Proceedings of the Nutrition Society (2011), **70**, 426–438 doi:10.1017/S0029665111001662
 First published online 22 August 2011

The annual Irish Section Postgraduate meeting hosted by the University of Ulster was held at White Horse Hotel, Derry/Londonderry on 16–18 February 2011

Irish Section Postgraduate Symposium

Pathogenic obesity and nutraceuticals

K. P. Conroy*, I. M. Davidson and M. Warnock

Department of Dietetics, Nutrition and Biological Sciences, Queen Margaret University, Edinburgh, Queen Margaret Drive, Musselburgh EH21 6UU, UK

Over a decade of intense research in the field of obesity has led to the knowledge that chronic, excessive adipose tissue expansion leads to an increase in the risk for CVD, type 2 diabetes mellitus and cancer. This is primarily thought to stem from the low-grade, systemic inflammatory response syndrome that characterises adipose tissue in obesity, and this itself is thought to arise from the complex interplay of factors including metabolic endotoxaemia, increased plasma NEFA, hypertrophic adipocytes and localised hypoxia. Plasma concentrations of vitamins and antioxidants are lower in obese individuals than in the non-obese, which is hypothesised to negatively affect the development of inflammation and disease in obesity. This paper provides a review of the current literature investigating the potential of nutraceuticals to ameliorate the development of oxidative stress and inflammation in obesity, thereby limiting the onset of obesity complications. Research has found nutraceuticals able to positively modulate the activity of adipocyte cell lines and further positive effects have been found in other aspects of pathogenic obesity. While their ability to affect weight loss is still controversial, it is clear that they have a great potential to reverse the development of overweight and obesity-related comorbidities; this, however, still requires much research especially that utilising well-structured randomised controlled trials.

Nutraceuticals: Polyphenols: Obesity: Inflammation: Adipose tissue

Obesity is considered the epidemic of the 21st century and worldwide in 2008 approximately 1·5 billion adults were classed as overweight, with a third of these classed as obese, numbers which are expected to increase over the next 5–10 years[1]. Having significant associations with CVD, type 2 diabetes mellitus (T2DM) and cancer[2], obese individuals have been found to have a substantially higher use of healthcare services than the non-obese[3]; therefore, as prevalence increases, so will the burden on healthcare systems. It is now widely recognised that obesity is characterised by a chronic, low-grade, systemic inflammatory response stemming from enlarged adipose tissue (AT) depots, and this is thought to be involved in the development of obesity-related pathologies[4]. Furthermore, plasma levels of vitamins and antioxidants are lower in the obese[5,6] and an inverse relationship has been shown between serum total antioxidant capacity and waist circumference[7], research also indicates the modulatory effects of vitamins and antioxidants on the immune system[8] and it may be that reduced levels have a role in the development of inflammation and ultimately disease, in obesity.

Current pharmacotherapy for obesity primarily involves Orlistat and Sibutramine; however, their side effects, combined with the uncertain long-term effects associated with their use, have prompted research into alternatives. The term 'nutraceuticals' was originally defined as 'a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of disease'[9]. This term encompasses substances that are not traditionally recognised nutrients (e.g. vitamins and minerals), but that have been found to have positive physiological effects on

Abbreviations: AT, adipose tissue; C/EBP, cytidine-cytidine-adenosine-adenosine-thymidine-enhancer-binding protein; EGCG, epigallocatechin-3-O-gallate; ER, endoplasmic reticulum; HIF, hypoxia-inducible factor; LPS, lipopolysaccharide; sNEFA, saturated NEFA; T2DM, type 2 diabetes mellitus; TLR, Toll-like receptor; UPR, unfolded protein response.

***Corresponding author:** K. P. Conroy, fax +44 131 4740000, email kconroy@qmu.ac.uk

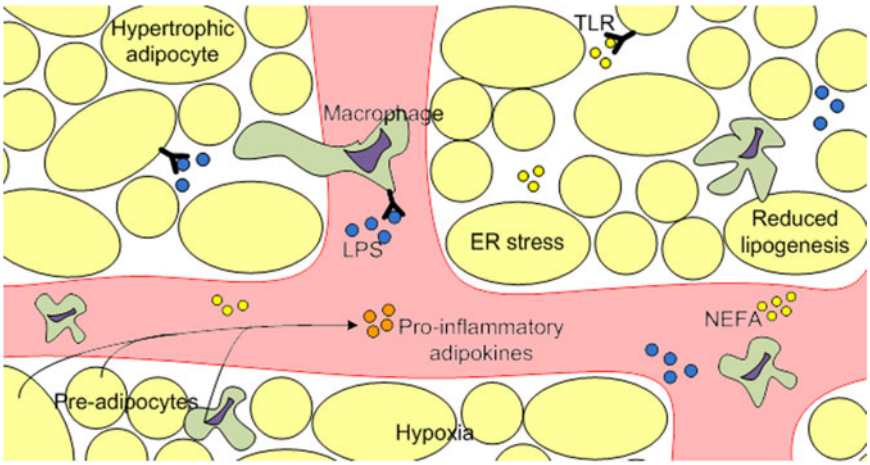

Fig. 1. (Colour online) The development of pathogenic adipose tissue in obesity is a complex interplay of many factors. LPS, lipopolysaccharide; ER, endoplasmic reticulum; TLR, Toll-like receptors.

the body[10] and includes plant phytochemicals and phenolics. There is currently no coherent, international definition of a nutraceutical; however, over the last decade, there has been a surge in their marketing, sales and research and as a result there is a requirement for governing bodies to define this area in order to uphold regulatory laws. It is generally regarded that a nutraceutical is a food component consumed in a unit dose form such as tablets, capsules or liquids and includes those from botanical sources[10]. Polyphenols are now known to act as signalling molecules and have been found to affect cellular function and modulate gene expression in relation to cancer[11] and neurodegenerative disease[12]. However, research into the potential use of nutraceuticals in the treatment of chronic inflammatory diseases such as obesity has only recently been undertaken and as such there is still much to be investigated.

Adipose tissue in obesity

AT comprises mature adipocytes and non-fat stromovascular cells including fibroblasts, endothelial cells, preadipocytes and tissue resident macrophages[13]. Originally thought of as connective tissue where excess energies were stored as TAG, in the last decade, the endocrine function of AT has been demonstrated and it is now known to produce numerous products collectively called 'adipokines' involved in energy metabolism, inflammatory response and cardiovascular activity[14,15]. The two major adipokines secreted are leptin and adiponectin.

Leptin is a protein product of the *ob* gene initially known for its role in regulating appetite[16]. In obesity, circulating levels are increased in proportion to fat mass[17,18], possibly due to increased expression of the *ob* gene and elevated leptin secretion[19,20]. Women have higher-serum leptin concentrations than men regardless of percent body fat or fat mass[21,22], gender differences also seen in obese children[23]. Leptin shares homology with some pro-inflammatory cytokines and is indeed regarded as such; the leptin receptor is expressed by immune cells[24,25] and in human subjects circulating levels of leptin are positively associated with those of C-reactive protein, a marker of inflammation[26]. Adiponectin is regarded as anti-inflammatory and also regulates insulin sensitivity[14]. Normal-weight individuals have high circulating levels of adiponectin; however, this decreases as adiposity increases[27] and levels also negatively correlate with insulin resistance, T2DM and CVD[28]. Adiponectin synthesis is increased by weight loss and thiazolidinediones, used in the treatment of T2DM, conversely TNFα and IL-6 reduce adiponectin synthesis[29,30]. In human subjects, there is an inverse correlation between plasma C-reactive protein levels and adiponectin[26,31,32]. Furthermore, in mice, adiponectin gene knockdown results in diet-induced insulin resistance[33] and an increased inflammatory response to dextran sulfate sodium-induced colitis[34] and tissue ischaemia[35].

Chronic excessive energy intake leads to AT expansion through both hypertrophy and hyperplasia, and in adults hypertrophy seems to dominate[36,37]. In some adults, however, hyperplasia can be predominate, which is thought to result in the development of a metabolically benign form of obesity[38]. Dysregulated secretion of adipokines occurs as obesity develops and there is a general shift in adipokine and cytokine production towards a pro-inflammatory composition. This is thought to be mediated by the activation of tissue-resident macrophages in addition to a significant infiltration of other immunocytes, predominantly macrophages[39] although the triggering factors for this are, as yet, unclear. However, the main factors implicated in the initiation of inflammation and oxidative stress in obesity are thought to be metabolic endotoxaemia, increased plasma NEFA, hypertrophic adipocytes and increased AT hypoxia[13] (Fig. 1). These factors do not develop in isolation and there are most likely mechanisms involved which act to feed-forward these processes.

Metabolic endotoxaemia

It is now well known that there is a post-prandial inflammatory response, especially following meals high in fat

and carbohydrate[40]. Macronutrient intake has also been shown to induce pro-inflammatory changes in the immunocytes of normal-weight subjects, a response that is greater and more prolonged in the obese[41], and which is not seen following consumption of a meal rich in fruit and fibre[42]. Recent research suggests that this may be due to the presence of Toll-like receptor (TLR) stimulants, such as bacterial lipopeptides and lipopolysaccharides (LPS), which have been found primarily in meat and processed food products even though they are fit for consumption[43]. Microbiota of the gut has recently been identified as a triggering factor of inflammation in obesity, and indeed for the development of obesity itself. Germ-free mice, which contain no gut microbiota, have 42% less total body fat than conventionally raised mice; however, re-colonisation with microbiota from normal mice, increased their total body fat content by 57%[44]. It is thought that microbiota aid the absorption of monosaccharides and induce hepatic lipogenesis, promoting energy storage with a subsequent increase in adiposity[44].

