

The Summer Meeting of the Nutrition Society, hosted by the Rowett Research Institute and the University of Aberdeen, was held at the Aberdeen Exhibition and Conference Centre, Aberdeen on 3–6 July 2006

Plenary Lecture

The interplay between nutrients and the adipose tissue

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The importance of adipose tissue in health as well as disease has been demonstrated in several studies recently, and it has become appropriate to use the term ‘adipose organ’ when referring to adipose tissue as a whole. The obesity epidemic, with a marked increase in the incidence of the metabolic syndrome leading to diabetes type 2 as well as cardiovascular complications, has stimulated considerable interest in adipose tissue biology. Moreover, several studies in different species have shown that limited energy intake is associated with less inflammation, improved biomarkers of health and a marked increase in longevity. In addition, there is convincing evidence that an optimal amount of adipose tissue is essential for many body functions such as immune response, reproduction and bone quality. Some nutrients and their metabolites are important as energy sources as well as ligands for many transcription factors expressed in adipose tissue, including all energy-providing nutrients both directly and indirectly as well as cholesterol, vitamin E and vitamin D. In particular, fatty acids can be effectively taken up by adipocytes and they can interact with several transcription factors crucial for growth, development and metabolic response, e.g. PPAR α , $-\delta$ and $-\gamma$, sterol regulatory element-binding proteins 1 and 2 and liver X receptors α and β). Moreover, glucose is also readily taken up and stored as fatty acids via lipogenesis in adipocytes. It is known that some metabolic signals released as proteins from adipose tissue (adipokines) are important for normal as well as pathological responses to the amount of energy stored in the adipose organ. The future challenge will be to understand the function of adipose tissue in energy homeostasis and the interplay with nutrients in order to be able to give optimal advice for the prevention and treatment of obesity.

Energy homeostasis: Nutrients: Adipose tissue: Adipokines: Fatty acids

During evolution famine has been a substantial threat to survival. Adipocytes enable the storage of large amounts of fat for use when food is scarce. In modern times many individuals face a different challenge, i.e. overnutrition and a sedentary lifestyle, and the negative health consequences have become more prevalent. Excessive intake of energy-dense foods high in fat and/or sugar combined with low physical activity is associated with the development of obesity (Drevon *et al.* 2000; Saris *et al.* 2000). The amount as well as the type of dietary fatty acids may affect lipid homeostasis and fat deposition (Hill *et al.* 1992). Obesity is becoming an extensive public health problem in most countries, particularly in economically-advanced countries.

The prevalence of obesity in Europe is alarming, as demonstrated by recent health statistics in Norway (Meyer & Tverdal, 2005) and the UK (Rennie & Jebb, 2005), which show that about 15 and 25% of the adult population respectively are classified as obese (BMI >30 kg/m²). The prevalence of obesity is even higher in the USA, with about one-third of adults classified as obese (Baskin *et al.* 2005). Furthermore, there has been a very rapid escalation in the obesity epidemic over the past two to three decades, with the incidence rising 3-fold in Norway (Drevon *et al.* 2000) and the UK (Prentice & Jebb, 1995). Obesity is associated with increased risk of conditions such as type 2 diabetes, CHD, hypertension, dyslipidaemia (which are

Abbreviations: RA, retinoic acid.

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Table 1. Adipose tissue depot locations (modified after Abate & Garg, 1995)

Subcutaneous*	Intra-abdominal*	Perirenal
Abdomen	Omental	Perinodal
Inguinal	Mesenteric	Epidural
Axillar	Retroperitoneal	Periarticular
Extremities	Intrathoracic	Retro-orbital
Temporal	Mediastinal	Crista galli
Buccal	Epicardial	Bone marrow
Palm	Retrosternal	
Sole		

*These depots are very sensitive to shifts in energy balance, and they are often enlarged in obesity.

often included in the so-called metabolic syndrome), gall stones, certain types of cancer (breast and colon), osteoarthritis, non-alcoholic steatohepatitis, sleep apnoea, infertility and many psychological conditions. Moreover, there is a marked reduction in life expectancy of the order of several years. With an increasing amount of body fat there is an increasing risk of developing type 2 diabetes in particular; the likelihood of developing this disease increases 10-fold at a BMI of 30 kg/m².

Type 2 diabetes mellitus is diagnosed in about 20% of pubertal children referred to diabetic clinics in the USA (Arslanian, 2002). The metabolic syndrome is identified in ≤30% of obese children. Signs of the metabolic syndrome in children tend to continue into adulthood, and non-alcoholic steatohepatitis is an increasing clinical problem in obese children and adolescents (Malecka-Tendera & Mazur, 2006).

Adipose tissue structure and distribution

Adipose tissue is unique to vertebrates. It is found in most mammals, birds, reptiles and amphibians, and a variety is found in some species of fish. Furthermore, in insects the fat body found in larvae as well as in adults shares some homology with adipose tissue. In man adipose tissue deposition begins towards the end of fetal life. A very lean healthy adult may have as little as 3–4% body fat, whereas a lean adult on average has about 10–15 kg adipose tissue and an obese individual with leptin receptor deficiency can accumulate >70% body mass as fat (Clement *et al.* 1998).

