Adipokines: implications for female fertility and obesity

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Abstract

Obesity is associated with a diverse set of metabolic disorders, and has reproductive consequences that are complex and not well understood. The adipose tissue-produced leptin has dominated the literature with regards to female fertility complications, but it is pertinent to explore the likely role of other adipokines – adiponectin and resistin – as our understanding of their biological functions emerge. Leptin influences the developing embryo, the functioning of the ovary and the endometrium, interacts with the release and activity of gonadotrophins and the hormones that control their synthesis. In this review such biological actions and potential roles of the adipokines leptin, adiponectin and resistin are explored in relation to female fertility and the complexity of the obese metabolic state.

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Introduction

The worldwide incidence of obesity continues to escalate, despite increased awareness and global efforts to understand and confront its origins. In essence, dysregulated energy homeostasis stems from a societal reduction in physical activity, an increase in the accessibility of, and overindulgence in, energy-dense foods, combined with a myriad of genetic, social and economic complicating factors. The mechanisms that control energy metabolism and body fat mass are inherently linked to those that govern fertility and stem back to the evolutionary drive to survive in times of limited food supply. The rising incidence of obesity and associated metabolic disturbances highlights a loss of control in this homeostatic system, which has effects on reproduction, the biology of which remains ill-defined but in desperate need of understanding.

Metabolic disorders such as the development of insulin resistance result from the increasing incidence of obesity, and have serious ramifications on the progression of lifetime health problems such as type II diabetes, cardiovascular disease, dyslipidemia and hypertension. A significant proportion of the infertile or sub-fertile population are obese or overweight (Hamilton-Fairley *et al.* 1992, Zaadstra *et al.* 1993, Pettigrew & Hamilton-Fairley 1997, Norman & Clark 1998, Crosignani *et al.* 2002), with a plethora of reproductive complications including menstrual dysfunction and anovulation (Hartz *et al.* 1979, Lake *et al.* 1997) and miscarriage (Wang *et al.* 2002). The development of obesity and insulin resistance commonly go hand-in-hand with the development of fertility

problems, but it is the link between this metabolic state and infertility that remains to be defined.

Adipose tissue functions as a highly specialised, endocrine and paracrine organ producing an array of adipokines, as well as eliciting cell mediated effects via pro-inflammatory and anti-inflammatory cells, producing various cytokines and chemokines. Such factors have local and systemic biological effects, influence insulin sensitivity and the development of diseases such as atherosclerosis. This review will focus on these adipokines and female fertility, regarding their complex interactions with energy metabolism at the level of the hypothalamus, the pituitary, and peripheral tissues including the gonads, skeletal muscle and adipose tissue. In the last decade the study of one of these adipokines, leptin, has highlighted the interaction with female reproduction. Here, the links between excessive adiposity with obesity and associated metabolic states such as insulin resistance, and interactions with aspects of female fertility will be explored in the context of leptin and two new adipokines, adiponectin and resistin.

Insulin resistance, adipokines and fertility in the obese

The mechanisms contributing to the impaired physiological effects of insulin commonly described with obesity can be manifest peripherally in muscle and adipose tissue or in the liver. Metabolic consequences evident with the development of insulin resistance include increased

circulating free fatty acids via elevated lipolysis of triglycerides in adipose tissue and lipoproteins (rich in triglycerides) in other tissues, impaired glucose uptake in muscle and adipose tissue, overproduction of glucose by the liver and overproduction of insulin by pancreatic β -cells. The obese state is also characterised by features of chronic inflammation, particularly elevated circulating levels of cytokines and inflammatory markers, such as C-reactive protein. Various inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α), and nuclear receptors including peroxisome proliferator-activated receptor- γ (PPAR- γ) have been implicated in the aetiology of insulin resistance associated with obesity. Furthermore the role of adipokines including leptin, resistin and adiponectin with obesity and insulin resistance is emerging (Kadowaki *et al.* 2003, Greenfield & Campbell 2004, Eckel *et al.* 2005).

Evidence supporting an interrelationship between insulin and fertility exists (Gong 2002, Hunter *et al.* 2004) but the mechanistic actions of dysregulated insulin functioning at a physiological and cellular level as associated with obesity, remain obscure. The adipokines resistin and adiponectin have been touted as this link, because they modulate glucose homeostasis, fat homeostasis, influence insulin action, and thus may potentially mechanistically link obesity, insulin resistance and fertility.