In trying to further identify the causative factors for post-prandial inflammation, research indicates that it may be absorption of the endotoxin LPS, released during the death of Gram-negative bacteria within the gut; this is also proposed to have a role in the development of obesity and inflammation[45]. In mice, a high-fat or high-carbohydrate meal increases plasma endotoxin levels[45]. Similarly, in human subjects, consumption of a high-fat meal has been found to increase plasma levels of endotoxin[42,46] and positive correlations have been found between energy or fat intake and plasma endotoxin levels in healthy men[47]. One study has further shown there to be a difference between fatty acids in increasing plasma LPS concentrations. Genetically obese JCR:LA-cp (James C Russell corpulent) rat fed a diet containing either 5% or 10% PUFA had significantly lower levels of LPS-binding protein than those on the isoenergetic, lipid-balanced control diets[48]. It would be interesting to elucidate if PUFA have similar properties in human subjects.

This significant increase in plasma LPS in response to diet composition has been termed as 'metabolic endotoxaemia'[45]. Plasma levels of LPS-binding protein, a marker of endotoxaemia, are significantly higher in obese human subjects and are associated with metabolic syndrome and T2DM[49]. Research in mice has found that a high-fat or high-carbohydrate diet increases the Gram-negative bacteria population of the gut along with increasing plasma levels of LPS[45]. Conversely, modulation of gut flora by antibiotics reduced metabolic endotoxaemia in diet-induced and the genetically obese *ob/ob* mice[50]. The binding of LPS to TLR4 on enterocytes triggers its phagocytosis and it is subsequently translocated across the intestinal barrier and into the lymph; from there LPS is packaged into chylomicrons along with dietary lipids and transported around the body[51]. Indeed, one study conducted in fasting normal-weight, healthy individuals has found that while intake of water, orange juice or a glucose drink has no effect on plasma endotoxin concentrations, consumption of cream increased plasma LPS levels[52]. It has also been shown in the genetically obese mouse models, *ob/ob* and *db/db*, that high-fat feeding and LPS can increase intestinal wall permeability, elevating endotoxin levels in the portal circulation[50,53]. Recent research suggests that it is gut microbiota that mediate this effect, by modulating the intestinal endocannabinoid system[54]. In obese mice, blockade of the endocannabinoid receptor, CB_1 led to a reduction in gut permeability with a concomitant reduction in plasma LPS, which was also seen following prebiotic administration[54].

Although it has recently been shown that tea catechins such as epigallocatechin-3-O-gallate (EGCG)[55], anthocyanins and anthocyanidins[56] have a moderate affinity for endocannabinoid receptors at concentrations <50 μM, there is, as yet, no research into their ability to modulate gut permeability and thereby reduce plasma LPS levels. Furthermore, limited research has been conducted investigating their ability to limit the increases in LPS found following a high-energy meal. A small study using normal-weight, healthy subjects investigated plasma changes in endotoxin levels, inflammation and oxidative stress following consumption of a high-fat, high-carbohydrate meal with water, a glucose drink or orange juice[57]. Consumption of orange juice abrogated the increase in plasma endotoxin, inflammation and oxidative stress which was seen with glucose drink and water intake[57]. In a similar study, healthy, normal-weight individuals were given a nutritional supplement containing resveratrol (major polyphenol of red-wine grapes) and muscadine grape polyphenols along with a high-fat, high-carbohydrate meal. The supplement ameliorated the increase in plasma LPS-binding protein and endotoxin concentrations associated with intake of such a meal, along with reducing monocytic expression of TLR4[58]. The results of these studies indicate the merit of further research into this area and due to the extended post-prandial inflammatory response seen in obesity, should be extended to include this population.

TLR are transmembrane proteins that recognise microbial components such as bacterial LPS and flagellin and also possibly endogenous ligands released during inflammation[59]. TLR4 is thought to mediate cellular response to LPS, and TLR2 is regarded as the main receptor for Gram-positive bacterial and fungal cell well components[60]; however, LPS activation of TLR4 on 3T3-L1 murine adipocytes has been found to induce the expression of TLR2, leading to an increase in IL-6 gene expression[60]. TLR expression has been observed in AT and adipocytes from normal-weight and obese human subjects and these are responsive to LPS, resulting in the activation of NF-κB signalling, which regulates immune and inflammatory responses, and subsequent cytokine release[61–63]. In mice fed a high-fat diet, knockdown of TLR ameliorated the increase in adiposity, reducing serum insulin concentrations and circulating markers of inflammation, although the mechanisms behind this are not fully understood[64].

The bioactive xanthones of the mangosteen fruit, α- and γ-mangostin, have recently been found to abrogate the activation of NF-κB signalling following incubation with LPS, with a concomitant reduction in pro-inflammatory gene expression in human adipocytes, *ex vivo*[65]. Furthermore, α-tocopherol treatment of 3T3-L1 cells stimulated with LPS abrogated production of the cytokine, IL-6[66]. Plant compounds have also been found to reduce

LPS-activation of immunocytes. Stimulation of the human acute monocytic leukemia cell line THP-1 with LPS increased the expression and secretion of TNFα and IL-6, which was significantly reduced by treatment with the common polyphenol, cyanidin 3-O-β-glucoside[67]. EGCG is also known to be anti-inflammatory and abrogates the macrophage inflammatory response to LPS. Recent research suggests that this is mediated by its ability to inhibit TLR signalling by down-regulating TLR4 expression[68].

NEFA

Elevated plasma NEFA are a feature of obesity thought to result from increased AT basal lipolytic activity[69], which is in turn due to increased adipocyte size[70] and cellular hypoxia[71]. Historically, increased plasma NEFA have been connected with obesity[72] and T2DM[73] although further investigations have failed to find any significant associations[74]. Regardless, there is much research to indicate the ability of NEFA to impair the insulin responsiveness of tissues including the muscle and liver, which is thought to result from the inhibition of GLUT translocation caused by the intracellular accumulation of fatty acid metabolites[75]. The polyphenolic compounds, EGCG[76] and naringenin[77], have been shown to increase GLUT translocation in rat L6 skeletal muscle cells, thereby enhancing glucose uptake; this has also been found in 3T3-L1 adipocytes treated with the phenolic acid, gallic acid, derived from seabuckthorn[78]. Conversely, in isolated rat adipocytes, the polyphenols catechin-gallate, myricetin and quercetin, widely present in fruits and vegetables, have been shown to directly interact with GLUT4, reducing glucose transport[79]; however, this has not been replicated *in vivo*. In a fructose-fed rat model of insulin resistance, AT concentrations of GLUT4 were reduced by 58 % compared to the control group; however, in those supplemented with green-tea powder, GLUT4 levels were not significantly different from the controls (19 %) thereby increasing insulin sensitivity[80]. Further to this, the induction of insulin resistance in rats by 48 h intravenous infusion of a TAG emulsion, inhibited the translocation of GLUT4 in both adipose and skeletal muscle tissue. However, this was abrogated in both tissues with the co-injection of 10 mg/kg EGCG; additionally there was a concomitant improvement in insulin-induced glucose uptake[81].

Recently it has been found that normal fasting NEFA levels are maintained in abdominally obese men through a reduction in lipolytic enzyme expression and therefore reduced fasting state NEFA release[82]. However, it was further found that post-prandial fatty acid uptake by AT was significantly reduced, which is attributed to a down-regulation of fat storage mechanisms and resulted in a substantial increase in plasma NEFA following a meal[82]. This is proposed to lead to an increase in ectopic fat deposition; however, this requires further research[82]. Phytochemicals such as luteolin, a flavonoid found in olive oil and carrots[83], resveratrol[84] and theaflavins found in black tea[85] have been found to limit lipid accumulation in human liver HepG2 cells. This has also been found with curcumin treatment of human Hep3B cells[86] and EGCG treatment of primary mouse hepatocytes[87]. The proposed mechanism of action is thought to be activation of AMP-activated protein kinase α signalling pathway, which subsequently inhibits fatty acid and cholesterol synthesis and up-regulates fatty acid oxidation and glycolysis, thereby regulating cellular energy balance[88].

There are a number of animal studies indicating the benefits of phyotchemicals in reducing liver lipotoxicity. Supplementation of the genetically obese KK/A^{y} mice with rhaponticin, extracted from rhubarb, reduced plasma NEFA and TAG levels in addition to preventing the development of liver steatosis[89]. Theaflavin treatment of rats fed a high-fat diet ameliorated the development of liver steatosis with a concomitant reduction in plasma NEFA and TAG, which was shown to be mediated through activation of AMP-activated protein kinase signalling[85]. In a rat model of liver steatosis, where treatment with carbon tetrachloride induces liver fat accumulation and hepatic cell death, prior feeding with an apricot extract significantly attenuated this[90]. Olive leaf extract has also been shown to attenuate the development of liver steatosis in a high-fat fed rat model of obesity, with a concomitant reduction in plasma TAG; however, circulating NEFA levels were not affected[91]. Resveratrol supplementation of rats with diet-induced liver steatosis significantly reduced fat deposition in the liver[92]. None of these studies investigated alterations in adipose or muscle tissue gene expression of lipid-processing mechanisms, which given the recent findings in obese human subjects[82] would be pertinent. Furthermore, there are, as yet, few studies investigating their effects in human subjects.

