Mechanistic links between obesity, diabetes, and blood pressure: Role of perivascular adipose tissue

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Mechanistic links between obesity, diabetes and blood pressure: Role of perivascular adipose tissue

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List of abbreviations

5HT: serotonin
AAT: aortic adipose tissue
ACE: angiotensin converting enzyme
AdipoR1: adiponectin receptor 1
AdipoR2: adiponectin receptor 2
AGT: angiotensinogen
AMPK: 5' adenosine monophosphate-activated protein kinase
Ang 1-7: angiotensin 1-7
Ang II: angiotensin II
APJ: apelin receptor
ATP: adenosine triphosphate
BAT: brown adipose tissue
BATIRKO: brown adipose tissue specific insulin receptor knockout mice
BMI: body mass index
CCL2: C-C motif chemokine ligand 2
cDCs: conventional dendritic cells
CNS: central nervous system
CSE: cystathionine-γ-lyase
CVD: cardiovascular disease
DCs: dendritic cells
EAT: epicardial adipose tissue
EFS: electrical field stimulation
eNOS: endothelial nitric oxide synthase
ET-1: endothelin 1
FFAs: free fatty acids
FGF-21: fibroblast growth factor 21
GAT: gluteofemoral adipose tissue
H_2O_2: hydrogen peroxide
H_2S: hydrogen sulphide
HIF-1α: hypoxia inducible factor-1α
iBAT: interscapular brown adipose tissue
ICAM-1: intercellular adhesion molecule 1
IGF-1: insulin-like growth factor 1
IL-6: interleukin 6
IL-8 interleukin 8
IL-10: interleukin 10
ILC2s: type-2 innate lymphoid cells
IMAT: intramuscular adipose tissue
iNOS: inducible nitric oxide synthase
IRS2: insulin receptor substrate 2
JNK: c-Jun N-terminal kinase
LPS: lipopolysaccharide
MBV: microvascular blood volume
Metrnl: meteorin-like
MetS: metabolic syndrome
NADPH: nicotinamide adenine dinucleotide phosphate
NE: norepinephrine
NET: norepinephrine transporter
nNOS: neuronal nitric oxide synthase
NO: nitric oxide

NPY: neuropeptide Y
OCT: organic cation transporter
PAI-1: plasminogen activator inhibitor 1
PAME: palmitic acid methyl ester
pDCs: plasmacytoid dendritic cells
PI3K: phosphatidylinositol 3 kinase
PKB: protein kinase B
PPARγ: peroxisome proliferator-activated receptor-γ
PVAT: perivascular adipose tissue
RAAS: renin-angiotensin-aldosterone system
ROS: reactive oxygen species
SAT: subcutaneous adipose tissue
SERT: serotonin transporter
SNS: sympathetic nervous system
STZ: streptozotocin
T2D: type 2 diabetes
TNFα: tumour necrosis factor alpha
UCP-1: uncoupling protein 1
VAT: visceral adipose tissue
VEGF: vascular endothelial growth factor
VSMCs: vascular smooth muscle cells
WAT: white adipose tissue

1. Abstract

Obesity is increasingly prevalent and is associated with substantial cardiovascular risk. Adipose tissue distribution and morphology play a key role in determining the degree of adverse effects, and a key factor in the disease process appears to be the inflammatory cell population in adipose tissue. Healthy adipose tissue secretes a number of vasoactive adipokines and anti-inflammatory cytokines, and changes to this secretory profile will contribute to pathogenesis in obesity. In this review, we will discuss the links between adipokine dysregulation and the development of hypertension and diabetes, and explore the potential for manipulating adipose tissue morphology and its immune cell population to improve cardiovascular health in obesity.

2. Introduction

2.1. The clinical problem

Acculturated societies are entering a dangerous time with the rapidly increasing rates of obesity in populations leading to soaring levels of type 2 diabetes (T2D), hypertension, heart disease and stroke, as well as some cancers. Life expectancy extensions have plateaued in many developed countries (709) and the cost of treating these diseases is placing an enormous burden on healthcare systems globally. Cardiovascular disease (CVD) is the leading cause of death worldwide (276) and obesity and its associated vascular complications such as hypertension and T2D, are some of the major risk factors associated with CVD (431). Worldwide almost 2 billion adults are overweight (39%) and 650 million are obese (13%) (748). Even more concerning are the statistics for the young: 41 million children under age 5 are classed as obese and 340 million adolescents are obese. Whilst there are some rare genetic conditions, the most common causes are environmental and include high calorie diets, and low physical activity. The obvious implication should be that this is preventable (484, 545).

As an example hypertension affects 1 in 3 adults worldwide (547). According to The Framingham Heart Study, 60-70% of essential hypertension results from obesity (274), and obese patients are 3.5 times more likely to develop high blood pressure (367). In addition, T2D affects 347 million people worldwide (749), and obese individuals have a seven-fold increased risk of developing the condition (2). Approximately 50% of diabetic patients die of CVDs such as heart disease and stroke (473).

Our contemporary understanding of obesity centres on a time when our ancestors were exposed to “cycles of feast or famine” (494): genes predisposing to obesity were beneficial to survival by allowing increases in energy stores in the form of expanding fat deposition during times of plentiful food availability, which could be utilised during times of famine. Variations in weight in the animal kingdom continue to serve this pro-survival purpose. For example, in hibernating mammals such as the Brown Bear, voracious eating modulated by the dark/light cycle stimulation, and hypothalamic hormones such as melatonin, induces short-term obesity and insulin resistance in preparation for the six months of sleep when temperatures fall. However, now human populations in the developed world have constant and ready access to high energy foods stuffs (154, 494), and the consequences are all too obvious; chronic diseases and significant associated cardiovascular morbidity and mortality, often requiring multiple drug therapies or revascularization interventions (603).

An additional layer of complexity is added to this area when it becomes clear that not all obese individuals develop any of the diseases associates with the phenotype. Indeed, multiple studies have reported an “obesity paradox”, whereby some obese patients exhibit lower mortality rates than expected with CVD (447). Such people have been termed ‘metabolically healthy obese’, and lack the expected abnormalities associated with obesity such as hypertension, dyslipidemia, hypercholesterolemia, insulin resistance and glucose intolerance. It is clear that simple measurements such as body mass index (BMI) are not

necessarily the best predictors of CVD compared to measures such as blood pressure and lipid profiles, and patient family history (750). It has been suggested that it is the degree of inflammation present in adipose tissue depots that determines cardiovascular disease susceptibility (359, 428, 505, 616) and opens the intriguing prospect of manipulating the adipose tissue inflammasome as a novel therapeutic approach to combatting obesity-related diseases, which we shall discuss below.

2.2. Adipose distribution determines cardiovascular risk

In obesity the distribution of fat is important in determining the adverse effects of adiposity. Visceral adipose tissue (VAT) is associated strongly with insulin resistance, dyslipidemia, and hypertension (87, 214, 598, 787), independent of subcutaneous adipose tissue (SAT) and overall BMI, i.e. even in individuals with a normal BMI increased VAT is severely detrimental, and in "lean" patients with T2D and visceral adiposity, their mortality rates are double those of a non-diabetic obese patient (110, 486). These patients are referred to as "metabolically unhealthy lean" subjects. This highlights the limitations of the BMI, because it does not differentiate between adipose tissue mass and lean muscle mass. Interestingly, in rats fed a high-fructose diet there was no change in overall bodyweight, but visceral adipocytes were hypertrophied, and this was accompanied by the development of leptin resistance and metabolic syndrome (MetS) (97, 220). These changes have been attributed to fructose-induced downregulation of glucocorticoid receptor expression, and reduced lipolysis (368). Nevertheless, there is still a positive correlation between VAT, BMI, and waist circumference (105). Most importantly, increases in VAT and SAT are associated with chronic systemic inflammation, in particular increased production of pro-inflammatory cytokines such as tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6) (60, 782).

Another depot which is positively correlated with BMI and waist circumference is epicardial adipose tissue (EAT), but it can be increased greatly in lean individuals (31). The thickness of EAT is positively associated with increased fasting insulin, diastolic blood pressure, coronary artery disease, and atrial fibrillation (60, 291, 292, 775). As with VAT, EAT is a source of several pro-inflammatory markers such as TNFα and IL-6, independent of BMI (446). In contrast, increased gluteofemoral adipose tissue (GAT) mass is associated with a protective role in metabolic and cardiovascular risk (433, 604). Studies have demonstrated that increased GAT is associated with lower cholesterol, reduced glucose and insulin levels, and reduced vascular calcification and arterial stiffness (571, 624-626, 669). It is likely that these effects are driven by secretion of beneficial adipokines such as leptin and adiponectin (91). It has been suggested that reduced GAT, such as that observed in Cushing's syndrome, could actually be detrimental (433, 624).

In addition, another important factor in the metabolic consequences of obesity is the ability of adipose tissues to expand (reviewed by Hammarstedt *et al.* (259)). Adipose tissue has a limited ability to recruit new adipocytes, and once this limited is reached the existing adipocytes will hypertrophy; leading to a dysfunctional phenotype associated with inflammation, insulin resistance, and dyslipidemia. Indeed some studies have suggested that adipocyte cell size rather than number is a strong predictor of metabolic dysfunction (24, 415, 794). Reinforcing this suggestion are studies in patients with defective adipose tissue expansion, which conclude that these patients are at a higher risk of developing CVD (136, 417, 607). The ability of an individual to expand their adipose tissues is likely to be governed by genetics in addition to environmental factors (635).

The close associations between adiposity and cardiovascular risks indicate an important role of adipose tissue structure and phenotype in the disease process promoted by obesity. The focus of this review will be to examine the mechanisms of adipose tissue function on the vasculature, including the local effects of adipokines on the vasculature and the contribution of adipokines released into circulation. We will then explore the links between adipose tissue dysfunction and hypertension and T2D.

3. Adipose tissue phenotypes and functions

3.1. Classical phenotypes: White and brown

Although originally thought to be an organ designed for energy storage, adipose tissue is recognised now as a highly important for a number of processes, such as metabolism, body weight homeostasis, and modulation of vascular tone (13, 131, 345). Adipogenesis, the process by which pre-cursor cells of mesenchymal origin differentiate into mature adipocytes, occurs throughout life, which means that an increase in adipose tissue deposition can occur in response to need, for example, when increased energy exceeds consumption (245).

Classically there are two types of adipose tissue, white and brown which differ in morphology and function (Figure 1). White adipocytes are unilocular, and their lipid content is organised into one large droplet, whereas brown adipocytes are multilocular and contain many lipid droplets (127, 491, 492). White adipocytes are approximately 30-130µm in diameter, and are therefore much larger than brown adipocytes which are only 20-40µm. In addition, white cells are spherical, whereas brown are elliptical. The large unilocular structure of white adipocytes means that the cytoplasm consists mostly of lipid, with a compressed, “cup-shaped” nucleus, whereas in a brown adipocyte the nucleus is round. The biggest difference in the morphology of these cells lies in the mitochondrial content. White adipocytes contain small and elongated mitochondria, whereas brown adipocytes are densely populated with mitochondria filled with a large number of cristae (127). These differences in mitochondrial populations are significant for the different adipocyte functions discussed below. Notably, both cell types contain a large number of pinocytic vesicles for endocytosis.

Traditionally brown adipose tissue (BAT) is thought to play an important role in body temperature regulation by producing heat, via uncoupling electron transport from the generation of adenosine triphosphate (ATP) within its large number of cristae-dense mitochondria (344). Some studies have suggested an endocrine function for BAT, as its transplantation into various mouse models of obesity has exhibited beneficial effects on their metabolic profiles (410, 412, 637), which will be discussed within this review. BAT is highly vascularised by capillaries, allowing efficient dispersal of heat generated by mitochondria (127, 131, 583). The vasculature and its high mitochondrial content is what gives BAT its colour. In humans, is it is widely accepted that most functional BAT disappears between infancy and adulthood (780); however, experiments subjecting adult humans to cold exposure demonstrate that BAT is still present in supraclavicular and spinal regions, and still has the ability to regulate body temperature.

White adipose tissue (WAT) is distributed widely throughout the human body. It provides insulation and mechanical support by surrounding organs and muscles (131) and is important also in energy storage, particularly in the form of free fatty acids (FFAs), during times of excessive dietary intake. When there is an increase in energy expenditure or fasting, lipolysis occurs, and the lipid stores in WAT are broken down to release FFAs which are utilised in energy production. It is here where the relevance of elongated mitochondria becomes apparent, because they are implicated in macroautophagy; that is the breakdown of cells (239), which includes the process of lipolysis to mobilise FFAs. Equally important is the role of WAT as an endocrine organ (131, 223, 665). WAT secretes (locally and systemically), and expresses receptors for a number of hormones, cytokines, and enzymes, which play significant roles in biological processes such as metabolism, inflammation, and modulation of vascular tone. One of these factors is leptin, which is vital in satiety signalling (215). Interestingly, *ob/ob* mice lacking leptin (secreted from WAT) are susceptible to WAT hypertrophy and hyperplasia in obesity, whereas *db/db* mice lacking the leptin receptor are only susceptible to hypertrophy (313), indicating that WAT-derived leptin may be crucial for adipocyte proliferation.

VAT and SAT depots previously discussed, including mesenteric and epididymal adipose tissue, are largely white (751) as are skeletal muscle depots. However, they each have unique secretory profiles (343). VAT expresses greater levels of inflammatory cytokines such as IL-6, whereas secretion of the adipokines leptin and adiponectin are larger in the SAT depots. In addition, expression of various receptors such as angiotensin II (Ang II) and β-adrenoceptors are greater in VAT. It is likely that these differences account for variations in endocrine function, and disease development.

3.2. Non-classical phenotypes: Beige and pink

Obesity and T2D are associated with the pathological "whitening" of adipose tissue, where white adipocytes hypertrophy and brown adipocytes undergo apoptosis (129, 503). Evidence has emerged recently that WAT depots can be stimulated to differentiate into "beige" adipocytes (Figure 1), which resemble BAT with increased expression of uncoupling protein-1 (UCP-1), thereby enabling thermogenesis (278, 724). Interventions which promote the beiging of WAT are correlated positively with metabolic improvements in both humans and animals (263, 410, 463). For example, within patients, BAT activity is inversely correlated with BMI (713), and cold exposure in lean T2D patients improves glucose uptake in WAT and skeletal muscle (263). Moreover, BAT activity is negatively correlated with both total adipose tissue mass and VAT mass alone, and as discussed previously, an abundance of VAT is linked to higher cardiovascular and metabolic risks. Interestingly, whilst the activity of BAT is reduced in obese subjects, the fact that some activity persists suggests that this tissue could be a promising target for the treatment of obesity and its associated metabolic complications, which will be discussed later.

A fourth phenotype, the pink adipocyte, has been proposed by Giordano *et al*., (236). During pregnancy and lactation, changes in hormones stimulate the transformation of mammary WAT, a process which has been dubbed "pinking" by Giordano. White adipocytes develop epithelial-features and transform into lobulo-alveolar glandular structures, which secret milk (474) (Figure 1). It is suggested that these glandular cells meet the definition of an adipocyte as they are still capable of storing large amounts of lipid. They are exclusive to female SAT breast depots during pregnancy, and at the macroscopic level they are pink; hence the new term. Lineage tracing using transgenic fluorescent markers has confirmed that around 70% of the alveolar glandular cells arising during pregnancy originate from white adipocytes (474). Moreover, this pinking process is reversible, and the glandular cells revert back to white adipocytes. This transformation process has been followed using transplantation studies of pure white adipocytes (devoid of stem cells) into pregnant mice, and the adipocytes did indeed become glandular tissue (148). Whereas white and brown adipocytes express the lipid-droplet associated protein perilipin 1 (70), pink adipocytes express perilipin 2, the adipose differentiation-related protein (578). Similar to white adipocytes, pink adipocytes express the calcium binding protein family S-100b (623) which is important in the unilocular structure of white adipocytes (44, 162), and most importantly they produce leptin (48). This pink adipocyte-derived leptin is secreted in milk, and studies have indicated that leptin in milk from lactating mothers is vital in preventing obesity in neonates (523). Giordano *et al*., (236) have suggested that pinking may be beneficial in breast cancer. Peroxisome proliferator activated receptor-γ (PPAR-γ) has been indicated as essential in the differentiation of the pre-adipocyte cell line 3T3-L1 into mature adipocytes (778), and it has been shown that in secretory mammary cells, a loss of PPAR-γ creates a tumorigenic environment (26). However, currently this is speculative and the links between PPAR-γ, pinking and cancer have not yet been investigated.

4. Perivascular adipose tissue: A complex structure

Perivascular adipose tissue (PVAT) is a highly dynamic and metabolically active tissue surrounding a number of vascular beds, with the exception of neural and pulmonary vasculature (13, 64). It is not known why these two vascular beds are devoid of PVAT. PVAT

is thought to be a differentiated continuation of the highly plastic vascular adventitia (176), and the close proximity between the two tissues likely allows a degree of crosstalk. Typically healthy PVAT comprises adipocytes, microvasculature, stem cells, nerves, and inflammatory mediators such as macrophages and eosinophils, although the exact phenotype depends on anatomical location and will vary significantly with pathogenesis (13, 92, 222, 246, 660).

Also, the composition of PVAT with regard to WAT or BAT will depend on location. Human EAT adipose tissue surrounding coronary arteries bears most resemblance to WAT, although the adipocytes appear smaller than those in SAT and VAT depots (116). In addition, EAT differs greatly to VAT and SAT in its expression profiles: low levels of adiponectin, and high levels of IL-6 and C-C motif chemokine ligand 2 (CCL2), and in coronary artery disease, this is associated with a higher infiltration of macrophages (37). The low expression of adiponectin in EAT has been linked to hypertension, and myocardial infarction (510, 539, 676).

The composition of PVAT surrounding the aorta varies with location, and is thought to influence the distribution of atherosclerosis (519). In rodents, thoracic aortic PVAT comprises BAT, whereas abdominal aortic PVAT in both humans and rodents is a mixture; mostly WAT and some BAT (92, 205, 223, 519). The phenotype of human thoracic aortic PVAT is unclear, with some studies reporting no PVAT (128), some reporting WAT (229), and others reporting BAT (203). Importantly, the human abdominal aorta is most susceptible to development of atherosclerotic plaques and aneurysmal dilatation, and abdominal adipose tissue has a much greater expression of a number of inflammatory markers such as TNFα, CCL2 and IL-6, as well as the adipokine leptin (519). These inflammatory profiles worsen with aging.

The phenotype of PVAT is altered in obesity. White adipocytes in particular are susceptible to hypertrophy as they are the main site of energy storage (131), and previously we have shown that adipocytes in rat mesenteric PVAT are enlarged in obesity (99), as well as increased in number (246). Moreover, some studies have shown that obesity drives BAT of the aorta to resemble WAT (541). As discussed in section 2.2, adipocyte size is a more important marker of metabolic disease than number, indicating that hypertrophy of adipocytes in PVAT will have metabolic consequences. Importantly, the immune cell population in PVAT is vastly altered in obesity, and this will be discussed further below.