Different adipose tissue depots (Bjorneboe *et al.* 1986) probably have different functions based on their anatomical location (Table 1). For example, it is likely that the retro-orbital fat depot, located behind the eye, has a different function from the visceral adipose tissue depots (surrounding internal organs). There is fairly good evidence that there is higher risk of developing myocardial infarction associated with visceral obesity than with fat accumulated subcutaneously around the hip (Yusuf *et al.* 2005). This difference in risk may be related to a lower expression of leptin, leptin receptor, adipsin, adiponectin, acylating-stimulating protein, cholesteryl ester transfer protein in visceral adipose tissue *v.* subcutaneous adipose tissue. On the other hand, higher expression of IL-6 and -8, plasminogen-activator inhibitor-1, PPAR γ , resistin and 11-hydroxysteroid dehydrogenase type 1 is observed in

Table 2. Different cell types in adipose tissue

Adipocytes
White: TAG storage, one large lipid droplet
Brown: heat producing, many mitochondria
Adipocyte precursor cells
Preadipocytes
Pericytes: potential precursors of preadipocytes
Stem cells
Immune cells
Macrophages
Dendritic cells
Mast cells
Lymphocytes
Granulocytes
Fibroblasts
Endothelial cells in capillaries
Nerve cells

visceral adipose tissue *v.* subcutaneous adipose tissue (Schaffler *et al.* 2005).

Adipose tissue comprises several cell types

Although the distinctive feature of adipose tissue is the adipocytes, there are several types of cells present in adipose tissues, including pericytes, preadipocytes, white and brown adipocytes, fibroblasts, endothelial cells, immune cells such as macrophages, dendritic cells, mast cells, granulocytes and lymphocytes, in addition to nerve cells linked to the autonomous nervous system (Table 2).

Adipocytes are derived from mesenchymal stem cells (probably pericytes) and acquire intracellular lipid droplets during differentiation (Cinti, 1999a). Essentially, all eukaryotic cells are capable of forming small lipid droplets, although the capacity for lipid-droplet storage is greatly enhanced in adipocytes.

Mature white adipocytes comprise ≤85% of the adipose tissue mass and can accommodate much larger lipid droplets than any other cell type (Fig. 1). In contrast to most other cell types adipocytes have a considerable capacity for expansion. When filled with lipids white adipocytes are approximately spherical. They differ in size, having diameters of ≤100 μ m, which is larger than most other cell types. The unilocular lipid droplet can represent approximately 90% of the cell volume of a white adipocyte. In a typical mature white adipocyte the nucleus and other organelles are compressed against the cell membrane (Cinti, 1999a).

Brown adipocytes (Fig. 1) are clustered together to form what is termed brown adipose tissue, which appears brown because of the large number of mitochondria in the cytoplasm of these cells (Cinti, 1999a). Brown adipocytes have a unique metabolism in which the flow of protons through the inner mitochondrial membrane bypasses the ATP synthase via uncoupling protein 1, which uncouples oxidative phosphorylation and the energy produced by the protons as they are channelled through the inner mitochondrial membrane is released as heat (Cannon & Nedergaard, 2004).

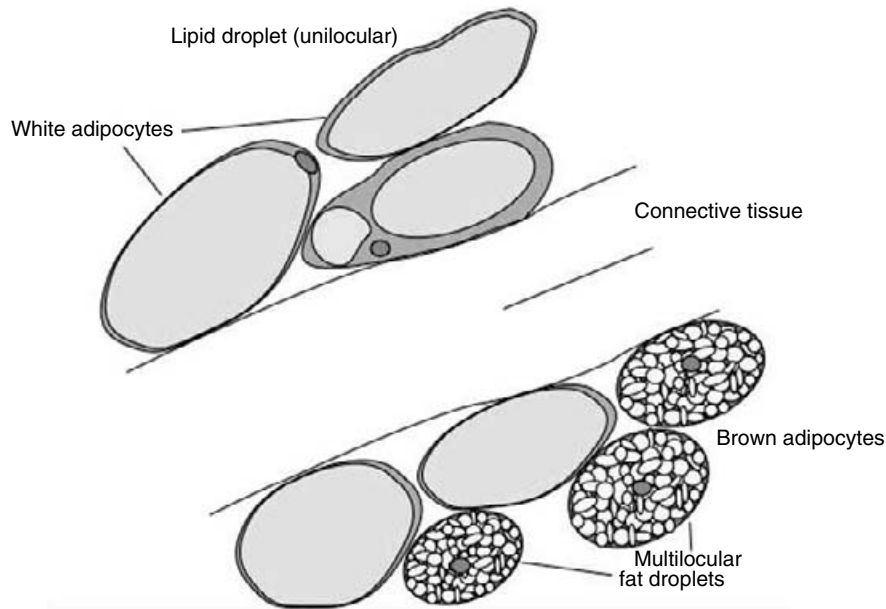


Fig. 1. White and brown adipocytes containing unilocular and multilocular lipid droplets, respectively.

Table 3. Adipose tissue functions

Store very large amounts of energy with little volume and weight
Store cholesterol, and vitamins D and E
Mechanical protection
Thermic insulation
Release very many hormones (adipokines)
Regulate metabolism: brown adipocytes can uncouple mitochondria and produce heat

White adipose tissue depots contain variable amounts of brown adipocytes depending on age, species and environmental conditions. Recent data (Cinti, 2005) have demonstrated the plasticity of the adipose organ, and under particular conditions fully differentiated white adipocytes can transdifferentiate into brown adipocytes, and vice versa. All adipocytes of the adipose organ express a specific adrenoceptor termed α_3 adrenoceptor, and treatment of genetically-obese and diet-induced obese rats with α_3 adrenoceptor agonists ameliorates their pathological condition, and is accompanied by the appearance of brown adipocytes in white areas of the adipose organ. This drug-induced modification of the anatomy of the organ is also demonstrated in rats and dogs by treatment with PPAR γ agonists. The transformation of white adipose tissue into brown adipose tissue in rats treated with α_3 adrenoceptor agonists is a result of direct transformation of differentiated unilocular adipocytes (Cinti, 2005).

