Adipokine inflammation and insulin resistance: the role of glucose, lipids and endotoxin

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Abstract

Adipose tissue is an active endocrine organ, and our knowledge of this secretory tissue, in recent years, has led us to completely rethink how our body functions and becomes dysregulated with weight gain. Human adipose tissue appears to act as a multifunctional secretory organ with the capacity to control energy homoeostasis through peripheral and central regulation of energy homoeostasis. It also plays an important role in innate immunity. However, the capability to more than double its original mass to cope with positive energy balance in obesity leads to many pathogenic changes. These changes arise within the adipose tissue as well as inducing secondary detrimental effects on other organs like muscle and liver, including chronic low-grade inflammation mediated by adipocytokines (adipokine inflammation). This inflammation is modulated by dietary factors and nutrients including glucose and lipids, as well as gut bacteria in the form of endotoxin or LPS. The aim of this current review is to consider the impact of nutrients such as glucose and lipids on inflammatory pathways, specifically within adipose tissue. Furthermore, how nutrients such as these can influence adipokine inflammation and consequently insulin resistance directly through their effects on secretion of adipocytokines (TNFα, IL6 and resistin) as well as indirectly through increases in endotoxin is discussed.

Key Words
- Adipokine
- Insulin resistance
- Inflammation
- Lipotoxicity
- Endotoxin

Journal of Endocrinology
(2013) **216**, T1–T15

Evolution and inflammation

Chronic low-grade inflammation is thought to be key in the pathogenesis of insulin resistance, type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) that is associated with obesity-mediated diabetes (Hotamisligil 2006, Ouchi *et al*. 2011). The role of adipose tissue as an endocrine organ, secreting numerous hormones and pro-inflammatory cytokines (adipokines), seems to be central to subclinical inflammation in adipose tissue. And while obesity exacerbates this process, the mediators and underlying mechanisms for this appears to be a complex multifactorial phenomenon (Hotamisligil 2006, Nishimura *et al*. 2009, Ouchi *et al*. 2011).

It is clear that during weight gain, our normal physiological response to inflammatory insults misalign but our understanding as to why this occurs is incomplete. It is clear that immunity has an important protective role within the human body, and an inflammatory response coordinates more efficient wound healing as well as response to infections. From an evolutionary perspective,

http://www.joe.endocrinology-journals.org
DOI: 10.1530/JOE-12-0498

Published by Bioscientifica Ltd.
This paper is one of three papers that form part of a thematic review section on Adipokines. The Guest Editor for this section was Simon Dunmore, Diabetes and Metabolic Disease Research Group, University of Wolverhampton, UK.

the immune function is heavily preserved across species with *Drosophila melanogaster* (commonly known as the fruit fly) providing valuable insight into immune function. Approximately 75% of human disease-related genes have a recognisable match in the genome of *Drosophila* (Reiter *et al*. 2001), and *Drosophila* have been used as a genetic model for several human disease mechanisms underlying aging, oxidative stress, immunity, T2DM and heart disease (Tanji & Ip 2005, Kühnlein 2010, Diop & Bodmer 2012). The *D. melanogaster* immune system can be divided into two innate immune responses: humoral and cell mediated. The former is a systemic response mediated through the Toll and immune deficiency (Imd) pathways, which are parallel systems for detecting microbes. The Toll and Imd pathways are homologous to the mammalian Toll-like receptor (TLR) and tumour necrosis factor receptor (TNFR) signalling pathways respectively and are essential for *Drosophila* to survive infection. Spatzle, a known ligand for the Toll pathway in flies, is produced in response to Gram-positive bacteria, parasites and fungal infection. Upon infection, pro-Spatzle is cleaved by protease Spatzle processing enzyme (SPE) to become active Spatzle, which then binds to the Toll receptor located on the cell surface of the fat body and the haemocytes and dimerises for activation of downstream nuclear factor-kappa B (NF-κB) signalling pathways (a key factor that regulates the transcription of numerous pro-inflammatory cytokines/adipokines). Although the pathway of innate immune activation via TLRs is different in mammalian physiology, it leads to the same activation of the NF-κB signalling pathways (Tanji & Ip 2005, O'Neill *et al*. 2009). Of note, the *Drosophila* fat body performs the function of the mammalian liver, haematopoietic, immune system and adipose tissue as one whole unit; in mammals, each of these tissues have become highly specialised, yet their functions often overlap, particularly in the case of immunity, which in both the *Drosophila* and the mammal are vital to survival (Hotamisligil 2006). Therefore, the need to conserve the immune functions across species and evolution appears paramount. Specifically, in the case of human adipose tissue, this tissue is an active site of innate immune response, through activation of TLRs and downstream NF-κB signalling, with the pre-adipocytes preserving phagocytic type qualities and responding to inflammatory insults. In addition, adipose tissue also contains a large number of macrophages and thus may support the function as a first line of defence against superficial wounds or stimuli. As adipose tissue may lie directly underneath the basal epidermal membrane, across the human body, this would allow a quick inflammatory response to wound damage and limit infection effectively. From an evolutionary perspective, in mammals, the subcutaneous locality of adipose tissue to promote local wound healing would seem an advantage. However, obesity alters normal physiology and development of abdominal adipose tissue appears to exacerbate the inflammatory response, and the underlying cause for this has been the subject of considerable research.