Most studies of PVAT in humans use subcutaneous biopsies, although there are a number using internal mammary artery or saphenous vein; harvested for coronary bypass procedures (reviewed by Xia *et al.* (756)). These depots consist of WAT. Our group is particularly interested in mesenteric PVAT. Mesenteric adipose tissue surrounds vessels supplying the gut, and is therefore a VAT depot (751), although its white adipocytes are relatively small (~40μM in rats) compared with other VAT depots (524). In humans mesenteric PVAT is difficult to access for in-depth comparisons, but it is thought to be most similar to omental fat (a VAT depot). Expression of lipolytic genes is high in omental adipose, and metabolic responses are faster than that of SAT depots (524). Therefore, unsurprisingly, both basal- and catecholamine-induced lipolysis is greater in VAT, including in omental adipose (16). Differentiation of the pre-adipocytes in mesenteric depots is slower than SAT, but higher than in omental adipose tissue (673) and expression of vascular endothelial growth factor (VEGF), which is vital for angiogenesis in expanding adipose tissue depots, is higher in VAT than SAT (774). Importantly, the ability of expanding adipose depots to develop new blood vessels is reduced in obesity (230). In mesenteric adipose tissue, TNFα-induced apoptosis was increased compared with other VAT depots (674), which has significant implications when the increased expression of TNFα in obesity is considered.

5. PVAT releases vasoactive factors

Originally it was thought that PVAT provided mechanical support for the vasculature;

however, there is substantial evidence that PVAT releases factors that are vital in regulating vascular tone (629). At first glance, a simple review of the vast literature on the properties of PVAT can appear somewhat confusing or contradictory because there are reports of both vasorelaxant and pro-contractile properties. Now we know that PVAT can behave differently, depending on the specific species and vascular beds being studied. The distinctive properties of PVAT are dependent also on the way the tissue is stimulated. A number of studies in various arteries including skeletal muscle and mesenteric resistance arteries, the superior mesenteric artery, and the thoracic aorta, have reported that PVAT exerts a significant anti-contractile effect in response to vasoconstrictors (144, 224, 246, 682). That is to say that in a simple organ bath or myography studies, in the presence of PVAT a small artery constricts significantly less than an adjacent skeletonised vessel when challenged with a vasoconstrictor. This effect will play a paracrine role in regulating vascular resistance, and therefore blood pressure and nutrient delivery to skeletal muscle. Loss of this PVAT function will lead to an increase in vascular tone, and may contribute to development of hypertension and T2D (786).

There is evidence that the vasorelaxant property can be attributed to a number of adipokines being secreted from PVAT as well as a contribution from the 'sponging effect' of PVAT, transporting vasoconstrictors such as norepinephrine (NE) into the adipocytes and away from vascular smooth muscle cells (VSMCs) (595) (discussed further below). In addition, a small component of the anti-contractile effect observed in isolated arteries in an organ bath is due to PVAT forming a physical barrier to exogenously applied stimuli, although this is unlikely to have any significance *in vivo* (734). However, we know from using exogenously applied PVAT and solution transfer studies that PVAT is releasing transferable factors (424, 595). Whilst no single factor has been identified yet as primarily responsible for the PVAT anti-contractile effect, a number of potential candidates have been suggested with both endothelium-dependent and -independent mechanisms (227). Also, whilst white and brown adipocytes differ in their functions and secretory profiles, the anti-contractile effect has been observed in both types of depot (166, 222, 419). Below is discussed the evidence for a number of proposed anti- and pro-contractile factors released from PVAT, and their roles in blood pressure, metabolism and inflammation (see Table 1 for summary). We will include studies of other adipose depots, as the pattern of adipokine expression is likely to be similar; therefore, these studies may be applicable to PVAT (in particular VAT studies) even if not yet studied specifically in the vasculature. In addition, there will be an endocrine contribution from adipokines released into circulation from other depots which should be considered (see Figure 2 for a schematic of adipokine effects on vascular tone).

5.1. Adiponectin

In 1995 Scherer *et al.* (596) were the first to discover 'adipocyte complement-related protein of 30 kDa' (Acrp30) within 3T3-L1 adipocytes and murine adipose tissue. This protein was soon after termed 'adipose most abundant gene transcript 1' (apM1) owing to its transcript being the most highly expressed in the mRNA of human adipose tissue (429). Now more commonly known as adiponectin, this protein is a vasodilator adipokine which is predominantly produced by adipocytes. There is substantial evidence for the role of adiponectin as a PVAT-derived anti-contractile factor. Replication of the PVAT anti-contractile effect can be achieved in mouse PVAT-denuded mesenteric resistance arteries using the exogenous application of recombinant mouse globular adiponectin (246, 424, 595). Furthermore, in PVAT intact vessels challenged with NE or by electrical field stimulation (EFS), the addition of a blocking peptide for the adiponectin type-1 receptor (AdipoR1) abolishes the PVAT anti-contractile effect. Moreover, we have demonstrated that electrical stimulation of mesenteric PVAT stimulates secretion of adiponectin via activation of adipocyte β_3-adrenoceptors by nerve-derived NE (595). To further investigate the importance of adiponectin, we employed the use of an adiponectin knockout mouse. Here the EFS-induced anti-contractile effect was absent, and the mice exhibited a hypertensive and hyperglycemic phenotype. In addition, the EFS-induced anti-contractile effect in small resistance arteries persisted in endothelium-denuded vessels, indicating that the adiponectin

mediated anti-contractile effect is endothelium-independent (595).

Adiponectin is secreted in a number of polymeric forms with varying molecular weights: hexameric, multimeric, trimeric, and globular (216, 369, 430). The globular form arises from proteolytic cleavage of the full form (216), and it is globular adiponectin that we have used to replicate the anti-contractile effect (246, 424, 595). However, globular adiponectin is less abundant in the circulation than multimeric isoforms (216). The biological functions of the different adiponectin isoforms are unclear; however, individual isoforms have different effects on the degree of 5' adenosine monophosphate-activated protein kinase (AMPK) activation in VSMCs and endothelial cells to induce vasodilation (372, 754, 764). In addition, the isoforms have varying effects on glucose metabolism. Multimeric isoforms are associated with improved insulin sensitivity, as well as simulating glucose uptake into skeletal muscle, and inhibiting hepatic cell glucose release, whereas globular adiponectin appears to have no effect (522). Instead of glucose metabolism, globular adiponectin appears to play a role in stimulating fatty acid metabolism (216, 522, 693, 764). Interestingly, Kim *et al.* (351) found that crossing the leptin deficient *ob/ob* mouse with a transgenic mouse containing a deletion in the collagenous domain of adiponectin to increase plasma adiponectin, resulted in rescuing the diabetic phenotype, and blood glucose was normalised. Moreover despite its healthy phenotype this new strain of mouse actually exhibited increased adiposity through hyperplasia of SAT, rather than hypertrophy.

There are two adiponectin receptors: type 1 (AdipoR1) and type 2 (AdipoR2). Both AdipoR1 and AdipoR2 are ubiquitously expressed, with expression of each being highest in skeletal muscle and the liver respectively (531, 763). AdipoR1 is located on both endothelial and VSMCs and it is activation of these receptors which will stimulate a number of pathways such as VSMC differentiation and growth (157, 158, 391). In terms of modulating VSMC contraction, activation of AdipoR1 stimulates the production of AMPK (640). Adiponectin mediated AMPK activation may vary with the location or type of PVAT. Deletion of the AMPK α1 subunit in mice caused a significant reduction in the anti-contractile effect of aortic BAT, and markedly reduces circulating adiponectin (20). Conversely, deletion of the AMPK α2 subunit reduces the anti-contractile effect of WAT surrounding skeletal muscle resistance arteries, and decreased insulin sensitivity (144). The effects of AMPK α1 deletion have not been studied in WAT.

The roles of AMPK are twofold: first, increased phosphorylation of endothelial nitric oxide synthase (eNOS) in both the endothelium and VSMCs, leading to increased production of nitric oxide (NO) (640). Second, in VSMCs AMPK regulates opening of large conductance calcium-activated potassium channels (206). NO from endothelial cells can diffuse to the VSMC, or feedback onto the NO signalling within adipocytes. In the VSMC, NO stimulates soluble guanylate cyclase, leading to an increase in the production of protein kinase G. Protein kinase G will phosphorylate large conductance calcium-activated potassium channels on the VSMC membrane (218), and alongside AMPK, will increase the opening of these channels, leading to hyperpolarization and relaxation.

Studies using mice deficient in either AdipoR1 or AdipoR2 reveal that these receptors must play different roles in metabolism. Whilst a high fat diet results in severe obesity and reduced glucose clearance in the AdipoR1 knockout mouse, the AdipoR2 knockout mouse is resistant to obesity and shows improved glucose clearance (66, 531). Interestingly, these studies have also revealed that AdipoR2 plays a vital role in revascularization following ischemic hind limb injury, whereas AdipoR1 appeared to have no effect (531). These results suggest that it is likely to be AdipoR1 that plays a more important role in modulating vascular tone.

In hypertension, adiponectin levels are low and are increased with anti-hypertensive therapy (777), indicating the importance of adiponectin in modulating peripheral resistance and blood pressure. Likewise in obesity plasma adiponectin is reduced (29). In addition,

adiponectin appears to augment the effects of insulin and is reduced in diabetes (375, 517). More importantly, the reduction in plasma adiponectin in obesity and diabetes occurs early, implicating hypoadiponectinemia in the pathogenesis of these diseases (286). As mentioned previously, globular adiponectin increases fatty acid oxidation in muscle (216), and full length adiponectin stimulates glucose utilization (764). Moreover, in adiponectin knockout mice, we have demonstrated a hypertensive and hyperglycemic phenotype despite normal body weight (595). Interestingly, as previously discussed high fructose diets have been associated with increased VAT and MetS, and one study has indicated that the high fructose diets induce adiponectin resistance, as well as an increasing expression of other pro-inflammatory adipokines (436). In the KKAy genetic mouse model of obesity there is overexpression of adiponectin and reduced blood pressure (510), again highlighting the importance of adiponectin as a therapeutic target in obesity-related hypertension.

Adiponectin is generally considered an anti-inflammatory adipokine (692), and this role has been implicated in protection against hyperglycemia in endothelial cells (7, 758). This is likely due to reduced reactive oxygen species (ROS) production, as adiponectin has been shown to reduce TNFα-induced ROS production in phagocytes (117). Interestingly, despite adiponectin's protective effects against TNFα, their tertiary structures appear similar (113). In addition to adiponectin's protective effects against TNFα, it has been shown in cardiac cells to activate macrophage autophagy (549). Antonopoulos *et al*. have demonstrated that application of adiponectin to human internal mammary artery directly supressed nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, and consistent with other studies found an inverse correlation between circulating adiponectin levels and NADPH oxidase (25). Interestingly, they found a paradoxical positive correlation between NADPH oxidase activity and the adiponectin gene (ADIPOQ) expression. Using co-culture studies, Antonopoulos *et al.* determined that NADPH oxidase products will increase PPAR-γ mediated expression of ADIPOQ as a protective mechanism to supress further local NADPH oxidase activity.

Studies using various vasoconstrictors such as phenylephrine, NE and serotonin (5HT), suggest that the mechanism of the anti-contractile effect is agonist-dependent. In the adiponectin knockout mouse, the NE- and EFS-induced anti-contractile effect is absent, whereas the 5HT-induced effect persists (196, 595). Furthermore, addition of the adiponectin blocking peptide to rat PVAT intact vessels antagonises the anti-contractile effect elicited with NE, but has no effect on vessels stimulated with 5HT (743). This suggests that other PVAT-derived factors may play a role in the 5HT-induced effect.

5.2. Leptin

Leptin is another highly secreted adipokine, which is known to play a vital role in regulating appetite and body weight (83). Its central actions include its effects on the hypothalamus resulting in appetite suppression (558), and leptin deficient *ob/ob* mice are severely obese and diabetic, although normotensive (438). A similar phenotype is observed in *db/db* mice, which is deficient in leptin receptors (358). Leptin secretion is directly proportionate to adipocyte size (184), therefore in obesity where adipocytes are enlarged, leptin is profoundly increased. However, instead of reducing appetite and therefore obesity, obese subjects demonstrate leptin resistance (256, 401), which will lead to further, rapid increases in adiposity. The exact mechanisms of leptin resistance remain unclear, but may be due to an inability in crossing the blood brain barrier (43), or reduced cellular responses (485),

Leptin secretion is modulated via a number of factors, including insulin and TNFα, which will increase secretion, and β_3-adrenoceptors, which decrease leptin secretion (437). Three splice variants of the leptin receptor exist in humans, and six in the mouse, which belong to the cytokine receptor family. However, it is the long form known as OB-Rb which regulates the majority of leptin's effects on the central nervous system (CNS) and the periphery, including the vasculature (63, 294). In addition to effects on the vasculature, leptin is known to affect cytokine production and angiogenesis. Therefore, leptin resistance in obesity may

exacerbate hypoxia and inflammation.

Leptin shares a similar long-chain helical structure to a number of inflammatory cytokines such as IL-6, and it is likely that it is this structural similarity that enables leptin to regulate immune responses (379). The OB-Rb receptor is present on a number of immune cell populations, including macrophages and lymphocytes, and exerts a stimulatory effect on immune cell activation (527). As previously mentioned TNFα increases leptin secretion, creating a pro-inflammatory loop. During starvation, circulating leptin is reduced and the immune response is impaired; however, this impairment can be prevented by exogenous administration of leptin (287). Therefore in obesity, where leptin expression is high, leptin could be contributing to chronic inflammation of adipose tissue.

Leptin can induce vasodilation via both endothelium-dependent and -independent mechanisms (399). In aortic and mesenteric arteries pre-constricted with phenylephrine, leptin induces vasodilation which is absent in endothelial-denuded vessels, indicating the presence of leptin receptors on endothelial cells (397). In the aorta, leptin-induced vasodilation could be blocked using NOS inhibitors. Similarly, leptin induces vasodilation in rat and canine coronary arteries, which again was absent in endothelial-denuded arteries and blocked by NOS inhibition (357). These data suggest that leptin-induced vasodilation in the aorta and coronary arteries is dependent upon the eNOS isoform. Immunoblotting studies have suggested that leptin induces release of NO from endothelial cells via phosphorylation of eNOS (710). However, in mesenteric arteries NOS inhibition has no effect on leptin-induced vasodilation, but could be blocked by a non-specific endothelium-derived hyperpolarising factor inhibitor (Brefeldin A), indicating a NOS-independent mechanism of vasodilation in mesenteric arteries (397). Interestingly, in pharmacologically sympathectomised rats leptin injections have a hypotensive effect (397). In addition, infusion of leptin into healthy human males increases forearm blood flow (489), indicating that a balance between leptin's effects on the CNS and periphery is vital in blood pressure modulation.

Chronically elevated leptin may result in vasoconstriction through effects on endothelin-1 (ET-1). ET-1 is a vasoconstrictor produced by endothelial cells, and application of leptin to cultured human endothelial cells has demonstrated a dose-dependent increase in ET-1 secretion (554). Moreover, expression of the ET_A receptor, which mediates the vasoconstrictor effects of ET-1, is increased in VSMCs treated with leptin (320).

As well as effects on the endothelium, leptin appears to have a direct effect on VSMCs. Leptin receptors are present on cultured rat VSMCs and the vasodilator effect of leptin on rat aortic rings constricted with Ang II persists in the absence of endothelium (212). Similarly, in internal mammary arteries and saphenous veins from patients with coronary artery disease leptin induced an endothelium-independent vasodilation (95, 469). However, the effects of leptin have not been tested in these arterial beds from healthy patients. Leptin also contributes to VSMC hypertrophy via ET-1, which may increase peripheral resistance (788).

The evidence suggests that at least in the aorta, leptin derived from the surrounding BAT may be responsible for the PVAT anti-contractile effect induced by some vasoconstrictors such as Ang II, phenylephrine, and NE (212, 224, 397). However, it is unlikely that leptin is the anti-contractile factor released by 5HT, as in leptin receptor knockout mice the 5HT-induced anti-contractile effect persists (413). Interestingly, in the spontaneously hypertensive rat loss of PVAT anti-contractile function is accompanied by reduced expression of leptin in the PVAT, and reduced eNOS activation, again highlighting the importance of adipocyte-derived leptin in blood pressure regulation (224).

5.3. Nitric oxide

NO is a widespread and commonly known vasodilator, which is synthesised by three NOS

enzymes; endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) (459). The iNOS isoform is the only isoform of the three to be Ca^{2+}-independent, and its activity can be stimulated in most cell types by inflammatory cytokines, which means that iNOS plays a role in the pathology of many inflammatory diseases (210). The nNOS isoform is present in central and peripheral neurons, and nNOS-derived NO acts as a neurotransmitter and contributes to central regulation of blood pressure. The eNOS isoform in primarily located in endothelial cells, hence the name, and has been shown to have anti-atherosclerotic effects as well as participating in the local control of blood pressure (210). However, recent studies have indicated that eNOS is also present in PVAT, and PVAT is able to directly produce NO to exert an effect on afferent vessels (142, 235, 755). The source of NO in PVAT is widely regarded as from the microvasculature; however, we hypothesise that adipocytes may be able to synthesise NO. In addition, recent unpublished studies by our group have indicated that sympathetic nerves are a source of NO in PVAT (via nNOS). Further study is required to delineated the exact sources of NO and compare their importance. As discussed in section 5.1, NO stimulates soluble guanylate cyclase, leading to phosphorylation of large conductance calcium-activated potassium channels on the VSMC membrane via protein kinase G, leading to hyperpolarization and relaxation.

Previously we have demonstrated that the PVAT anti-contractile effect stimulated by NE in mesenteric resistance arteries is NOS dependent (100, 246, 424). When PVAT is incubated with a non-specific NOS inhibitor, the anti-contractile effect is completely abolished. Whilst specific pharmacological inhibition of eNOS has not yet been possible, we have tested the effects of a nNOS inhibitor, which had no effect (100). Moreover, in global eNOS knockout mice the NE induced PVAT anti-contractile effect is absent. Other studies have shown that the eNOS knockout mouse is hypertensive (638), insulin resistant and hyperglycemic (611).

Below the role of adipocyte β_3-adrenoceptors in lipolysis and vascular tone is discussed, but it should be highlighted here that we and others have shown that β_3-adrenoceptors stimulate production of NO in PVAT (100, 108), and β_3-adrenoceptor stimulation induces PVAT-dependent hyperpolarizations in VSMCs which can be blocked using a NOS inhibitor (734). Also, there is speculation that NO may increase adiponectin secretion through its effects on adipocyte mitochondrial biogenesis (255, 743).

It is thought that early in obesity there is an adaptive increase in NO which may preserve vascular function (235). In a high fat feeding mouse model of obesity, insulin and leptin, which are elevated in obesity, stimulate NO production from mesenteric PVAT. In PVAT intact arteries, there is an enhanced response to NO-dependent vasodilators in animals fed a high fat diet, compared to normal diet animals. However, with chronic obesity increased superoxide production results in a reduction in NO bioavailability (12).

A low amount of NO is generally considered to be anti-inflammatory, and regulates expression of a number of immune cells including eosinophils, and inhibits inflammatory cytokine production (73, 434, 435). However, high levels produced by iNOS can be pro-inflammatory and even toxic (253). Large amounts of NO will be rapidly oxidised, increasing peroxynitrite, which has a cytotoxic effect and may cause DNA damage and induce apoptosis (254).