Characterisation of fasting plasma NEFA in healthy, normal-weight individuals has found that SFA comprise just over half (56 %) of the total NEFA concentration, and of this fraction palmitate predominates[93]. Further research has found that consumption of a saturated NEFA (sNEFA)-rich diet by abdominally obese participants for 8 weeks resulted in an increase in AT inflammatory gene expression compared to those on a MUFA-rich diet[94]. In cell culture, sNEFA have been shown to induce release of pro-inflammatory cytokines from macrophages[95,96] and in adipocytes, increase reactive oxygen species generation and TNFα, IL-6 and monocyte chemotactic protein-1 gene expression along with reducing adiponectin gene expression[97–99]. TNFα has been found to decrease adipocyte insulin sensitivity, which increases lipolysis and therefore plasma levels of NEFA[100,101]. Even short-term exposure of adipocytes to TNFα stimulates lipolysis through increased inducible nitric oxide synthase expression, which in turn up-regulates nitric oxide production and subsequently phosphorylates and activates hormone-sensitive lipase[102]. Further research has found that immunocyte response to LPS, mediated by TLR4 activation, is approximately three-fold higher in those pre-treated with sNEFA than those treated with either sNEFA or LPS alone[103]. A positive feedback loop is proposed whereby sNEFA released from adipocytes activate macrophages, stimulating further release of TNFα and IL-6 and these in turn cause inflammatory changes in adipocytes[104].

Studies *in vitro* have shown that sNEFA activate TLR2 and TLR4 on adipocytes and macrophages triggering c-Jun

N-terminal kinase and NF-κB pro-inflammatory signalling cascades resulting in pro-inflammatory cytokine production[105–108]. However, recent research suggests that it may be LPS contamination of the fatty acid-free bovine serum albumin, a reagent commonly used to complex with sNEFA in *in vitro* studies, which stimulates TLR4 as uncomplexed sNEFA had no effect on TLR-dependent signalling[109]. Although this is a matter that requires further clarification, numerous cell and animal studies do show that sNEFA are able to elicit a pro-inflammatory response; furthermore, these low levels of LPS may better represent the *in vivo* milieu[110]. There are, as yet, limited studies investigating the inhibitory effects of phytochemicals on the pro-inflammatory response of macrophages or adipocytes to sNEFA. However, as mentioned previously, studies in both adipocytes and macrophages have shown that phytochemicals, such as α- and γ-mangostin[65], α-tocopherol[66] and EGCG[68], are able to inhibit signalling pathways downstream of LPS-mediated TLR activation, ameliorating pro-inflammatory gene expression.

Adipocyte hypertrophy

Hypertrophic adipocytes have been associated with hypertension[111] and an increased risk of CVD[112], and further research in human subjects and mice has found that adipocyte size positively correlates with degree of AT inflammation[113–116]. Hypertrophic adipocytes isolated from human subjects have been found to have altered gene expression[117] leading to increased secretion of pro-inflammatory factors and altered adipokine secretion[118–120]. Anti-obesity research has investigated the ability of nutraceuticals to promote adipocyte apoptosis and inhibit adipocyte differentiation, thereby reducing AT accumulation. The two most well-studied transcription factors regulating adipogenesis are PPARγ and cytidine-cytidine-adenosine-adenosine-thymidine-enhancer-binding proteins (C/EBP)[121]. PPARγ is considered to be essential and adequate for the induction of adipocyte differentiation and has two isoforms, PPARγ1 and PPARγ2, whose distinct roles are yet to be elucidated. Members of the C/EBP family are either anti- or pro-adipogenic and include C/EBPα, C/EBPβ, C/EBPγ and C/EBPδ. Their expression is necessary for the development of adipocyte insulin sensitivity[122] and while they are important for adipogenesis, the presence of PPARγ is still required.

The anti-adipogenic potential of various natural compounds has been investigated and many have been found to inhibit adipocyte differentiation. The addition of curcumin, the major polyphenol found in turmeric, to rodent models of obesity has been shown to reduce body weight gain and ameliorate the development of diabetes[123,124]. This is thought to be due to its ability to suppress adipocyte differentiation and indeed this has been found in studies using the murine 3T3-L1 cell line, with a concomitant down-regulation of PPARγ[125,126]; however, in another study utilising 3T3-L1 cells, these transcriptional markers were not affected[124]. A recent comprehensive investigation into the ligand activity of curcumin found it to have no binding activity at the PPARγ ligand-binding site and subsequently no effect on adipocyte differentiation[127]. These disparities in curcumin activity are most likely related to the different extractions used as some studies have utilised purified curcumin, while others have prepared ethanolic extracts of turmeric which may contain other active compounds.

The green-tea polyphenol, EGCG, induces cancer cell apoptosis and has been shown to increase weight loss and reduce fat accumulation in both human[128] and rodent obesity studies[129,130]. In one study, administration of EGCG to the diets of high-fat fed rats abrogated the development of glucose intolerance with a concomitant increase in PPARγ gene expression; however, contrastingly, administration of green tea suppressed PPARγ gene expression[131]. In 3T3-L1 cells, investigations have attributed the anti-obesity effects of EGCG to its ability to induce adipocyte apoptosis and inhibit adipocyte differentiation and proliferation, through down-regulation of PPARγ and C/EBPα[132–134]. The concentrations used in these studies ranged from 0 to 200 μM; however, one study found that EGCG administration at 0·5–10 μM, while having no effect on cell activity, enhanced expression of genes related to adipocyte differentiation and insulin sensitivity and reduced fat accumulation[135]. In human subjects, studies investigating the bioavailability of green-tea polyphenols following consumption of green-tea solids in water have found the maximum plasma concentration of EGCG to be <1 μg/ml[136,137]; therefore, studies carried out in cells using lower levels of EGCG may better mimic physiological levels.

However, is the inhibition of adipocyte differentiation truly beneficial? Recent research has indicated that in the moderately obese (BMI 26–36 kg/m^2), an increase in the number of smaller adipocytes may also contribute to AT inflammation. In the study, abdominal AT biopsies were taken from healthy, moderately obese individuals and analysed for cell size distribution and inflammatory gene expression[138]. Adipocyte size was not found to be associated with inflammatory gene expression, instead an increase in the proportion of smaller adipocytes predicted the expression of inflammatory genes, which was independent from sex, insulin resistance and BMI, although this association was stronger in insulin-resistant than insulin-sensitive individuals[138]. A total of eight inflammatory genes were analysed and of these CD14 and CD45 are specific for monocyte lineage cells, suggesting the acquisition of a monocytic phenotype by the smaller adipocytes. Previous research has found that pre-adipocytes acquire functional properties similar to macrophages when cultured in contact with one another and their gene profile has been found to be closer to macrophages than adipocytes[139]. As outlined in Fig. 2, there are many factors in pathogenic AT which may affect the normal differentiation of pre-adipocytes; this then results in the development of a pro-inflammatory, macrophage-like phenotype as indicated by the elevated secretion of cytokines and chemokines[140,141], most likely by activation of the key transcriptional regulator of inflammation, NF-κB[141]. Further research in subcutaneous AT biopsies obtained from obese individuals suggests that there is a failure of pre-adipocytes to differentiate[140,141], possibly caused by elevated levels of TNFα[140].

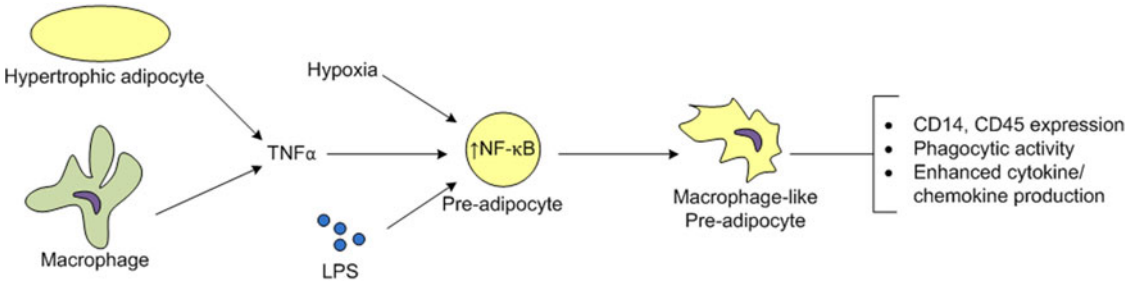

Fig. 2. (Colour online) Factors contributing to conversion of pre-adipocyte to one with macrophage-like activity. LPS, lipopolysaccharide.

LPS, high circulating levels of which are found in the obese or those following a high-fat meal, has also been found to affect adipocyte differentiation. Pre-adipocytes are known to have a macrophage-like phenotype and have a high gene expression and secretion of pro-inflammatory cytokines[142,143] in response to TNFα and LPS[139,144]. IL-6 expression levels were found to be higher in LPS-stimulated 3T3-L1 pre-adipocytes than in mature 3T3-L1 adipocytes[145], and continuous treatment of these cells with LPS impaired their differentiation[146]. Furthermore, in primary cultures of human adipocytes, LPS stimulation up-regulated pro-inflammatory cytokine mRNA, predominantly in the pre-adipocyte fraction and, as differentiation into mature adipocytes occurred pro-inflammatory cytokine expression decreased[144]. Moreover, the therapeutic effects of thiazolidinediones used in the treatment of diabetes have been attributed, in part, to their ability to increase adipocyte differentiation[147]. Treatment of genetically obese Zucker rats with the thiazolidinedione, troglitazone normalised hyperglycaemia and hyperinsulinaemia in addition to reducing AT levels of TNFα and leptin[1]. This was concomitant with an increase in the number of small adipocytes and a reduced number of large adipocytes, without alterations to the total weight of white AT[148].