Adipose tissue: a site of inflammation

From previous studies, it is well established that when there is an expansion of adipose tissue, such as that observed in obesity, there is a sustained inflammatory response accompanied by adipokine dysregulation, which leads to chronic subclinical inflammation as well as insulin resistance (Shoelson *et al*. 2006). Although BMI as a measure of obesity is a good predictor of all-cause and cardiovascular mortality, as recently described in two separate meta-analyses (ProspectiveStudiesCollaboration 2009, Berrington de Gonzalez *et al*. 2010), overall mortality and especially cardiovascular mortality seems to be better predicted by abdominal or central obesity in addition to BMI (Koster *et al*. 2008, Pischon *et al*. 2008, Czernichow *et al*. 2011). This highlights the importance of the site of deposition of adipose tissue and how the locality of the adipose tissue affects such function, as all fat depots are not equal in terms of their function and pathogenic nature. There are several sites of subcutaneous white adipose tissue, including the abdomen, thigh, mammary region, gluteofemoral adipose tissue as well as epidermal, while visceral abdominal depots comprise omentum, mesenteric and peri-renal adipose tissue. Adipose tissue also lies on the heart (epicardial adipose tissue) (Baker *et al*. 2009) and brown or beige/brite adipose tissue has recently been described in adult humans that, unlike white adipose tissue, provides the release of energy via non-shivering thermogenesis (Cypess *et al*. 2009, van Marken Lichtenbelt *et al*. 2009, Wu *et al*. 2012*a*).

Many previous studies have also described visceral adipose tissue activity as a key determinant of metabolic risk (Peiris *et al*. 1989, Després *et al*. 1990, 2000, Couillard *et al*. 1996, Wajchenberg 2000, Smith *et al*. 2001). However, many of these initial studies were examining triglyceride turnover in visceral fat as the marker of metabolic risk, and this may not be relevant for adipokine release or take into account the size of abdominal subcutaneous fat and the pathogenic nature of this tissue (Fisher *et al*. 2002, Harte *et al*. 2003*a*,*b*, McTernan *et al*. 2003, Kos *et al*. 2007, 2009, Jernås *et al*. 2009,

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DOI: 10.1530/JOE-12-0498

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Saiki *et al*. 2009, Carobbio *et al*. 2011, McGee *et al*. 2011). While gluteofemoral subcutaneous fat is considered to have a protective effect and reduce metabolic risk – with the classic pear-shaped obesity and lower waist:hip ratio (Manolopoulos *et al*. 2010) – abdominal subcutaneous adipose tissue appears to be more active than previously thought, secreting a multitude of pro-inflammatory adipocytokines (Fisher *et al*. 2002, Harte *et al*. 2003*a*,*b*, McTernan *et al*. 2003, Kos *et al*. 2007, 2009, Jernås *et al*. 2009, Saiki *et al*. 2009, McGee *et al*. 2011, Youssef-Elabd *et al*. 2012). There is expansion of the adipose tissue depots in obesity with both hyperplasia and hypertrophy, coupled with increased macrophage infiltration and, consequently, inflammation. Although obesity can lead to an expansion of the visceral depot to as much as 20% total fat mass, subcutaneous adipose tissue accounts for the remaining 80% and also responds to inflammatory insults (Mlinar & Marc 2011). Furthermore, while adipose tissue from lean individuals may preferentially secrete anti-inflammatory adipokines such as adiponectin, transforming growth factor β (TGFβ), interleukin 10 (IL10), IL4, IL13, ILRa and apelin, in obesity pro-inflammatory adipocytokines such as TNFα, IL6, leptin, visfatin, resistin, angiotensin II and plasminogen activator inhibitor 1 are released, as well as several interleukins (Ouchi *et al*. 2011) coupled with a reduction in secretion of anti-inflammatory adipokines (Table 1).

It would also appear that adipokines have different functions in normal-weight individuals and in the obese. In lean individuals, adipokines mediate physiological functions while in states of metabolic disease the adipokines have altered effects, modulating insulin resistance either directly by affecting the insulin signalling pathway or indirectly via stimulation of inflammatory pathways. Serine phosphorylation of insulin receptor substrate (IRS) 1 by various adipokines directly or via inflammatory pathways including the c-Jun N-terminal kinases (JNK) pathway and I-Kappa B kinase β (IKKβ)/NF-κB pathway disrupts the insulin signalling pathways, possibly giving rise to insulin resistance (Pirola *et al*. 2004, Tilg & Moschen 2008, Kalupahana *et al*. 2012).

Mediators of adipokine release and systemic inflammation

The importance of adipocytes and recruitment of macrophages into adipose tissue and their impact on innate immunity and the inflammation response are now widely recognised, even though there is controversy over the precise sequence of events in the pathogenesis and also the role of the different cells involved. There is also now a much improved understanding of the impact of glucotoxicity and lipotoxicity as key factors leading to the pathogenesis of obesity-mediated diabetes that is likely to be a consequence of subclinical inflammation in adipose tissue. Approaches to a reductionist explanation of the pathogenesis of 'diabesity' overlooks the sheer complexity of the disorder – the potential crosstalk of insults, such as glucose and lipids and their impact on inflammatory pathways. These next sections will elaborate on the impact of glucose, lipids and gut-derived bacteria – endotoxin – and their effects on inflammatory pathways, as this review evaluates the triple insult of these factors on T2DM pathology. Figure 1 gives an overview of the effect of glucose, lipids and endotoxin on adipokine inflammation and insulin resistance.