Since iNOS activity can be induced in most cell types, it is unsurprising that iNOS activity has been observed in multiple white and brown adipose tissue depots, including thoracic and aortic PVAT (22, 28, 326, 538, 567). Therefore, it is likely that adipose tissue inflammation in obesity may increase iNOS activity. It has been shown that iNOS plays a role in increasing insulin-stimulated glucose transport in skeletal muscle in response to cytokines (53), which might suggest that iNOS deficiency may contribute to the development of diabetes. Conversely, in cultured islet cells from the Zucker diabetic rat, when incubated with FFAs iNOS expression is greatly increased alongside reduced insulin secretion as a result of islet cell death. In iNOS knockout mice, animals fed a high fat diet are protected against insulin resistance, but still become hypertensive (504). These results suggest that

iNOS may be important in the development of hypertension; however, its role in diabetes appears to be more complex. During septic shock, iNOS activity is increased in response to lipopolysaccharide (LPS) and plays a large role in the development of hypotension associated with sepsis (747), again suggesting a clear link between iNOS and blood pressure. Although, whilst iNOS activity may be increased by inflammation in obesity, bioavailability of NO as a whole is reduced in obesity

There is evidence that NO contributes to adipocyte metabolism. In eNOS gene over-expressing mice fed a high fat diet, WAT hypertrophy was inhibited and metabolism was increased (588). Oxygen consumption and expression of mitochondrial proteins were increased, and FFAs were decreased. There was no effect on the expression of leptin; however, insulin levels were normal (588). In control mice fed a high fat diet, eNOS expression was reduced in adipose tissue but unchanged in skeletal muscle and the aorta. These results indicate clearly the importance of adipose eNOS in the pathology of obesity.

NO is rapidly broken down into nitrite and nitrates, and some studies have indicated that nitrates have anti-obesity and anti-diabetic effects (453, 568, 569). The nitrate-nitrite-nitric oxide pathway is associated with beiging of adipose tissue, which is discussed below. In eNOS deficient mice with MetS, dietary supplementation of nitrates reduced blood pressure, improved glucose tolerance, and reduced VAT (109). Clearly, improving secretion of adipose tissue-derived NO in obesity presents a promising therapeutic target.

5.4. Apelin

In the search for the endogenous ligand for the orphaned G-protein coupled receptor; APJ, which shares a similar structure to the angiotensin receptor, apelin was discovered (671). In the body it is found ubiquitously, and can be expressed in both human and mouse adipocytes (78). Moreover, its expression in both white and brown SAT and VAT depots is increased in obesity, and similar to insulin, expression is increased by fasting. Insulin has been shown to stimulate apelin production; therefore, it is likely that the hyperinsulinemia in obesity is responsible for increased apelin secretion. Interestingly, apelin injections in obese, diabetic mice actually increased glucose utilization, with no effect on insulin (164), suggesting a direct effect of apelin on glucose transporters.

The APJ receptor is widely expressed in the periphery and CNS (322), but studies on the effects of apelin on vascular tone and blood pressure are conflicting. In mesenteric arteries, the exogenous apelin fragment apelin-13 has no effect on resting arteries but will dilate arteries pre-constricted with the thromboxane agonist U46619, and this dilation is reduced by NOS inhibition (586). Similarly, apelin-13 administered intravenously into humans induces dilation of forearm resistance arteries, which can again be attenuated by NOS inhibition (305). However, in the human saphenous vein, apelin-13 induced vasoconstriction (332). It is possible that the function of apelin varies with vessel type, but the effects of apelin on blood pressure complicate the story further.

In rats injected with apelin-13 either intravenously or directly into the cerebral ventricle, mean arterial blood pressure was increased (322). However, in two other separate studies, rats injected with apelin-12 intravenously, blood pressure is reduced (120, 390). Similar results are observed in rats when apelin-12 is administered using a femoral cannula (672), and in mice with intraperitoneal injections of apelin-12 (298). It is worth noting that in the latter two studies, the hypotensive effects of apelin-12 could be reduced using NOS inhibitors. In addition, in APJ deficient mice, the vasoconstrictor response to Ang II is increased, and the vasopressor effect of Ang II is increased (298). The differences in the effects of apelin may be explained by the apelin fragments used in these studies; apelin-13 raised blood pressure, whereas apelin-12 reduced it. Various forms of apelin exist, and *in vivo* it is the long-form, apelin-36, which is most predominant (671); however, it is the shorter fragments which seem to elicit the most biological activity. Tatemoto *et al*. (671), the group which first discovered

apelin found that apelin-13 has the lowest EC_{50} and is therefore the most active, followed by apelin-17, then apelin-12. Apelin-17, when administered via femoral cannula has a similar hypotensive effect to apelin-12 (172). Messari *et al*. (172) concluded that the actions of apelin-17 were mediated via internalization of the receptor, and internalization triggers a second signalling cascade which reduces vascular tone and therefore blood pressure. They found that apelin-13 was less effective in inducing internalization of the receptor. In hypertensive patients with normal BMI, plasma apelin is reduced (405), which would indicate that the vasodepressor role of apelin is the most physiologically relevant. Further studies are required to conclusively understand the physiological importance of apelin and its various forms. Interestingly, in the ApoE knockout mouse model of atherosclerosis, apelin-13 reduced plaque formation, increased NO bioavailability and reduced systolic blood pressure (125), indicating an anti-atherosclerotic role for apelin.

Apelin expression correlates closely with oxidative stress and inflammation (784). Under normal conditions in cultured macrophages, apelin-13 down-regulates expression of TNFα and monocyte chemotactic proteins (770). In addition, when cultured under hypoxic conditions, the expression of these inflammatory proteins was still suppressed. A similar immunosuppressive effect of apelin-13 has been observed in ischemic stroke (759). These studies indicate that increased apelin expression in obesity could have beneficial effects on the inflammatory environment.

5.5. Visfatin

Visfatin is highly secreted by VAT, hence the name, and is secreted by PVAT (159, 529, 555), although in humans it is thought that it is the macrophage which is the greatest source of visfatin as opposed to adipocytes in rodents (137). Plasma visfatin is highly elevated in obesity (219), but can be reduced back to control levels again in non-diabetic obese patients with aerobic exercise (122). Expression of visfatin is upregulated in a number of inflammatory diseases, and can induce expression of TNFα and IL-6 in the microvasculature (421).

Visfatin appears to play a role in atherosclerosis, and is highly expressed in atherosclerotic plaques (353). It increases monocyte adhesion to endothelial cells, and promotes VSMC proliferation (722). This role of visfatin in VSMC proliferation may contribute to increased peripheral resistance. In patients with adrenal adenomas, visfatin expression is highly increased, and this is associated with increased blood pressure, hyperglycemia, and hyperinsulinemia (32). Similarly, in both hypertensive patients with normal weights, and obese subjects with hypertension, plasma visfatin is increased, suggesting a vasopressor effect (405). In the rat aorta, cumulative applications of visfatin induced eNOS dependent relaxation in arteries pre-constricted with NE (766), whereas in both human and rat mesenteric small resistance arteries, visfatin had no effect on the vasoconstrictor response to NE, but did impair acetylcholine-induced vasodilation (702). Therefore, it is likely that the vasopressor effects of visfatin are mediated via small resistance arteries.

As briefly mentioned, increased visfatin positively correlates with plasma insulin and blood glucose (32, 181, 506). Although, studies of visfatin on insulin signalling are contradictory and would suggest that elevated visfatin should be beneficial in obesity. One study has indicated insulin-mimetic effects of visfatin, and in cultured 3T3-F442A adipocytes, visfatin phosphorylated insulin receptors, increasing glucose transport (219). In addition, in visfatin deficient mice plasma glucose was significantly elevated. In diabetic rats, infusion with visfatin increased insulin signalling by increasing pancreatic β cell proliferation, and increased glucose metabolism and excretion (348). Further study is required to understand the contribution of visfatin to insulin resistance.

5.6. Omentin

Omentin is highly expressed in VAT, specifically, the omentum (773), although it is not yet known if PVAT secretes omentin. Little is known about the direct vascular effects of omentin; however, plasma omentin is reduced in obesity and negatively correlates with leptin, BMI, waist circumference and insulin resistance (150). In addition, omentin expression improves following diet-induced weight loss (472) and aerobic exercise (591), alongside improvements in insulin sensitivity and blood pressure. In cultured subcutaneous human adipocytes, application of omentin significantly enhanced insulin stimulated glucose transport (773). In rats, intravenous injection of omentin had no acute effect on blood pressure; however, it did suppress the vasopressor effects of NE and Ang II via a NOS dependent mechanism (336). In a separate study following 14 days of omentin injection in rats, blood pressure was reduced, and interestingly, adiponectin expression in adipose tissue was increased (89). As far as we know, there has been only one study on the direct effects of omentin on isolated arteries. In the rat aorta and the superior mesenteric artery, omentin attenuated NE-induced contractions, again through a NO dependent mechanism (768).

Omentin may be a useful target in improving the inflammatory status of adipose tissue in obesity. In both cultured VSMCs from the superior mesenteric and whole segments of the aorta, omentin significantly reduced TNFα expression, and TNFα-induced monocytic cell adhesion (337). Similar results have been observed in human endothelial cells whereby TNFα signalling was inhibited through activation of eNOS (767). These data suggest that adipocyte-derived omentin may play an important anti-inflammatory role in the vasculature.

5.7. Hydrogen sulphide

Aortic PVAT adipocytes and epididymal depot adipocytes are a source of the hydrogen sulphide (H_2S) synthesising enzyme cystathionine-γ-lyase (CSE) (185). H_2S can induce vasodilation of VSMCs via opening of ATP-sensitive K^+ channels (185), or via activation of endothelial intermediate conductance Ca^{2+} dependent K^+ channels (483). A number of vasoconstrictors including phenylephrine, 5HT and Ang II stimulate production of H_2S from aortic PVAT, and inhibition of CSE reduces the aortic PVAT anti-contractile effect in rats (185, 360), but not mice (360), which could be attributed to a slightly higher expression of CSE in rat aortic PVAT than mouse (360). In addition, activation of CSE enhanced the PVAT anti-contractile effect in the aorta but had no effect on PVAT denuded aorta (185). H_2S could therefore be key to the PVAT anti-contractile effect in large conductance arteries.

Plasma H_2S is reduced in the spontaneously hypertensive rate (769) and in a pharmacologically-induced mouse model of hypertension by oral administration of a NOS inhibitor (798). Exogenous administration of a H_2S donor to both models reduces blood pressure, indicating a key target in hypertension. In overweight patients, waist circumference is an independent predictor of plasma H_2S levels, and the two are negatively correlated (735). Surprisingly, changes in PVAT secretion of H_2S occur early in obesity. After only one month of a cafeteria diet in rats, H_2S production is increased and the PVAT anti-contractile effect is enhanced (54). After three months of cafeteria diet, CSE expression is downregulated, H_2S production is reduced, and PVAT function is lost.

At physiological levels H_2S has anti-oxidant effects (657). Interestingly, evidence suggests that early in diabetes, glucose stimulates increased CSE expression as a protective mechanism against oxidative stress (659). Incubation of endothelial cells, pancreatic islet cells, and vascular rings with high levels of glucose will increase CSE expression, and in vascular rings from CSE deficient mice, high glucose accelerates endothelial dysfunction (324, 656). Moreover, application of exogenous H_2S will protect against this effect. However, despite these beneficial of anti-oxidant effects of H_2S in diabetes, one study has demonstrated that H_2S reduced insulin-stimulated glucose transport into epididymal adipocytes (189). This same study indicated that in a diabetic rat model, upregulation of CSE negatively correlated with glucose uptake, and concluded that elevated H_2S contributes to insulin resistance. Taken together, these studies indicate a complex role of H_2S in diabetes. The beneficial vs detrimental effects of H_2S may be dependent on its concentration, as high levels of H_2S will lead to increased generation of free radicals and oxidants (658).

5.8. Hydrogen peroxide

The persistence of the 5HT-induced anti-contractile effect in endothelium-denuded vessels (413) indicated an endothelium-independent anti-contractile effect. Hydrogen peroxide (H_2O_2) is a known vasodilator in endothelium-denuded vessels via activation of soluble guanylate cyclase in smooth muscle. Therefore, it has been hypothesised that H_2O_2 plays an important role in this pathway (227). Gao *et al.* (227) investigated this hypothesis, and found that the phenylephrine-induced PVAT anti-contractile effect can be reduced using a H_2O_2 scavenger, and enhanced by increased production of H_2O_2 using superoxide dismutase. In health, H_2O_2 is present at non-toxic levels in adipose tissue; however, it is elevated in obesity (221). H_2O_2 is known to have cytotoxic effects at high levels as a result of its indiscriminate conversion to hydroxyl radicals (258). Via disruption of Ca^{2+} homeostasis, hydroxyl radicals will induce formation of DNA lesions. Oxidative stress as a result of hypoxia and increased FFAs (discussed further below) is thought to link obesity to insulin resistance and diabetes (17), and therefore, in obesity it is likely that oxidative stress is responsible for the increased H_2O_2 production in adipose tissue. In obese KKAy mice, both NADPH oxidase inhibitors and TNFα reduced H_2O_2 production in adipocytes (221). Moreover, adiponectin bioavailability was increased, alongside reductions in blood pressure and insulin resistance. Similarly in human and rodent skeletal muscle H_2O_2 production is increased and treatment of rodents with anti-oxidants attenuates insulin resistance (23). In cultured rat adipocytes, H_2O_2 stimulates glucose transport in a similar manner to insulin (126); however, prolonged exposure of 3T3-L1 adipocytes to H_2O_2 leads to insulin insensitivity (576).

5.9. Palmitic acid methyl ester

Palmitic acid methyl ester (PAME) is spontaneously released from PVAT and induces vasodilation of the aorta via K_v channels in an NO- and endothelium- independent manner (395). In addition, spontaneous release of PAME is Ca^{2+}-dependent, as release of PAME is significantly reduced in PVAT perfused with Ca^{2+}-free Krebs solution. In the spontaneously hypertensive rat PAME secretion from PVAT is reduced, and the vasodilator effect of exogenous PAME in these rats is significantly less than in control animals possibly indicating the involvement of PAME in hypertension. However, there is no effect of PAME on human mesenteric arteries (721).

Basal PAME turnover is increased in obesity; however, turnover is reduced in the presence of hyperinsulinemia (307). One study has indicated that PAME increased insulin secretion during hyperglycemia (530), however other studies indicated a negative effect of PAME on insulin signalling. In human adipose microvascular endothelial cells, PAME increased the expression of inflammatory cytokines IL-6, IL-8, and the intracellular adhesion molecule-1 (ICAM-1), as well as reducing insulin transport (537). Similarly, in cardiac muscle PAME inhibits basal and insulin-stimulated glucose transport (496). Ishi *et al.* (299) found that the mechanism of PAME-induced reduced insulin signalling was via degradation of key insulin signalling molecules including the insulin receptor. Therefore, it is likely that adipocyte-derived PAME contributes to insulin resistance in obesity.

5.10. Angiotensin 1-7

Both WAT and BAT are a source of Ang 1-7 (394). Ang 1-7 is well established in control of blood pressure through the renin-angiotensin-aldosterone system (RAAS), and adipose tissue is already recognised as RAAS organ (discussed further below) (521). As well as this contribution of adipocyte derived Ang 1-7 in circulation, it is likely that PVAT-derived Ang 1-7 plays a local role in regulating vascular tone. Studies have shown that Ang 1-7 antagonists attenuate the PVAT anti-contractile effect in aorta (393). In addition, inhibition of Mas receptors reduced the anti-contractile effect, and reduced the vasodilator effect of exogenous Ang 1-7 on PVAT denuded aorta (393, 394), indicating how the vasodilation is mediated. Importantly, the aortic PVAT anti-contractile effect is absent in Mas receptor knockout mice (393). In this review we will be discussing the consequences of autonomic

nervous system over activity in obesity; therefore, it is important to note here that Ang 1-7 has been shown to reduce nerve-stimulated NE overflow via Mas receptors (101), which may have implications in obesity.

In obesity and diabetes, expression of Ang 1-7 is reduced (264, 632). Some studies have indicated a potential therapeutic role of Ang 1-7 in diabetic rats. Oral administration reduced blood glucose and plasma insulin (589). There appears to be a degree of overlap between signalling pathways associated with insulin and with Ang 1-7, and this overlap is thought to enable Ang 1-7 to enhance insulin signalling (160). In addition, Ang 1-7 reduces oxidative stress in diabetic mice (55), indicating another mechanism by which Ang 1-7 may be useful in disease.

5.11. Chemerin

Chemerin is a pro-contractile adipokine that may play a significant role in the loss of PVAT vasorelaxant function. Secretion from human obese adipose tissue is significantly increased, is associated with insulin resistance and inflammation, and is a predictive marker of coronary artery disease (163, 617). In addition, its levels fall with loss of adipocyte mass following exercise, diet or bariatric surgery, and circulating levels of chemerin negatively correlate with glucose tolerance (112). In mice, chronic treatment with chemerin increased systolic blood pressure (376). The chemerin treatment increased VSMC proliferation and migration in the aorta via a ROS-dependent signalling pathway, which is likely to increase peripheral resistance, and therefore blood pressure (376).

Chemerin evokes direct vasoconstriction, as well as enhancing agonist-induced contractions in human and rat vessels through Gi proteins, resulting in the activation of L-type Ca^{2+} channels (190). Similarly, in the aorta, superior mesenteric, and small mesenteric resistance arteries, a chemerin receptor agonist induced vasoconstriction which was greatly increased in endothelium denuded arteries, which may indicate a role for chemerin in obese arteries where the endothelium is dysfunctional (725). This study also found that a chemerin receptor antagonist reduced the contractile response to phenylephrine and prostaglandin in vessels with intact PVAT, suggesting that endogenous chemerin does regulate vascular tone. Moreover, there is evidence that chemerin enhances sympathetic nerve-induced vasoconstriction (141). Using the superior mesenteric artery, chemerin receptor antagonists caused a reduction in the contractile responses to EFS in the presence of PVAT, and had no effect on PVAT denuded arteries. In addition, exogenous chemerin enhanced EFS-induced vasoconstriction in the artery (with and without PVAT), and this could be inhibited using an α-adrenergic receptor antagonist.

We have discussed chemerin's role in the vasculature, but its first known function was as a chemoattractant of macrophages and dendritic cells (745), and serum chemerin concentrations correlates with the levels of inflammatory cytokines such as IL-6 and TNFα independent of BMI (729). In addition, chemerin induces ICAM-1 and E-Selectin expression in endothelial cells (383). Whilst there is no evidence to directly implicate chemerin in the inflammation of adipose tissue in obesity, its chemoattractant roles make it likely to play a role.

Many studies have indicated a correlation between chemerin, obesity, and MetS (645, 729). Interestingly, one study in Mexican-American patients found a correlation between chemerin and T2D independent of BMI (80). Treatment of isolated human skeletal muscle cells with chemerin reduced glucose uptake and insulin secretion, by stimulating phosphorylation of insulin receptor 1 (606). As previously discussed, chemerin levels are significantly reduced following weight loss, and following bariatric surgery, the reduction in circulating chemerin is accompanied by a decrease in insulin resistance and blood glucose (605). Given that chemerin plays a role in inflammatory cell recruitment, insulin resistance and vasoconstriction, and its levels correlate with weight gain and drop following weight loss, chemerin is one of the major adipokines that could be targeted in therapeutic strategies to

treat MetS.