Adipose tissue consists of other cells, in addition to adipocytes. For example, preadipocytes are dispersed amongst the adipocytes and are precursor cells of brown and white adipocytes. Furthermore, adipose tissue is highly vascularized and brown adipose tissue has a particularly extensive capillary network. Adipose tissue is also richly innervated with several nerves entering the various depots, and brown adipose tissue is more innervated than the white adipose tissue. Monocytes, lymphocytes, granulocytes,

macrophages and dendritic cells are also present in adipose tissue, and many of the inflammatory cells can be recruited from the bone marrow with increasing size during the development of obesity (Weisberg *et al.* 2003). Communication between inflammatory cells and adipocytes, which may involve monocyte chemoattractant protein-1 (Kamei *et al.* 2006), is being intensively investigated.

Adipose tissue functions

Adipose tissue has several functions (Table 3) and is considered to be a vital organ.

From an evolutionary perspective long-term energy storage is an essential function of the adipose tissue. In a lean healthy individual the adipose tissue can provide fuel for several weeks (Table 4).

The adipocytes store TAG and release fatty acids by highly-regulated processes. The adipose tissue also stores cholesterol and lipid-soluble vitamins, in particular vitamins D and E (Dueland *et al.* 1983; Bjorneboe *et al.* 1986). Adipose tissue surrounding lymph nodes may have a function in the immune system (Pond, 2005). In addition, several non-protein hormones are produced in adipose tissue, e.g. sex steroids and glucocorticoids are produced from precursors in adipose tissue.

Brown adipose tissue is able to generate as much as 300 times more heat relative to tissue weight than other tissues. The abundance of brown adipose tissue peaks at about the time of birth and is less prominent after the postnatal period. The importance of brown adipose tissue in man is not known, but in rodents a functional brown adipose tissue is maintained throughout life (Cannon & Nedergaard, 2004).

TAG storage

TAG are the main constituents of lipid droplets in adipocytes, and a human adipocyte typically contains about

Table 4. Energy stores in man and the approximate duration of their capacity to provide energy for different activities

Energy store		May provide sufficient energy for:		
Storage form	Amount (g)	Inactivity	Walking	Running
Adipose tissue TAG	9000–15 000	34 d	11 d	3 d
Liver glycogen	80	3–5 h	1 h	18 min
Muscle glycogen	350–700	14–28 h	5–10 h	2–3 h
Blood and extracellular glucose	20	40 min	15 min	4 min
Protein	6000	15 d	5 d	1–3 d