Increased production and secretion of the satiety hormone leptin correlates with the amount of fat tissue in animals (Maffei *et al.* 1995, Considine *et al.* 1996). Ordinarily leptin functions to reduce food intake and maintain energy homeostasis, but in obesity the development of a state of leptin resistance results in a dysfunctional energetic state (Sahu 2004). Obese rodents have elevated serum resistin levels (Steppan *et al.* 2001, Steppan & Lazar 2002, Lee *et al.* 2005) but adipose mRNA resistin levels are generally lower or unchanged in these models (Juan *et al.* 2001, Le Lay *et al.* 2001, Masuzaki *et al.* 2001, Way *et al.* 2001, Milan *et al.* 2002, Lee *et al.* 2005), which may be explained by altered translational or post-translational modifications of resistin protein, or altered metabolic clearance of resistin. In humans obese individuals, or those with a higher body mass index (BMI), have higher serum and adipose expression levels of resistin (Savage *et al.* 2001, Azuma *et al.* 2003, Degawa-Yamauchi *et al.* 2003b, Yannakoulia *et al.* 2003), although not all studies confer (Lee *et al.* 2003) and in obese pigs, elevated adipose mRNA and protein levels have been reported (Chen *et al.* 2004). In contrast, serum and adipose expression levels of adiponectin are reduced in obese humans (Arita *et al.* 1999, Cnop *et al.* 2003, Diamond *et al.* 2004, Bullo *et al.* 2005), pigs (Jacobi *et al.* 2004) and rodents (Hu *et al.* 1996, Yamauchi *et al.* 2001). Studies investigating the interaction between levels of these adipokines with increased adiposity in obesity, and with nutrition and energy supply in humans and animal models are summarised in Table 1.

Biological functions of adipokines

Our understanding of the biological significance and functions of leptin, adiponectin and resistin is in its infancy. The potential interactions to regulate energy homeostasis are depicted in Fig. 1.

Leptin

Leptin, produced predominantly by adipose tissue, was first explored as a satiety signal regulating food intake and energy expenditure. Leptin binds to the long-form of the leptin receptor (Ob-Rb) in the hypothalamus, to reduce neuropeptide-Y (NPY) and agouti regulated protein (AgRP) activity, to increase pro-opiomelanocortin (POMC) and cocaine- and amphetamine related protein (CART) neuron activity, effectively reducing appetite and feed intake (Hakansson *et al.* 1996, Mercer *et al.* 1996, Cheung *et al.* 1997, Bjorbaek & Kahn 2004). Deficiencies in leptin signalling or functioning in the hypothalamus are thought to contribute to the development of obesity. A link with insulin resistance and fertility was described early on, with leptin deficient mice having increased adiposity, display severe insulin resistance and diminished fertility, both of which were restored with leptin administration, but not by calorie restriction or weight loss (Chehab *et al.* 1996, Mounzih *et al.* 1997).

In peripheral tissues, leptin generally has a fat metabolising role with limited direct effect on glucose metabolism. However, leptin antagonises insulin action and decreases its production by pancreatic β -cells (Seufert 2004), it indirectly affects glucose metabolism, for example glucose transport in skeletal muscle via the hypothalamus and central nervous system (Kamohara *et al.* 1997, Minokoshi *et al.* 1999). Evidence suggests that leptin increases lipolysis in adipose tissue and cells, and in skeletal muscle, but it appears less critical to liver function (Cohen *et al.* 2001). Leptin receptor signalling in peripheral tissues is not well understood but involves various transcription factors, such as activation of signal transducer and activator of transcription 1 (STAT1) and STAT3 in adipose tissue (Bendinelli *et al.* 2000) and of STAT3 and Akt in skeletal muscle (Maroni *et al.* 2003). Furthermore the increase in fatty acid oxidation by leptin in skeletal muscle has been attributed to the activation of the cellular nutrient-sensing AMP-activated protein kinase (AMPK) signalling pathway (Minokoshi *et al.* 2002, Steinberg *et al.* 2003).

Adiponectin

Adiponectin (previously termed by initial investigators: ACRP30; Scherer *et al.* 1995, AdipoQ; Hu *et al.* 1996, APM1; Maeda *et al.* 1996 and gbp28; Nakano *et al.* 1996), was first described in cultured murine adipocytes 3T3-L1 a decade ago (Scherer *et al.* 1995) and is abundantly produced by adipose tissue. The adiponectin gene is located on chromosome 3q27 (Saito *et al.* 1999), in a

Table 1 Tissue expression and circulating levels of the adipokines adiponectin, resistin and leptin, in genetic and diet-induced obesity, and the influence of nutrient restriction.