Supplementation of diet-induced obese rats with bitter melon extract powder or the thiazolidinedione, pioglitazone, prevented the development of hyperinsulinaemia and glucose intolerance[149]. The number of large adipocytes (>180 μm) was significantly lower in these two groups compared with those on the high-fat diet alone. In addition, the number of smaller adipocytes (60–100 μm) in the bitter melon group was similar to those fed the low-fat diet, which was significantly higher than the high-fat and thiazolidinedione-treated groups. Bitter melon powder had the added effect of reducing AT mass and lipid content, suggesting that lipogenesis within AT was also attenuated[149]. *In vitro* studies have identified further compounds able to enhance adipocyte differentiation. Phloretin, a flavonoid found in apples and strawberries, was found to increase TAG accumulation with an attendant up-regulation of PPARγ and C/EBPα, concomitantly increases in adiponectin expression and secretion were also found[150]. Found in citrus fruits, the flavone nobiletin has been shown to enhance 3T3-L1 differentiation; however, this was not due to any activity at PPARγ. Instead, nobiletin activated C/EBPβ, which is up-stream of PPARγ and induces its expression[151]. Further research clearly needs to be undertaken to fully determine the impact of individual cell populations within AT on adipose inflammation; however, it can be seen that failure of pre-adipocytes to differentiate can be detrimental with respect to either overloading of mature adipocytes rendering them hypertrophic or increasing the inflammatory pre-adipocyte population.

Adipose tissue hypoxia

Secondary to the development of hypertrophic adipocytes is AT hypoxia. Adipocytes can expand up to 150–200 μm in diameter[118] and the maximum diffusion distance of oxygen is 200 μm; therefore adipocyte hypertrophy can lead to AT hypoxia as their size may impair oxygen diffusion into the cell[4]. A recent study in obese human subjects has shown their abdominal AT to have a lower capillary density and oxygen partial pressure than lean subjects and this correlated negatively with percentage body fat and macrophage inflammatory protein-1 secretion, which is involved in inflammatory cell recruitment and release of pro-inflammatory cytokines[152]. Furthermore, the increase in AT blood flow associated with the postprandial state is not seen in the obese[82]. AT hypoxia is also found in rodent models of obesity, in addition to increased expression of hypoxia-regulated genes and dysregulated adipokine secretion[71,153,154]. Hypoxia-inducible factor (HIF)-1α and HIF-2α are transcription factors induced by hypoxia that affect angiogenesis, glycolysis, cell proliferation, apoptosis and inflammation[155,156]. Gene expression of HIF-1α has been positively correlated with body mass[157] and in adipocytes, HIF-1α and HIF-2α accumulation have been shown to promote the development of an insulin-resistant state by decreasing insulin receptor phosphorylation[158]. In adipocyte cell lines, hypoxia reduces NEFA uptake and increases lipolysis as well as inducing necrosis and apoptosis[71], pro-inflammatory cytokine production is also increased and adipokine secretion dysregulated[159,160]. Furthermore, the differentiation of pre-adipocytes is inhibited[161].

Production of angiogenic factors, such as vascular endothelial growth factor and platelet-derived growth factor, are increased in response to hypoxia[162,163] and circulating levels of these are found to be elevated in obese human subjects and mice[164,165]. A recent rodent study has shown that angiogenesis supports, and is essential for

adipogenesis and that they occur together in cell clusters; however, as fat mass increases hypertrophy dominates with a reduction in the occurrence of adipogenic/angiogenic cell clusters[166]. Nutraceuticals have been found to reduce the expression and activity of HIF in cancer cells[167] with the overall aim to reduce tumour angiogenesis and therefore growth; however, similar inhibition in AT may only serve to further exacerbate hypoxia. In ischaemia-reperfusion injury, the promotion of HIF and its downstream signalling targets is beneficial, limiting infarct size by stimulating angiogenesis[168]. The subunits of HIF, HIF-1α, HIF-2α and the recently discovered HIF-3α, differentially regulate adipogenesis[169]; however, their exact roles are, as yet, ill defined. The role of HIF and its subunits in AT dysfunction is a recent area of research and needs to be further understood before investigations into its regulation by nutraceuticals can get underway.

Adipocyte dysfunction

Researchers have attempted to establish what the fundamental triggering factor is that tips healthy AT towards one which is pro-inflammatory; one potential candidate is endoplasmic reticulum (ER) stress. Markers of ER stress occur in AT of both diet and genetically induced mouse models of obesity[170] and more recently in obese human subjects[171–173], and have been found to be reduced by weight loss[173]. Recently, ER stress has been linked with reduced secretion of adiponectin, a key adipokine in the regulation of insulin sensitivity and inflammation in obesity. Incubation of 3T3-L1 adipocytes with a protease inhibitor induced ER stress which resulted in a reduction in adiponectin synthesis through the activation of c-Jun N-terminal kinase signalling pathway and subsequent induction of activating transcription factor 3[174].

The ER is the principal site of protein synthesis within the cell, ensuring the transport and release of correctly folded proteins and within adipocytes, also facilitates lipid droplet formation[175–177]. An oxidative environment is present within the ER and is critical for disulfide bond formation and correct folding of proteins[177]. However, in reaction to disturbances such as nutrient deprivation, lipids and increased workload, unfolded proteins accumulate within the ER triggering the unfolded protein response (UPR), which results in reactive oxygen species accumulation and cellular oxidative stress[178]. This is mediated by three protein kinases, protein kinase RNA-like ER kinase, inositol-requiring 1α and activating transcription factor 6[176,177]. As a transient measure, the UPR initially reduces protein synthesis and translocation into the ER, followed by a longer-term increase in the ability of the ER to handle unfolded proteins. If protein misfolding persists or is excessive then cell death is triggered, usually through apoptosis[176,177].

The UPR is linked to inflammation through production and accumulation of reactive oxygen species, activation of the acute-phase response and activation of transcription factors regulating inflammatory signalling pathways such as NF-κB and c-Jun N-terminal kinase[175,179]. It is unknown as to what causes ER stress in obesity and there is little research into ER stress in the adipocyte; however, some causative factors may include nutrient deprivation, resulting from decreased vascular density, with concomitant hypoxia, and increased protein synthesis due to adipocyte hypertrophy[180]. Elevated NEFA levels may also be a culprit, as these have been shown to activate the UPR in other cell types, including pancreatic β-cells and hepatocytes[181–183]. Conversely, ER stress may also result in elevated blood lipid levels, and research has found that protease inhibition in adipocytes, which induces ER stress, suppresses TAG synthesis and the transcription of lipogenic genes[184].

Although antioxidants may promote ER stress by adversely affecting the oxidising environment of the ER, it has recently been shown that antioxidants could possibly have some benefit in reducing UPR-induced oxidative stress. One study investigated the expression of coagulation factor VIII, which is deficient in haemophilia A and is prone to misfolding in the ER[185]. It was found that factor VIII misfolding in the ER resulted in oxidative and ER stress *in vitro* in Chinese hamster ovary-(H9) cells with eventual apoptosis, which was attenuated by the addition of butylated hydroxyanisole, a phenolic, lipid-soluble antioxidant. An effect that was also mimicked *in vivo* in mice. Further to this, butylated hydroxyanisole treatment reduced the intracellular accumulation of misfolded factor VIII with a concomitant increase in functional factor VIII secretion, both *in vitro* and *in vivo*. Treatment of Chinese hamster ovary-H9 cells with ascorbic acid, which has weaker antioxidant properties than butylated hydroxyanisole, produced inconsistent results of less intensity[185].

In another study, oxidative and ER stress were induced in human umbilical vein endothelial cells by incubation in hyperglycaemic conditions[186]. Interestingly though, while treatment with ascorbic acid and α-tocopherol eliminated oxidative stress, no effect was found on ER stress, similar to the results found by Malhotra *et al.*[185]. This discrepancy may be due to the different cell lines used or, more likely, due to butylated hydroxyanisole having phenolic activity. Research in human colon cancer cell lines has shown that quercetin, a phenolic flavonoid, is able to reduce ER stress through the inhibition of the phosphoinositide 3-kinase pathway, which is not replicated by ascorbic acid or α-tocopherol[187]. In a cell-free study, oxidative stress resulted in the loss of function of the ER protein-folding enzyme, protein disulfide isomerase causing an accumulation of misfolded proteins which was prevented by the addition of the polyphenolic compounds, curcumin and masoprocol[188]. While it has recently been shown that reduced adiponectin secretion from adipocytes is due, in part, to ER stress, it has yet to be investigated whether antioxidants could ameliorate ER stress in the adipocyte and, in so doing, possibly re-assert an anti-inflammatory secretory pattern. Given the evidence, it seems unlikely that a compound with purely antioxidant activity would have this effect, and therefore polyphenolic compounds may have more benefit.