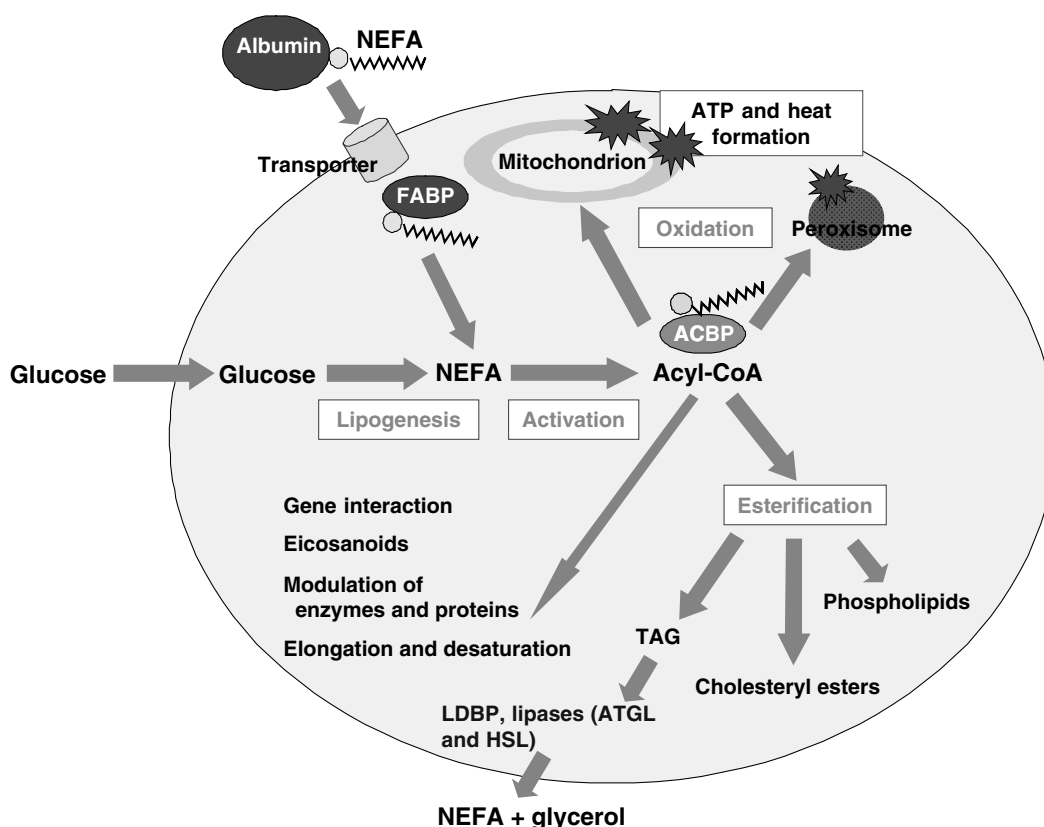


Fig. 2. Metabolism of fatty acids in adipocytes. NEFA are released from chylomicrons and VLDL by the action of lipoprotein lipase and taken up into cells mainly by protein carriers in the plasma membrane and transported intracellularly via fatty acid-binding proteins (FABP). NEFA are activated (acyl-CoA) before they can be shuttled via acyl-CoA-binding protein (ACBP) to mitochondria or peroxisomes for β -oxidation (formation of energy as ATP and heat), or to endoplasmic reticulum for esterification to different lipid classes. Acyl-CoA or certain NEFA may bind to transcription factors that regulate gene expression or may be converted to signalling molecules (eicosanoids). Glucose may be transformed to fatty acids if there is a surplus of glucose or energy in the cells. TAG are stored in lipid droplets covered with lipid droplet-binding proteins (LDBP) such as perilipin. Perilipin and hormone-sensitive lipase (HSL) are activated by phosphorylation by protein kinase A. Adipose tissue TAG lipase (ATGL) hydrolyses TAG, whereas HSL hydrolyses diacylglycerols. (Modified after Rustan & Drevon, 2005.)

1 μ g TAG. The fatty acids originate either from plasma TAG or from *de novo* lipogenesis (Fig. 2). TAG circulating in plasma in lipoprotein particles are hydrolysed to fatty acids outside the adipocyte by lipoprotein lipase attached to endothelial cells in the capillaries.

Glucose can be utilized for *de novo* lipogenesis and the resulting fatty acids are stored as TAG in the lipid droplets of adipocytes after esterification with glycerol 3-phosphate. In the fed state lipogenesis is stimulated by insulin. However, lipogenesis may contribute quantitatively to TAG

storage only under a shortage of fatty acids, which is not usually the case on a mixed diet with >20% energy from fat (Frayn, 2003).

Fatty acid release

Fatty acids are released by lipases from adipocytes into the bloodstream, e.g. during fasting. The lipases act on the surface of lipid droplets, and at least three lipases act sequentially to release three molecules fatty acids and one

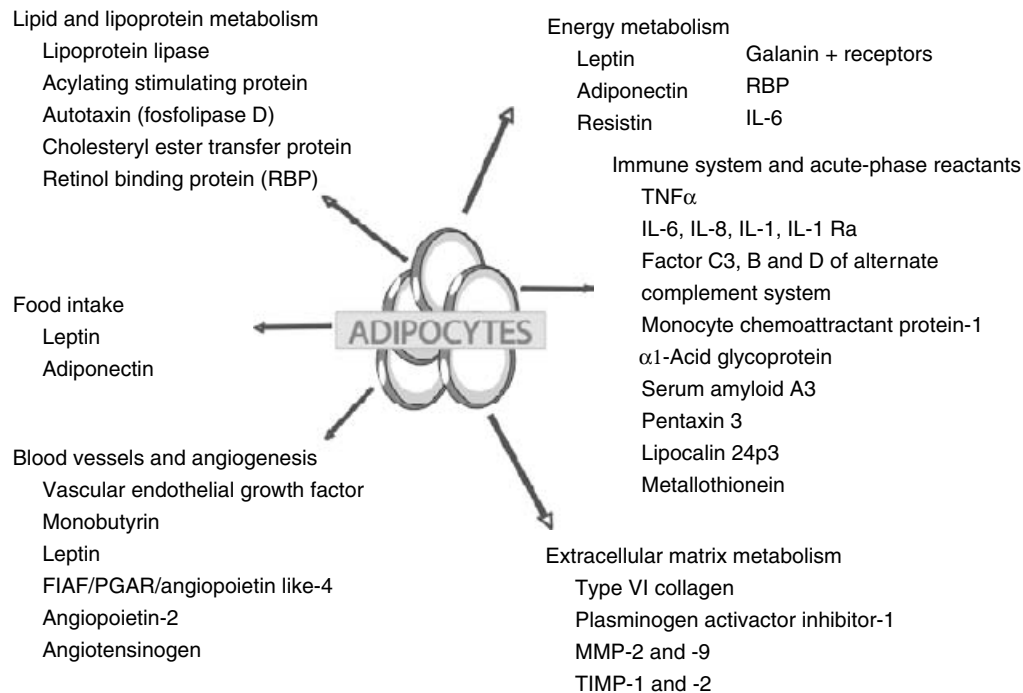


Fig. 3. Adipokines may act locally (autocrine or paracrine) and at the systemic (endocrine) level influencing a variety of biological processes including energy metabolism with carbohydrates as well as lipids, appetite, reproduction, immune function, angiogenesis and extracellular matrix metabolism. FIAF/PPAR γ angiopoietin-related gene (FIAF, PGAR and angiopoietin like-4 are alternative terms for the same factor); IL-1Ra, IL-1 receptor antagonist; MMP-2, MMP-9, matrix metalloproteinase-2 and -9 respectively; TIMP-1, TIMP-2, tissue inhibitor of metalloproteinases-1 and -2 respectively. (Modified after Lafontan, 2005.)

molecule glycerol from each molecule TAG. The first fatty acid is removed by adipose TAG lipase (Zimmermann *et al.* 2004), the second by hormone-sensitive lipase and the third by monoacylglycerol lipase (Frayn, 2003).

When intracellular levels of cAMP increase, hormone-sensitive lipase is phosphorylated by cAMP-dependent protein kinase and translocated to the surface of the lipid droplets. Moreover, the lipases may work in concert with putative lipid droplet-coating proteins, e.g. perilipin, mannose-6-phosphate receptor-binding protein 1 and adipose differentiation-related protein. Along with hormone-sensitive lipase, perilipin is phosphorylated, thus bringing about its restructuring or relocalization (Clifford *et al.* 2000). This process in turn may facilitate the translocation of hormone-sensitive lipase during activation and provide access to the lipid droplets (Sztalryd *et al.* 2003). In the fed state insulin inhibits this process of fatty acid release and hormone-sensitive lipase is dephosphorylated.