The effect of glucose on adipokine inflammation

The presence of T2DM or impaired glucose tolerant (IGT) confers a state of chronic low-grade inflammation as well as higher cardiovascular risk. A raised HbA1c, a measure of hyperglycaemia, has been linked with increased cardiovascular mortality and morbidity in various studies (Stratton *et al*. 2000, Selvin *et al*. 2004, Gerstein *et al*. 2005). Hyperglycaemia occurs in tandem with hyperinsulinaemia, although in T2DM subjects given low levels of exogenous insulin to produce normoglycaemia there was a reduction in TLR expression in mononuclear cells (Ghanim *et al*. 2008). However, hyperinsulinaemia has been associated with increased inflammation, for example in patients with T2DM. In healthy individuals, hyperinsulinaemic euglycaemic clamps resulted in a significantly increased IL6 response when endotoxin was infused (Soop *et al*. 2002). Furthermore, insulin is known to increase lipogenesis and increase triglyceride synthesis, further fuelling free fatty acid-mediated inflammation. Free fatty acids are also implicated in inflammation and insulin resistance, as described later in this review. While hyperglycaemia can induce oxidative stress (Dandona *et al*. 2007), studies have shown that acute hyperglycaemia can increase pro-inflammatory adipokines such as IL6 and TNFα levels in non-diabetic as well as IGT subjects (Esposito *et al*. 2002) and IL6 in non-diabetic and T2DM subjects (Ruge *et al*. 2009).

The activation of these pro-inflammatory factors has been investigated *in vitro*, with hyperglycaemic-type conditions shown to activate the innate immune pathway in abdominal subcutaneous adipose tissue as well as isolated abdominal subcutaneous adipocytes, as denoted

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DOI: 10.1530/JOE-12-0498

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Table 1 List of adipokines. Adapted and updated from Frühbeck *et al*. (2001) and Kusminski *et al*. (2007)

Adipokine	Function/effect	Distribution	Effect of obesity	Evidence
Leptin	Satiety signal. Promotes increased energy expenditure	Secreted predominantly by WAT, Sc AT > Om AT. Also derives from BAT, skeletal muscle, stomach and plasma	↑ In human obesity, correlates with BMI, ↓after fasting or weight loss	Meier & Gressner (2004) and Mantzoros *et al*. (2011)
Adiponectin	Improves energy homoeostasis, insulin sensitivity and glucose uptake. Anti-inflammatory properties	Secreted exclusively by adipocytes. mRNA and protein in Sc AT > Om AT. 2–3x greater secretion in females	↓ In mouse models of obesity and insulin resistance (ob/ob and db/db). ↓ In human obesity and T2DM. ↑ After weight loss	Fisher *et al*. (2002), Spranger *et al*. (2003) and Whitehead *et al*. (2006)
TNFα	Reduces insulin secretion and insulin sensitivity. Stimulates lipolysis	Predominantly expressed by macrophages. Also expressed by WAT adipocytes, Sc AT > Om AT	Correlates with BMI, ↑ in human obesity: obese (2X) > lean. ↓ Adipose differentiation	Hotamisligil *et al*. (1993), Hube & Hauner (1999) and Tzanavari *et al*. (2010)
IL6	Affects glucose and lipid metabolism. Improves insulin sensitivity and glucose tolerance	35% of the basal supply is derived from WAT. Produced by macrophages, fibroblasts, endothelial cells and skeletal muscle cells	↑ In morbidly obese patients. ↓ After weight loss	Fried *et al*. (1998), Bastard *et al*. (2000) and Eder *et al*. (2009)
Resistin	Affects glucose metabolism and causes insulin resistance in rodents. In humans, it acts more as a pro-inflammatory cytokine	In rodents, secreted by WAT. In humans, secreted in macrophages and WAT	↑ In human obesity, metabolic syndrome, T2DM and CVD	McTernan *et al*. (2002*a*, 2006) and Schwartz & Lazar (2011)
PAI-1	Potent inhibitor of fibrinolytic pathway	Expressed by Sc and Om AT. Positive correlation with abdominal adiposity	↑ In human obesity, metabolic syndrome and T2DM	Shimomura *et al*. (1996) and Alessi *et al*. (2007)
IL8	Neutrophil chemotaxis and degranulation. Pro-atherogenic	Predominantly macrophages and monocytes. Adipocytes: Om > Sc	↑ In obesity, positively correlates with BMI and TNFα	Straczkowski *et al*. (2002), Bruun *et al*. (2004) and Fain (2010)
RBP4	Implicated in insulin resistance as well as increased hepatic glucose output and impaired muscle insulin signalling	Secreted by adipocytes, macrophages and liver	↑ In obesity and insulin resistance	Yang (2005) and Graham *et al*. (2006)
TGFβ	Varied role in proliferation, differentiation, apoptosis and development	Multifunctional, produced by variety of cells. Inhibitor of differentiation	↑*ob/ob* and *db/db* mice. ↑ Preadipocyte cell proliferation, as with TNFα	Sporn *et al*. (1987) and Fain *et al*. (2005)
MCP1	Increases insulin resistance, macrophage infiltration in adipose tissue and hepatic steatosis	Secreted by WAT	↑ *ob/ob* and *db/db* mice. ↑ In obesity, T2DM and CVD	Kanda *et al*. (2006) and Panee (2012)
RANTES	Pro-inflammatory	Secreted by T cells, monocytes and to a lesser degree in WAT	No correlation of serum levels with obesity although ↑ gene expression in adipose tissue	Madani *et al*. (2009)
Visfatin/PBEF/ NAMPT	Pro-inflammatory and insulin mimicking	Secreted by adipocytes	↑ In obesity	Chang *et al*. (2011) and McGee *et al*. (2011)
Chemerin	Affects adipogenesis, inflammation as well as glucose metabolism	Secreted by WAT	↑ In obesity	Catalán *et al*. (2011) and Roman *et al*. (2012)
Vaspin	Improves insulin sensitivity	Secreted by WAT Om > Sc. Also secreted in skin, hypothalamus, pancreatic islets and stomach	↑ In obesity, insulin resistance and T2DM	Blüher (2012)
Nesfatin	Acts centrally to reduce appetite	Secreted in brain tissue, β cells and adipose tissue	↓ In obesity, T2DM and PCOS	Li *et al*. (2010), Ramanjaneya *et al*. (2010) and Deniz *et al*. (2012)
Omentin	Increases insulin sensitivity	Secreted by omental adipose tissue	↓ In obesity	de Souza Batista *et al*. (2007)