Conclusion

Despite the large amount of research into the development of pathogenic obesity, it is clear that this is a complex and

NS Proceedings of the Nutrition Society

dynamic process and as such, further research is required in order to fully understand the mechanisms involved. There are thought to be four key areas that are disturbed during AT expansion leading to the initiation of inflammation within AT; metabolic endotoxaemia, increased plasma NEFA, hypertrophic adipocytes and increased AT hypoxia. Adipocyte ER stress is hypothesised to precede the development of the aforementioned four areas. A role for nutraceuticals in reversing the development of inflammation in obesity is a subject of great interest, and from the research reviewed here their potential in this area is clear. Although having been subject to intensive research in other areas, grape seed and green-tea polyphenols appear to also be particularly effective in pathogenic obesity, limiting metabolic endotoxaemia and the detrimental effects of elevated NEFA. Newly characterised compounds such as α- and γ-mangostin and bitter melon extract were also found to have beneficial effects. However, as has been highlighted in this review, there is still much research that needs to be undertaken before the role of nutraceuticals in limiting the development of obesity-related comorbidities can be fully defined. In particular, further research in defined, obese populations using randomised controlled trials is essential.

Although initial research has focused on developing targeted interventions to limit the expansion of AT by reducing angiogenesis, inhibiting adipogenesis or promoting adipocyte apoptosis, this has a high risk of adverse side effects. It is, therefore, possibly more effective instead to direct research towards reversing the development of dysregulated AT activity in general, and in this respect, nutraceuticals may be the answer by providing a broader spectrum of treatment.

Acknowledgements

K.P.C. is supported by Queen Margaret University, Edinburgh. The authors state that there are no conflicts of interest. K.P.C. is the primary researcher and author of this manuscript. M.W. and I.M.D. are the supervisory team and proofread the manuscript.

References

1. WHO (2011) Obesity and Overweight. Available at http://www.who.int/mediacentre/factsheets/fs311/en/index.html
2. Guh D, Zhang W, Bansback N *et al.* (2009) The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health* **9**, 88.
3. Bertakis KD & Azari R (2005) Obesity and the use of health care services. *Obesity* **13**, 372–379.
4. Trayhurn P & Wood IS (2004) Adipokines: Inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* **92**, 347–355.
5. Aasheim ET, Hofso D, Hjelmesaeth J *et al.* (2008) Vitamin status in morbidly obese patients: A cross-sectional study. *Am J Clin Nutr* **87**, 362–369.
6. Panagiotakos DB, Pitsavos C, Yannakoulia M *et al.* (2005) The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. *Atherosclerosis* **183**, 308–315.
7. Chrysohoou C, Panagiotakos DB, Pitsavos C *et al.* (2007) The implication of obesity on total antioxidant capacity in apparently healthy men and women: The ATTICA study. *Nutr Metab Cardiovasc Dis.* **17**, 590–597.
8. Wintergerst ES, Maggini S & Hornig DH (2007) Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* **51**, 301–323.
9. DeFelice SL (1995) The nutraceutical revolution: Its impact on food industry R&D. *Trends Food Sci Technol* **6**, 59–61.
10. Gulati OP & Berry Ottaway P (2006) Legislation relating to nutraceuticals in the European Union with a particular focus on botanical-sourced products. *Toxicology* **221**, 75–87.
11. Ramos S (2008) Cancer chemoprevention and chemotherapy: Dietary polyphenols and signalling pathways. *Mol Nutr Food Res* **52**, 507–526.
12. Ramassamy C (2006) Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. *Eur J Pharmacol* **545**, 51–64.
13. Maury E & Brichard S (2010) Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol Cell Endocrinol* **314**, 1–16.
14. Fantuzzi G (2005) Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* **115**, 911–919.
15. Lago F, Dieguez C, Gomez-Reino J *et al.* (2007) Adipokines as emerging mediators of immune response and inflammation. *Nat Clin Pract Rheum* **3**, 716–724.
16. Friedman J (2002) The function of leptin in nutrition, weight and physiology. *Nutr Rev* **60**, s1–s14.
17. Considine RV, Sinha MK, Heiman ML *et al.* (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* **334**, 292–295.
18. Maffei M, Halaas J, Ravussin E *et al.* (1995) Leptin levels in human and rodent: Measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med* **1**, 1155–1161.
19. Hamilton BS, Paglia D, Kwan AYM *et al.* (1995) Increased obese mRNA expression in omental fat cells from massively obese humans. *Nat Med* **1**, 953–956.
20. Lonnqvist F, Arner P, Nordfors L *et al.* (1995) Overexpression of the obese (*ob*) gene in adipose tissue of human obese subjects. *Nat Med* **1**, 950–953.
21. Saad MF, Damani S, Gingerich RL *et al.* (1997) Sexual dimorphism in plasma leptin concentration. *J Clin Endocrinol Metab* **82**, 579–584.
22. Ostlund RE Jr, Yang JW, Klein S *et al.* (1996) Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* **81**, 3909–3913.
23. Hassink SG, Sheslow DV, de Lancey E *et al.* (1996) Serum leptin in children with obesity: Relationship to gender and development. *Pediatrics* **98**, 201–203.
24. Otero M, Lago Rcaa, Lago F *et al.* (2005) Leptin, from fat to inflammation: Old questions and new insights. *FEBS Lett* **579**, 295–301.
25. Sanchez-Margalet V, Martin-Romero C, Santos-Alvarez J *et al.* (2003) Role of leptin as an immunomodulator of blood mononuclear cells: Mechanisms of action. *Clin Exp Immunol* **133**, 11–19.
26. Sugiura K, Tamakoshi K, Yatsuya H *et al.* (2008) Contribution of adipocytokines to low-grade inflammatory state as expressed by circulating C-reactive protein in Japanese men: Comparison of leptin and adiponectin. *Int J Cardiol* **130**, 159–164.
27. Arita Y, Kihara S, Ouchi N *et al.* (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* **257**, 79–83.

28. Tilg H & Moschen AR (2008) Role of adiponectin and PBEF/visfatin as regulators of inflammation: Involvement in obesity-associated diseases. *Clin Sci* **114**, 275–288.
29. Bruun JM, Lihn AS, Verdich C *et al.* (2003) Regulation of adiponectin by adipose tissue-derived cytokines: *In vivo* and *in vitro* investigations in humans. *Am J Physiol Endocrinol Metab* **285**, E527–E533.
30. Maeda N, Takahashi M, Funahashi T *et al.* (2001) PPARγ ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* **50**, 2094–2099.
31. Ouchi N, Kihara S, Funahashi T *et al.* (2003) Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* **107**, 671–674.
32. Matsushita K, Yatsuya H, Tamakoshi K *et al.* (2006) Inverse association between adiponectin and C-reactive protein in substantially healthy Japanese men. *Atherosclerosis* **188**, 184–189.
33. Maeda N, Shimomura I, Kishida K *et al.* (2002) Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* **8**, 731.
34. Nishihara T, Matsuda M, Araki H *et al.* (2006) Effect of adiponectin on murine colitis induced by dextran sulfate sodium. *Gastroenterology* **131**, 853–861.
35. Shibata R, Sato K, Pimentel DR *et al.* (2005) Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med* **11**, 1096–1103.
36. Spalding K, Arner E, Westermark P *et al.* (2008) Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787.
37. van Harmelen V, Skurk T, Rohrig K *et al.* (2003) Effect of BMI and age on adipose tissue cellularity and differentiation capacity in women. *Int J Obes Relat Metab Disord* **27**, 889–895.
38. Stefan N, Kantartzis K, Machann J *et al.* (2008) Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med* **168**, 1609–1616.
39. Zeyda M & Stulnig TM (2007) Adipose tissue macrophages. *Immunol Lett* **112**, 61–67.
40. Margioris AN (2009) Fatty acids and postprandial inflammation. *Curr Opin Clin Nutr Metab Care* **12**, 129–137.
41. Patel C, Ghanim H, Ravishankar S *et al.* (2007) Prolonged reactive oxygen species generation and nuclear factor-{kappa}B activation after a high-fat, high-carbohydrate meal in the obese. *J Clin Endocrinol Metab* **92**, 4476–4479.
42. Ghanim H, Abuaysheh S, Sia CL *et al.* (2009) Increase in plasma endotoxin concentrations and the expression of Toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal. *Diabetes Care* **32**, 2281–2287.
43. Erridge C (2011) Accumulation of stimulants of Toll-like receptor (TLR)-2 and TLR4 in meat products stored at 5C. *J Food Sci* **76**, H72–H79.
44. Backhed F, Ding H, Wang T *et al.* (2004) The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci USA* **101**, 15718–15723.
45. Cani PD, Amar J, Iglesias MA *et al.* (2007) Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–1772.
46. Erridge C, Attina T, Spickett CM *et al.* (2007) A high-fat meal induces low-grade endotoxemia: Evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr* **86**, 1286–1292.
47. Amar J, Burcelin R, Ruidavets JB *et al.* (2008) Energy intake is associated with endotoxemia in apparently healthy men. *Am J Clin Nutr* **87**, 1219–1223.
48. Hassanali Z, Ametaj BN, Field CJ *et al.* (2010) Dietary supplementation of *n*-3 PUFA reduces weight gain and improves postprandial lipaemia and the associated inflammatory response in the obese JCR:LA-cp rat. *Diabetes Obes Metab* **12**, 139–147.
49. Sun L, Yu Z, Ye X *et al.* (2010) A marker of endotoxemia is associated with obesity and related metabolic disorders in apparently healthy Chinese. *Diabetes Care* **33**, 1925–1932.
50. Cani P, Bibiloni R, Knauf C *et al.* (2008) Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**, 1470–1481.
51. Neal MD, Leaphart C, Levy R *et al.* (2006) Enterocyte TLR4 mediates phagocytosis and translocation of bacteria across the intestinal barrier. *J Immunol* **176**, 3070–3079.
52. Deopurkar R, Ghanim H, Friedman J *et al.* (2010) Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care* **33**, 991–997.
53. Brun P, Castagliuolo I, Leo VD *et al.* (2007) Increased intestinal permeability in obese mice: New evidence in the pathogenesis of nonalcoholic steatohepatitis. *Am J Physiol Gastrointest Liver Physiol* **292**, G518–G525.
54. Muccioli GG, Naslain D, Backhed F *et al.* (2010) The endocannabinoid system links gut microbiota to adipogenesis. *Mol Syst Biol* **27**, 6.
55. Korte G, Dreiseitel A, Schreier P *et al.* (2010) Tea catechins' affinity for human cannabinoid receptors. *Phytomedicine* **17**, 19–22.
56. Korte G, Dreiseitel A, Schreier P *et al.* (2009) An examination of anthocyanins' and anthocyanidins' affinity for cannabinoid receptors. *J Med Food* **12**, 1407–1410.
57. Ghanim H, Sia CL, Upadhyay M *et al.* (2010) Orange juice neutralizes the proinflammatory effect of a high-fat, high-carbohydrate meal and prevents endotoxin increase and Toll-like receptor expression. *Am J Clin Nutr* **91**, 940–949.
58. Ghanim H, Sia CL, Korzeniewski K *et al.* (2011) A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. *J Clin Endocrinol Metab* **96**, 1409–1414.
59. Shizuo A, Kiyoshi T & Tsuneyasu K (2001) Toll-like receptors: Critical proteins linking innate and acquired immunity. *Nat Immunol* **2**, 675.
60. Lin Y, Lee H, Berg AH *et al.* (2000) The lipopolysaccharide-activated Toll-like receptor (TLR)-4 induces synthesis of the closely related receptor TLR-2 in adipocytes. *J Biol Chem* **11**; 275, 24255–24263.
61. Vitseva OI, Tanriverdi K, Tchkonia TT *et al.* (2008) Inducible Toll-like receptor and NF-[kappa]B regulatory pathway expression in human adipose tissue. *Obesity* **16**, 932–937.
62. Creely SJ, McTernan PG, Kusminski CM *et al.* (2007) Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *Am J Physiol Endocrinol Metab* **292**, E740–E747.
63. Bes-Houtmann S, Roche R, Hoareau L *et al.* (2007) Presence of functional TLR2 and TLR4 on human adipocytes. *Histochem Cell Biol* **127**, 131–137.
64. Davis JE, Gabler NK, Walker-Daniels J *et al.* (2008) Tlr-4 deficiency selectively protects against obesity induced by diets high in saturated fat. *Obesity* **16**, 1248–1255.
65. Bumrungpert A, Kalpravidh RW, Chitchumroonchokchai C *et al.* (2009) Xanthones from mangosteen prevent lipopolysaccharide-mediated inflammation and insulin resistance in primary cultures of human adipocytes. *J Nutr* **139**, 1185–1191.