5.12. Resistin

Similar to visfatin, resistin expression is greater in VAT than SAT (41), and is secreted by PVAT (458, 529). In rodents adipocytes are the main source of resistin compared with macrophages in humans (137). In addition, in humans resistin has clear pro-inflammatory effects, and will strongly increase expression of IL-6 and TNFα (75). There is a plethora of evidence for a role of resistin in insulin resistance in rodents. In cultured adipocytes, incubation with resistin impairs insulin-stimulated glucose uptake, and this effect can be blocked with resistin antibodies (647). In a diet-induced mouse model of obesity, these resistin antibodies improved blood glucose and insulin sensitivity. In addition, plasma resistin is increased in this model, and can be reduced using the anti-diabetic drug rosiglitazone (647). In normal mice, acute doses of resistin reduced glucose tolerance and insulin sensitivity. Interestingly resistin-deficient mice do not develop obesity, and high fat feeding has no effect on body weight or fat mass, and animals have improved glucose tolerance compared to normal mice (42). This is thought to be due to increased AMPK activity (42), and improved hepatic responsiveness to insulin (482, 550). Genetic over-expression of resistin in mice results in hyperglycemia. These studies indicate a clear link between resistin and T2D in rodents.

The role of resistin in T2D is less clear in man. Some studies report that resistin is elevated in human obesity, and is linked to a number of disease processes such as insulin resistance and coronary artery disease (96, 520). Others report that whilst resistin was increased in their obese cohorts, it was not linked to aetiology of T2D (592, 609). However, in cultured human VSMCs resistin increased proliferation (104), and in a study of human T2D it was reported that resistin expression was normal in the normotensive T2D patients, but elevated in hypertensive T2D patients (666), indicating a role for resistin in blood pressure modulation. Similarly, in a mouse model of hypoxia-induced hypertension, plasma resistin was elevated (677). In isolated arteries, application of resistin had no effect on pre-constricted aorta or superior mesenteric rings (233). However, insulin-induced vasodilation was impaired via a reduction in eNOS phosphorylation. A similar impairment was observed in coronary artery rings dilated with bradykinin (155). Therefore, resistin may present a useful target in the treatment of obesity-associated hypertension at least.

6. Sympathetic nervous stimulation of adipose tissue

6.1. Innervation of adipose tissue

Whilst there are a vast number of studies identifying vasoactive adipokines, there are fewer on the mechanisms of the release of these factors. The vasculature has a rich supply of sympathetic nerve fibres, and the secretion of catecholamines from the nerves modulates the contractile state of VSMCs. Sympathetic nerve-derived NE induces vasoconstriction via activation of α1-adrenoceptors on VSMCs, and it is well recognised that WAT responds to sympathetic nerve-derived catecholamines which play a vital role in lipolysis. Sympathetic denervation of WAT pads *in vivo* will increase lipid deposits (40, 213, 389, 573). Furthermore, electrical activation of sympathetic nerves in epididymal WAT *in vitro* will increase lipolysis, and the process can be attenuated by inhibition of β-adrenoceptors (134).

NE turnover is often used as a measure of sympathetic activity, and using this method it has been shown that under certain stimulatory conditions, such as food deprivation and cold exposure, sympathetic activity varies between anatomical locations of adipose tissue depots and morphology i.e. white or brown (86, 378, 499). Electrophysiological recordings have confirmed the activity of sympathetic nerves in both BAT and WAT (170, 501). A reduced level of glucose reduces sympathetic activity in BAT, therefore reducing thermogenesis and ATP utilization in BAT (170). In contrast, in WAT reduced glucose increases sympathetic

activity, therefore increasing lipolysis and the release of FFAs to be metabolised into ATP (501). These electrophysiological studies indicating a role for sympathetic innervation of adipose tissue are reinforced by radioligand binding studies. Radioligand uptake into human BAT is reduced following surgical disruption of the sympathetic nerve supply to the neck and thorax (232). Similar studies demonstrate a reduction in radioligand uptake into the same BAT regions using β-blockers to pharmacologically block sympathetic nerve activity (627). These studies indicate that sympathetic innervation of adipose tissue may be vital for uptake of various substrates.

The innervation of perivascular BAT has been well characterised histologically (107, 741). Early fluorescence histochemical studies reported nerve fibres which appear to make direct contact with BAT adipocytes (741), and electron microscopy studies have revealed catecholaminergic nerve plexuses in the extracellular space between brown adipocytes isolated from human perirenal BAT (400). Moreover, studies using tyrosine hydroxylase, a marker for catecholamine synthesis, demonstrated that autonomic nerves present in BAT are sympathetic nerves (107). However, the neuropeptide tyrosine, a marker for vascular sympathetic nerves, was negative in the BAT, suggesting that BAT and the vessels it surrounds are innervated by two separate populations of sympathetic nerves.

Extensive studies of the distribution of sympathetic nerve fibres within rat mesenteric, epididymis, omentum, and subcutaneous WAT have been conducted (621). This study found using fluorescence histochemistry that the arteries, arterioles, and capillaries were richly innervated by sympathetic nerves, particularly the mesenteric PVAT and epididymal fat. Similarly, we have demonstrated the strong expression of the sympathetic nerve marker dopamine hydroxylase in mouse mesenteric PVAT (595). However, electron microscopy studies in the Slavin & Ballard study (621) concluded that only 2-3% of adipocytes are innervated by the sympathetic nerves. In a conflicting study, confocal and fluorescent microscopy suggested that there is a high degree of direct contact between catecholaminergic nerves and rat epididymal, perirenal, mesenteric, and inguinal WAT (562). It is likely that the tight packing of adipocytes makes it difficult to visualise direct contact. Further study is required to determine definitively if autonomic nerves are directly innervating the adipocytes and influencing anti-contractile function.

Most tissues exhibit dual innervation by both branches of the autonomic nervous system; however, the evidence suggests that PVAT is predominantly innervated by sympathetic nerve fibres. Using immunohistochemical labelling in rodent retroperitoneal and epididymal WAT for adrenergic, cholinergic, nitrergic, and peptidergic nerves, Giordano *et al*. (237) concluded that 97-98% nerves supplying the adipose tissue are sympathetic nerves.

Viral transneuronal retrograde and anterograde tract tracers such as the pseudorabies virus and the H129 strain of the herpes-simplex virus-1 respectively, have been used to delineate the source of sympathetic nerve fibres in WAT (40, 499, 630). In anesthetised hamsters, WAT depots were exposed (epididymal and inguinal) and the virus was injected directly to infect the neurons. Immunocytochemistry revealed the pattern of neural infection, demonstrating that the nerves originate from the general CNS sympathetic outflow. They begin in the forebrain, including several hypothalamic regions (e.g. arcuate nucleus, ventral premammillary nucleus, dorsal hypothalamic area, dorsomedial nucleus of the hypothalamus and the suprachiasmatic nuclei) and portions of the midbrain (particularly at the level of the facial nerve, and in dorsal and ventral regions of the central grey) (40). Next they travel through the brain stem (nucleus of the solitary tract, lateral and rostroventrolateral reticular nuclei, and C1 region), down the spinal cord (intermediolateral cell group and central autonomic nucleus), and into the fat deposits. However, again it is unclear if the nerves are innervating the adipocytes or the vasculature.

Studies of the functional role for sympathetic nerves in the PVAT anti-contractile effect indicate that involvement may vary with anatomical location or adipocyte phenotype. In conductance arteries, EFS of PVAT to activate sympathetic nerve fibres has effects

dependent upon location (682). Electrical stimulation of the superior mesenteric artery demonstrated that PVAT exerts an anti-contractile effect on the vessel, whilst stimulation of the larger abdominal aorta exhibited a pro-contractile effect of PVAT. Aside from the obvious difference in vessel sizes, the differences here could also be attributed in part to the adipose phenotype; the mesenteric PVAT comprises white adipocytes, whereas abdominal aortic PVAT does contain some brown adipocytes. Likewise, recently we have shown that in the WAT of small mesenteric resistance arteries, EFS induces an anti-contractile effect which is dependent upon sympathetic nerve activity (595). However, in a conflicting study using the superior mesenteric artery a pro-contractile effect of WAT was evident (228). It is worth noting that these studies used distinctly different stimulation protocols; we used 20V (595), and Gao *et al*. (228) used 150V. This may suggest that increased stimulation may alter PVAT function. Interestingly, in the Torok *et al.* (682) study the EFS-induced anti-contractile effect in the superior mesenteric artery was absent in spontaneously hypertensive rats, indicating a role for PVAT dysfunction in hypertension.

The aforementioned tract tracer studies also identified sensory nerve afferents in adipose tissue (51, 630). It is likely that the function of these nerves is to sense products of catecholamine-induced lipolysis, and feedback on the CNS in order to modulate lipolysis. However, recently it has been suggested that sensory nerves in adipose tissue may be crucial in vasodilation (4). In pre-constricted arteries, EFS elicited PVAT dependent vasorelaxation in mesenteric arteries. Abu Bakar *et al*. (4) attributed these effects to calcitonin gene-related peptide, secretion of which was increased from mesenteric adipose tissue by the sensory nerve activator capsaicin. In a separate study, sensory nerves in adipose tissue have been shown to be leptin sensitive, and adipocyte-derived leptin increases sensory nerve activity (481). In obesity, circulating leptin is elevated and many obese individuals exhibit leptin insensitivity (525). This may suggest that leptin insensitivity in obesity may result in a loss of this newly discovered PVAT-dependent vasodilatory function of sensory nerves. However, this has yet to be investigated.

6.2. The adrenergic system in PVAT

Evidence suggests that adipocytes contain a complete adrenergic system including adrenergic receptors, transporters, and metabolic enzymes. This system may play a vital role in the vasocontractile functions of PVAT.

As described above, WAT responds to sympathetic nerve-derived catecholamines to induce lipolysis and this process is regulated through adipocyte β_3-adrenoceptors (562, 570) (Figure 3). In addition, thermogenesis in BAT can be stimulated using β_3-adrenoceptor agonists (139). Originally β_3-adrenoceptors, seven transmembrane domain G-protein coupled receptors, were thought only to play a role in the metabolic functions of adipocytes (153); however, *in vivo* studies in rodents and dogs have demonstrated that CL-316,243, a specific β_3-adrenoceptor agonist, induces hypotension (614). *In vitro*, this agonist has been shown to induce PVAT-dependent relaxations in pre-constricted mesenteric resistance arteries (84). The agonist had no effect on vessels with PVAT removed. Studies using other, less specific β_3-adrenoceptor agonists *in vitro*, induced vasorelaxation of the rat aorta and carotid, which could be blocked using the β_3-adrenoceptor antagonist SR59230A, but not $\beta_{1/2}$-adrenoceptor antagonists (426, 515, 688). In the aorta this effect was endothelium and NO –dependent. These studies suggest that functional β_3-adrenoceptors are present in the endothelium of larger, conductive vessels; however, these larger vessels are not important in modulating blood pressure. In endothelium-denuded mesenteric resistance arteries, electrophysiological studies using the agonist *in vitro* reveal PVAT-dependent hyperpolarizations of VSMC (734). Interestingly, these electrophysiological effects of the β_3-adrenoceptor agonist are absent in adiponectin deficient-mice, which may suggest that in health, activation of β_3-adrenoceptors will stimulate adiponectin secretion from adipocytes. To confirm these findings, we have recently used pharmacological manipulation of β_3-adrenoceptors in contractile studies of mesenteric resistance arteries with and without PVAT (100, 595). We demonstrated that adipocyte β_3-adrenoceptors do play a vital role in the PVAT anti-contractile effect, and

activation of these receptors by sympathetic nerve-derived NE triggers the release of the vasodilator adiponectin (Figure 3).

Studies of the molecular structure of β_3-adrenoceptors show that the rodent and human receptors show high homology (79% identical) (153). However, expression of β_3-adrenoceptor mRNA in human adipocytes is low as compared with rodent adipocytes (152, 697). Whilst mRNA expression may be low, histological studies have confirmed the presence of β_3-adrenoceptors in lean and obese human WAT (147). β_3-adrenoceptor agonists stimulate lipolysis in cultured human WAT (608), confirming that these receptors play a functional role despite low mRNA expression.

In addition to β_3-adrenoceptors, all other adrenoceptor subtypes ($\alpha_{1/2}$, $\beta_{1/2}$) are present on adipose tissue (380) (Figure 3). The α-adrenoceptors are inhibitory; coupled negatively to adenylyl cyclase, and the β-adrenoceptors are stimulatory; coupled positively to adenylyl cyclase. The expression profiles with regard to white and brown adipocytes vary slightly, whilst white adipocytes express more α_1- than α_2-adrenoceptors, the opposite is true for brown adipocytes (380). All adipocyte adrenoceptors play a role in lipolysis; α-adrenoceptors inhibit lipolysis, β-adrenoceptors stimulate lipolysis, as well as playing a number of other roles including modulating thermogenesis and glycogenesis (reviewed by Lafontan & Berlan (380)).

Receptors for some non-adrenergic, non-cholinergic neurotransmitters have been found on WAT, in particular purinergic and neuropeptide-Y (NPY) receptors (92). Adipogenesis can be stimulated by NPY, contributing to increased fat deposits, particularly in the abdomen, and lipolysis can be regulated by purinergic receptors. It is possible that these receptors play a role in the release of a number of vasoactive adipokines, and it has already been shown that purinergic receptors stimulate leptin secretion from adipocytes (92), which as discussed plays a vital role in satiety signalling. Conversely, NPY activity increases food intake (261), and in obesity chronic elevation of NPY will cause a reduction in leptin signalling, therefore further increasing food intake (464).

There is evidence of catecholamine uptake and metabolism within adipocytes. This system was first identified by Pizzinat *et al.* (540), who confirmed the presence of monoamine oxidases A and B; the enzymes which catalyse catecholamine metabolism. In mammary adipose, monoamine oxidase A was found to be the most active; therefore it is likely to be the predominant isozyme in degrading NE within adipocytes. Using high performance liquid chromatography NE uptake into PVAT adipocytes can be measured (34). In the presence of corticosterone, an inhibitor of organic cation transporter (OCT) 3, NE uptake was significantly reduced. We have investigated the functional role of OCT3 in PVAT, and found that one mechanism behind PVAT's anti-contractile function is the sequestering of NE via OCT3 into adipocytes (a "sponging" effect), therefore reducing the amount of NE which reaches the blood vessel to exert contraction (595) (Figure 3). More recently, Ahmad *et al.* found that adipocytes from PVAT express vesicular monoamine transporters, and are therefore able to store this NE (15). Interestingly, retroperitoneal adipocytes (a VAT depot) did not express vesicular monoamine transporters, indicating that PVAT may be unique in its ability to store catecholamines in comparison to other adipose tissue depots.

OCT3 plays a predominant role in extraneuronal transport of NE, among other substrates, into the periphery (uptake$_2$) (247). OCT3 belongs to solute carrier family SLC22A, alongside OCT1 and OCT2 (296, 316). Each of these transporters plays an important role in neurotransmitter uptake into the periphery, as well as a number of drugs. Each transporter varies slightly in its endogenous substrates. In terms of classical neurotransmitters, OCT1 will transport 5HT, whereas OCT2 is responsible for the transport of dopamine. OCT3 however, will transport both of these aforementioned transmitters, as well as NE (18). In 2006, an extensive study was carried out on the expression of OCT1, OCT2, and OCT3 in fourteen tissues taken from mice (21). Whilst OCT1 mRNA and OCT2 mRNA were only found to be expressed in the liver and kidney, indicating that these transporters are likely to

be important in excretion, low levels of OCT3 mRNA were found in all fourteen tissues including the heart, lung, and small and large intestines, confirming this transporter to be much more widespread in the periphery. Similar results have also been reported in the rat (340) and human (271, 711). There are no reports of expression of OCT1 or 2 being expressed in adipose tissue; however, OCT3 has been shown to be highly expressed in BAT (82), and we have confirmed its expression in the WAT surrounding mouse mesenteric arteries (595).

Some studies have indicated the presence of the norepinephrine transporter (NET) in BAT (354, 465). King *et al*., (354) indicated that cold exposure of isolated rat BAT significantly decreased the uptake capacity of NET in BAT after 3 days, with no change in affinity, indicating that the transporters may be downregulated during cold exposure. Mirbolooki *et al*. (465) investigated the potential of targeting BAT metabolism in obesity by testing the effects of NET inhibitor atomoxetine *in vivo* on fasted and unfasted rats. In fasted animals, atomoxetine significantly reduced radioligand uptake, and BAT temperature was increased, alongside a reduction in glucose. By using a β_3-adrenoceptor inhibitor, Mirbolookie *et al.* (465) confirmed that as a result of reduced NE uptake, a greater concentration of NE was present in the synapse, which increased activation of β_3-adrenoceptors on the adipocytes; increasing BAT metabolism. There has been only one study of NET in WAT, conducted by Ayala-Lopez *et al*. (34). In this study, a pro-contractile effect of PVAT in response to tyramine was demonstrated in the superior mesenteric artery, which was attenuated by NET inhibitors. Interestingly, western blotting revealed that NET is present in PVAT as a whole, but not in the isolated adipocytes. This may indicate that the beneficial effects of NET inhibition on BAT metabolism may be a result of NET expression in other cells types, and not on the adipocyte.

Studies have indicated that adipocytes may also be a source of NE. The use of tyramine as a sympathomimetic demonstrated that both aortic BAT and superior mesenteric WAT release functional NE, as well as 5HT, and dopamine (35). Similarly, stress in rats induced by repeated immobilization increased production of NE in various fat depots including both BAT and WAT depots (708). In both of these studies, transport of these transmitters into vesicles was dependent on vesicular monoamine transporters (35, 708). Removal of the celiac ganglion had no effect on their production, indicating that the production of these neurotransmitters was independent of sympathetic nerve firing (35). It is possible that the adipose tissue-derived dopamine and 5HT may be a source of the pro-contractile effects of PVAT seen in some vascular beds. However, caution is required in attributing the production of these transmitters to adipocytes, as PVAT comprises of a number of cell types including an immune cell population (11, 246). Macrophages, eosinophils and lymphocytes alone have been shown to produce NE (318, 498, 744); therefore, it is possible that other cell types play a role in the production of these chemical messengers.

As indicated above, adipose tissue appears to be a source of 5HT, and adipose tissue does express the 5HT transporter (SERT) (34, 651). In addition, treatment with 5HT *in vivo* in female rats has been shown to induce weight loss, via increased secretion of leptin (651). Similarly, in 5HT knockout rats, female rats demonstrate significant increases in adiposity, whereas male rats did not gain weight (283). Surprisingly, this increase in adiposity was not accompanied by hyperglycemia or hyperinsulinemia, even when challenged with a high fat diet. However, in SERT knockout mice, obesity was accompanied by glucose intolerance and insulin resistance (792), indicating a vital species difference. The importance of these findings lies in the prevalence of obesity in depressed patients, as it is well established that reduced expression of SERT in humans and animals is indicated in depression (88, 726).

The ability of adipocytes to produce dopamine is interesting when the role of dopamine in eating behaviour is considered. Acute increases in dopamine levels have been indicated in “rewarding” behaviours, such as eating palatable foods (231, 275). Dopamine feeds back in the nucleus accumbens, where it mediates reinforcement mechanisms i.e. seeking more reward/food. However, chronic over-eating results in adaptations that reduce dopamine

release, and instead of a decrease in consumption, it leads to an increase in reward-seeking behaviour in an attempt to increase dopamine, commencing a vicious circle of compulsive over-eating (231). The specific role of adipocyte-derived dopamine in obesity and compulsive over-eating has not been investigated.