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Table 1 *Continued*

Adipokine	Function/effect	Distribution	Effect of obesity	Evidence
Apelin	Improves insulin sensitivity mainly acting in skeletal muscle and adipocytes in mice	Produced in a wide range of tissue	↑ In obesity, impaired glucose tolerance and T2DM. ↓ After weight loss following diet or bariatric surgery	Boucher *et al*. (2005), Castan-laurell *et al*. (2012)

AT, adipose tissue; WAT, white adipose tissue; BAT, brown adipose tissue; Sc, subcutaneous; Om, omental; T2DM, type 2 diabetes mellitus; PCOS, polycystic ovarian syndrome; CVD, cardiovascular disease; TNFα, tumour necrosis factor α; IL6, interleukin 6; PAI-1, plasminogen activator inhibitor 1; IL8, interleukin 8; TGFβ, transforming growth factor β; MCP1, monocyte chemotactic protein 1; RANTES, regulated on activation, normal T cell expressed and secreted protein; PBEF, Pre B cell colony-enhancing factor; NAMPT, nicotinamide phosphoribosyltransferase.

by increased TLR4 receptor expression as well as NF-κB and IKKβ activity (Youssef-Elabd *et al*. 2012). Studies in monocytes have also shown that high-glucose conditions increased the production of IL6 and TNFα (Morohoshi *et al*. 1996), increased the mRNA and protein expression of TLR2 and TLR4 and activated the NF-κB pathway (Dasu *et al*. 2008).

Studies have further demonstrated that a change in diet, which impacts on glucose levels and subsequently lowers insulin levels, also reduces systemic inflammation (Bouché *et al*. 2002, Qi *et al*. 2006, de Mello *et al*. 2008, Heggen *et al*. 2012, Neuhouser *et al*. 2012). While it is established that a lower glycaemic index (GI) weight loss diet tends to reduce both the rate of absorption of glucose