	Adiponectin			Resistin			Leptin		
	mRNA and/or protein	Circulating levels	Author	mRNA and/or protein	Circulating levels	Author	mRNA and/or protein	Circulating levels	Author
Obese	↓	↓	Liu <i>et al.</i> 2003	↑		Savage <i>et al.</i> 2001		↑	Pagano <i>et al.</i> 2005
Human		↓	Pagano <i>et al.</i> 2005		–	Helibronn <i>et al.</i> 2004	↑	↑	Maffei <i>et al.</i> 1995
		↓	Arita <i>et al.</i> 1999	–	–	Pagano <i>et al.</i> 2005	↑	↑	Considine <i>et al.</i> 1996
Rodent (diet-induced)	↓	↓	Makimura <i>et al.</i> 2002	↓		Le Lay <i>et al.</i> 2001		↑	Maebuchi <i>et al.</i> 2003
		↓	Makimura <i>et al.</i> 2002	–	↑	Lee <i>et al.</i> 2005			
	↓	↓	Yamauchi <i>et al.</i> 2001	↓	↑	Rajala <i>et al.</i> 2004			
				↓	↓	Maebuchi <i>et al.</i> 2003			
				↓		Makimura <i>et al.</i> 2002			
Rodent (genetic)		↓	Maebuchi <i>et al.</i> 2003	↓		Milan <i>et al.</i> 2002		↑	Maebuchi <i>et al.</i> 2003
	↓		Milan <i>et al.</i> 2002	↓	↑	Rajala <i>et al.</i> 2004		↑	Wallenius <i>et al.</i> 2002
				↓		Maebuchi <i>et al.</i> 2003			
Pig				↑		Chen <i>et al.</i> 2004	↑	↑	McNeel <i>et al.</i> 2000
Nutrient restriction	↑	–	Liu <i>et al.</i> 2003		–	Monzillo <i>et al.</i> 2003			Viguerie <i>et al.</i> 2005
Humans		–	Garaulet <i>et al.</i> 2004		–	Lee <i>et al.</i> 2003		↓	Maffei <i>et al.</i> 1995
		↑	Raitakari <i>et al.</i> 2004					↓	Wadden <i>et al.</i> 1998
		↓	Wolfe <i>et al.</i> 2004				↓	↓	Considine <i>et al.</i> 1996
	↓	–	Xydakis <i>et al.</i> 2004						
Rodents	↓		Makimura <i>et al.</i> 2002	↓		Milan <i>et al.</i> 2002		↓	Maffei <i>et al.</i> 1995
	↑		Milan <i>et al.</i> 2002	↓	↓	Rajala <i>et al.</i> 2004			
				↓		Makimura <i>et al.</i> 2002			
Pig				↓		Chen <i>et al.</i> 2004			

↑ = increased levels; ↓ = decreased levels; – = no change in levels of adipokines.

Figure 1 The potential interactions between adipokines and energy homeostasis. Expanded adipose tissue with obesity generally relates to an increase (↑) in leptin (L) and resistin (R) production, and a decrease (↓) in adiponectin (A) production, to stimulate (+), inhibit (−) or have an as yet unknown (?) effect on energy metabolism. The potential interactions between these adipokines and the adipose tissue, skeletal muscle, liver and pancreas in obesity may have direct effects (solid arrows) and indirect effects (dashed arrows) on energy homeostasis.

region recently mapped as a susceptibility locus for type II diabetes and adiposity (Kissebah *et al.* 2000, Vionnet *et al.* 2000), and is thought to potentially link obesity to insulin resistance. Receptors for adiponectin, AdipoR1 and AdipoR2, were discovered recently in mice (Yamauchi *et al.* 2003) and a third receptor, t-cadherin, has also been identified, although the tissue distribution and functional significance of the latter remain to be elucidated (Hug *et al.* 2004).

Adiponectin functions as an insulin sensitising agent by reducing hepatic glucose production and enhancing insulin action in the liver (Berg *et al.* 2001, Combs *et al.* 2001). Furthermore, adiponectin reduces the activity of gluconeogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase), and reduces fatty acid oxidation in the liver (Combs *et al.* 2001, Yamauchi *et al.* 2002). A direct effect on insulin production is yet to be determined, however AdipoR1 are expressed in islets cells of the pancreas (Kharroubi *et al.* 2003) and adiponectin treatment of *in vitro* cultured islet cells from normal and high-fat fed rats, showed a differential response in insulin production suggesting an alternative role in insulin resistant states (Winzell *et al.* 2004). Adiponectin increases fatty acid oxidation in the liver, via a reduction in CD36 expression, reducing fatty-acid influx

and liver triglycerides (Yamauchi *et al.* 2001). In skeletal muscle a reduction of triglyceride accumulation involves increased expression of proteins that transport lipids (CD36), fuel oxidation (acyl-CoA oxidase) and energy dissipation (uncoupling protein 2; UCP2) (Fruebis *et al.* 2001, Yamauchi *et al.* 2001). Although not completely defined, post-receptor signalling involving AMPK and downstream acetyl-CoA carboxylase (ACC), p38 mitogen-activated protein kinase (MAPK) and PPAR- α is described in skeletal muscle, liver and adipocytes (Tomas *et al.* 2002, Yamauchi *et al.* 2002, Wu *et al.* 2003, Yamauchi *et al.* 2003) and are thought to regulate glucose and lipid metabolism.