Adipose tissue as a source of adipokines

Adipose tissue expresses several receptors that allow it to respond to signals from traditional hormones as well as the autonomous nervous system (Trayhurn *et al.* 2006). Moreover, the adipose tissue is the site of expression and secretion of a range of biologically-active proteins termed adipokines. Some of the most studied adipokines are leptin, adiponectin, resistin, IL and TNF α (Fig. 3).

Thus, adipose tissue contains the biological machinery necessary for the handling of a major proportion of energy metabolism as well as communication with most other organs. The present review will focus on some aspects of resistin, adiponectin and leptin, in particular the interaction between nutrients and the expression of these adipokines.

Resistin

Steppan *et al.* (2001) discovered resistin when screening for adipocyte-derived factors that may cause insulin resistance. They looked for genes in 3T3-L1 cells that were both induced during adipogenesis and down-regulated in mature adipocytes by the anti-diabetic thiazolidinedione drugs, which enhance insulin sensitivity in liver, muscle and adipose tissue, and are ligands for the PPAR nuclear receptor, which is highly expressed in adipocytes. One of the genes that matched both criteria in 3T3-L1 cells encoded a protein that was secreted by adipocytes and was found in mouse serum; it was termed resistin. The expression of resistin increases with increasing mass of adipose tissue. The resistin gene is identical to the *FIZZ3* gene discovered earlier by Holcomb *et al.* (2000). Although there are several observations that are compatible with a role for resistin in the development of insulin resistance in rodents as well as in man, there are data that support the notion that the major function of resistin in man may be related to inflammation (Weisberg *et al.* 2003).

Resistin like other RELM proteins comprises 105–114 amino acids and is characterized by a specific pattern made up of ten cysteine residues (Holcomb *et al.* 2000). It circulates in the plasma as a trimer or a hexamer (Patel *et al.* 2004).

Only two genes of the RELM family have been identified in the human genome that share homology with their mouse and rat counterparts: resistin, which is also known as *RETN*; *RELM β* , which is also termed *RETNLB* (Holcomb *et al.* 2000; Weisberg *et al.* 2003). In contrast to findings in mice, the human resistin gene has its highest expression in bone marrow, whereas expression in adipose tissue is much lower than that in mouse adipose tissue (Patel *et al.* 2003). Low expression of resistin has also been observed in several tissues including lung, breast and placenta (Yura *et al.* 2003; Haugen *et al.* 2006).

Obesity and resistin

There is a strong correlation between serum concentrations of resistin and resistin mRNA expression in abdominal subcutaneous adipose tissue from obese subjects (Heilbronn *et al.* 2004). Thus, despite the low level of expression in adipose tissue, there is a link between adipose tissue mass and circulating levels of resistin, and obesity is an important determinant of resistin levels in human subjects.

Diabetes and resistin

Serum resistin is increased in subjects with type 2 diabetes compared with subjects without diabetes (McTernan *et al.* 2003). Plasma resistin levels are also increased in patients with Cushing's syndrome (central adiposity and insulin resistance) as compared with control subjects matched for body mass (Krsek *et al.* 2004). However, no correlation has been found between plasma resistin levels and insulin sensitivity in human subjects. Several polymorphisms in the resistin gene have been studied, some of which are located in the 5' flanking region (G–638A, A–537C, C–420G and G–358A) and affect circulating levels of resistin (Cho *et al.* 2004; Osawa *et al.* 2004). The –420G genotype is specifically recognized by the transcription factors Sp1 and Sp3, leading to increased resistin promoter activity and serum resistin levels. The –420G/G genotype has been associated with type 2 diabetes (Osawa *et al.* 2004). Plasma resistin levels of women are higher than those of men, and it is possible that the physiology of resistin differs between the genders. In a group of women who were not diabetic the –420C/C genotype was found to be associated with a higher body mass than the –420G allele carriers (Mattevi *et al.* 2004).

Resistin may inhibit insulin-mediated glucose uptake in human cells (Bajaj *et al.* 2004; McTernan *et al.* 2003). In line with animal studies treatment of subjects with type 2 diabetes with thiazolidinedione drugs causes a decrease in plasma resistin concentration, which is positively correlated with the reduction in hepatic fat content and improvement in hepatic insulin sensitivity (Bajaj *et al.* 2004). Furthermore, thiazolidinediones inhibit resistin expression in macrophages and adipocytes *in vitro*

(McTernan *et al.* 2003). In summary, it is not yet clear whether resistin has a role in insulin resistance and the development of type 2 diabetes in human subjects.

Inflammation and resistin

Patients with severe inflammatory disease have elevated levels of resistin and there is a correlation between plasma resistin concentration and markers of inflammation (Stejskal *et al.* 2003). Obesity is characterized by the expression of weak chronic inflammation, and this condition may cause insulin resistance. If macrophages rather than adipocytes are the main source of resistin in human subjects, resistin could be a link between insulin resistance and inflammation. Macrophages resident in adipose tissue may prove to play an important role in the development of insulin resistance (Xu *et al.* 2003). Macrophages in adipose tissue show an increase in numbers during obesity and are responsible for most of the TNF α expression in adipose tissue and substantial amounts of inducible NO synthase and IL-6 expression (Weisberg *et al.* 2003).

