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.

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, Zaatstra 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
circularing 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 aetiologies 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, Stepan & 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.

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Adiponectin mRNA and/or Protein</th>
<th>Circulating Levels</th>
<th>Author</th>
<th>Resistin mRNA and/or Protein</th>
<th>Circulating Levels</th>
<th>Author</th>
<th>Leptin mRNA and/or Protein</th>
<th>Circulating Levels</th>
<th>Author</th>
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<td>Obese Human</td>
<td>↓</td>
<td>↓</td>
<td>Liu et al. 2003</td>
<td>↑</td>
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<td>Savage et al. 2001</td>
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<td>Pagano et al. 2005</td>
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<td>Pig</td>
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<td>Makimura et al. 2002</td>
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<td>↑</td>
<td>Le Lay et al. 2001</td>
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<td>↑</td>
<td>Maebuchi et al. 2003</td>
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<tr>
<td>Rodents</td>
<td>↓</td>
<td>–</td>
<td>Raitakari et al. 2004</td>
<td></td>
<td></td>
<td>Lee et al. 2003</td>
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<td>↑</td>
<td>Wadden et al. 1998</td>
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<tr>
<td>Pig</td>
<td></td>
<td></td>
<td>Wolfe et al. 2004</td>
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<td>↑</td>
<td>Considine et al. 1996</td>
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<td></td>
<td>↑</td>
<td>–</td>
<td>Xydakis et al. 2004</td>
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<td>Milan et al. 2002</td>
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<td>↑</td>
<td>Maffei et al. 1995</td>
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<td>Makimura et al. 2002</td>
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<td>Rajala et al. 2004</td>
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<td>Milan et al. 2002</td>
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<td>Makimura et al. 2002</td>
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<td></td>
<td></td>
<td></td>
<td>Chen et al. 2004</td>
<td></td>
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</tbody>
</table>

↑ = increased levels; ↓ = decreased levels; – = no change in levels of adipokines.
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 (Gerstmayer 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 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 poly-cystic 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.
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 adenohypophysial 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 cells and tissues has not been investigated.
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.

<table>
<thead>
<tr>
<th>Adiponectin mRNA and/or protein</th>
<th>Circulating levels</th>
<th>Authors</th>
<th>Resistin mRNA and/or protein</th>
<th>Circulating levels</th>
<th>Authors</th>
<th>Leptin mRNA and/or protein</th>
<th>Circulating levels</th>
<th>Authors</th>
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<tbody>
<tr>
<td>Female vs males</td>
<td>↑</td>
<td>Arita et al. 1999</td>
<td>↓</td>
<td>Nogueiras et al. 2003a,b</td>
<td>↑</td>
<td>Armellini et al. 2000</td>
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<td></td>
<td>↑</td>
<td>Huang et al. 2004</td>
<td>↑</td>
<td>Yannakoula et al. 2003</td>
<td>↑</td>
<td>Gui et al. 2004</td>
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<td></td>
<td>↑</td>
<td>Combs et al. 2003</td>
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<td>Gui et al. 2004</td>
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<td>Degawa-Yamauchi et al. 2003a</td>
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<td>↑</td>
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<td>↑</td>
<td>Nogueiras et al. 2003a</td>
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<td>Qian et al. 1999</td>
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<td></td>
<td>↑</td>
<td>Gui et al. 2004</td>
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<td>Gui et al. 2004</td>
<td>↑</td>
<td>Kristensen et al. 1999</td>
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<td>Androgens</td>
<td>–</td>
<td>Gui et al. 2004</td>
<td>↑</td>
<td>Ging et al. 2001</td>
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<td>Gui et al. 2004</td>
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<td>↑</td>
<td>Nishizawa et al. 2002</td>
<td>↑</td>
<td>Gui et al. 2004</td>
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<td>Murakami et al. 1995</td>
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<td></td>
<td>↑</td>
<td>Bottner et al. 2004</td>
<td>–</td>
<td>–</td>
<td>↑</td>
<td>Kristensen et al. 1999</td>
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<tr>
<td>PCOS vs normal†</td>
<td>–</td>
<td>Orio et al. 2003</td>
<td>↑</td>
<td>Seow et al. 2004</td>
<td>–</td>
<td>Carmina et al. 2005</td>
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<td></td>
<td>↑</td>
<td>Sieminska et al. 2004</td>
<td>↑</td>
<td>Seow et al. 2005</td>
<td>↑</td>
<td>Rensberg et al. 2002</td>
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</table>

↑ = 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 (Pelleymounter 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 circulating 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.

2002). Furthermore in humans, blood leptin levels correlate closely with those of progesterone throughout the menstrual cycle, and with both oestradiol and human chorionic gonadotrophin (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 undernutrition (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 signaling 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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