP.[78] In addition, visfatin levels positively correlate with obesity indices in women of reproductive age.[79] However, its levels correlate with BMI in visceral fat but negatively in subcutaneous fat, possibly due to different regulation of visfatin production in the two distinct fat depots. In the ovaries, visfatin is expressed primarily in human granulosa cells (hGCs), in the tumor cell line KGN, in human cumulus cells and in oocytes. Interestingly, the concentration of visfatin in follicular fluid is associated with the number of mature oocytes.[80] The insulin sensitizer metformin elevates the levels of visfatin transcript within human granulosa cells.[81]

Direct effects of resistin on the female gonad

Resistin is expressed in the porcine ovary, where it directly affects ovarian steroidogenesis.[82] Gonadotropins and gonadal steroids stimulate the production of ovarian resistin, while IGF1 suppresses it.[82] Resistin levels[83] are positively associated with polycystic ovary syndrome (PCOS). The ratio of adiponectin to resistin levels positively correlates with plasma FSH and LH and negatively with free androgen index in women with PCOS.[84]

Direct effects of chemerin on the female gonad

The primary function of chemerin, identified as an adipokine in 2007,[85] involves chemoattraction of macrophages and dendritic cells during the immune response. It is implicated in the regulation of adipogenesis, adipocyte metabolism and glucose metabolism in mouse models of obesity and diabetes.[86] Chemerin

regulates insulin secretion and insulin, in turn, and induces chemerin secretion from adipocytes. In humans, chemerin acts as a pro-inflammatory adipokine by directly affecting adipocytes in which it is induced by TNFa,[87] and also by enhancing macrophage adhesion.[88] Circulating levels are increased in obesity, type 2 diabetes, the metabolic syndrome and cardiovascular disease and are positively correlated with biomarkers of inflammation, including CRP, TNFa, IL-6, as well as leptin and resistin.[89,90] Chemerin (RARRES2) and its receptors chemokine-like receptor 1 (CMKLR1), G protein-coupled receptor-1 (GPR1) and -2 (GPR2) are present in bovine ovarian cells (granulosa cells, theca cells, corpus luteum and oocytes),[91] while chemerin and CMKLR1 are expressed in rat and human ovarian cells.[92,93] Chemerin and resistin down-regulate steroidogenesis in bovine ovarian cells,[91,94] wherees chemerin does so by up-regulating prohibin in rat ovarian cells.[92]

Chemerin has been associated with obesity and PCOS.[95,96] Our studies have shown that ovarian and circulating chemerin levels are elevated in a chronically androgenized rat model and that chemerin suppresses FSH-induced steroidogenesis.[92] However, whether and how chemerin is involved in antral follicular growth arrest has not as yet been documented. Chronic androgen administration increases chemerin and CKMLR1 expression that is involved in the induction of antral follicle growth arrest. The latter response is characterized by dysregulated interactions of survival (p-Akt, XIAP, PARP) and proapoptotic (PTEN, caspase-3) factors in a cell-specific manner. This hyperandrogenic state is also accompanied by marked changes in follicle structure, including up-regulation of calpain expression and decreased cytoskeletal proteins, apoptotic deletion of granulosa cells and oocytes and the survival and retention of theca cells.

In addition to its role in the control of ovarian follicular growth, chemerin is important in the regulation of follicular steroidogenesis.[5] It has been reported that chemerin inhibits FSH-induced aromatase expression and estrogen secretion in granulosa cells and that this influence is mediated through increased expression and action of the mitochondrial protein.[5] This observation, together with our present findings that elevated chemerin levels and down-regulated aromatase expression are positively related to increased granulosa cell apoptosis in dihydrotestosterone-treated rats, supports the hypothesis that chemerin plays a paracrine and/or autocrine-regulatory role in the ovary and contributes to the dysfunction of the ovarian function.

Direct effects of obesity on the male gonad

Male fertility, especially the quality of semen, is seriously declining in the developed countries. Among other environmental factors, obesity is positively associated with defective spermatogenesis. Males consuming high-energy diets exhibit sperm cell defects, spermatogenesis arrest and spermatozoa with mitochondrial dysfunction and high levels of reactive oxygen species,[97] while overtly obese men have low total and free testosterone and reduced sperm concentration, sperm count and motility.[98] Caloric restriction in obese men exerts a beneficial effect on their fertility via improvement of overall testicular function and by a reduction of the conversion of testosterone to β-estradiol by aromatase activity in adipose tissue.[99]

Limited information is available on the crosstalk between adipokines and male fertility. Adiponectin and its receptors are also expressed by most cells in male gonads including Leydig cells, spermatozoa and epididymis. Adiponectin protects Leydig cells from the detrimental effects of pro-inflammatory cytokines by suppressing nuclear factor-κB signaling via induction of AMPK.[100] Finally, visfatin induces Leydig cell steroidogenesis in *in vitro* models.[101]

CONCLUSIONS

Overall, there is accumulating evidence that adipose tissue has a pleiotropic effect on the HPG axis affecting fertility at multiple levels. Further research will shed light on the mechanisms involved and provide methods for prevention or amelioration of the detrimental effects of obesity on the HPG axis and fertility.

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