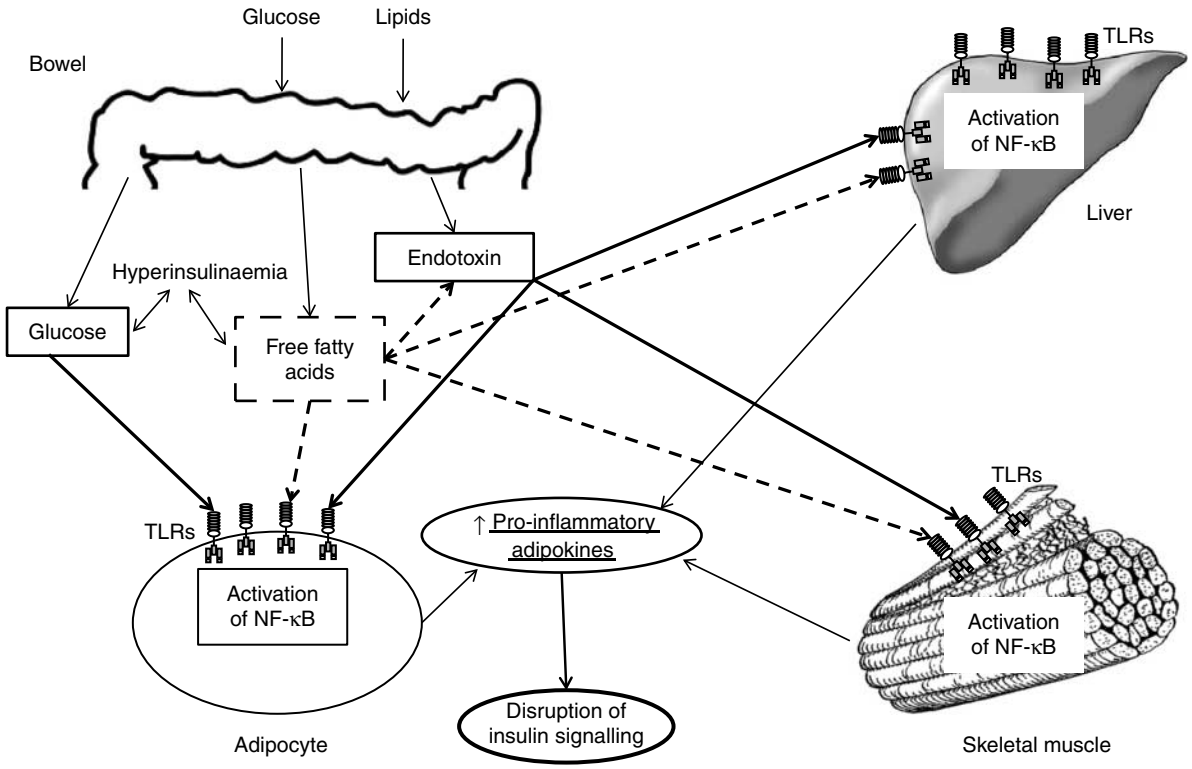

Figure 1
Overview of the effect of glucose, lipids and endotoxins on inflammation in the adipocyte, liver and skeletal muscle. Dietary glucose and lipids result in absorption of glucose, free fatty acids and leakage of endotoxins into the systemic circulation. Glucose activates NF-κB in the adipocytes via TLR activation, whereas free fatty acids and endotoxins activate NF-κB in the adipocytes, liver and skeletal muscle via TLR activation. Increased glucose results in hyperinsulinaemia, which in turn can result in an increased level of free fatty acids. Free fatty acids also have a role in increasing the endotoxin levels. Activation of NF-κB leads to release of pro-inflammatory adipokines from the adipocytes, liver and muscle, which in turn leads to disruption in insulin signalling in all three tissues, leading to insulin resistance.

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DOI: 10.1530/JOE-12-0498

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into the body and glucose load into tissue, subsequently reducing hyperinsulinaemia, there is also an observed reduction in systemic inflammation. Previous studies utilising a mouse model of obesity (C57BL/6J) have shown this, with the obese mice being fed a high-fat and either a low- or high-GI diet over 13 weeks. As such, the low-GI diet led to significant weight loss, improved glucose tolerance and insulin sensitivity. Although both diets had an equal calorie intake, the low-GI diet was accompanied by a significant reduction in systemic leptin levels and a marked rise in adiponectin levels (van Schothorst *et al*. 2009). Similar findings have been observed in humans with overweight/obesity, metabolic syndrome or T2DM. Where weight loss was induced via a low-GI diet, this again led to a systemic reduction in pro-inflammatory adipocytokines. Weight loss was shown to reduce expression of genes involved in NF-κB activation, which, in turn, led to improvements in insulin sensitivity (Bouché *et al*. 2002, Qi *et al*. 2006, de Mello *et al*. 2008, Heggen *et al*. 2012, Neuhouser *et al*. 2012).

The effect of lipids on adipokine inflammation

It is well established how vital controlling cholesterol is to reduce cardiovascular risk; the advent of statins profoundly highlighted this with a reduction in serum cholesterol being directly correlated with a marked reduction in cardiovascular risk and a reduced inflammatory profile (Pedersen *et al*. 2000, Hsia *et al*. 2011, Sever *et al*. 2011). More generally, lipotoxicity has been shown to play a major role in the pathogenesis of insulin resistance, with raised circulating free fatty acids associated with increased insulin resistance, as first suggested by Randle *et al*. (1963). Continued raised systemic free fatty acids can lead to lipid accumulation in adipose tissue and ectopic deposition of lipids, especially in the muscle and liver, which can ultimately lead to whole-body insulin resistance, this being concurrent with systemic inflammation. In muscle, the excess systemic free fatty acids are thought to mediate insulin resistance via disruption of the insulin signalling pathway via serine phosphorylation of IRS-1, as demonstrated in previous mouse model studies (Morino *et al*. 2008). While in the liver, excess systemic free fatty acids mediate increased intracellular diacylglycerol, which, in turn, results in lower insulin-stimulated liver glycogen synthesis and decreased suppression of hepatic gluconeogenesis (Boden *et al*. 2005). Parallel to this, free fatty acids also appear to induce inflammation through activation of the NF-κB inflammatory pathway, which can mediate insulin resistance, with both inflammation and insulin resistance being alleviated by high-dose salicylates through inactivation of IKKβ (Kim *et al*. 2001, Yuan *et al*. 2001, Shoelson *et al*. 2003).

Studies *in vitro* have also enhanced our insight into the effect of fatty acids on inflammatory pathways with the downstream capacity to induce insulin resistance via pro-inflammatory cytokine production. Studies have suggested that saturated fatty acids (SFAs) act as ligands for several members of the TLRs leading to activation of putative inflammatory pathways (Lee *et al*. 2001, Lee & Hwang 2006). This has been highlighted in several cell types such as the monocyte/macrophage cell, where SFA treatment led to activation of the innate immune pathway via TLR4 to induce downstream NF-κB activity as well as expression of cyclooxygenase 2 (COX2) and other inflammatory markers (Lee *et al*. 2001). Furthermore, in *in vitro* studies of human adipocytes, SFAs also activate TLR4 and NF-κB leading to downstream pro-inflammatory adipokine production (Youssef-Elabd *et al*. 2012). Similar findings for activation of TLR pathways by fatty acids have been noted in liver as well as muscle with detrimental effects (Szabo *et al*. 2005, Shi *et al*. 2006, Reyna *et al*. 2008, Hommelberg *et al*. 2010).