6.3. Autonomic dysfunction in obesity

A large number of studies agree that the SNS becomes pathologically overactive in obesity (432, 622) due to an imbalance in the hypothalamic-pituitary axis (123). The mechanisms contributing to this imbalance have been reviewed in depth (398, 622), and may include changes in the secretion of adipokines such as leptin and adiponectin from adipocytes. Typically, leptin has a stimulatory effect on SNS activity, and secretion is increased in obesity, whereas adiponectin has an inhibitory effect on SNS activity, but is reduced in obesity.

Measurement of SNS activity in skeletal muscle is commonly used, and increased nerve activity has been shown to correlate with increased body mass index and percentage of body fat (244, 315, 597). In cardiac and renal nerves, increased sympathetic nerve activity is observed in obese hypertensive patients (577). Moreover, the degree of over activity appears to vary with the location of increased adiposity, and abdominal and visceral fat deposits are associated with the greatest increases in nerve activity (678). Interestingly, sympathetic over activity in obesity also results in reduced sympathetic responsiveness to other stimuli such as cold exposure.

What is most concerning is the early onset of sympathetic over activity. After only 12 days of high fat feeding in rats, lumbar sympathetic nerve activity is elevated (478); independent of weight gain. Studies in non-obese humans reveal a similar increase in SNS activity with small increases in body weight (143). Prolonged SNS activity may result in desensitisation of adrenoceptors and loss of function. For example, β-adrenoceptors in cardiac tissue become desensitised due to SNS over activity, leading to heart failure (542). Similarly, SNS over activity will result in hypertension (467, 679), which can be reduced in a dog model of obesity by renal sympathetic denervation (329). This is of particular relevance to adipocyte β_3-adrenoceptors in PVAT, as desensitization of these receptors in obesity will result in reduced adiponectin release.

As discussed previously, sympathetic nerve-derived catecholamines play a vital role in lipolysis, and this process is impaired in obesity (387), particularly in SAT and skeletal muscle adipose depots (277, 508, 566). As a result, the enhanced need for energy storage in obesity will result in an increase in adipocyte size in all adipose depots including PVAT, resulting in hypoxia and inflammation (discussed further below). One proposed mechanism of impaired lipolysis is a reduction in the expression of adipocyte β_2-adrenoceptors on the adipocyte membrane (50, 311, 312), possibly due to desensitization caused by autonomic over-activity. The specific effects of altered lipolysis in obesity on PVAT adipocytes have not been studied.

Whilst catecholamine-induced lipolysis is impaired in SAT, basal lipolysis is increased (565). The inflammatory cytokines TNFα and IL-6 have been shown to stimulate lipolysis (385, 689), and adiponectin has an inhibitory effect on basal lipolysis (727). Therefore, the increase in inflammatory cytokines and reduction in circulating adiponectin in obesity are likely to contribute to increased basal lipolysis. More importantly, catecholamine-induced lipolysis in VAT is increased (30). The resulting increase in serum FFAs will increase the risk of developing T2D (361, 381). In particular, elevated FFAs contribute to increased adiposity in skeletal muscle, which is also associated with the development of insulin resistance. Whilst the specific effects of FFAs on adiposity in PVAT have not yet been studied, both PVAT and skeletal muscle adipose contains white adipocytes; therefore, we would predict a similar effect of FFAs in PVAT. Increased circulating leptin in obesity appears to be another contributor to increased basal lipolysis, as the application of leptin to *ob/ob* adipocytes

induces lipolysis (217, 416). It is also worth noting that leptin inhibits the anti-lipolytic effects of insulin (477).

As discussed above, adipocytes express α_2-adrenoceptors which when activated exert an inhibitory effect on lipolysis (380). In human obesity, expression of α_2-adrenoceptors is increased (444, 445). To examine the importance of this change in expression, α_2-adrenoceptors were over-expressed in β_3-adrenoceptor deficient mice (700). When fed a high fat diet, the result of this transgenic combination was an obese mouse, with no insulin resistance, and most surprisingly; the increased adiposity was purely as a result of adipocyte hyperplasia, and no hypertrophy was observed. Previously, activation of α_2-adrenoceptors using the selective agonist UK14304 has been shown to increase proliferation of pre-adipocyte cell-lines *in situ*, via release of lysophosphatidic acid (701). Together, these studies suggest that the increased expression of α_2-adrenoceptors in obesity may play a role in the recruitment of adipocyte precursors, leading to hyperplasia.

It is uncertain which comes first in obesity; reduced catecholamine-induced lipolysis, or increased adiposity (361). In human obese males impaired catecholamine-induced lipolysis persists following diet-induced weight loss (67). In addition, obese children demonstrate resistance to catecholamine-induced lipolysis (79). More importantly, in a study by Hellström *et al.* (272), lipolysis was studied in lean subjects with and without obese parents, and it was found that the lean off-spring of obese parents were resistant to catecholamine-induced lipolysis. Collectively these data indicate that reduced catecholamine-induced lipolysis occurs early in obesity, which fits with the rapid onset of sympathetic over activity following a short period of high fat feeding in rats discussed above (478). However, it is possible that impaired catecholamine-induced lipolysis acts as a compensatory mechanism to limit FFA release. Whilst circulating FFAs are increased, the degree to which they are increased is less than would be expected if all fat depots were releasing their FFA stores (76, 304, 310, 599).

7. Immune cells in PVAT

True to the complexities of adipose tissue being an endocrine organ in its own right and its function, type and location being subtly different throughout the body, the immune cell component within these tissues is also diverse and dynamic. The contribution of immune cells to adipose tissue function is so significant, that 'immunometabolism' is a research area within its own right. The close proximity of PVAT to lymphoid organs allows a degree of crosstalk, which means the immune content of PVAT is likely to be rapidly adjusted in response to energy needs and nutrient availability (294) For the purpose of this review, we will focus on the significance of immune cells residing in PVAT and how they may contribute to physiology and pathophysiology.

Immune cells form part of the stromal vascular fraction which communicates with adipocytes to regulate the release of the vasoactive substances, as discussed previously, leading to a host of physiological effects including energy metabolism and vascular reactivity. PVAT contains cells of the innate and adaptive immune systems (451). Macrophages, neutrophils, dendritic cells, eosinophils, natural killer cells, innate lymphoid cells, and B and T cells have all been identified within adipose tissue (Figure 4). Although numbers of these vary, nearly all have been shown to be affected by the metabolic state of the host and will be discussed below. Through understanding what resident immune cells exist in adipose tissue and how populations respond to the metabolic challenge of obesity, we can understand how immune cells can contribute to vascular dysfunction resulting from obesity and the associated cardiovascular risk.

7.1. Macrophages

Macrophages are considered to be late-responders in the dynamic immune cell changes which occur in response to high fat diet (502) and are the most studied of the adipose-derived immune populations. They represent the largest percentage of immune cells within the stromal fraction, and are both increased in number (730, 760) and activated/polarised in obesity, through their response to other immune populations and in response to autocrine signals (476). It is likely that their role is adipose tissue depot dependent (370, 480) and is mediated through direct communication with adipocytes and subsequent adipokine release, as macrophage-gene expression in other tissues is little changed in response to diet (760).

Macrophages demonstrate significant plasticity and their physiology adjusts to environmental cues, as well as innate and adaptive immune responses. Despite the M1/M2 dichotomy being broadly accepted, it is noteworthy that clear definition of macrophage populations has become increasingly difficult (476) and new markers of macrophages are still being identified (302). With this in mind, macrophage polarization in itself is thought to be a vital part of the pro-inflammatory switch in response to diet, and increased number of M1 macrophages has been linked with the development of insulin resistance (516) and hypertension (268, 493). On the other hand, M2 macrophages are important in adipose tissue homeostasis through their role in adipocyte turnover (201), lipid buffering (366) and as catecholamine stores which can increase sympathetic drive within PVAT (498).

The complex nature of hypertension often makes it difficult to determine how macrophages in PVAT vary between obesity and hypertension, as the two often co-exist. However, studies in the spontaneously hypertensive rat demonstrate that circulating macrophages were increased, and treatments which reduced macrophage numbers had anti-hypertensive effects (407). Comparable to obesity, circulating monocyte-related pro-inflammatory markers are significantly elevated in hypertensive lean patients (528). Also, macrophage accumulation has been linked to target end organ damage resulting from hypertension (289). Activation of the Ang II receptor on macrophages suppresses their M1 polarization as a mechanism of damage limitation, and pro-inflammatory macrophages are known to contribute to RAAS-dependent hypertension (reviewed by Harwani (267)).

The role of macrophages in mediating the altered PVAT function is demonstrated by studies in which mice with depleted macrophages are unable to respond to inflammatory stimuli to the same extent as their wild-type counterparts (742). The release of pro-inflammatory cytokines from M1 macrophages impacts on vasculature through their effects on endothelial and VSMCs. Resistance artery endothelial dysfunction has been shown to result from the iNOS activity of PVAT derived–M1 macrophages and its reduction of H_2S bioavailability (106). Macrophage derived interleukin-17 has been proposed to contribute to vascular remodelling (797). Furthermore, resistin, which is predominantly expressed by macrophages in human PVAT (533) shows a positive correlation between plasma levels and blood pressure in subjects with and without T2D (666, 680), as well as being linked to other complications of obesity as discussed in section 5.12. There remains a wealth of avenues to exploit with regards to macrophage populations, yet due to their late-responder role it may be more useful to consider how they respond to other immune populations if we are to fully optimise their therapeutic potential.

7.2. Neutrophils

Neutrophils are a poorly understood population of cells with regard to adipose tissue and vascular function. These early responders in the immune response have been shown to increase in response to high fat feeding; they comprise 1% of the stromal fraction in lean, which increases to 2% in obese phenotypes, with most evidence indicating that this expansion is transient (193). Neutrophil numbers also decrease following bariatric surgery (58). The contribution made to inflammation in adipose tissue appears to be depot specific, with there being more of a contribution to the inflammatory response in VAT than SAT. Neutrophils are considered as key to the early polarization of macrophages in response to high fat feeding through stimulating CCL2 and TNFα secretion. Furthermore, elastase secretion by neutrophils was documented to contribute to glucose intolerance and insulin

resistance via insulin receptor substrate-1 downregulation (667). However, the potential of neutrophils as direct regulators of PVAT function is relatively underexplored despite interesting observations in both human and animal studies. Observations that neutrophil accumulation in the microvasculature correlates to blood pressure in obese females (347, 618), alongside evidence that neutrophil depletion in hypertensive models slows disease progression in mice through visfatin and IL-8 mechanisms may implicate a more significant role for neutrophils than initially thought (308). Our own work has identified PVAT-derived NO as a key modulator of vascular function (99, 743), and as increased numbers of circulating neutrophils have been shown to reduce NO (448), it would be interesting to explore this early response to a high fat diet further.

7.3. Dendritic cells

Dendritic cells (DCs) are sub-classified into myeloid or conventional DCs (cDCs) and plasmacytoid DCs (pDCs), and act as antigen presenting cells throughout the body (644). Similar to neutrophils, DCs exist in negligible numbers in the lean phenotype, yet despite population increases in some adipose sites to levels comparable to macrophages in response to high fat diet (121, 639), little is known regarding their contribution to adipose tissue physiology. It is likely that this area of immunometabolism has been confounded by difficulties around the refined identification of DCs from macrophages as they express similar markers; traditionally $F4/80^{+}CD11b^{+}$ have been used to defined adipose tissue macrophages (366), yet this does not exclude other leukocytes. This is highlighted in a study which showed that CD11c+ cell induction correlates with insulin resistance (61); however, as CD11b and F4/80 expression overlaps with macrophages, it is difficult to delineate the direct contribution made by DCs (121). The study which seeks to more intuitively define immune cells suggests that DCs play an independent role in mediating adipose function due to adipose tissue DC pathways relating to antigen presentation and cytokine signalling remaining elevated independently of macrophage pathways (121). Adipose tissue-derived chemerin acts through three receptors, CMKLR1 (also known as ChemR23), chemokine receptor-like 2 (CCRL2), and G protein-coupled receptor 1 (GPR1) (175). CMKLR1 is expressed in macrophages, DCs, adipocytes and VSMCs; pDCs respond to the chemoattractant signal of chemerin (175, 179) and interestingly, activation of its CMKLR1 has been shown to increase vascular tone (341, 731), resulting in hypertension (795). The accumulation of DCs in alveolar lesions of human and experimental pulmonary arterial hypertension (536) may implicate the recruitment of PVAT DCs to affect changes to the vasculature. A very recent study has looked at these cells in the *db/db* rat, and as predicted, the increased population of DCs in PVAT was linked to an impairment of the anti-contractile activity in PVAT (552). Despite this early evidence, the direct contributory role of these cells is yet to be fully explored, and early evidence may suggest that it is the interaction with macrophages which is important to down-stream changes in PVAT function and vascular tone.

7.4. Mast cells

Mast cell populations in adipose tissue are shown to increase in obesity, although to a lesser extent than macrophages. Their potential role in contributing to the vascular effects of adipose tissue is implicated by their close association with the vasculature in both human and animal adipose (408). Furthermore, the study demonstrated that pharmacological mast cell stabilizers reduced diet-induced body weight gain and enhanced glucose tolerance. There are few studies which have examined mast cells in the vasculature; however, with regard to hypertension specifically, mast cells in cardiac hypertrophy have been identified (420). Accumulation of these cells around the pulmonary vasculature has been observed in patients with pulmonary hypertension (762). Mast cell degranulation has been shown to increase peripheral resistance in placental arteries (102) which may suggest a link with increased numbers in obese PVAT and enhanced vascular tone. Furthermore, they have been implicated in mediating a microvascular response to systemic hypoxia (643). Taken together their modulation of lipolysis, insulin resistance, angiogenesis and oxidative

metabolism (408, 502, 740) earmarks this class of immune cells as interesting, but an under explored target in the field of immunometabolism.

7.5. Eosinophils

Eosinophils are another innate-immune cell type which reside in adipose tissue anchored by integrins. However, unlike other populations, their numbers decrease with high fat feeding (744). The role of eosinophils as potentially critical regulators of metabolic homeostasis is beginning to unfold, alongside a new understanding of the nature of eosinophils is as a collection of subtypes, defined by different markers, morphology, and function. The recent review by Abdala-Valencia *et al.* explores the emerging role of eosinophils in much more detail (1). With regards to PVAT-derived eosinophils and their contribution to vascular physiology, eosinophil-deficient ΔdblGATA-1 mice (783) exhibit elevated peripheral mean arterial pressure and impaired glucose tolerance, both of which can be rescued by intraperitoneal injection of purified exogenous eosinophils (eosinophil reconstitution) (744). Notably, the anti-contractile effect of mesenteric PVAT is also lost in ΔdblGATA-1 mice, and consistent with *in vivo* findings, the anti-contractile effect of PVAT is restored by the reconstitution of eosinophils (744). The role of the eosinophil as an independent regulator of adipose tissue function is controversial; many studies suggest that the interleukin-4 secretion of resident eosinophils sustains M2 polarization, thereby maintaining adipose tissue homeostasis (762). However, our data suggest the pro-relaxant effect of eosinophils was due to their ability to secrete catecholamines which stimulate β_3-adrenoceptors on adipocytes, which in turn induces the release of the vasorelaxant mediators adiponectin and NO (744). Eosinophils are also an abundant source of 15-lypoxygenase which may contribute to function (187). The counterintuitive negative correlation of adipose tissue mass with eosinophil number confounds the understanding of this little appreciated immune cell population, however, true to many physiological systems; it is likely that balance is central to homeostasis.

7.6. T and B cells

The combined populations of B and T cells make up the second largest group of immune cells residing in the adipose tissue after adipose tissue macrophages (739). Simply, obesity is associated with increased numbers of total T (753) and B cells (739), however, there are some small subpopulations, such as Tregs, which have been implicated with inhibiting adipose tissue inflammation which are reduced following high fat diet (197). There are three T cell populations which have been identified in adipose, CD8+, Th1 and Tregs (reviewed by Schipper *et al.* (600)). Their expression appears to be depot specific and it is considered that the ratio of populations is key to driving the inflammatory response in response to diet (452) as T regs are associated with increased insulin sensitivity, whereas CD8+ and Th1 populations stimulate macrophage polarization (560) and modulation of oxidative metabolism respectively (740). Several studies have linked T cell populations residing in adipose tissue with hypertension; CD4+ and CD8+ subpopulations express higher levels of pro-inflammatory cytokines (252, 460) which contribute to PVAT dysfunction and increased vascular constriction through changes to the endothelium (736).

B cells are found in low numbers within the adipose tissue and are increased with obesity where it is thought their modulation of other immune cells has implications on metabolic status of adipose tissue. Numbers of B2 cells ordinarily outweigh B1; however, both populations increase shortly after the initiation of a high fat diet. This increase included total B cells, B1a cells, and B2 cells (167). Interestingly, the absence of B cells in a mouse model of obesity protects animals from disease despite weight gain (739). There are no direct studies of B cells and obesity-induced hypertension; however, studies in models of pre-eclampsia have shown that B cell depletion was associated with lower circulating TNFα and ET-1 levels (133). Further to this, B-cells in VAT have been shown to release IL-10, supporting the adipocyte-immune crosstalk in response to diet (14). These pieces of evidence identify an interesting research avenue in the immune-adipose-vascular field.

8. Drivers of inflammation of adipose tissue in obesity

The metabolic status of adipose tissue is the main driver of inflammation suggesting that immune cells can act as invigilators of the adipocyte environment through their recognition (e.g. by toll-like receptors) of molecular signals, including hypoxia, lipids and adipocyte death/stress (Figure 4). When inflammation is present, it has been shown to lead to loss of bioavailability of dilator factors in PVAT, including adiponectin (226, 238, 246).

8.1. Hypoxia

Hypoxia within the tissue has been proposed as an underlying cause of adipose tissue dysfunction, moving the tissue toward a pro-inflammatory phenotype (reviewed by Trayhurn & Wood (685)). The hypertrophic expansion of adipocytes is not accompanied by a similar rate of increase in angiogenesis, which results in some adipocytes being outside the reach of oxygen diffusion from the existing vasculature, leading to areas of hypoxia within the adipose depot (241). The subsequent increase in hypoxia inducible factor-1α (HIF-1α) acts as a 'call to arms' for the early responders in the immune response (130, 257, 414). In theory, stabilization of HIF-1α in hypoxia should promote activation of angiogenesis (284, 532); however, in adipose tissue induction of HIF-1α seems to largely promote inflammation and fibrosis (257).

Piminidazole staining of adipose tissue in animal models of obesity seems to confirm that hypoxia is present, however, direct measures of oxygen tension are less conclusive and furthermore, these studies are yet to be recreated in human participants (280). It is likely that different depots respond differently to levels of oxygen tension. When subjected to hypoxia *in vitro*, the loss of PVAT function in obesity can be replicated in small resistance arteries from mice and rats (246, 742), indicating the importance of hypoxia-induced changes to the PVAT environment. Moreover, this loss of function can be reversed *in vitro* using antioxidants and cytokine antagonists (10, 246, 742). One characteristic of hypoxia in obesity is an increase in expression of pro-inflammatory cytokines such as TNFα and IL-6 (284, 684), and application of antibodies for these cytokines can reverse PVAT dysfunction in hypoxia (246). In addition, TNFα expression is increased in both human and mouse obesity (246, 285, 761), which will increase oxidative stress (140, 793). Furthermore, hypoxia is known to disable the production of NO by eNOS via the oxygen-dependent pathway (423), which aligns with our own findings that NO bioavailability is compromised in obesity (99). The loss of PVAT-derived relaxant function in response to hypoxia appears to be driven by inflammatory mediators as in the absence of macrophages (742) there is no response to experimental hypoxia, indicating the importance of macrophages in the inflammatory process of PVAT. Work from Agabiti-Rosei *et al.* whereby melatonin was exploited for its antioxidant properties, showed improved PVAT function in two different animal models, which was accompanied by decreased oxidative stress and inflammation (8, 9).