66. Lira F, Rosa J, Cunha C *et al.* (2011) Supplementing alpha-tocopherol (vitamin E) and vitamin D_3 in high fat diet decrease IL-6 production in murine epididymal adipose tissue and 3T3-L1 adipocytes following LPS stimulation. *Lipids Health Dis* **10**, 37.
67. Zhang Y, Lian F, Zhu Y *et al.* (2010) Cyanidin-3-O-β-glucoside inhibits LPS-induced expression of inflammatory mediators through decreasing IκBα phosphorylation in THP-1 cells. *Inflamm Res* **59**, 723–730.
68. Hong Byun E, Fujimura Y, Yamada K *et al.* (2010) TLR4 signaling inhibitory pathway induced by green tea polyphenol epigallocatechin-3-gallate through 67-kDa laminin receptor. *J Immunol* **185**, 33–45.
69. Nielsen S, Guo Z, Johnson M *et al.* (2004) Splanchnic lipolysis in human obesity. *J Clin Invest* **113**, 1582–1588.
70. Arner P (2005) Human fat cell lipolysis: Biochemistry, regulation and clinical role. *Best Pract Res Clin Endocrinol Metab* **19**, 471–482.
71. Yin J, Gao Z, He Q *et al.* (2009) Role of hypoxia in obesity-induced disorders of glucose and lipid metabolism in adipose tissue. *Am J Physiol Endocrinol Metab* **296**, E333–E342.
72. Opie LH & Walfish PG (1963) Plasma free fatty acid concentrations in obesity. *New Engl J Med* **268**, 757–760.
73. Fraze E, Donner CC, Swislocki ALM *et al.* (1985) Ambient plasma free fatty acid concentrations in noninsulin-dependent diabetes mellitus: Evidence for insulin resistance. *J Clin Endocrinol Metab* **61**, 807–811.
74. Charles M, Fontbonne A, Thibult N *et al.* (2001) High plasma nonesterified fatty acids are predictive of cancer mortality but not of coronary heart disease mortality: Results from the Paris prospective study. *Am J Epidemiol* **153**, 292–298.
75. Samuel VT, Petersen KF & Shulman GI (2010) Lipid-induced insulin resistance: Unravelling the mechanism. *Lancet* **375**, 2267–2277.
76. Zhang ZF, Li Q, Liang J *et al.* (2010) Epigallocatechin-3-O-gallate (EGCG) protects the insulin sensitivity in rat L6 muscle cells exposed to dexamethasone condition. *Phytomedicine* **17**, 14–18.
77. Zygmunt K, Faubert B, MacNeil J *et al.* (2010) Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK. *Biochem Biophys Res Commun* **398**, 178–183.
78. Vishnu Prasad CN, Anjana T, Banerji A *et al.* (2010) Gallic acid induces GLUT4 translocation and glucose uptake activity in 3T3-L1 cells. *FEBS Lett* **584**, 531–536.
79. Strobel P, Allard C, Perez-Acle T *et al.* (2005) Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. *Biochem J* **386**, 471–478.
80. Wu LY, Juan CC, Hwang L *et al.* (2004) Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in a fructose-fed rat model. *Eur J Nutr* **43**, 116–124.
81. Li Y, Zhao S, Zhang W *et al.* (2011) Epigallocatechin-3-O-gallate (EGCG) attenuates FFAs-induced peripheral insulin resistance through AMPK pathway and insulin signaling pathway *in vivo*. *Diabetes Res Clin Pract* (In the Press).
82. McQuaid SE, Hodson L, Neville MJ *et al.* (2011) Down-regulation of adipose tissue fatty acid trafficking in obesity. *Diabetes* **60**, 47–55.
83. Liu JF, Ma Y, Wang Y *et al.* (2011) Reduction of lipid accumulation in HepG2 cells by luteolin is associated with activation of AMPK and mitigation of oxidative stress. *Phytother Res* **25**, 588–596.
84. Shang J, Chen L, Xiao F *et al.* (2008) Resveratrol improves non-alcoholic fatty liver disease by activating AMP-activated protein kinase1. *Acta Pharmacol Sin* **29**, 698–706.
85. Lin CL, Huang HC & Lin JK (2007) Theaflavins attenuate hepatic lipid accumulation through activating AMPK in human HepG2 cells. *J Lipid Res* **48**, 2334–2343.
86. Kim T, Davis J, Zhang AJ *et al.* (2009) Curcumin activates AMPK and suppresses gluconeogenic gene expression in hepatoma cells. *Biochem Biophys Res Comm* **388**, 377–382.
87. Collins QF, Liu HY, Pi J *et al.* (2007) Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase. *J Biol Chem* **282**, 30143–30149.
88. Carling D (2004) The AMP-activated protein kinase cascade – a unifying system for energy control. *Trends Biochem Sci* **29**, 18–24.
89. Chen J, Ma M, Lu Y *et al.* (2009) Rhaponticin from rhubarb rhizomes alleviates liver steatosis and improves blood glucose and lipid profiles in KK/Ay diabetic mice. *Planta Medica* **75**, 472–477.
90. Ozturk F, Gul M, Ates B *et al.* (2009) Protecive effect of apricot (*Prunus armeniaca* L.) on hepatic steatosis and damage induced by carbon tetrachloride in Wistar rats. *Br J Nutr* **102**, 1767–1775.
91. Poudyal H, Campbell F & Brown L (2010) Olive leaf extract attenuates cardiac, hepatic, and metabolic changes in high carbohydrate-, high fat-fed rats. *J Nutr* **140**, 946–953.
92. Bujanda L, Hijona E, Larzabal M *et al.* (2008) Resveratrol inhibits nonalcoholic fatty liver disease in rats. *BMC Gastroenterol* **8**, 40.
93. Staiger H, Staiger K, Stefan N *et al.* (2004) Palmitate-induced interleukin-6 expression in human coronary artery endothelial cells. *Diabetes* **53**, 3209–3216.
94. van Dijk SJ, Feskens EJ, Bos MB *et al.* (2009) A saturated fatty acid-rich diet induces an obesity-linked pro-inflammatory gene expression profile in adipose tissue of subjects at risk of metabolic syndrome. *Am J Clin Nutr* **90**, 1656–1664.
95. Laine P, Schwartz E, Wang Y *et al.* (2007) Palmitic acid induces IP-10 expression in human macrophages via NF-κB activation. *Biochem Biophys Res Commun* **358**, 150–155.
96. Haversen L, Danielsson KN, Fogelstrand L *et al.* (2009) Induction of proinflammatory cytokines by long-chain saturated fatty acids in human macrophages. *Atherosclerosis* **202**, 382–393.
97. Ajuwon KM & Spurlock ME (2005) Palmitate activates the NF-{kappa}B transcription factor and induces IL-6 and TNF{alpha} expression in 3T3-L1 adipocytes. *J Nutr* **135**, 1841–1846.
98. Subauste AR & Burant CF (2007) Role of FoxO1 in FFA-induced oxidative stress in adipocytes. *Am J Physiol Endocrinol Metab* **293**, E159–E164.
99. Takahashi K, Yamaguchi S, Shimoyama T *et al.* (2008) JNK- and I{kappa}B-dependent pathways regulate MCP-1 but not adiponectin release from artificially hypertrophied 3T3-L1 adipocytes preloaded with palmitate *in vitro*. *Am J Physiol Endocrinol Metab* **294**, E898–E909.
100. Zhang HH, Halbleib M, Ahmad F *et al.* (2002) Tumor necrosis factor stimulates lipolysis in differentiated human adipocytes through activation of extracellular signal-related kinase and elevation of intracellular cAMP. *Diabetes* **51**, 2929–2935.
101. Permana PA, Menge C & Reaven PD (2006) Macrophage-secreted factors induce adipocyte inflammation and insulin resistance. *Biochem Biophys Res Commun* **341**, 507–514.
102. Lien CC, Au LC, Tsai YL *et al.* (2009) Short-term regulation of tumor necrosis factor-{alpha}-induced lipolysis in 3T3-L1 adipocytes is mediated through the inducible nitric oxide synthase/nitric oxide-dependent pathway. *Endocrinology* **150**, 4892–4900.