A transgenic mouse model generating a 2–3 fold elevation of circulating adiponectin levels improved hepatic insulin sensitivity (Combs *et al.* 2004), although studies using adiponectin knock-out models are yet to demonstrate a clear relationship with glucose homeostasis, under various control and dietary treatments (Kubota *et al.* 2002, Ma *et al.* 2002, Maeda *et al.* 2002).

Resistin

The discovery of resistin (also known as FIZZ3 and adipocyte specific secretory factor; ADSF) was concurrent in three separate groups, focusing on aspects of lung

inflammation (Holcomb *et al.* 2000), adipocyte differentiation (Kim *et al.* 2001) and screening targets of the insulin sensitising drug thiazolidinedione (Steppan *et al.* 2001). Despite the initial promise of resistin as the link between obesity and diabetes (Steppan *et al.* 2001), the discovery of low inter-species sequence homology (Gerst-mayer *et al.* 2003), different chromosomal location of the gene between species (pig; Cepica *et al.* 2002, rat; Lin *et al.* 2003, bovine; Komatsu *et al.* 2003, Otieno *et al.* 2005) and differing sites of synthesis between species (Kim *et al.* 2001, Nagaev & Smith 2001, Savage *et al.* 2001, Steppan *et al.* 2001, McTernan *et al.* 2002, Fain *et al.* 2003, Patel *et al.* 2003), have resulted in some confusion in relation to resistin's role in the development of obesity and insulin resistance. The majority of studies investigating a wider metabolic role of resistin is limited to rodents and humans, but data should be interpreted with caution when comparing these models and when extrapolating to other species.

In rodents resistin is abundantly expressed in adipose tissue and has been linked to reduced insulin tolerance, via increased hepatic glucose production through increased hepatic gluconeogenic enzymes PEPCK and G6Pase, and decreased AMPK activity (Rajala *et al.* 2003, Banerjee *et al.* 2004, Muse *et al.* 2004). Furthermore, resistin decreases glucose uptake by adipocytes (Steppan *et al.* 2001) and skeletal muscle (Moon *et al.* 2003, Pravenec *et al.* 2003) indicating that muscle, adipose tissue and liver contribute to impaired glucose sensitivity in rodents. In contrast, resistin mRNA expression in human adipocytes is comparably low (Nagaev & Smith 2001, Savage *et al.* 2001, McTernan *et al.* 2002). Although resistin altered proliferation of cultured human adipocytes (Ort *et al.* 2005), it did not affect glucose uptake or Akt phosphorylation (Ort *et al.* 2005), which raises the possibility that in humans resistin is not directly involved in glucose homeostasis in adipocytes. Resistin is however highly expressed in macrophages and monocytes (Savage *et al.* 2001, Patel *et al.* 2003) suggesting it may influence insulin resistance via effects on inflammation. Therefore, in rodents the direct role of resistin in obesity and glucose utilisation is more apparent than in humans, where it may be related to the functioning of adipose tissue rather than insulin resistance *per se*.

Adipokines and fertility

Evidence supporting a link between adipose-secreted adipokines and female fertility may be considered at four levels (Fig. 2) and is discussed here in this context; a) central effects on the hypothalamus and pituitary, b) peripheral effects on the ovary and reproductive tract, c) direct effects on the oocyte and the embryo and d) effects during pregnancy. Table 2 summarises our knowledge to date concerning the influence of sex hormones, puberty and the reproductive disorder polycystic ovary syndrome

(PCOS) on levels of leptin, adiponectin and resistin, in tissues and in circulation.

Fertility of transgenic and knock-out models

The first experiments to raise interest in adipokines and reproduction involved the reinstatement of fertility of otherwise infertile ob/ob mice (which do not produce leptin), with the exogenous administration of leptin to both female (Chehab *et al.* 1996) and male (Mounzih *et al.* 1997) mice. Transgenic female mice expressing 2–3 times the normal circulating levels of adiponectin are infertile (Combs *et al.* 2004) although the extent and nature of this fertility defect are not defined. Furthermore, various studies whereby adiponectin levels are ablated fail to describe any adverse fertility effects (Kubota *et al.* 2002, Ma *et al.* 2002, Maeda *et al.* 2002). The manipulation of resistin expression to increase or decrease protein levels in adipose tissue or liver, had no reported effect on fertility (Pravenec *et al.*, 2003, Banerjee *et al.* 2004, Rangwala *et al.* 2004). Thus a comprehensive study of any infertility or sub-fertility in the adiponectin or resistin modified models are yet to be completed but are warranted given the alignment of physiological functions of both adipokines with leptin.