While more than one mechanism may induce insulin resistance, the role of the innate immune pathway appears key to how inflammation may mediate the pathogenesis of insulin resistance within different human tissues (Lee *et al*. 2001, Szabo *et al*. 2005, Lee & Hwang 2006, Shi *et al*. 2006, Reyna *et al*. 2008, Hommelberg *et al*. 2010, Youssef-Elabd *et al*. 2012). Previous rodent studies have also examined the pathogenesis of insulin resistance via modulation of the innate immune pathway (Poggi *et al*. 2007, Tsukumo *et al*. 2007). Specifically, when wild-type mice and *Tlr4* knockout (KO) mice were fed a high-fat diet, both maintained a similar body weight, body fat content, insulin and serum-free fatty acid levels compared with mice fed on a low-fat diet. However, the *Tlr4* KO mice had lower activation of the NF-κB pathway and reduced cellular insulin resistance compared with the wild-type mice, suggesting the importance of the innate immune pathway in inducing insulin resistance (Kim *et al*. 2007). The effects shown in the *Tlr4* KO mice have also been observed in *Tlr3* KO mice; again these mice were fed a high-fat diet yet showed improved insulin sensitivity, lipid profile and reduced hepatic steatosis compared with wild-type mice (Wu *et al*. 2012*b*).

The effect of endotoxin on adipokine inflammation

Classically, Gram-negative bacterial fragments derived from the outer cell membrane (also referred to as LPS

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DOI: 10.1530/JOE-12-0498

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or endotoxin) have been used to stimulate an inflammatory response, as a positive control, in many *in vitro* experiments. It is also well documented that endotoxin stimulates the innate immunity pathway through the activation of TLRs via several proteins, including the LPS binding protein (LBP), CD14 and myeloid differential protein 2 (MD2). This leads to intracellular activation of NF-κB and resulting pro-inflammatory cytokines (Creely *et al*. 2007, Baker *et al*. 2009, Youssef-Elabd *et al*. 2012). However, understanding of how gut-derived endotoxin affect metabolic function has changed in recent years, as studies have considered the direct impact of endotoxin as a systemic inflammatory insult. Endotoxin is known to have a strong affinity for chylomicrons (lipoproteins that transport dietary lipids including long chain SFAs through the gut wall) and, as such, can cross the gastrointestinal mucosa coupled to damaging lipoproteins. Once in the circulation, endotoxin has been shown to mediate metabolic dysfunction in several tissues including adipose tissue, liver and muscle.

While there are several long-established risk factors that contribute to metabolic dysfunction, such as hyperglycaemia, raised triglycerides and reduced HDL-cholesterol associated with insulin resistance, other 'primary inflammatory mediators' may also be relevant – including endotoxin. Within this context, chronic low-grade inflammation has been considered as another factor, coupled with obesity, insulin resistance and a raised immune response (Ouchi *et al*. 2011). The impact of adipose tissue on the immune response appears clear as *in vitro* studies, using human adipocytes, have shown that endotoxin can stimulate TLRs and NF-κB inflammatory pathways. This, in turn, leads to secretion of pro-inflammatory adipokines, with the response impacted by weight gain or loss (Creely *et al*. 2007, Dixon *et al*. 2008). In normal circumstances, only small amounts of endotoxin will cross from the intestinal lumen into the systemic circulation and the absorbed endotoxin will rapidly be removed by monocytes, particularly resident Kupffer cells within the liver. However, a compromised liver, due to ectopic fat deposition, has diminished capacity to remove the endotoxin, which can directly aggravate liver disease exacerbated by weight gain (Rao *et al*. 2004, Harte *et al*. 2010), leading to increased circulating endotoxin. Thus, a combination of dietary lipoprotein patterns and an increase in circulating endotoxin mediate chronic low-grade systemic inflammation that could activate the TLR pathway to induce downstream insulin resistance. As lipoprotein patterns would appear to alter circulating endotoxin levels, recent studies have begun to evaluate this across different insulin resistance states to examine the impact of feeding. Interestingly, a single high-fat meal did alter endotoxin levels across the different subgroups analysed. The rise in circulating endotoxin levels was ~20% more in the IGT subjects and obese groups compared with the non-obese control (NOC) group, while subjects with T2DM experienced as much as 125% higher endotoxin levels than NOC, even at 4 h post-meal in the T2DM group (Harte *et al*. 2012). In addition to this, previous cross-sectional *in vivo* studies have shown that endotoxin appears to correlate with markers and conditions of insulin resistance, with endotoxin appearing to act as a predictive metabolic biomarker of T2DM (Dixon *et al*. 2008, Al-Attas *et al*. 2009, Miller *et al*. 2009, Harte *et al*. 2010, Pussinen *et al*. 2011). Taken together, the *in vivo* and *in vitro* studies highlight the impact of endotoxin on the inflammatory pathways to promote secretion of pro-inflammatory adipocytokines to exacerbate the insulin-resistant state (Brun *et al*. 2007, Creely *et al*. 2007, Dixon *et al*. 2008, Al-Attas *et al*. 2009, Baker *et al*. 2009, Miller *et al*. 2009, Harte *et al*. 2010, 2012).