8.2. Lipids

Between 20 (461) and 50% (198) of circulating FFAs are a result of spill-over. Lipid spill-over and increased plasma lipid concentration are recognised as a danger signal by the immune system. Despite adipocytes increasing in size to accommodate the effects of over-nutrition, storage capacity is exceeded, resulting in lipid spill-over, ectopic storage and subsequent lipotoxicity (225, 377). How lipid spill-over can impact on vascular function is unclear; however, studies which have identified increases in inflammatory gene expression (406, 687), changes in sympathetic drive (204) and activation of an innate immune response support a contributory role to hypertension (648).

Toll-like receptor (TLR) signalling, which plays an important role in the innate immune response, has linked dietary fatty acids to MetS, and adipocytes have been shown to express a broad panel of TLRs (352). It is beyond the scope of this review to discuss in

detail the role of TLRs in the immune-adipocyte interaction. However, in relation to circulating FFAs, high fat feeding and subsequent elevated lipids have been shown to increase adipose-depot specific expression of TLR2 and TLR4 in the VAT of animal models (352, 479, 631). Up-regulation of TLR expression in obese animals has been linked with downstream NFκB activation, which itself has been associated with impaired vascular function (330). Further mechanisms linking TLR signalling with hypertension include: changes in Ca^{2+} signalling contributing to enhanced contractility, activation of adventitial fibroblasts resulting in ROS and cytokine release, and changes to endothelial signalling (411, 646). These mechanisms have all been proposed as potential pathways by which chronic TLR activation due to lipid spill-over may be linked to hypertension.

Interestingly, circulating FFAs reduce NO production by the endothelium production via protein kinase C dependent activation of NADPH oxidase (297); whether there is a similar impact on adipose-derived NO remains to be elucidated. They have also been documented to impact on adipokine expression including adiponectin, leptin and resistin, directly via transcription factors or indirectly via fatty acid oxidation, synthesis, or storage (165). Therefore, there is potential that vascular dysfunction resulting from lipid spill-over may be a consequence of these changes (350).

8.3. Adipocyte cell death and stress

Obesity is associated with the cell death of adipocytes via apoptosis and/or necrosis (129, 650). This is due to, at least in part, stress signals associated with nutrient overload and ensuing endoplasmic reticulum stress (686). The associated increase in unfolded protein aggregates and trafficking initiates apoptosis if homeostasis within the endoplasmic reticulum is not maintained (6, 791). Dying adipocytes may contribute to the recruitment of immune cells or release adipocyte-associated damage-associated molecular patterns to activate inflammasomes *in situ* (654) but this remains unclear (39, 188).

The presence of multinucleate giant cells has been shown in the adipose tissue of obese humans (129) and animal models (760), indicative of persistent macrophage activation. We have shown that macrophage activation is essential to the loss of the PVAT anti-contractile function in experimental hypoxia (742). As mentioned earlier, there is also an accumulation of macrophages in obese adipose tissue in humans and animal models (10, 11, 99, 730). Two fundamental pathways of apoptosis are activated in adipose tissue; inhibition of adipocyte cell death in Bid (a pro-apoptotic gene) knockout mice is sufficient to protect against development of insulin resistance through protection of adipose tissue from macrophage infiltration (19); however, no data on vascular changes is available. What is clear, is that diet-induced obesity is associated with increased cell death (188), and it is likely that the impact this has on adipose tissue inflammation and subsequent hypertension is depot specific, representative of the true diversity of function and form adipose tissue throughout the body (650).

9. PVAT dysfunction may contribute to development of hypertension

The mechanisms behind obesity-related hypertension are not yet fully understood; however, there are a number of pathways, such as increased SNS activity, RAAS dysfunction, and adipokine dysregulation, which may be involved (11) (Figure 5). It is important to note here that PVAT does surround renal arteries, and in addition to releasing vasodilators, PVAT is a source of NE which will alter renal vascular function (563), and may influence renal control of blood pressure. Currently, there is no direct evidence implicating loss of PVAT function in obesity-related hypertension. In this section, we will discuss the evidence for the role of PVAT in modulation of blood pressure.

9.1. PVAT dysfunction correlates with elevated blood pressure

PVAT inflammation is common to both obese and lean hypertensive mice, and has been implicated in the development of vascular dysfunction (460). In this regard, elevated vascular tone, resulting from PVAT dysfunction as a result of inflammation, would be expected to increase peripheral resistance and thus systemic blood pressure (145, 238, 327, 610) (Figure 5). Notably, obese patients with concomitant hypertension have been found to have elevated peripheral vascular resistance compared with obese non-hypertensive patients (450). These findings suggest that inflammation-induced PVAT dysfunction in obese patients may be responsible for increased peripheral vascular resistance, and thus the establishment of clinical hypertension. Indeed, we have widely reported that loss of healthy PVAT function in obesity is positively correlated with increased blood pressure in rodent models of diet-induced obesity (12, 99, 744). In brief, animals were fed a high fat diet to establish an environmental model of obesity. Vessel segments from their mesenteric beds were assessed and the degree of contraction of their adjacent skeletonised vessel was quantified. We reported a correlation between this derived figure and systemic blood pressure. This meant that as the animals gained weight and lost their PVAT anti-contractile effect, there was an attendant elevation in blood pressure. We have reported a similar correlation between PVAT dysfunction and increased blood pressure in humans (10). This remains the most convincing evidence of a link between weight gain and PVAT function correlating with a rise in blood pressure. Regardless of weight gain, as previously mentioned PVAT anti-contractile function is lost in spontaneously hypertensive rats (682), stressing the importance of PVAT function in blood pressure homeostasis.

9.2. Adipokine dysregulation effects on blood pressure

In section 5, we discussed the roles of various adipokines and their direct effects on the vasculature in detail. As well as contributing to local modulation of vascular tone, these adipokines will have systemic effects via their release into circulation. Here we will briefly summarise the key evidence that dysregulation in adipokine levels may contribute to hypertension. The majority of adipokines discussed in section 5 are vasodilators: adiponectin, leptin, NO, omentin, H_2S, H_2O_2 and PAME. All of these adipokines, with the exception of leptin and H_2O_2 are downregulated in obesity. Adiponectin (595), eNOS (638) and iNOS (504) knockout mice are hypertensive, which is the most convincing evidence that these adipokines are important in modulating blood pressure. Chronic injections of omentin into rats reduces blood pressure (89). In the spontaneously hypertensive rat, production of PAME (395) and H_2S is reduced in adipose tissue (769), and treatment with a H_2S donor improves blood pressure. All of these studies indicate that adiponectin, NO, omentin, PAME, and H_2S help keep blood pressure low, and when their expression is reduced in obesity, this may contribute to development of hypertension (Figure 5). Whilst the vasodilator leptin is increased in obesity, obesity is associated with leptin insensitivity. H_2O_2 is also increased in obesity; however, the cytotoxic effects of H_2O_2 likely overshadow any vasodilator effects.

Visfatin, chemerin, and resistin are all vasoconstrictors, and their expression is increased in obesity. In normal weight human patients, plasma visfatin is elevated in hypertensive subjects and not normotensive subjects (405). Similarly, in human T2D patients, plasma resistin is reduced in normotensive subjects, and increased in hypertensive subjects (666). In mice, chronic chemerin treatment elevates blood pressure (376). These studies indicate that these adipokines are vasopressors, and therefore upregulation in obesity likely contributes to hypertension (Figure 5).

The RAAS system in PVAT will be discussed below; however, it is worth noting here that PVAT is a source of the vasoconstrictor Ang II (288), and release of Ang II from PVAT is increased in spontaneously hypertensive rats (393), indicating a direct role for adipocyte-derived Ang II in hypertension.

9.3. The RAAS within PVAT

In addition to an intrinsic adrenergic system, PVAT contains its own RAAS system, including angiotensin converting enzyme (ACE), angiotensin receptors, and angiotensinogen (AGT) (11), and it is reported that adipocyte-derived AGT may contribute directly to plasma AGT, which modulates blood pressure (442) (Figure 5). In the AGT-deficient hypotensive mouse model (668), when an adipocyte specific promotor is used to drive expression of AGT in adipose tissue, plasma AGT is increased, and the previously low blood pressure in these mice is normalised (442). In addition the mice exhibited increased adiposity, indicating that AGT plays a role in adipose tissue expansion and indeed, in obesity AGT mRNA expression is increased (704). Whereas a positive correlation exists between AGT and BMI in humans, obesity has no effect on the expression of ACE or angiotensin receptors in adipose tissue (234). As previously discussed, TNFα and FFAs are elevated in obesity, and in the Ob1771 pre-adipocyte cell line these components have been shown to increase AGT expression (33, 584).

Importantly in the context of MetS and hyperinsulinemia, some studies have indicated a role for insulin in increasing AGT expression in hepatic cells (668). In adipose tissue, the stimulatory effects of insulin on AGT are less clear, and conflicting. In a streptozotocin (STZ)-induced diabetic rat model, application of insulin increased AGT expression *in vivo* (111). Similarly, in 3T3-L1 cell lines, insulin again increases AGT expression (314). However, in 3T3-F442A and Ob1771 cells, insulin reduced AGT expression (33). Moreover, in isolated cells obese Zucker rats, insulin had no effect on AGT expression.

Eplerenone, an aldosterone receptor antagonist, has been shown to reduce hypertension in a canine model of diet-induced obesity (149). Previously, we have shown that eplerenone rescues hypoxia-induced PVAT dysfunction by reducing macrophage infiltration of PVAT (742). In addition, treatment with eplerenone reduces ROS generation, and increases adiponectin expression in obese adipose tissue (251). Since eplerenone is an aldosterone antagonist, these studies indicate that adipocyte-derived aldosterone, which is elevated in obesity (85), may contribute to the inflammatory environment in obese PVAT.

9.4. PVAT effects on arterial stiffness

PVAT-derived adipokines, in particular adiponectin, leptin and resistin, may be linked to increased vessel stiffness in obesity and hypertension (580) (Figure 5). Abdominal obesity and increased VAT strongly correlate with increased arterial stiffness in the femoral and brachial arteries (649), and increased EAT in lean hypertensive patients was associated with decreased coronary artery compliance (365). These studies indicate that adiposity and adipokines may be closely related with the process of arterial stiffness, which includes accumulation of collagen and elastin, and calcification (388, 691).

As previously discussed, adiponectin exerts protective effects on the vasculature by increasing eNOS activation (7, 758); however, its protective role in vascular stiffness does not end there. Adiponectin has been shown to suppress VSMC proliferation and migration and prevents vascular stenosis (443), which may suggest interactions with collagen. Therefore, reduced plasma adiponectin in obesity and hypertension may contribute to arterial stiffness, and adiponectin does have a negative correlation with arterial stiffness in hypertensive patients (694, 695).

Similarly, increased leptin (which occurs in obesity, resulting in leptin insensitivity) is positively associated with increased arterial stiffness (441, 737) and leptin deficient *ob/ob* mice exhibit reduced arterial compliance (619). In isolated VSMCs from rat, treatment with leptin enhanced expression of a number of extracellular matrix proteins such as collagen I and fibronectin (441), which may contribute to remodelling and stiffness.

PVAT-derived resistin is secreted from both adipocytes and macrophages (533, 647), therefore unsurprisingly, resistin is increased in obesity, and is positively correlated with arterial stiffness (772). Resistin plays a substantial pro-inflammatory role and is associated

with endothelial dysfunction in atherosclerosis through its associations with vascular adhesion molecule-1, ICAM-1, and ET-1 (333). The links between resistin and arterial compliance have not been fully explored, but it is likely that its pro-inflammatory role contributes significantly.

10. The role of PVAT in the pathophysiology of diabetes

PVAT has been proposed to regulate glucose uptake, based on several bodies of indirect evidence. In this context, several relevant depots of PVAT with specialized functions are intramuscular, mesenteric, pancreatic and periaortic BAT (Figure 6a). These PVAT depots regulate important determinants of insulin resistance and T2D: muscle perfusion, liver inflammation, insulin secretion and basal metabolic rate. In the next section we will discuss the relationship between PVAT and these traits one by one.

10.1. Regulation of muscle insulin sensitivity by perivascular adipose tissue

Resistance to insulin-stimulated whole body glucose disposal is a strong risk factor for T2D (454) and a key step in its pathogenesis (77). While insulin stimulates glucose uptake in multiple tissues, the majority of insulin-stimulated glucose disposal takes place in muscle (5).

In 2005, one of us proposed that perivascular adipose tissue in muscle contributes to regulation of muscle insulin sensitivity and causes insulin resistance, i.e. reduced insulin-stimulated glucose uptake (786). This hypothesis was based on correlations between insulin resistance and accumulation of intramuscular fat, measured by magnetic resonance imaging as intramuscular fat (620) or by computed tomography as intra- and intermuscular adipose tissue (IMAT) (462). Accumulation of IMAT independently increases the risk of incident diabetes, demonstrating its relevance for glucose metabolism (462).

Examining a variety of muscles including the cremaster, gracilis and vastus lateralis muscles, we observed that IMAT is in large part PVAT situated around A1 and A2 arterioles at the proximal end of the muscle microcirculation (455, 786). In healthy human muscle the exact anatomical location is not as clearly defined because of the limited availability of healthy muscle specimens, but both IMAT and PVAT are situated around the larger arterioles similarly to other mammals (457).

The endocrine and paracrine effects of adipose tissue have been recognized since the demonstration that targeted reduction of glucose uptake in adipocytes causes muscle insulin resistance (3). Moreover, adipose tissue inflammation, commonly observed in obesity (285) reduces muscle glucose uptake (279, 699).

Adipose tissue-dependent regulation of muscle insulin sensitivity is mediated by both impairment of glucose uptake into myocytes and reduction of delivery of insulin and glucose to myocytes (349). The latter is a function of the muscle microcirculation, a well-known physiological regulator of muscle metabolism and function during exercise. In general, microvascular properties that determine extraction of blood constituents are the density of microvessels (546), blood flow (169) and the microvascular blood content or hematocrit (716). In healthy endothelium, insulin has been shown to stimulate all of these microvascular properties, albeit not simultaneously. Within 10-20 minutes, insulin induces vasodilation of muscle resistance arteries (456, 696). Within the same time frame, insulin increases the hematocrit of the muscle microcirculation (171, 716). Prolonged hyperinsulinemia of ~2 hours enhances bulk limb blood flow (47), and eNOS expression within 6-24 hours (202, 371), while it stimulates angiogenesis during exposure of days (180).

Particularly the effects of insulin on microvascular blood volume (MBV) and transendothelial insulin transport are strongly and causally related to whole-body insulin sensitivity (49, 373, 455). In rats fed a high-fat diet, impairment of insulin's (micro)vascular effects precedes metabolic insulin resistance (795). In mice, mimicking this impairment by deletion of

endothelial insulin receptors mildly reduced insulin-stimulated glucose disposal (362, 712), while deletion of insulin receptor substrate 2 (IRS2) in endothelium causes a stronger decrease in whole-body insulin sensitivity (373). This indicates that post receptor insulin signaling in endothelium more strongly contributes to insulin sensitivity than insulin receptor expression or activity.

Insulin's actions within the vessel wall are primarily mediated by the endothelium (178), specifically NO (790) and ET-1 (195). Data from endothelium-specific insulin receptor knockout (VENIRKO) mice have shown that insulin regulates 40-60 percent of eNOS expression and ~50 percent of ET-1 expression in the heart and the aorta (712), showing the importance of this signaling pathway for vascular physiology.

The signaling pathways of insulin-stimulated NO synthesis has been well characterized. In endothelial cells insulin activates the insulin receptor, which upon autophosphorylation binds the insulin receptor substrates 1 and 2, activating phosphatidylinositol 3 kinase (PI3K). Activation of PI3K induces translocation of PKB to the cell membrane, which phosphorylates eNOS at serine 1177/1179 to enhance NO production (156, 373, 789). This signaling pathway of insulin seems to be conserved between different parts of the vasculature, as it has been demonstrated in aortic (720), arteriolar (38) and retinal (544) endothelial cells.

The signaling events controlling insulin-induced ET-1 release have not been characterized as extensively as insulin-stimulated eNOS activation, but involve the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling cascade (178, 543) and are independent from PI3K and PKB (177). This is relevant to perfusion defects in T2D, as impairment of vascular insulin signaling primarily affects the vasodilator branch of insulin signaling (176, 309, 543). In human subjects, this selective vascular insulin resistance is demonstrated by an insulin-stimulated decrease in MBV in subjects with T2D, which has been observed in both skeletal muscle (173) and in the heart (602). Similarly, insulin-stimulated ET-1 release from endothelial cells is preserved in subjects with T2D (194). Inhibition of endothelin activity has been shown to improve glucose disposal in one study (418), but interventions that enhanced muscle perfusion without improving myocellular glucose uptake have largely shown neutral effects on overall insulin sensitivity in T2D (173).

PVAT and its products contribute to this selective impairment of insulin's vasodilator effects in human and experimental insulin resistance and T2D. In isolated muscle resistance arteries of obese human subjects, vasoactive effects of insulin examined in the pressure myograph were similar to those observed in obese Zucker rats, yet only in the presence of adjacent PVAT (456). To explain this, post receptor insulin signaling in both myocytes and endothelial cells is controlled by a host of adipokines secreted by PVAT including FFAs, cytokines and hormones. PVAT-derived, insulin-sensitizing adipokines that enhance muscle MBV include adiponectin and its effector protein AMPK in endothelium (144, 246). PVAT-derived, insulin-desensitizing factors that reduce muscle MBV are inflammatory factors such as tumor necrosis factor alpha (246, 285) as well as FFAs (72).

In addition to effects on insulin delivery to myocytes, PVAT-derived adipokines likely regulate myocellular insulin sensitivity. As previously discussed in section 5.1, in internal mammary arteries from patients with T2D, it has been shown that adiponectin suppresses local production of reactive oxygen species, particularly superoxide production by NADPH oxidase (25). This is relevant to insulin resistance and T2D, as the NADPH oxidase subunit nox2 mediates diet-induced myocellular insulin resistance in mice (633). Both obesity and T2D are associated with systemic oxidative stress (221, 338). As already discussed, Antonopoulos *et al.*, indicated that NADPH oxidase products stimulates upregulation of the adiponectin gene as a protective mechanism against further local NADPH oxidase activity (25). We know that human skeletal muscle PVAT does express adiponectin (Figure 7), but whether expression of adiponectin is different between intramuscular PVAT of healthy and T2D subjects is not known. Finally, IMAT isolated from obese subjects was shown to decrease insulin-stimulated glucose uptake in primary myotubes, with similar potency to VAT (581). Along with this glucoregulatory role of IMAT, it was shown to be more similar in

adipokine secretion to VAT than SAT; secreting more saturated fatty acids and diacylglycerol. Whether the IMAT in this study was PVAT draining into muscle tissue, and whether the glucoregulatory effect was different between lean and obese subjects, is unknown; but, adipose tissue in close proximity to muscle is clearly capable of regulating myocellular insulin sensitivity.