103. Schwartz EA, Zhang WY, Karnik SK *et al.* (2010) Nutrient modification of the innate immune response: A novel mechanism by which saturated fatty acids greatly amplify monocyte inflammation. *Arterioscler Thromb Vasc Biol* **30**, 802–808.
104. Suganami T, Nishida J & Ogawa Y (2005) A paracrine loop between adipocytes and macrophages aggravates inflammatory changes: Role of free fatty acids and tumor necrosis factor {alpha}. *Arterioscler Thromb Vasc Biol* **25**, 2062–2068.
105. Shi H, Kokoeva M, Inouye K *et al.* (2006) TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest* **116**, 3015–3025.
106. Nguyen MTA, Favelyukis S, Nguyen AK *et al.* (2007) A Subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. *J Biol Chem* **282**, 35279–35292.
107. Suganami T, Yuan X, Shimoda Y *et al.* (2009) Activating transcription factor 3 constitutes a negative feedback mechanism that attenuates saturated fatty acid/Toll-Like receptor 4 signaling and macrophage activation in obese adipose tissue. *Circ Res* **105**, 25–32.
108. Han CY, Kargi AY, Omer M *et al.* (2010) Differential effect of saturated and unsaturated free fatty acids on the generation of monocyte adhesion and chemotactic factors by adipocytes. *Diabetes* **59**, 386–396.
109. Erridge C & Samani NJ (2009) Saturated fatty acids do not directly stimulate Toll-like receptor signaling. *Arterioscler Thromb Vasc Biol* **29**, 1944–1949.
110. Kennedy A, Martinez K, Chuang CC *et al.* (2009) Saturated fatty acid-mediated inflammation and insulin resistance in adipose tissue: Mechanisms of action and implications. *J Nutr* **139**, 1–4.
111. Berglund G, Ljungman S, Hartford M *et al.* (1982) Type of obesity and blood pressure. *Hypertension* **4**, 692–696.
112. Lonn M, Mehlig K, Bengtsson C *et al.* (2010) Adipocyte size predicts incidence of type 2 diabetes in women. *FASEB J* **24**, 326–331.
113. Cinti S, Mitchell G, Barbatelli G *et al.* (2005) Adipocyte death defines macrophage localisation and function in adipose tissue of obese mice and humans. *J Lipid Res* **46**, 2347–2355.
114. Cancello R, Henegar C, Viguerie N *et al.* (2005) Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* **54**, 2277–2286.
115. Weisberg SP, McCann D, Desai M *et al.* (2003) Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* **112**, 1796–1808.
116. Lee YH, Nair S, Rousseau E *et al.* (2005) Microarray profiling of isolated abdominal subcutaneous adipocytes from obese *vs* non-obese Pima Indians: Increased expression of inflammation-related genes. *Diabetologia* **48**, 1776–1783.
117. Jernas M, Palming J, Sjoholm K *et al.* (2006) Separation of human adipocytes by size: Hypertrophic fat cells display distinct gene expression. *FASEB J* **20**, 1540–1542.
118. Skurk T, Alberti-Huber C, Herder C *et al.* (2007) Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* **92**, 1023–1033.
119. Cancello R & Clement K (2006) Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. *BJOG* **13**, 1141–1147.
120. Gustafson B, Hammarstedt A, Andersson CX *et al.* (2007) Inflamed adipose tissue: A culprit underlying the metabolic syndrome and atherosclerosis. *Arterioscler Thromb Vasc Biol* **27**, 2276–2283.
121. Rosen ED & MacDougald OA (2006) Adipocyte differentiation from the inside out. *Nat Rev Mol Cell Biol* **7**, 885–896.
122. Wu Z, Rosen ED, Brun R *et al.* (1999) Cross-regulation of C/EBP[alpha] and PPAR[gamma] controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Mol Cell* **3**, 151–158.
123. Weisberg S, Leibel R & Tortoriello D (2008) Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. *Endocrinology* **149**, 3549–3558.
124. Ejaz A, Wu D, Kwan P *et al.* (2009) Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *J Nutr* **139**, 919–925.
125. Zhao J, Sun XB, Ye F *et al.* (2011) Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. *Mol Cell Biochem* **10**, 1–10.
126. Lee YK, Lee WS, Hwang JT *et al.* (2008) Curcumin exerts antidifferentiation effect through AMPKα-PPARγ in 3T3-L1 adipocytes and antiproliferatory effect through AMPKα-COX-2 in cancer cells. *J Agric Food Chem* **57**, 305–310.
127. Narala V, Smith M, Adapala R *et al.* (2009) Curcumin is not a ligand for peroxisome proliferator-activated receptor-γ. *Gene Ther Mol Biol* **13**, 20–15.
128. Wolfram S, Wang Y & Thielecke F (2006) Anti-obesity effects of green tea: From bedside to bench. *Mol Nutr Food Res* **50**, 176–187.
129. Wolfram S, Raederstorff D, Wang Y *et al.* (2005) TEAVIGO (epigallocatechin gallate) supplementation prevents obesity in rodents by reducing adipose tissue mass. *Ann Nutr Metab* **49**, 54–63.
130. Bose M, Lambert JD, Ju J *et al.* (2008) The major green tea polyphenol, (−)-epigallocatechin-3-gallate, inhibits obesity, metabolic syndrome, and fatty liver disease in high-fat-fed mice. *J Nutr* **138**, 1677–1683.
131. Chen N, Bezzina R, Hinch E *et al.* (2009) Green tea, black tea, and epigallocatechin modify body composition, improve glucose tolerance, and differentially alter metabolic gene expression in rats fed a high-fat diet. *Nutr Res* **29**, 784–793.
132. Furuyashiki T, Nagayasu H, Aoki Y *et al.* (2004) Tea catechin suppresses adipocyte differentiation accompanied by down-regulation of PPARgamma2 and C/EBPalpha in 3T3-L1 cells. *Biosci Biotechnol Biochem* **68**, 2353–2359.
133. Moon HS, Chung CS, Lee HG *et al.* (2007) Inhibitory effect of (−)-epigallocatechin-3-gallate on lipid accumulation of 3T3-L1 cells. *Obesity* **15**, 2571–2582.
134. Lin J, Della-Fera MA & Baile CA (2005) Green tea polyphenol epigallocatechin gallate inhibits adipogenesis and induces apoptosis in 3T3-L1 adipocytes. *Obesity* **13**, 982–990.
135. Sakurai N, Mochizuki K, Kameji H *et al.* (2009) (−)-Epigallocatechin gallate enhances the expression of genes related to insulin sensitivity and adipocyte differentiation in 3T3-L1 adipocytes at an early stage of differentiation. *Nutrition* **25**, 1047–1056.
136. Lee MJ, Maliakal P, Chen L *et al.* (2002) Pharmacokinetics of tea catechins after ingestion of green tea and (−)-epigallocatechin-3-gallate by humans. *Cancer Epidemiol Biomarkers Prev* **11**, 1025–1032.
137. Yang CS, Chen L, Lee MJ *et al.* (1998) Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer Epidemiol Biomarkers Prev* **7**, 351–354.