Adipokine action

The following highlights key adipokines with Table 1 detailing a comprehensive list of adipokines along with their key functions.

Leptin was one of the first proteins discovered to be secreted from adipose tissue, by the identification and sequencing of the *ob* gene from the *ob/ob* mouse (Zhang *et al*. 1994). Daily injection of the peptide in *ob/ob* mice resulted in a rapid reduction in food intake, body mass and percentage body fat but maintained lean muscle mass, increased energy expenditure and restored euglycaemia and reproductive function, confirming that it had an important role in energy homoeostasis and storage (Campfield *et al*. 1995, Halaas *et al*. 1995, Pelleymounter *et al*. 1995). However, leptin levels were noted to be increased in obese subjects, with little or no impact to regulate energy homoeostasis, which coined the well-established phrase 'leptin resistance' in obesity (Friedman & Halaas 1998). While this has dominated much of the literature on leptin, leptin was initially shown to have a pro-inflammatory function when studies observed that recombinant leptin activated human T lymphocytes and monocytes (Santos-Alvarez *et al*. 1999, Martín-Romero *et al*. 2000). More recently, leptin has also been shown to activate human B cells to secrete TNFα, IL6 and IL10 via the JAK2, STAT3, p38MAPK and ERK signalling pathways (Agrawal *et al*. 2011). The pro-inflammatory nature of

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DOI: 10.1530/JOE-12-0498

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leptin has been noted in several studies, with i.v. injection of endotoxin inducing a sudden rise in leptin levels (Landman *et al*. 2003, Xiao *et al*. 2003), as well as endotoxin-induced fever and anorexia in rats, again, inducing an increase in leptin levels as part of the inflammatory response (Sachot *et al*. 2004).

TNFα is a pro-inflammatory cytokine, and it was the first adipocyte-derived factor that suggested a link between obesity, inflammation and T2DM (Hotamisligil *et al*. 1993). Although originally thought to be mainly secreted by adipocytes, it is now thought that the majority of TNFα is secreted by macrophages (Weisberg *et al*. 2003). TNFα is thought to play an important role in insulin resistance by reducing insulin-stimulated tyrosine phosphorylation of the insulin receptor and IRS1 in muscle and adipose tissues, but not in the liver, thus promoting insulin resistance (Hotamisligil *et al*. 1994). In humans, TNFα levels are higher in plasma and adipose tissue of subjects with obesity, and circulating levels reduce with weight loss (Kern *et al*. 1995, Ziccardi *et al*. 2002). TNFα levels were also found to positively correlate with other markers of insulin resistance (Hivert *et al*. 2008); nonetheless acute treatment with TNFα inhibitor in obese subjects with T2DM reduced other systemic inflammatory markers without reducing insulin resistance (Dominguez *et al*. 2005). More recently, assessment of anti-TNFα inhibitor treatment, over the long term, given to subjects with metabolic syndrome, has shown to improve fasting blood sugar and also increase adiponectin levels, confirming a role for TNFα in obesity-related insulin resistance in humans (Stanley *et al*. 2011).

IL6 appears to have dual functions, depending on the tissue and metabolic state. In skeletal muscle, during exercise, it acts to increase glucose uptake resulting in muscle hypertrophy and myogenesis and AMPK-mediated fatty acid oxidation, as well as having an anti-inflammatory effect (Starkie *et al*. 2003, Kelly *et al*. 2004). While in adipose tissue and hepatic tissue, IL6 is shown to be a pro-inflammatory adipokine. It increases insulin resistance by up-regulating suppressor of cytokine signalling 3 (SOCS3), which, in turn, impairs insulin-induced insulin receptor and IRS1 phosphorylation (Senn *et al*. 2002, 2003, Rotter *et al*. 2003).

IL6 is positively correlated with increasing body mass and plasma-free fatty acids (Fried *et al*. 1998), with reduction in circulating IL6 following weight loss (Bastard *et al*. 2000, Ziccardi *et al*. 2002). IL6 has been shown to be raised in subjects with T2DM and also increases the risk of future development of T2DM (Pradhan *et al*. 2001). As such, IL6 appears to have different actions that may be due to acute or chronic effects (acute exercise vs chronic release in obesity), the different tissue-specific action (liver vs muscle), or the source of IL6 (adipose tissue vs muscle), all of which appear to influence both inflammation and insulin resistance status.

Resistin is a cytokine with a molecular structure similar to adiponectin (Patel *et al*. 2004) and has a clear role in mice, affecting glucose homoeostasis and acting as a mediator of insulin resistance (Steppan *et al*. 2001, Schwartz & Lazar 2011). However, its role in human adipose tissue has had a much more conflicted history (Nagaev & Smith 2001, Savage *et al*. 2001, McTernan *et al*. 2002*a*, 2006, Schwartz & Lazar 2011). While initially considered not be to be present in the adipocyte, subsequent studies have shown its presence and regulation (Nagaev & Smith 2001, Savage *et al*. 2001, McTernan *et al*. 2002*a*,*b*,*c*, 2003, Al-Daghri *et al*. 2005, Baker *et al*. 2006, Kusminski *et al*. 2007), although its role in humans appears more related to an inflammatory role than being an important factor regulating glucose metabolism. *In vitro* studies in isolated abdominal subcutaneous adipocytes have shown an increase in resistin secretion following treatment of the adipocyte with endotoxin (LPS). In addition, treatment of adipocytes with recombinant human resistin increased release of IL6, TNFα as well as expression of TLR2, IKKβ and JNK, suggesting a possible role for resistin in pro-inflammatory mechanisms in the adipocyte via both the NF-κB and the JNK pathways (Kusminski *et al*. 2007).