In summary, adiponectin from intramuscular PVAT contributes to control of insulin-dependent muscle perfusion and of insulin-stimulated glucose uptake in myocytes. In experimental T2D, this control is impaired by local inflammation, providing targets for improvement of muscle insulin sensitivity in T2D.

10.2. Mesenteric PVAT and liver metabolism

Abdominal obesity, or accumulation of VAT, is commonly associated with insulin resistance and T2D. These associations have been explained by the portal hypothesis, which states that products of intra-abdominal adipose tissue drain into the portal circulation, triggering liver inflammation, liver insulin resistance and fasting hyperglycemia (57). This hypothesis has been put forward after elegant studies showing that fatty acid infusion into the portal vein reduced liver and whole-body insulin sensitivity (191). More recently, the role of intraabdominal adipose tissue was confirmed by studies showing that transplantation of intraabdominal fat of lean mice to the portal vein of obese mice improved insulin sensitivity (363), and that transplantation of intraabdominal fat from obese mice to the portal vein of lean mice decreased it (579). Interestingly the latter effect was critically dependent on the presence of IL-6 in the transplanted adipose tissue, yet was not accompanied by liver inflammation (579). These data suggest that products of intraabdominal adipose tissue regulate liver insulin sensitivity, and that inflammation of intraabdominal adipose is critical to this regulatory effect.

The principal intraabdominal adipose tissue depots draining into the portal circulation are omental and mesenteric adipose tissue (300). Mesenteric adipose tissue is predominantly perivascular, especially in lean individuals and animal models (Figure 6b). Mesenteric PVAT is the most inflammation-prone adipose tissue depot (742), and growth and low-grade inflammation of mesenteric adipose tissue has been associated with vascular dysfunction and T2D (57). In the liver, activity of the pro-inflammatory transcription factor NFκB is another early event during development of obesity, and triggers whole-body insulin resistance by enhancing production of cytokines such as TNFα and IL-6 (103).

The exact causes of inflammation of mesenteric PVAT in obesity and T2D are not known, however, in addition to the drivers discussed previously, infiltration of microbiota from the gut is a likely to be another contributor (266). Similar to the transplantation approach taken to test the portal hypothesis described above, exchange of gut microbiota between lean and obese individuals has provided evidence that gut microbiota regulate glucose metabolism. In man, transplantation of gut microbiota from lean to obese individuals can improve glucose metabolism (719), depending on the composition of the microbial transplant and the host of the microbiome (364). In mice, inducing obesity by a high-fat diet reduces epithelial barrier function in the colon, triggering a sequence of infiltration of bacteria via lymphatic vessels into mesenteric adipose tissue and resulting in depot-specific inflammation (382). The relationship between lymphatic transport in the mesentery and mesenteric PVAT inflammation is further supported by evidence that reinforcing the lymphatic endothelial barrier by the adipokine apelin reduces mesenteric PVAT inflammation (594). During high fat diet, the local inflammatory response in mesenteric PVAT is characterized by a shift in immune cells from eosinophilic granulocytes to DCs and neutrophils (207) and increased expression of TNFα and IL-6 (382). In an intriguing recent study, it was demonstrated that specific inhibition of expansion of mesenteric adipose tissue reduces intestinal barrier function and liver fat metabolism (732). The gut microbiome determines mesenteric adipose tissue expansion and inflammation (732), which in turn are critical determinants of risk of

T2D (103, 364). Taken together, these studies suggest continuous interplay between mesenteric adipose tissue, the gut microbiome and the intestinal wall, determining β cell function and liver steatosis.

10.3. Mesenteric adipose tissue and β cell function

The strongest predictor of future T2D in normoglycemic individuals is pancreatic β cell function, i.e. glucose-stimulated insulin secretion (192, 663). VAT is strongly linked to β cell function and risk of T2D, independently from body weight (495). The pancreas contains substantial amounts of adipose tissue even in healthy individuals (273), and both visceral and pancreatic fat relate to β cell function (273). Nevertheless pancreatic fat tissue has not been found to relate to β cell function in all studies (636), indicating that other VAT depots are more relevant to insulin secretion.

The most relevant of these visceral depots is likely to be mesenteric adipose tissue, a recently recognized separate organ (132) that is anatomically connected to the pancreas by the superior mesenteric artery (512). In T2D, the decrease in β cell density is most pronounced in the "head" part of the pancreas (723), which is perfused by the superior mesenteric artery (512). In experimental studies, substances administered through the mesenteric artery have been shown to efficiently reach and influence the β cells (664), confirming communication between the mesentery and endocrine pancreas through the mesenteric artery.

The products of mesenteric PVAT influencing β cell function are likely pro- and anti-inflammatory agents, as sterile inflammation is characteristic of islets in T2D (161). The anti-inflammatory C-X-C motif chemokine 10 is produced by mesenteric adipose tissue (182), whereas mesenteric PVAT also produces IL-6 and C-reactive protein (208).

In contrast to insulin-stimulated glucose disposal in muscle, adiponectin plays a minor role in mesenteric-pancreatic communication as the adiponectin gradient across the mesentery is small (182, 208). Similarly, there is little release of TNFα, resistin, and CCL2. Important questions regarding the relationship between mesenteric fat and insulin secretion remain, as β cell function has not yet been evaluated during specific manipulation of mesenteric PVAT.

10.4. Periaortic adipose tissue and resting energy expenditure

Adipose tissue does not only display substantial variation in paracrine and endocrine function and cellular consistency, but also in metabolism, secondary to mitochondrial density and uncoupling. While WAT is anabolic with a low mitochondrial density and metabolic rate, BAT carries a catabolic function and contributes to regulation of body temperature (705). As previously discussed, relatively recently BAT was discovered in adult human subjects, responding to cold exposure (705). Moreover, increasing BAT activity was proposed as a novel avenue for preventing and treating T2D (138, 139).

A relevant and representative BAT depot in adult subjects and experimental models of obesity is thoracic periaortic or paraaortic adipose tissue (AAT), which in contrast to PVAT in the mesentery and leg muscles has a high mitochondrial density and correspondingly high metabolic rate (728). Already half a century ago, it was recognized that AAT produced heat, regulating body temperature and metabolism (661). As such, AAT is a PVAT depot with a morphology and function distinct from PVAT in the abdomen and limbs.

In human obesity and aging, BAT activity is decreased (705). Similarly, decreased BAT activity has been shown around the thoracic aorta in aging human subjects and experimental models of obesity (541). An increased volume of AAT, indicative of decreased metabolic activity, has been observed in subjects with pre-diabetes and T2D (771), and in the Framingham study volumes of AAT were found to be strongly related to VAT as well as

fasting plasma glucose (396). The former relationship shows that the properties of thoracic brown PVAT and visceral WAT are related, despite their different metabolic phenotypes.

The mechanisms by which BAT, including AAT, lowers plasma glucose are presently known to be two-fold: metabolism of FFAs and glucose, and secretion of specific adipokines. The metabolism of FFAs by BAT determines glucose metabolism reduces accumulation of triglycerides, or lipotoxicity, muscle and the pancreas (269). For an extensive discussion of regulation of glucose metabolism by BAT, the reader is referred to other reviews (601). Regarding fatty acid metabolism of adipose tissue, it should be noted that this can be decreased ("whitening") (71) or increased ("browning") (56, 463) in many depots. Therefore, the distinction between metabolic phenotypes of adipose tissue is not absolute, but mitochondrial fatty acid metabolism a regulated property of PVAT and other adipose tissue depots.

The metabolism of PVAT is linked to its secretory function (463). BAT produces specific hormones, or "BATokines" which regulate metabolism and function of other organs (discussed further below) (323, 715). These products of BAT include fibroblast growth factor 21 (FGF-21), endocannabinoids and the well-known adipokine adiponectin (715). Boosting adipose tissue metabolism by β-adrenergic agonism increases secretion of adiponectin (463), showing that the metabolic and secretory function of adipose tissue are regulated by shared mechanisms.

11. Reversing PVAT dysfunction: Manipulating the inflammasome and targeting adipokines

The incidence of weight regain in obese individuals following weight loss is high. In a study of 204 patients subjected to dietary interventions for weight loss, the average weight regain after 2 years was 70% (548). More alarmingly, in one bariatric surgery study; a more extreme method of weight loss, approximately 28% of the 64 patients exhibited significant weight regain after 2 years (52). These studies emphasise the importance of discovering novel therapeutics in obesity-related disorders in place of weight loss strategies.

11.1. Sympathetic stimulation

It is widely accepted that the parasympathetic nervous system plays an important role in the inflammatory reflex (reviewed by Pereira & Leite (535)), and there is an emerging body of evidence to suggest that the sympathetic nervous system plays a vital role in immunosuppression. Multiple studies have established that adrenoceptors are present on splenocytes (331, 339, 662), which will respond to sympathetic nerve-derived NE. In addition, splenic sympathetic denervation has been shown to enhance plasma TNFα production in rats when challenged with LPS (339, 439). Similarly, activation of splenic sympathetic nerves using interferon-α will suppress natural killer cell cytotoxicity (331). Sympathetic inputs to other immune organs, including the thymus, bone marrow, and lymph nodes have been well characterised using retrograde tract-tracing techniques (93, 151, 572).

As discussed previously M1 macrophages play a role in obese PVAT dysfunction. Adrenoceptors present on macrophages regulate TNFα production, and inhibition of sympathetic outflow using reserpine will increase LPS-induced TNFα production from macrophages (293, 662). Similarly, sympathetic activation using isoprenaline will increase circulating IL-6 (468). In addition to macrophages, adrenoceptors (particularly β_2-adrenoceptors) have been confirmed to be present on both T and B cell subtypes, both of which are present in obese PVAT (374, 490, 738). These results indicate an intricate connection between sympathetic nerves and the inflammatory reflex, and therefore it is possible that sympathetic dysfunction in obesity may exacerbate the inflammatory response in PVAT, leading to loss of function.

Sympathetic nerve activation by exercise in obesity is associated with beneficial effects on tachycardia, hypertension, and diabetes, as a result of reduced sympathetic over activity in obesity (270, 471). In addition, sympathetic activation is associated with reduced food intake (678) and when exercise is combined with caloric restriction, the reduction in sympathetic over activity is more pronounced (146). It is possible that exercise-induced weight loss may play a role in the beneficial effects of exercise on health in obesity. As previously discussed, lipolysis is regulated by the sympathetic nervous system, and in response to exercise lipolysis will increase due to greater energy expenditure (317). Exercise has also been shown to have beneficial effects on contractility of the vasculature. In pigs with high cholesterol and atherosclerosis, exercise training on treadmills improved the response of coronary arteries to the vasodilator ET-1 (94).

Multiple studies have demonstrated that exercise has an anti-inflammatory effect. In a high fat fed mouse model of obesity, forced exercise on a treadmill reduced macrophage infiltration and induced a phenotypic switch from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages (334, 335). In addition, TNFα and T cell expression were reduced in epididymal fat pads. Similarly, macrophage infiltration of skeletal muscle is reduced in a similar feeding and exercise study (587). Interestingly, all three of these studies exhibited anti-inflammatory effects of exercise that were independent of weight loss. Voluntary exercise in obese mice yields the same reduction in circulating TNFα, as well as producing improvements in glucose tolerance and insulin sensitivity (81). In obese human patients, exercise in combination with caloric restriction induced weight loss and again a reduction in TNFα, as well and IL-6 (321). Interestingly, exercise training in healthy rats increased eNOS expression in aortic PVAT (27), presenting a potential mechanism by which exercise may restore PVAT function in obesity.

The beneficial effects are not limited to chronic exercise; obese rats subjected to one three-hour swimming session demonstrated reduced circulating LPS, TNFα and interleukin-1, and resulted in improved insulin signalling (513). In addition, similar to in chronic exercise studies previously discussed, a phenotypic switch from M1 macrophages to M2 macrophages was observed in adipose tissue.

11.2. Helminth infection

As previously discussed, it is known that eosinophils reside within healthy adipose tissue and that high-fat feeding diminishes the population of eosinophils within VAT (742, 744, 752). However, the application of exogenous eosinophils to diet-induced obese mice has not yet been investigated. Thus, future studies implementing the induction of a hypereosinophilic state (eosinophilia) within obese animals are therefore required. In this regard, helminth infection offers physiological means of inducing eosinophilia (752). Wu *et al*. (752) have demonstrated that in the helminth model of eosinophilia, visceral adiposity is decreased, whilst insulin sensitivity and glucose tolerance are improved, post-clearance of helminth infection in diet-induced obese mice. Wu *et al*. propose that the beneficial effects of eosinophilia are attributed to an induced phenotypic switch of pro-inflammatory M1 macrophages, to anti-inflammatory M2 macrophages. We have been unable to confirm this (744). More recently, helminth infection of high fat diet fed mice with *Heligmosomoides polygyrus* had direct effects on the expression of key genes involved in lipid metabolism (652). There was an upregulation of UCP-1 in adipose tissue, akin to “beiging” of WAT, along with suppression of glucose and triglyceride levels.

Shen *et al*. (613) have shown that previous helminth infection significantly reduces the risk of later-life development of the MetS and its constituents, including hypertension, within healthy Chinese men. Furthermore indigenous South American Tsimane adults, over two-thirds of whom have intestinal helminth infections (69), exhibit a low prevalence of CVD, including hypertension (325). This is in stark contrast to individuals from typically more developed Western populations, in whom helminth infection is rare, circulating eosinophils are low, and MetS and hypertension prevalent (328). These studies indicate that helminth-induced

eosinophilia could be a useful therapeutic tool in obesity, although there are not yet any studies on the specific effects of helminth infection on PVAT.

11.3. Pharmacological intervention

A recent study in mice has demonstrated that pharmacological intervention is useful in restoring PVAT function in obesity. Obesity was established using a high fat diet, before treating with a compound which has been shown to increase eNOS phosphorylation for the last four weeks of feeding (757). Treatment with this compound successfully reversed dysfunction of the BAT surrounding the thoracic aorta, independent of fat mass. Whilst there were no measurements of blood pressure or glucose tolerance in this study, it is possible that with further investigation this compound could be useful in treating hypertension and T2D, and may be applicable to humans. As discussed in section 5.3, eNOS may increase secretion of adiponectin from PVAT (734, 743), and in humans following statin therapy plasma adiponectin is increased (124). It has been proposed that statin therapy enhances eNOS expression (209, 403); therefore, it is possible that therapies which target eNOS in obesity may improve adiponectin bioavailability.

The effects of infliximab, a TNFα blocking antibody, on adiponectin expression have been tested in the STZ-induced diabetic mice (488). In this model, inflammation in PVAT was associated with reduced adiponectin synthesis and dysregulation in adiponectin receptor expression. In addition, eNOS phosphorylation was impaired. These changes occurred after only 1 and 2 weeks of diabetes onset, highlighting the detrimental effects of acute changes to PVAT function (488). However, treatment with infliximab normalised expression of adiponectin and its receptors, and improved eNOS activity, indicating another potentially useful compound in the vascular complications of obesity. Despite this, whilst TNFα-induced loss of PVAT function in rat vessels could be restored by infliximab, we have previously found that *in vitro* incubation with infliximab does not restore the anti-contractile effect of PVAT from obese patients with MetS (246). Given the acute nature of the aforementioned intervention and the chronic disease state of the human vessels, this is perhaps somewhat unsurprising. As such, our findings do not conclusively prohibit a therapeutic role for infliximab (or indeed other TNFα-targeting therapies), and so further research into TNFα neutralization is warranted.

Enhancing H_2S production in PVAT may present another promising target. In cafeteria diet fed rats, H_2S production was reduced and PVAT anti-contractile function was lost in the aorta (54). However, treatment with the anti-diabetes drug rosiglitazone restored CSE activity, increasing H_2S production, and restoring PVAT function. Similarly, atorvastatin has been shown to increase H_2S production and enhance the phenylephrine-induced PVAT anti-contractile effect in healthy rat aorta (746), although the effect of statins on H_2S in obese PVAT has not been investigated.

Incubation of isolated rat PVAT with activators of AMPK increases eNOS phosphorylation and adiponectin secretion, and reduces expression of pro-inflammatory cytokines TNFα, CCL2, and IL-6 (118, 655). In addition, incubation of PVAT with AMPK activators before applying the PVAT to isolated aortic rings improved acetylcholine-induced vasodilation. More importantly, oral administration of AMPK activators reduced aortic PVAT mass, and improved responsiveness of the aorta to acetylcholine (118, 655). These data suggest that targeting AMPK may also be therapeutically useful in obesity.

11.4. Weight loss: Surgical and dietary

In human bariatric surgery patients, we and others have shown significant improvement in PVAT inflammation (10, 211). IL-6 and TNFα expression are reduced, and bioavailability of circulating adipokines such as adiponectin and NO are improved. In addition, one study has indicated increased expression of adiponectin receptors (475). These changes are accompanied by reversal of diabetic status (68).

Bariatric surgery completely reverses the loss of PVAT function in human small subcutaneous arteries six months post-surgery (10). Moreover, in these patients there were improvements in adiponectin bioavailability and insulin sensitivity, and a number of inflammatory mediators such as macrophages and TNFα were reduced. These positive changes resulted in significant reductions in blood pressure, indicating that restoring PVAT function may restore normal regulation of vascular tone. Interestingly, whilst the patients had lost weight, they were still in the obese BMI range (10). This suggests that there is more to weight-loss than purely loss of mass, and other factors such as the reduced adipocyte size and a reduction in PVAT inflammation as a consequence of a more balanced oxygen supply may be the fundamental trigger leading to our observation.

Similar improvements in blood pressure and insulin sensitivity can be induced using sleeve gastrectomy in diet-induced obese rats (470), although the effects of this surgery on adiponectin bioavailability and inflammation of adipocytes have not been studied in this model.

However, due to expense and risk, bariatric surgery is not readily available to all patients until all other methods of weight loss i.e. diet and exercise, have been exhausted. The effects of caloric restriction on PVAT function in a rat model of obesity have been characterised, and it was found that even after returning to normal weight, PVAT function was not restored (99). However, following an extended weight maintenance period of four weeks, the PVAT did regain some of its anti-contractile function and this was again accompanied by a reduction in TNFα expression and increased NO bioavailability. With further long-term study, a full reversal of PVAT damage may be achievable using caloric-restriction.

12. Beiging of adipose tissue

12.1. Therapeutic potential of BAT activation

Whilst BAT has been shown to be protective against insulin resistance, type 1 and type 2 diabetes, obesity, hyperlipidemia and atherosclerosis (56, 249, 412) the role of BAT on blood pressure is little-investigated, and it would appear that no studies have demonstrated that increased BAT activity is associated with improved blood pressure in hypertensive obese patients, or indeed animals. In most human studies of BAT activation, improved blood pressure, if measured, has rarely been a primary outcome. Of the studies which have measured blood pressure and BAT activity, or ostensible BAT activity, the vast majority have employed cold-exposure to activate BAT and as such have been principally concerned with transient, reactive changes in blood pressure, rather than long-term adaptation (355, 514). Furthermore, cold-exposure is well-known to elevate blood pressure, as evidenced by the phenomenon of seasonal (winter) hypertension (46, 90). Although, factors other than environmental temperature have been proposed to contribute to this affect e.g. vitamin D, catecholamines and serum cholesterol (186, 557). Thus, the use of cold-exposure to activate BAT has undoubtedly impeded the accurate assessment of the role of BAT activity in the regulation of blood pressure. Nonetheless, Orava *et al*. (514) found that cold-exposure did not increase the blood pressure of obese subjects whose BAT activity was also concomitantly elevated in response to cold. In contrast, a cold-induced hypertensive effect was observed in obese subjects whose BAT activity did not increase upon cold-exposure (514). BAT activity may therefore protect against cold-induced hypertension in obese subjects. Additionally, it should also be noted that winter hypertension particularly affects the elderly in whom BAT activity is reduced (135). Indeed, Kingma *et al*. (355) found that elderly individuals, who did not elicit increased energy expenditure through non-shivering thermogenesis (an indicator of BAT activity), exhibited greater cold-stimulated elevations in systolic blood pressure compared with young individuals (355). As such, the activation of BAT in response to cold-exposure may counteract cold-induced hypertension within the

general population. In this regard, it would seem logical that an enhanced ability to defend body temperature through increased BAT thermogenesis would reduce the importance of peripheral vasoconstriction for heat retention. However, the matter of interest herein is more so whether BAT can protect against hypertension under normal environmental conditions.