There have been few studies of the direct effect of fatty acids on the expression of resistin in adipocytes. As increased plasma NEFA concentrations are associated with insulin resistance (Lam *et al.* 2003), the effects of individual NEFA on the expression of resistin mRNA have been examined in cultured murine 3T3-L1 adipocytes (Haugen *et al.* 2005). The NEFA tested were not found to increase resistin expression, but both arachidonic acid and EPA were shown to reduce resistin mRNA levels. Arachidonic acid was found to be by far the most potent NEFA, reducing resistin mRNA levels to approximately 20% of the control levels at concentrations of 60–250 μ M. Selective inhibitors of cyclooxygenase-1 and mitogen-activated protein kinase were found to counteract the arachidonic acid-induced reduction in resistin mRNA levels. Transient overexpression of sterol-regulatory element binding protein-1a was shown to activate the resistin promoter, but no reduction in the abundance of mature sterol-regulatory element binding protein-1 was found after arachidonic acid exposure. Both actinomycin D and cycloheximide were found to abolish the arachidonic acid-induced reduction of resistin mRNA levels, indicating a dependence on *de novo* transcription and translation. These data suggest that reductions in resistin mRNA levels involve a destabilization of the resistin mRNA molecule. An inhibitory effect of arachidonic acid and EPA on resistin expression may explain the beneficial effect on insulin sensitivity of ingesting PUFA.

Leptin

Early studies have shown that fasting and feeding enhance and reduce plasma leptin concentrations respectively (Kolaczynski *et al.* 1996; Weigle *et al.* 1997). Although it is known that plasma leptin concentrations are correlated with the amount of adipose tissue in the body, relatively little information is available on the long-term effects of diet on leptin concentrations. The Oslo Diet and Exercise Study has investigated whether changes in dietary energy sources and exercise-mediated energy expenditure, alone

or in combination, affect plasma leptin concentrations (Reseland *et al.* 2001a). In a randomized, 2×2 factorial trial 186 men with enhanced risk of developing CVD were divided into four groups: diet; exercise; a combination of diet and exercise; control. Data on dietary intake, physical fitness and demographics were collected and plasma leptin concentrations were measured before and after an intervention period of 1 year. Plasma leptin concentrations, BMI and fat mass were found to be decreased in association with long-term reductions in food intake as well as increased physical activity. When values were adjusted for either BMI or fat mass a highly significant ($P < 0.001$) reduction in plasma leptin concentration was found after both the diet intervention and the exercise intervention. No interaction was found between the interventions, suggesting a direct and additive effect of changes in diet and physical activity on plasma leptin concentrations. Thus, long-term changes in lifestyle consisting of decreased intake of dietary fat and increased physical activity reduce plasma leptin concentrations in human subjects beyond the reduction expected as a result of changes in fat mass. This finding might indicate enhanced leptin sensitivity, which might be promoted by the newly-described PTP1B (a tyrosine phosphatase) regulating body mass and adiposity primarily through actions in the brain (Bence *et al.* 2006). Neuronal PTP1B also regulates adipocyte leptin production and is probably essential for the development of leptin resistance.

In a small dietary intervention study lasting 16 weeks (Mori *et al.* 2004) a daily fish meal providing 3.65 g *n-3* fatty acids as part of a weight-reducing regimen was found to be more effective in reducing plasma leptin levels than either the fish meal or the weight-reducing regimen alone. Reductions in leptin were found to be related to the substantial fall in blood pressure observed with the fish meal and weight-loss intervention.

The extension of studies in the Oslo Diet and Exercise Study population to include the measurement of other adipokines and cytokines (MH Rokling-Andersen, JE Reseland, MB Veierød, SA Anderssen, DA Jacobs Jr, P Urdal, JO Jansson and CA Drevon, unpublished results) has shown that plasma adiponectin levels are higher in the subjects who have improved their diet and physical activity as compared with the controls. Plasma adiponectin levels are unaltered, whereas BMI and fat mass decrease after a reduction in energy intake and increased physical activity, whereas the adiponectin concentration is reduced in the control group. Both diet and exercise intervention result in stable plasma adiponectin levels ($P < 0.01$ and $P = 0.07$, respectively) and a decrease in body fat mass ($P < 0.001$ and $P < 0.01$, respectively), but after adjustment for changes in body fat mass no effects on adiponectin are observed ($P > 0.15$). Thus, 1 year after implementing changes in diet and exercise plasma adiponectin levels are increased, which can be largely explained by a reduced body fat mass.

The previous studies on leptin in the Oslo Diet and Exercise Study (Reseland *et al.* 2001a) have prompted further examination of whether specific intervention with a daily supplement of 5 g marine *n-3* PUFA would affect leptin levels in plasma (Reseland *et al.* 2001b). It was

found that after 6 weeks plasma leptin concentrations of male smokers are unchanged. Changes in dietary intake of SFA are positively correlated with changes in plasma leptin levels, whereas for changes in the intake of PUFA the correlation is negative. Dietary intake of *n-3* PUFA-enriched diet for 3 weeks, as compared with a lard-enriched diet, reduces plasma leptin concentration and leptin mRNA expression in rat epididymal adipose tissue (Reseland *et al.* 2001b). In the human trophoblast cell line (BeWo) *n-3* PUFA has a dose- and time-dependent effect on leptin expression (Reseland *et al.* 2001b). Incubation with EPA and DHA (1 mM) for 72 h reduces leptin expression by 71% and 78% respectively, as compared with the control. There is no effect on the expression of the signal transducing form of the leptin receptor. In BeWo cells transfected with the human leptin promoter *n-3* PUFA reduce leptin promoter activity, whereas SFA and MUFA have no effect on leptin promoter activity (Reseland *et al.* 2001b). The transcription factors PPAR γ and sterol-regulatory element binding protein-1 mRNA are reduced after incubation with *n-3* PUFA, whereas the expression of CCAAT/enhancer-binding protein α is unchanged. DHA-reduced leptin expression is abolished in BeWo cells grown in cholesterol-free medium. Thus, *n-3* PUFA decrease leptin gene expression both *in vivo* and *in vitro*. The direct effects of PUFA on leptin promoter activity indicate a specific regulatory action of fatty acids on leptin expression.