Adipokine role in maturation and action of the hypothalamus and pituitary

Serum levels of leptin at puberty are generally increased in mice (Chehab *et al.* 1997), pigs (Qian *et al.* 1999) and cattle (Garcia *et al.* 2002), and are positively correlated to age of first period in women (Matkovic *et al.* 1997). Although there are some exceptions (Bronson 2001, Cheung *et al.* 2001) it is generally hypothesised that an elevation in leptin to a threshold level permits the activation of the hypothalamic–pituitary axis and the onset of puberty. Similar to serum levels of leptin, the expression of resistin in adipose tissue and the pituitary increased peri-pubertally in rodents (Morash *et al.* 2002, Nogueiras *et al.* 2003a). Plasma adiponectin levels in mice increase at puberty (Combs *et al.* 2003) in contrast to declining serum levels in boys and girls throughout puberty (Bottner *et al.* 2004). The mechanism responsible for the increase in mice appears to be common for both sexes, as the removal of the gonads prior to puberty did not affect its timing (Combs *et al.* 2003). Therefore a role for adipokines at the central level of the hypothalamus and pituitary in the regulation of pubertal development and subsequent cyclic female fertility is likely, and is explored herein.

Leptin's central role in fertility influences GnRH secretion by the hypothalamus and the pituitary secretion of gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Nagatani *et al.* 1998). The availability of nutrients influences this central effect, with fasting causing a decrease in leptin and LH levels in numerous species and the restoration of LH pulsatility

Figure 2 The potential interactions between adipokines and female reproduction. Expanded adipose tissue with obesity leads to an increase (↑) in leptin and resistin production, and a decrease (↓) in adiponectin production. The potential interactions between these adipokines and the hypothalamus, pituitary, ovary, oocyte and embryo, and the female reproductive tract may have direct effects (solid arrows) and indirect effects (dashed arrows) on female reproduction.

following leptin administration (Ahima *et al.* 1996, Amstalden *et al.* 2000, Henry *et al.* 2001, Whisnant & Harrell 2002). In the well-fed ruminant (Henry *et al.* 2001, Amstalden *et al.* 2002) and pig (Barb *et al.* 2004), leptin administration failed to alter LH secretion, in contrast to data in well-fed rodents. Experiments conducted *in vitro* using tissue from well-fed rodents and pigs, showed that leptin stimulated the release of gonadotrophin-releasing hormone (GnRH) from hypothalamic explants and cells (Yu *et al.* 1997, Barb 1999, Woller *et al.* 2001) and stimulated LH and FSH release from adenohypophyseal explants and cells (Yu *et al.* 1997, Barb 1999, De Biasi *et al.* 2001, Ogura *et al.* 2001), suggesting both the hypothalamus and the pituitary as central sites of leptin action. However, similar experiments using cells and explants from well-fed cattle showed no change in GnRH or gonadotrophin secretion in response to the administration of leptin (Amstalden *et al.* 2005). Thus, the central role of

leptin and the interactions between species and nutritional status remain to be explored further but suggest the possible development of central leptin resistance in ruminants when energy balance is positive or neutral (Amstalden *et al.* 2005).

Any prediction of a central role for adiponectin or resistin, interacting with GnRH and gonadotrophin production, or regulating energy metabolism is premature at this stage. However, a small number of studies have investigated expression and activity of these adipokines in cells from the hypothalamus and the pituitary. Studies using cultured rat hypothalamic neurons, failed to show a stimulatory effect of adiponectin on the production of various neurotransmitters involved in central energy metabolism, and this was in contrast to the enhanced production in response to resistin (Brunetti *et al.* 2004). Resistin mRNA expression has been localised to the pituitary and the hypothalamus, but expression of adiponectin by these

Table 2 The influence of sex hormones, puberty and the reproductive disorder poly-cystic ovary syndrome (PCOS) on levels of leptin, adiponectin and resistin, in tissues and in circulation.