138. McLaughlin T, Deng A, Yee G *et al.* (2010) Inflammation in subcutaneous adipose tissue: Relationship to adipose cell size. *Diabetologia* **53**, 369–377.
139. Charriere G, Cousin B, Arnaud E *et al.* (2003) Preadipocyte conversion to macrophage. *J Biol Chem* **278**, 9850–9855.
140. Isakson P, Hammarstedt A, Gustafson B *et al.* (2009) Impaired preadipocyte differentiation in human abdominal obesity: Role of Wnt, tumor necrosis factor-α, and inflammation. *Diabetes* **58**, 1550–1557.
141. Lacasa D, Taleb S, Keophiphath M *et al.* (2007) Macrophage-secreted factors impair human adipogenesis: Involvement of proinflammatory state in preadipocytes. *Endocrinology* **148**, 868–877.
142. Cousin B, Andre M, Casteilla L *et al.* (2001) Altered macrophage-like functions of preadipocytes in inflammation and genetic obesity. *J Cell Physiol* **186**, 380–386.
143. Cousin B, Munoz O, Andre M *et al.* (1999) A role for preadipocytes as macrophage-like cells. *FASEB J* **13**, 305–312.
144. Chung S, LaPoint K, Martinez K *et al.* (2006) Preadipocytes mediate lipopolysaccharide-induced inflammation and insulin resistance in primary cultures of newly differentiated human adipocytes. *Endocrinology* **147**, 5340–5351.
145. Harkins JM, Moustaid-Moussa N, Chung YJ *et al.* (2004) Expression of interleukin-6 is greater in preadipocytes than in adipocytes of 3T3-L1 cells and C57BL/6J and ob/ob mice. *J Nutr* **134**, 2673–2677.
146. Poulain-Godefroy O & Froguel P (2007) Preadipocyte response and impairment of differentiation in an inflammatory environment. *Biochem Biophys Res Commun* **356**, 662–667.
147. Lehmann JM, Moore LB, Smith-Oliver TA *et al.* (1995) An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). *J Biol Chem* **270**, 12953–12956.
148. Okuno A, Tamemoto H, Tobe K *et al.* (1998) Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *J Clin Invest* **101**, 1354–1361.
149. Huang L, Hong Y, Wong Y *et al.* (2008) Bitter melon (*Momordica charantia* L.) inhibits adipocyte hypertrophy and down regulates lipogenic gene expression in adipose tissue of diet-induced obese rats. *Br J Nutr* **99**, 230–239.
150. Hassan M, Yazidi CE, Landrier JF *et al.* (2007) Phloretin enhances adipocyte differentiation and adiponectin expression in 3T3-L1 cells. *Biochem Biophys Res Commun* **361**, 208–213.
151. Saito T, Abe D & Sekiya K (2007) Nobiletin enhances differentiation and lipolysis of 3T3-L1 adipocytes. *Biochem Biophys Res Commun* **357**, 371–376.
152. Pasarica M, Sereda O, Redman L *et al.* (2009) Reduced adipose tissue oxygenation in human obesity: Evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. *Diabetes* **58**, 718.
153. Hosogai N, Fukuhara A, Oshima K *et al.* (2007) Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. *Diabetes* **56**, 901–911.
154. Rausch ME, Weisberg S, Vardhana P *et al.* (2007) Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int J Obes* **32**, 451–463.
155. Patel S & Simon M (2008) Biology of hypoxia-inducible factor-2a in development and disease. *Cell Death Differ* **15**, 628–634.
156. Weidemann A & Johnson R (2008) Biology of HIF-1a. *Cell Death Differ* **15**, 621–627.
157. Maumus M, Sengenes C, Decaunes P *et al.* (2008) Evidence of *in situ* proliferation of adult adipose tissue-derived progenitor cells: Influence of fat mass microenvironment and growth. *J Clin Endocrinol Metab* **93**, 4098–4106.
158. Regazzetti C, Peraldi P, Gremeaux T *et al.* (2009) Hypoxia decreases insulin signaling pathways in adipocytes. *Diabetes* **58**, 95–103.
159. Wang B, Wood IS & Trayhurn P (2008) Hypoxia induces leptin gene expression and secretion in human preadipocytes: Differential effects of hypoxia on adipokine expression by preadipocytes. *J Endocrinol* **198**, 127–134.
160. Ye J, Gao Z, Yin J *et al.* (2007) Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. *Am J Physiol Endocrinol Metab* **293**, E1118–E1128.
161. Kim KH, Song MJ, Chung J *et al.* (2005) Hypoxia inhibits adipocyte differentiation in a HDAC-independent manner. *Biochem Biophys Res Commun* **333**, 1178–1184.
162. Lolmede K, Dunand de Saint Front V, Galitzhy J *et al.* (2003) Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes. *Int J Obes* **27**, 1187–1195.
163. Wang B, Wood I & Trayhurn P (2007) Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. *Pflugers Archiv* **455**, 479–492.
164. Silha JV, Krsek M, Sucharda P *et al.* (2005) Angiogenic factors are elevated in overweight and obese individuals. *Int J Obes* **29**, 1308–1314.
165. Pang C, Gao Z, Yin J *et al.* (2008) Macrophage infiltration into adipose tissue may promote angiogenesis for adipose tissue remodeling in obesity. *Am J Physiol Endocrinol Metab* **295**, E313–E322.
166. Nishimura S, Manabe I, Nagasaki M *et al.* (2007) Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels. *Diabetes* **56**, 1517–1526.
167. Singh R & Agarwal R (2003) Tumor angiogenesis: A potential target in cancer control by phytochemicals. *Curr Cancer Drug Targets* **3**:205–217.
168. Paul SAM, Simons JW & Mabjeesh NJ (2004) HIF at the crossroads between ischemia and carcinogenesis. *J Cell Physiol* **200**, 20–30.
169. Hatanaka M, Shimba S, Sakaue M *et al.* (2009) Hypoxia-inducible factor-3α functions as an accelerator of 3T3-L1 adipose differentiation. *Biol Pharm Bull* **32**, 1166–1172.
170. Ozcan U, Cao Q, Yilmaz E *et al.* (2004) Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **306**, 457–461.
171. Sharma NK, Das SK, Mondal AK *et al.* (2008) Endoplasmic reticulum stress markers are associated with obesity in nondiabetic subjects. *J Clin Endocrinol Metab* **93**, 4532–4541.
172. Boden G, Duan X, Homko C *et al.* (2008) Increase in endoplasmic reticulum stress-related proteins and genes in adipose tissue of obese, insulin-resistant individuals. *Diabetes* **57**, 2438–2444.
173. Gregor M, Yang L, Fabbrini E *et al.* (2009) Endoplasmic reticulum stress is reduced in tissues of obese subjects after weight loss. *Diabetes* **58**, 693–700.
174. Koh EH, Park JY, Park HS *et al.* (2007) Essential role of mitochondrial function in adiponectin synthesis in adipocytes. *Diabetes* **56**, 2973–2981.
175. Gregor MF & Hotamisligil GS (2007) Thematic review series: Adipocyte biology. Adipocyte stress: The endoplasmic reticulum and metabolic disease. *J Lipid Res* **48**, 1905–1914.

176. Ron D & Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* **8**, 519–529.
177. Xu C, Bailly-Maitre B & Reed J (2005) Endoplasmic reticulum stress: Cell life and death decisions. *J Clin Invest* **115**, 2656–2664.
178. Haynes CM, Titus EA & Cooper AA (2004) Degradation of misfolded proteins prevents ER-derived oxidative stress and cell death. *Mol Cell* **15**, 767–776.
179. Zhang K & Kaufman R (2008) From endoplasmic reticulum stress to the inflammatory response. *Nature* **454**, 455–462.
180. Kaufman R (2002) Orchestrating the unfolded protein reponse in health and disease. *J Clin Invest* **110**, 1389–1398.
181. Wei Y, Wang D, Topczewski F *et al.* (2006) Saturated fatty acids induce endoplasmic reticulum stress and apoptosis independently of ceramide in liver cells. *Am J Physiol Endocrinol Metab* **291**, E275–E281.
182. Karaskov E, Scott C, Zhang L *et al.* (2006) Chronic palmitate but not oleate exposure induces endoplasmic reticulum stress, which may contribute to INS-1 pancreatic {beta}-cell apoptosis. *Endocrinology* **147**, 3398–3407.
183. Das SK, Chu WS, Mondal AK *et al.* (2008) Effect of pioglitazone treatment on endoplasmic reticulum stress response in human adipose and in palmitate-induced stress in human liver and adipose cell lines. *Am J Physiol Endocrinol Metab* **295**, E393–E400.
184. Parker RA, Flint OP, Mulvey R *et al.* (2005) Endoplasmic reticulum stress links dyslipidemia to inhibition of proteasome activity and glucose transport by HIV protease inhibitors. *Mol Pharmacol* **67**, 1909–1919.
185. Malhotra J, Miao H, Zhang K *et al.* (2008) Antioxidants reduce endoplasmic reticulum stress and improve protein secretion. *Proc Natl Acad Sci USA* **105**, 18525–18530.
186. Sheikh-Ali M, Sultan S, Alamir AR *et al.* (2010) Effects of antioxidants on glucose-induced oxidative stress and endoplasmic reticulum stress in endothelial cells. *Diabetes Res Clin Pract* **87**, 161–166.
187. Natsume Y, Ito S, Satsu H *et al.* (2009) Protective effect of quercetin on ER stress caused by calcium dynamics dysregulation in intestinal epithelial cells. *Toxicology* **258**, 164–175.
188. Pal R, Cristan EA, Schnittker K *et al.* (2010) Rescue of ER oxidoreductase function through polyphenolic phytochemical intervention: Implications for subcellular traffic and neurodegenerative disorders. *Biochem Biophys Res Commun* **392**, 567–571.

NS Proceedings of the Nutrition Society