Retinoic acid (RA) is a ligand for some nuclear receptors and its effect on the expression of leptin has been examined in adipocytes of murine and human origin (Hollung *et al.* 2004). After incubation of murine 3T3-L1 adipocytes with 1 and 10 mM-all-*trans* RA for 48 h the expression of leptin mRNA is reduced by 56% and 65% respectively, whereas the secretion of leptin to the culture medium is reduced by 38% and 77% respectively. In human adipose tissue explants incubation with 1 mM-all-*trans* RA for 24 h reduces leptin mRNA expression levels by 55% and leptin secretion by 25%. In 3T3-L1 cells after incubation with RA mRNA expression levels for the transcription factors PPAR γ , retinoid X receptor α , and RA receptor α are increased, whereas in human adipose tissue explants mRNA levels for these transcription factors are unchanged. In two other leptin-expressing cell systems (the human placental trophoblast cell line BeWo and normal human primary osteoblasts) there is no effect of RA on leptin mRNA expression, but in BeWo cells leptin secretion is reduced by 64% after 24 h incubation with 10 mM-all-*trans* RA. Thus, all-*trans* RA reduces both the expression and secretion of leptin in human and rodent adipose tissue. In human BeWo cells or primary osteoblasts leptin mRNA expression levels are not changed by all-*trans* RA, indicating a tissue-specific regulation of leptin mRNA expression by all-*trans* RA.

Adiponectin

Structure

Adiponectin, an approximately 30 kDa polypeptide consisting of an N-terminal signal sequence followed by a variable domain, a collagen-like domain and a C-terminal

globular domain, was first described by Scherer *et al.* (1995). In the central region of the collagen-like domain there are fifteen Gly-X-Y repeats, whereas at the beginning and end of the domain there are seven Gly-X-Pro repeats. Recombinant adiponectin produced by mammalian cells has a higher biological activity than bacterially-produced adiponectin, suggesting that post-translational modifications may be important. Lysine residues in the collagen-like domain are glycosylated to yield multiple isoforms of adiponectin with relevance for biological activity (Wang *et al.* 2002).

The adiponectin superstructure resembles a bouquet of flowers, in which three protomers form a trimer that comprises a globular head domain and a collagen triple helix 'stalk' and six trimers form a multimer that resembles a 'bouquet'. The smallest adiponectin complex, referred to as the low-molecular-weight form, is simply a pair of trimers. A group of larger adiponectin complexes is referred to as the high-molecular-weight form, which is a diverse group of multimers comprising two to three pairs of trimers (Cinti, 1999b).

Physiological conditions

Adiponectin levels display a diurnal variation, with a nocturnal decline starting in the late evening and continuing throughout the night to reach the lowest point in the early morning (Gavrila *et al.* 2003). Pre- and post-menopausal women have higher plasma levels of adiponectin than men (Nishizawa *et al.* 2002). It is possible that low levels of adiponectin are related to the high risk of insulin resistance and atherosclerosis in men. A negative correlation has been observed between plasma concentrations of the adiponectin monomer and BMI in both men and women (Arita *et al.* 1999; Weyer *et al.* 2001). Plasma adiponectin levels are also reduced in adolescent obesity (Weiss *et al.* 2003). Among obese patients who have undergone gastric partition surgery body-weight reduction is accompanied by a reduction in plasma adiponectin levels (Yang *et al.* 2001). Plasma adiponectin levels are increased in anorexia nervosa (Delparte *et al.* 2003). However, in severe anorexia nervosa the adiponectin level increases gradually until BMI is about 16 kg/m² and then decreases subsequently (Iwahashi *et al.* 2003).

Subjects with type 2 diabetes have lower adiponectin levels than subjects without diabetes (Hotta *et al.* 2000; Weyer *et al.* 2001), and among subjects without diabetes there is an association between high adiponectin levels and insulin sensitivity (Tschrirter *et al.* 2003). Adiponectin mRNA levels are reduced in omental and subcutaneous adipose tissue of obese patients with type 2 diabetes compared with lean and obese subjects who are normoglycaemic (Hu *et al.* 1996). Also, low adiponectin levels are associated with gestational diabetes mellitus before and after it develops (Ranheim *et al.* 2004; Retnakaran *et al.* 2004; Williams *et al.* 2004).

In a study of patients with different forms of lipodystrophies (Haque *et al.* 2002) serum adiponectin levels were found to be lower among patients with diabetes compared with subjects without diabetes. In Pima Indians plasma adiponectin is negatively associated with insulin

receptor tyrosine phosphorylation in muscle biopsies (Stefan *et al.* 2002). Prospectively, low adiponectin levels in Pima Indians are associated with a decrease in insulin sensitivity and insulin receptor tyrosine phosphorylation increases the risk of developing type 2 diabetes (Lindsay *et al.* 2002; Stefan *et al.* 2002), and this outcome is not associated with increased adiposity (Vozarova *et al.* 2002). Plasma adiponectin concentrations are lower among individuals who subsequently develop type 2 diabetes than among controls (Spranger *et al.* 2003).