	Adiponectin			Resistin			Leptin		
	mRNA and/or protein	Circulating levels	Authors	mRNA and/or protein	Circulating levels	Authors	mRNA and/or protein	Circulating levels	Authors
Female vs males		↑	Arita <i>et al.</i> 1999	↓		Nogueiras <i>et al.</i> 2003a,b		↑	Armellini <i>et al.</i> 2000
		↑	Huang <i>et al.</i> 2004		↑	Yannakoulia <i>et al.</i> 2003	↑		Gui <i>et al.</i> 2004
	↑	↑	Combs <i>et al.</i> 2003	↑		Gui <i>et al.</i> 2004		↑	Degawa-Yamauchi <i>et al.</i> 2003a
Puberty	↑	↑	Gui <i>et al.</i> 2004	↑		Morash <i>et al.</i> 2002		↑	Chehab <i>et al.</i> 1997
		↓	Combs <i>et al.</i> 2003	↑		Brown <i>et al.</i> 2005		↑	Garcia <i>et al.</i> 2002
			Bottner <i>et al.</i> 2004	↑		Nogueiras <i>et al.</i> 2003a		↑	Qian <i>et al.</i> 1999
Oestrogen		↓	Combs <i>et al.</i> 2003	↓		Huang <i>et al.</i> 2005	↑		Matkovic <i>et al.</i> 1997
	↑	–	Gui <i>et al.</i> 2004	↓	–	Gui <i>et al.</i> 2004	↑	–	Kristensen <i>et al.</i> 1999
Androgens	–	–	Gui <i>et al.</i> 2004	↑		Ling <i>et al.</i> 2001	↑		Gui <i>et al.</i> 2004
		↓	Nishizawa <i>et al.</i> 2002	–	–	Gui <i>et al.</i> 2004	–	↑	Murakami <i>et al.</i> 1995
		↓	Bottner <i>et al.</i> 2004				–		Gui <i>et al.</i> 2004
		↓	Page <i>et al.</i> 2005						Kristensen <i>et al.</i> 1999
PCOS vs normal†		–	Orio <i>et al.</i> 2003	↑		Seow <i>et al.</i> 2004		–	Murakami <i>et al.</i> 1995
		↓	Carmina <i>et al.</i> 2005		↑	Carmina <i>et al.</i> 2005		–	Carmina <i>et al.</i> 2005
		↓	Sieminska <i>et al.</i> 2004		–	Seow <i>et al.</i> 2005		–	Chapman <i>et al.</i> 1997
		↓	Sepilian & Nagamani 2005		↑	Munir <i>et al.</i> 2005		↑	Remsberg <i>et al.</i> 2002
								↑	Vicennati <i>et al.</i> 1998
									Brzechffa <i>et al.</i> 1996

↑ = increased levels; – = decreased levels; - = no change in levels of adipokines.

† PCOS and normal ovulating women were BMI and age matched.

tissues has not yet been reported. Resistin expression levels were low in mouse pituitary at birth, increasing to peak levels at puberty, in contrast to the consistent expression by cells of the hypothalamus throughout development (Morash *et al.* 2002). The changes in expression by the pituitary around the time of puberty require signals from the hypothalamus, as was demonstrated by an absence of resistin expression in peri-pubertal mice with ablated hypothalamic cells (Morash *et al.* 2002). Furthermore, the reduction in pituitary levels of resistin in obese mice compared with control mice (Morash *et al.* 2004) and the co-localisation of resistin protein in rodent hypothalamus with neurons involved in feeding behaviour (Wilkinson *et al.* 2005) give weight to a link between resistin and the central control of feeding and obesity. Although a report in male rodents suggests that expression of resistin in the testis is regulated by the pituitary hormones LH and FSH (Nogueiras *et al.* 2004), like studies in female reproductive tissue are yet to be documented. Further exploration of resistin's role in central energy metabolism, and gonadotrophin production will undoubtedly provide insight into its function in puberty attainment and the regulation of female fertility.

The central expression of adiponectin and its receptors in the hypothalamus and pituitary are yet to be completely explored but studies in mice suggest unaltered feed intake by mice lacking (Kubota *et al.* 2002, Maeda *et al.* 2002) or mice over-expressing (Combs *et al.* 2004) adiponectin protein. In addition, both the central and peripheral administration of adiponectin protein failed to influence feed intake of obese mice (Masaki *et al.* 2003). This was in contrast to similar studies of leptin, whereby its central function via the hypothalamus resulted in reduced intake of food in well-fed ruminants (Henry *et al.* 1999, Morrison *et al.* 2001), pigs (Barb *et al.* 1998, Ramsay *et al.* 2004, Weber & Spurlock 2004) and rodents (Pellemounter *et al.* 1995, Mistry *et al.* 1997). As discussed in the Adiponectin section above, one known pathway through which adiponectin functions in peripheral tissues is via the cellular nutrient-sensor AMPK. Leptin too operates via this pathway, and in the hypothalamus it inhibits AMPK activation causing a reduction in food intake (Andersson *et al.* 2004). In contrast to this central action, leptin stimulates AMPK activation in skeletal muscle, (Minokoshi *et al.* 2002), a stimulation mirrored by adiponectin in various peripheral tissues (Tomas *et al.* 2002, Yamauchi *et al.* 2002, Wu *et al.* 2003). Given that both adipokines function to stimulate AMPK in peripheral tissues, it is conceivable that adiponectin in fact influences energy utilisation centrally via the same AMPK mechanism as leptin in the hypothalamus.