New 'kines' on the block

The following sections represent some brief insights into recent additions to the adipokine family, which, akin to other adipokines, appear to impact on inflammation and insulin resistance.

Apelin is a peptide that is produced in a wide range of tissues with positive effects on insulin sensitivity, glucose uptake and lipolysis in skeletal muscle as well as adipose tissue (Boucher *et al*. 2005, Dray *et al*. 2008, Yue *et al*. 2011, Attané *et al*. 2012). However, studies in humans have shown an increase in plasma apelin levels in obesity, morbid obesity, impaired glucose tolerance and T2DM with a reduction in apelin levels accompanying weight loss following diet or bariatric surgery. These findings suggest the presence of resistance to apelin, in a similar fashion to insulin and leptin (Heinonen *et al*. 2005, Li *et al*. 2006, Castan-Laurell *et al*. 2008, Erdem *et al*. 2008, Soriguer *et al*. 2009, Zhang *et al*. 2009).

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Apelin has also been shown to have a pro-inflammatory role with a close positive correlation demonstrated between apelin and TNFα levels, as well as other pro-inflammatory cytokines (Malyszko *et al*. 2008, Heinonen *et al*. 2009, Yu *et al*. 2012). Apelin expression also closely correlates with TNFα in adipose tissue of lean and obese individuals, and *in vitro* studies of cultured human adipose tissue explants show an up-regulation of apelin in response to TNFα (Daviaud *et al*. 2006). Further *in vitro* studies in human umbilical vein endothelial cells (HUVECs) suggest an increase in adhesion molecules (VCAM and ICAM) by apelin via the NF-κB and JNK pathways, further supporting its role as a pro-inflammatory adipokine (Lu *et al*. 2012).

Omentin is another new peptide that is produced in omental but not subcutaneous adipose tissue and exists in two isoforms, omentin 1 and omentin 2. Omentin 1 represents the predominant circulating form and positively affects insulin sensitivity, which is reduced in subjects with obesity and T2DM compared with lean subjects (de Souza Batista *et al*. 2007, Shibata *et al*. 2012). Omentin is thought to be an anti-inflammatory adipokine and acts by inhibiting TNFα-induced expression of adhesion molecules in endothelial cells by inhibiting the ERK/NF-κB pathway (Zhong *et al*. 2012), while in vascular smooth muscle cells omentin inhibits TNFα action via inhibition of p38 and JNK pathways (Kazama *et al*. 2012). Taken together, this suggests that omentin may have a positive role to play to reduce inflammation in normal physiology.

Chemerin is a novel adipokine that has been shown to play a role in the regulation of adipogenesis and adipocyte metabolism (Goralski *et al*. 2007), as well as a role in glucose homoeostasis – as noted by studies on glucose intolerance in *ob/ob* and *db/db* mice (Ernst *et al*. 2010). In humans, however, chemerin seems to have a direct action on inflammation in adipocytes rather than glucose homoeostasis, as use of recombinant TNFα seems to induce chemerin secretion from adipocytes (Catalán *et al*. 2011). In other inflammatory cell types, such as macrophages, chemerin causes a pro-inflammatory action through increasing macrophage adhesion to VCAM-1 and fibronectin (Hart & Greaves 2010). As such, in subsequently considered coronary artery disease patients, where inflammation had progressed, circulating chemerin levels were noted to be positively correlated with multiple markers of inflammation including TNFα, IL6, C-reactive protein (CRP), leptin and resistin, affirming its pro-inflammatory function (Lehrke *et al*. 2009). In separate studies of T2DM subjects at risk of CVD, analysis of their circulating chemerin levels also revealed positive associations with inflammatory markers, including TNFα CRP, leptin and resistin (Weigert *et al*. 2010, Yu *et al*. 2012). These combined studies indicate a pro-inflammatory function for chemerin, which appears exacerbated in metabolic disease states.

Conclusion

This current review has examined the importance of inflammatory pathways that can impact on adipokine function leading to insulin resistance. It is clear that through 'overnutrition', glucose, lipids and endotoxin can affect different tissues to mediate an aberrant inflammatory response and advance the pathogenesis of insulin resistance and metabolic disease. While it is evident that adiposity exacerbates this developing inflammatory state, compromised further by ectopic fat disposition, it is, perhaps, the continual insults from our dysfunctional diets that provide the key targets for intervention. Reducing the burden of inflammatory insults on our adipose tissue may subsequently impact on our long-term health to reduce the encumbrance of metabolic disease.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements
The authors would like to acknowledge University Hospitals Coventry and Warwickshire NHS Trust and Birmingham Science City.

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Received in final form 31 October 2012
Accepted 16 November 2012
Accepted Preprint published online 16 November 2012

www.joe.endocrinology-journals.org
DOI: 10.1530/JOE-12-0498

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