The accumulation of lipid in muscle cells is associated with insulin resistance, and there is a negative relationship between adiponectin and intramyocellular lipid content in a paediatric population (Weiss *et al.* 2003). Adiponectin does not contribute to the exercise-related improvements in insulin sensitivity (Hulver *et al.* 2002; Yatagai *et al.* 2003). Adiponectin is inversely correlated with abdominal visceral fat mass and insulin resistance in patients infected with HIV who are undergoing highly-active anti-retroviral therapy (Addy *et al.* 2003; Sutinen *et al.* 2003; Tong *et al.* 2003). On the other hand, in a study of subjects with type 1 diabetes serum adiponectin levels were found to be higher than those of healthy control subjects (Imagawa *et al.* 2002).

Subjects with coronary artery disease have lower adiponectin levels than healthy subjects (Hotta *et al.* 2000). Male patients with hypoadiponectinaemia have a 2-fold increase in prevalence of coronary artery disease, independent of well-known risk factors for coronary artery disease such as type 2 diabetes, dyslipidaemia, hypertension, smoking and increased BMI (Kumada *et al.* 2003). Adiponectin inhibits the TNF α inflammatory response of endothelial cells by inhibiting NF- κ B signalling via a cAMP-dependent pathway (Ouchi *et al.* 2000). Patients undergoing haemodialysis have elevated plasma adiponectin levels, and among these patients plasma adiponectin levels are lower in those patients who prospectively experience new cardiovascular events than in patients who are event free (Zoccali *et al.* 2002). In women without diabetes low plasma adiponectin concentrations are associated with dyslipidaemia such as high TAG levels and low HDL-cholesterol levels in serum (Matsubara *et al.* 2002).

In post-menopausal women low levels of adiponectin are associated with higher levels of high-sensitivity C-reactive protein and IL-6, which are inflammatory mediators and markers of increased cardiovascular risk (Engeli *et al.* 2003). Low adiponectin levels are also linked to endothelial dysfunction in human subjects (Ouchi *et al.* 2003; Shimabukuro *et al.* 2003).

Circulating levels of adiponectin depend on synthesis in adipose tissue, as well as clearance, possibly via the kidneys. Adiponectin levels are increased in patients with nephrotic syndrome, and proteinuria is strongly related to circulating adiponectin levels in patients with nephrotic and non-nephrotic renal diseases (Zoccali *et al.* 2003). Urinary adiponectin excretion amounts are increased in patients with nephropathy, whereas serum adiponectin levels are also elevated, perhaps as a result of compensatory enhanced synthesis (Koshimura *et al.* 2004).

Lifestyle intervention focused on low-fat diets can reduce the risk of developing type 2 diabetes (Tuomilehto

et al. 2001). Dietary composition as part of overall lifestyle may affect abnormalities in pregnancy such as gestational diabetes mellitus and pre-eclampsia. Increased fat intake during pregnancy has been associated with the development of impaired glucose tolerance and gestational diabetes mellitus in human subjects (Saldana *et al.* 2004) and in rats (Holemans *et al.* 2004). Observational studies of pre-eclampsia suggest that various nutrients are associated with pre-eclampsia. For example, high intake of energy, sucrose and PUFA may be involved in the development of the disorder (Clausen *et al.* 2001). However, in a recent review (Roberts *et al.* 2003) it is argued that targets for nutritional investigation based on the current knowledge of pathophysiology are warranted.

Adipokines may link the adipose tissue and reproductive function (Budak *et al.* 2006). One possible role of adiponectin is to ensure energy supply and to regulate energy needs for normal reproduction and pregnancy. Cord blood adiponectin levels are much higher than the serum levels in children and adults, and are positively correlated with fetal birth weights (Sivan *et al.* 2003). To address this hypothesis, adiponectin and other adipokines have been studied in various pathological states during pregnancy (Ranheim *et al.* 2004; Haugen *et al.* 2006).

A recent study (Haugen *et al.* 2006) has investigated whether adipokine levels are altered in pre-eclampsia and whether insulin sensitivity is affected. Maternal plasma concentrations of adiponectin, resistin and leptin and their mRNA expression were monitored in the abdominal adipose tissue and placenta from two groups of patients undergoing caesarean section: (1) women with pre-eclampsia; (2) healthy pregnant women (control group). Compared with the control group the women with pre-eclampsia were found to have higher concentrations of several adipokines: adiponectin, 50%; resistin, 22%; leptin, 52%. Similar mRNA levels of adiponectin, resistin and leptin were found in abdominal subcutaneous adipose tissue in the two groups. Moreover, resistin mRNA levels in the placenta were not found to be different between the groups, whereas leptin mRNA levels were found to be higher in placentas from women with pre-eclampsia compared with the controls. Thus, increased plasma concentrations of adipokines in pre-eclampsia may not relate to altered expression levels in adipose tissue. In contrast to resistin, leptin mRNA levels in the placenta were found to be increased in pre-eclampsia.

A comparison of women with gestational diabetes mellitus and healthy pregnant women (Ranheim *et al.* 2004) has shown that plasma adiponectin concentrations among lean control subjects are 51% higher than those of corresponding individuals with gestational diabetes mellitus. In line with this observation adiponectin mRNA levels in abdominal subcutaneous adipose tissue were found to be higher in healthy pregnant women as compared with women with gestational diabetes.

Summary

Dietary factors may influence the expression of adipokines *in vivo* as well as *in vitro*. Supply of total energy, total fat, different types of fatty acids and eicosanoids, RA and

nicotine linked to the adrenergic hormonal response may all influence the expression of adipokines in adipose tissue, as well as the plasma concentration of adipokines. Thereby dietary factors can change many biological systems with extensive physiological consequences.

Altered levels of, or sensitivity to, adipokines may alter appetite, glucose tolerance, fatty acid oxidation and angiogenesis (Iversen *et al.* 2002; Reseland *et al.* 2001c).

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