The underlying cause of reduced fertility in models of diet-induced obesity are important because unlike the *ob/ob* and *db/db* monogenic mutations researched extensively to date, human and rodent obesity results from complex interactions between genetics and the environment. Such obesity is often characterised by high circulat-

ing levels of leptin and increased leptin resistance (Halaas *et al.* 1997, Van Heek *et al.* 1997, Heymsfield *et al.* 1999, Hukshorn *et al.* 2000). A report by Tortoriello and colleagues discussed the development of leptin resistance and acquired obesity in a diet-induced animal model of obesity, with a rare and specific focus on fertility (Tortoriello *et al.* 2004). Diet-induced obesity exerted a greater effect on fertility in female mice compared with males. This was linked more closely to hyperleptinemia than hyperinsulinemia, and was overcome with GnRH stimulation, suggesting causes other than ovarian or uterine dysfunction for the infertility observed in this model (Tortoriello *et al.* 2004). Despite previous studies of diet-induced obesity in rodents failing to agree with regards to altered hypothalamic leptin receptor expression (El-Haschimi *et al.* 2000, Martin *et al.* 2000), the cause of infertility in this study was related to decreased leptin receptor expression and increased neuropeptide-Y levels in the hypothalamus, that is, reduced central leptin sensitivity and decreased GnRH pulsatility.

Adipokine role in the ovary and reproductive tissue

In general, the effects of adipokines on the process of ovulation, ovarian steroidogenesis and the maintenance of pregnancy have received limited attention. Reduced ovulation rate in *in vivo* experiments in which leptin was administered to intact rats, and *in vitro* culture studies of whole ovaries perfused with leptin, indicate a direct role for leptin in the ovulation process, independent of any change in steroid production (Duggal *et al.* 2000). In addition a recent report in mice that were deficient in GnRH indicated an effect of leptin on ovulation independent of GnRH and LH that involved a local function in the ovary, such as induction of ADAMTS-1 (a disintegrin and metalloproteinase with a thrombospondin-like motif), although other undefined hypothalamic pathways could not be excluded (Barkan *et al.* 2005). As yet, there are no similar mechanistic studies of the function of resistin or adiponectin in the process of ovulation. Furthermore, data concerning serum and local levels of adipokines in the ovary, with regards to the anovulatory disorder in humans poly-cystic ovary syndrome (PCOS) are not always clear, as is summarised in Table 2. Therefore, this remains as a significant area for future investigation.

The fat-soluble steroid hormones are produced by ovary cell steroidogenesis, and the adipocyte derived adipokines may have a localised function in this process. Expression of both leptin mRNA and protein in granulosa and theca cells, support this possibility (Cioffi *et al.* 1997, Karlsson *et al.* 1997). Leptin influences steroidogenesis in isolated ovarian cells by modulating the metabolic actions of insulin and IGF-I and the stimulatory actions of gonadotrophins in cattle (Spicer & Francisco 1997, 1998, Spicer *et al.* 2000), pig (Gregoraszczuk *et al.* 2003, 2004), rodent (Zachow & Magoffin 1997, Duggal *et al.* 2002) and human (Agarwal *et al.* 1999, Guo *et al.* 2001, Tsai *et al.*

2002). Furthermore in humans, blood leptin levels correlate closely with those of progesterone throughout the menstrual cycle, and with both oestradiol and human choriongonadotrophin (hCG) throughout pregnancy (Hardie *et al.* 1997).

A role for adiponectin in ovarian steroidogenesis is yet to be described but an interaction is likely given the negative effects of testosterone on circulating adiponectin in humans (Lanfranco *et al.* 2004, Page *et al.* 2005) and mice (Nishizawa *et al.* 2002). Such an interaction has been demonstrated by resistin, which has stimulatory effects on testosterone production by cultured human theca cells that synergise with insulin (Munir *et al.* 2005). Furthermore, resistin dose-dependently increased the production of testosterone by cultured rat testis (Nogueiras *et al.* 2004), and the adrenal androgen dehydroepiandrosterone (DHEA) reduced mRNA expression of resistin in adipose tissue taken from rats (Kochan & Karbowska 2004).

Studies of the expression and activity of adipokines in the oviduct and endometrium are limited to leptin. Leptin and its receptors (mRNA and protein) are expressed in the oviduct (Kawamura *et al.* 2002, Craig *et al.* 2005) and the endometrium (Gonzalez *et al.* 2000, Kawamura *et al.* 2002, Cerevo *et al.* 2005), suggesting possible involvement in endometrial receptivity for the developing embryo.

Adipokine role in oocyte quality and embryo development

The discovery of leptin expression in mature human oocytes, combined with a post-ovulatory surge in its circulating levels (Cioffi *et al.* 1997), indicate that leptin may also effect maturation of the oocyte and influence early embryo development. Studies in humans, rodents and pigs have shown mRNA and/or protein expression for the leptin receptors in oocytes and developing early embryos (Kawamura *et al.* 2002, Cerevo *et al.* 2005, Craig *et al.* 2005), and leptin expression itself in the rodent blastocyst (Cioffi *et al.* 1997, Ryan *et al.* 2002), with some variability related to species. Some conflict surrounds the nature of leptin's direct role in oocyte maturation, in different rodent species and between cultured whole follicles and oocytes (Ryan *et al.* 2002, Duggal *et al.* 2002, Swain *et al.* 2004). There are also conflicting reports concerning whether leptin enhances (Kawamura *et al.* 2002) or impedes (Fedorcsak & Storeng 2003) development of the pre-implantation mouse embryo but in the pig, leptin improves oocyte nuclear maturation via the MAPK pathway and increases embryo development *in vitro* (Craig *et al.* 2004).

Adiponectin receptors R1 and R2 are weakly expressed in the pig ovary (Lord *et al.* 2005), and to date this is the only documentation of expression in ovarian tissue or oocytes. Given that AMPK activity has been described in oocytes, coincident with germinal vesicle breakdown and induction of meiosis in preparation for fertilisation

(Downs *et al.* 2002), adiponectin may be involved in regulation of oocyte nutrient-sensing via the AMPK pathway. There have been no reports to date of resistin expression in the ovary, oocyte or embryo of any species. This highlights a basic gap in our knowledge of how adipokines may regulate nutrient use for the developing oocyte and embryo.

Adipokines in pregnancy

Pregnancy invokes a large shift in maternal metabolism, which enables the provision of appropriate nutrients to the developing fetus as well as providing for physiological maintenance of the mother and preparation for lactation. Investigation of adipokines such as leptin, adiponectin and resistin in this metabolic shift is not a focus of this review but is an important aspect of fertility reviewed most notably for the role of leptin (Sagawa *et al.* 2002). The developing placenta expresses both leptin and its receptor (Masuzaki *et al.* 1997, Senaris *et al.* 1997) and placental resistin production has been reported recently in humans (Yura *et al.* 2003). Resistin serum and placental levels increases as pregnancy progresses (Yura *et al.* 2003), which is in contrast to levels of leptin (Masuzaki *et al.* 1997). These levels correlate with the state of reduced insulin sensitivity often developed in the latter stages of pregnancy, thus contributing to successful development of the fetus (Yura *et al.* 2003). Adiponectin and its receptors (R1 and R2) have also recently been localised to the placenta of humans and rats (Caminos *et al.* 2005), and the uterus of pigs (Lord *et al.* 2005). In the rat, placental expression of adiponectin mRNA increased during pregnancy and decreased in response to feed restriction, whereas the AdipoR2 receptor expression decreased during pregnancy but remained unchanged during under-nutrition (Caminos *et al.* 2005), adding support for numerous roles of these adipokines in the maintenance of a normal pregnancy.

Conclusion

The adipokines leptin, adiponectin and resistin produced by adipose tissue and altered with obesity, clearly influence energy homeostasis and undoubtedly affect female fertility. Leptin alters GnRH and gonadotrophin production, and has a complexity of roles in the functioning of the ovary and endometrium, as well as in embryo development. The expansive influence on female fertility uncovered by leptin research has potential implications for other adipokines, which themselves operate similarly to regulate energy metabolism. The paucity of information implicating a role for adiponectin and resistin at any central or local level of female reproduction makes any firm statements at this time precarious in nature. That aside, current limited data implicate resistin in placental and ovarian function, and its localisation in the brain, suggest possible peripheral and central effects in the control of

energy metabolism and fertility. Evidence to date does not support a central role for adiponectin but recently the expression of its receptors in the ovary and its signalling via the AMPK nutrient-sensing pathway in other peripheral tissues, indicate future avenues for adiponectin research. Finally, amongst all the unknowns and anomalies regarding the biological activities of these adipokines in female fertility, there is but one point of clarity-adipokine research in relation to reproduction is very fertile ground for future exploration.

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