From a thermal perspective, modern individuals live largely at thermoneutrality (~30-31°C) courtesy of indoor-living, clothes and heating systems (263, 355). Thus, it is perhaps relevant that van der Lans *et al.* (703) found that cold-acclimated healthy men and women exhibited lower mean arterial pressure at thermoneutrality compared with non-cold-acclimated individuals (703). As such, boosting BAT activity via intermittent cold-exposure may beneficially impact upon long-term blood pressure.

In the context of treating metabolic disease, intermittent cold-exposure has already been demonstrated to activate BAT and transiently improve short-term glucose tolerance in high fat diet fed mice (561). Moreover, short-term cold acclimation of metabolically healthy obese subjects (263), and overweight subjects with T2D (262), via intermittent cold-exposure, has been shown to increase cold-induced glucose uptake into BAT and skeletal muscle, and increase peripheral insulin sensitivity, respectively. Accordingly, intermittent cold-exposure has been proposed to protect against the development of obesity-associated insulin resistance and hyperglycemia (263). Furthermore, given the importance of insulin in regulating vascular tone, particularly within skeletal muscle arteries (see section 10), such cold-exposure-induced metabolic improvements would also be expected to positively influence blood pressure. However, whilst cold-exposure is considered to be the safest (785) most physiological, and most powerful (781) way of inducing BAT activity and adipose tissue beiging, it should be noted that at least one previous study on rats has demonstrated apparent irreversible cold-induced hypertension, which persists at least up to 4 weeks post-exposure (612). Thus, this would indicate that the severity, duration and frequency of bouts of cold-exposure should be carefully considered, particularly in hypertensive subjects.

Nonetheless, with regard to PVAT, cold-exposure has been demonstrated to elicit a number of metabolic benefits. For example, cold-exposure has been found to induce thermogenesis within the aortic PVAT of ApoE knockout mice, thus improving lipid clearance (114). Moreover, within high fat fed ApoE knockout mice, cold-exposure has been demonstrated to protect against atherosclerosis and improve endothelial function through the release of PVAT-derived prostacyclin, a known atheroprotective vasodilator. These metabolic improvements appeared to occur without a reduction in the gene expression of pro-inflammatory cytokines within the aortic PVAT. However, Reynés *et al*. (564) have reported that cold-exposure induced an anti-inflammatory response in the aortic PVAT of ferrets; an animal model used for the similarity between their adipose tissues and those of humans. A recent study on high fat fed rats has also confirmed that *in vivo* cold-exposure elicits an anti-inflammatory response within aortic PVAT, as TNFα and IL-6 gene expression was decreased, whilst phosphorylation of AMPK was enhanced (404). Additionally, cold-exposure induced further beiging of this mixed-phenotype PVAT depot, as evidenced by an increase in the protein expression of UCP1. In mice, the beiging of aortic PVAT in response to cold-exposure has been shown to be modulated by miR-146b-3p, as antagomir-induced knockdown of this microRNA impairs cold-induced beiging *in vivo*, whilst *in vitro* transfection with a miR-146b-3p mimetic elicits the beiging of cultured primary adipocytes (526).

Given that increased amounts of VAT, such as omental and mesenteric adipose tissue, are typically linked to a higher risk of developing obesity-associated complications, such as hypertension and T2D (64, 65, 214), the ability to beige these adipose tissue depots through cold-exposure represents an intriguing therapeutic opportunity and is arguably of greater interest than beiging other adipose tissues. Notably, VAT is less sensitive to cold-induced beiging compared with other adipose tissue depots, such as SAT (718). However, it has been reported that *in vivo* cold-exposure is still capable of beiging VAT, including mesenteric PVAT, within animal models (36, 45, 295, 707). In this regard, Vargovic *et al*. (707) found that up to 7 days cold-exposure induced the expression of tyrosine hydroxylase, β_3-

adrenoceptors and UCP1 within the mesenteric PVAT of rats. This was concomitant with the infiltration of M2 macrophages into PVAT, and an increase and decrease in the gene expression of anti-inflammatory and pro-inflammatory cytokines, respectively. In contrast, whilst it remains to be determined if VAT can undergo cold-induced beiging in humans, non-obese patients with phaeochromocytomas (which produce excess catecholamines) exhibit extensive beiging of mesenteric PVAT (119, 319), demonstrating that human mesenteric PVAT is capable of undergoing sympathetically-mediated beiging. As such, cold-exposure, which is known to induce sympathetic activity, may also confer the same benefits.

Moving away from cold-exposure and its aforementioned confounding haemodynamic effects, other animal models also hint at a possible role for BAT in the regulation of blood pressure, and moreover allow for longer term conclusions to be drawn from the contribution of BAT activity. For example, a recent study by Tsai *et al*. (690) demonstrated that a heterozygous mutation in PPAR-γ (PparγP465L/+), which is associated with severe insulin-resistance and hypertension in humans, reduces interscapular BAT and also causes hypertension in mice. Nonetheless, whilst this might suggest a possible link between BAT and blood pressure regulation, these mice also exhibited elevated angiotensinogen gene expression within an expanded subcutaneous adipose tissue depot. Thus, given the role of the RAAS in the pathogenesis of hypertension this latter phenotypic change could be of greater significance (174, 675).

Another animal model which suggests a possible role for BAT and beige adipose tissue in blood pressure regulation is the perilipin-1 knockout mouse which exhibits dysfunctional PVAT, vascular dysfunction and hypertension (800). Phosphorylation of perilipin-1 by protein kinase A is known to be important in the regulation of BAT thermogenesis in response to adrenergic stimulation, as inability to phosphorylate perilipin-1 reduces BAT thermogenesis by approximately 70% (634). Additionally, overexpression of perilipin-1 in white adipocytes induces a brown adipocyte-like phenotype, complete with the upregulation of UCP1 (the molecular effector of BAT thermogenesis), and increases whole body energy expenditure (593). Unfortunately, blood pressure was not assessed in these animals, but it would be intriguing to know if perilipin-1 overexpression is capable of protecting against the development of hypertension in diet-induced obese animals. With respect to this, perilipin-1 overexpression has been shown to protect against diet-induced obesity (466), and as a consequence this may confer a more favourable haemodynamic status. Nonetheless, the role of perilipin-1 is somewhat unclear, as another group have reported that loss of perilipin-1 protects against diet-induced obesity (670), and the expression of perilipin-1 has been reported to be increased within obese human adipose tissue (342).

The examples presented above generally discuss the potential to improve elevated blood pressure through the upregulation of BAT activity, in other words increased BAT thermogenesis; which depends upon UCP1. However, Thoonen *et al*. (681) found that the blood pressure of UCP1 knockout mice and wild-type mice did not differ (681). If BAT is capable of ameliorating hypertension, then this suggests that such a benefit would not be due to UCP1, or indeed BAT thermogenesis, directly. As such, factors secreted by BAT, so-called “BATokines” (brown adipocyte-derived adipokines; reviewed by (683, 715)), such as FGF-21, insulin-like growth factor 1 (IGF-1), and IL-6, may be of greater importance (discussed below). With respect to this, the acute nature of most cold-exposure studies, which are predominantly concerned with activating BAT thermogenesis, would be unlikely to reveal any BATokine-mediated effects on blood pressure; as these changes would undoubtedly result from longer term adaptations involving more complex signalling pathways and the involvement of numerous tissues and cell types.

12.2. SNS activation and BAT transplant

The sympathetic dysfunction which accompanies obesity significantly contributes to the dysfunctional “whitening” of adipose tissue via perturbed metabolic homeostasis, in part via disrupted lipid homeostasis. In this regard, catecholamine-induced lipolysis and

thermogenesis are decreased in obesity (386, 387, 585, 713), whilst *de novo* lipogenesis increases in response to overfeeding (449, 776). The latter most likely results from the upregulation of genes involved in fatty acid synthesis, such as fatty acid synthase; upregulation of which has been observed in both the adipose tissue of obese patients (59) and adipocytes from genetically obese (*fa/fa*) rats (74). The resultant accumulation of FFAs within adipose tissue (due to increased production and lack of clearance) would be expected to promote adipose tissue whitening, leading to adipocyte hypertrophy and subsequently adipose tissue hypoxia, which is commonly implicated in the pathogenesis of obesity (246, 284, 427, 532). Additionally, saturated FFAs, such as palmitate, which are present in large quantities within hypertrophied adipocytes, are capable of inducing local adipose tissue inflammation (653). Importantly, an unfavourable circulating FFA profile, which is often observed in obesity and the MetS (500, 590, 796) predisposes to hypertension (183) and contributes to endothelial-dysfunction (641, 642). As such, redressing this imbalance in fatty acid homeostasis by correcting SNS function is an attractive approach for treating obesity-associated hypertension. One such way of achieving this could be to take advantage of brown and/or beige adipose tissue, as a recent study has demonstrated that cold-induced stimulation of BAT activity improves the circulating FFA profile in men, along with glucose uptake and insulin sensitivity (301). Furthermore, transplantation of BAT has also been shown to improve the circulatory FFA profile of obese mice (412).

Delineating the ability of BAT to confer metabolic improvements has been greatly aided through BAT transplantation studies (249, 346, 410, 412), which on the whole precludes interference from other concomitant changes that would be expected to occur via adipose tissue beiging and BAT activation protocols, such as cold-exposure or the systemic administration of β_3-adrenoceptor agonists. These studies have shown that *in vivo* BAT transplants (BATplants) can reverse type 1 diabetes (249, 250) and diet-induced obesity (412, 637, 799). Additionally, BATplants can also protect against genetic obesity (410), atherosclerosis (346), glucose intolerance and insulin resistance in high-fat diet-induced type 2 diabetic mice (412, 637). These benefits were at least in part attributable to enhanced fatty acid oxidation and glucose uptake within metabolic tissues such as endogenous interscapular BAT (iBAT) (412, 637). This therefore suggests that signals from the implanted BAT are capable of stimulating endogenous BAT activity. In this regard, removal or denervation of adipose tissue has been shown to affect sympathetic outflow to other adipose tissue depots (265, 615). Thus, the presence of new adipose tissue may yield a similar response, whereby, for example, the implantation of BAT might cause neural adaptations in endogenous BAT. Importantly, Zhu *et al*. (799) have demonstrated that BAT transplantation confers resistance to diet-induced obesity by increasing whole-body sympathetic activity (799). However, this was achieved in a tissue-specific manner, whereby NE turnover (a marker of sympathetic activity) was increased in the heart, liver, mesenteric WAT and iBAT, but not within epididymal, retroperitoneal and inguinal WAT. NE turnover was also found to be differentially increased across various skeletal muscles.

Given that lipid mobilization from distinct WAT depots in response to sympathetic stimulation is known to exhibit regional heterogeneity (306), the findings of Zhu *et al*. (799) suggest that lipids are preferentially liberated from VAT, and that the release of these lipids may be important in fuelling the concomitant stimulation of BAT thermogenesis. Thus, the benefits of BAT transplantation would be two-fold: Firstly, a reduction in visceral adiposity, which would otherwise predispose to the development of obesity-associated complications, such as hypertension (64, 65, 214). Secondly, diet-induced thermogenesis is restored, which serves to expend the accumulation of excess energy through over-nutrition via the generation of heat in order to maintain a healthy bodyweight (497, 575). On the subject of bodyweight, it should also be noted that transplantation of BAT into healthy mice did not result in them becoming underweight (799), suggesting that the effects exerted by transplanted BAT specifically correct the pathways involved in the development of diet-induced obesity. Finally, Zhu *et al*. (799) showed that NE-stimulated energy expenditure, which serves as a surrogate marker for whole-body sympathetic nerve activity (717), was higher in obese mice who had received BATplants than those who had not, indicating that the former were more sensitive

to adrenergic stimulation as they were able to increase whole-body sympathetic activity to a greater extent (799). With respect to this, Liu *et al*. (410) found that transplantation of BAT significantly increased β_3-adrenoceptor expression in subcutaneous and epididymal WAT, suggesting that BAT transplantation enhances the sensitivity of peripheral tissues to sympathetic stimulation. Thus, BATplants may also help to restore sympathetic responsiveness, which, as discussed previously, is impaired in obesity (432, 622).

The manner by which transplanted BAT communicates with the host to improve sympathetic activity and metabolic function remains in question. However, interestingly, Stanford *et al*. (637) found that whilst BAT transplantation reduced adiposity, enhanced glucose tolerance and improved the circulating lipid profile in already healthy wild-type mice, these effects were abolished when BAT from IL-6 knockout mice was transplanted (637). Mice who received BAT from wild-type donors were also found to exhibit elevated plasma NE, IL-6 and FGF-21, whereas those who received BAT from IL-6 knockout mice did not. Thus, transplanted BAT appears to exert its beneficial effects on metabolic homeostasis via IL-6. In support of this, cultured brown adipocytes are capable of producing IL-6 in response to adrenergic stimulation (98), and transgenic mice which overexpress IL-6 have reduced adiposity and improved metabolic health compared with wild-type mice, particularly when challenged with a high-fat diet (425, 582). Importantly, IL-6 is a centrally-acting pyrogen capable of crossing the blood-brain barrier, and intracerebroventricular injection of IL-6 has been shown to increase sympathetic outflow (402), core body temperature and oxygen consumption in rats (574). This ability of IL-6 in stimulating BAT thermogenesis is highlighted by the fact that cold-induced increases in energy expenditure (733) and UCP1 expression within inguinal WAT (356) are blunted within IL-6 knockout mice. Furthermore, IL-6 is pro-lipolytic, in that it stimulates the liberation of FFAs from WAT (281, 534). No doubt this contributes to the decrease in adipocyte size that is observed following BAT transplantation (637) or IL-6 overexpression (425, 582). As such, transplantation of BAT may improve sympathetic activity via secreting IL-6, whereby the secreted IL-6 acts in an endocrine manner upon the CNS to increase sympathetic outflow to adipose tissues which in turn serves to increase WAT lipolysis and BAT thermogenesis. In the context of obesity-associated hypertension, such restoration of sympathetic activity would be expected to reduce adiposity and therefore alleviate adipose tissue hypoxia and inflammation, both of which are strongly implicated in this pathology (242, 243, 246, 427).

12.3. Inflammation and the immune system

At this juncture it should be noted that both bariatric surgery (556), and flavonoids such as those contained within the aforementioned WS 1442 (282, 487, 757, 785) have been demonstrated to beige adipose tissue. Thus, beiging PVAT appears to reduce inflammation and therefore could rescue PVAT function in obesity.

The ability of healthy BAT to preserve vascular function and protect against adipose tissue inflammation can be demonstrated using mice with BAT-specific ablation of the insulin receptor (BATIRKO mice). Interestingly, these mice develop BAT atrophy and increased visceral adiposity with an attendant elevation in plasma and adipose tissue levels of the pro-inflammatory cytokine TNFα (240). Moreover, these mice also develop insulin resistance and vascular dysfunction. Notably, the aortae of BATIRKO mice are characterised by impaired endothelial relaxation, macrophage infiltration and the elevated expression of inflammatory and endothelial activation markers which are known to be regulated by TNFα, such as ET-1, ICAM-1, iNOS, plasminogen activator inhibitor 1 (PAI-1), and CCL2. Accordingly, Gomez-Hernandez *et al*. (240) further found that administering BATIRKO mice with an anti-TNFα antibody improved vascular insulin sensitivity and vascular function, in part via reducing the expression of the aforementioned inflammatory and endothelial activation markers.

Furthermore, compared with other adipose tissue depots, BAT has been shown to be more resistant to diet-induced obesity-associated inflammation (203), and the transplantation of

BAT has been shown to exert anti-inflammatory effects (249, 250). Gunawardana *et al*. (250) were the first to demonstrate that the transplantation of embryonic BAT into STZ mice reduces inflammation of endogenous WAT and restores euglycemia (250). In this regard, immunofluorescent staining of WAT revealed that levels of the pro-inflammatory cytokines IL-6 and TNFα were lower in the WAT of mice implanted with BAT compared with mice which were not. Importantly, the post-transplant WAT levels of IL-6 and TNFα were comparable to those of healthy mice, and adipocyte diameters were also similar. Interestingly, mice which did not achieve euglycemia, even after receiving embryonic BAT, did not exhibit such changes post-transplant, strongly indicating that the ability of BAT to restore glucose homeostasis is dependent upon its anti-inflammatory properties. Thus, in addition to restoring the healthy anti-contractile function of PVAT, the benefits of remediating adipose tissue inflammation to combat hypertension are also likely to involve improved glucose tolerance, as impaired glucose homeostasis is known to predispose to the development of hypertension in diabetes and the MetS (145, 327, 610, 786).

The anti-inflammatory manner by which BAT transplantations are able to restore euglycemia is not fully known. However, concomitant with reduced WAT inflammation, Gunawardana *et al*. (250) also observed that plasma adiponectin, leptin and IGF-1 levels were elevated post-transplant, and proposed that glucose regulation is achieved as a result of this altered hormone profile. Both adiponectin (511, 518, 714) and IGF-1 (250) are known to exert anti-inflammatory effects. Interestingly, post-transplant, IGF-1 levels were elevated within the BATplant itself and also to some degree in the surrounding WAT (250). This suggests that IGF-1 secreted from transplanted BAT could contribute to reducing systemic adipose tissue inflammation and thereby help to ameliorate obesity-associated hypertension. However, Gunawardana *et al*. (250) concede that that the enhanced plasma levels of IGF-1 are more likely a result of elevated leptin production from new, healthy WAT, as leptin has been demonstrated to induce IGF-1 expression (168, 250, 260, 628).

As previously discussed, circulating adiponectin is reduced in obesity, hypertension, and T2D, whilst adiponectin gene expression within the PVAT of human internal mammary arteries from patients with T2D is elevated, and is positively correlated with NADPH oxidase activity through what is believed to be a mechanism which protects against ROS-mediated vascular damage (25). Therefore, the ability of BAT transplantation to increase plasma adiponectin levels in non-obese diabetic mice as observed by Gunawardana *et al*. (250), is of particular interest. In addition, chronic cold-exposure induces adipose tissue beiging via augmenting local adiponectin production within SAT. Moreover, adiponectin knockout mice exhibit impaired cold-induced beiging (290). Importantly, another study, by Liu *et al*. (410), has demonstrated that implanting BAT into the dorsal subcutaneous region of genetically obese *ob/ob* mice also increases plasma adiponectin levels and furthermore protects against the development of obesity and excess subcutaneous adiposity. Whilst blood pressure was not measured in these mice post-BATplant, it is tempting to believe that transplantation of BAT could confer haemodynamic benefits, not least through elevating circulating adiponectin levels which may counteract oxidative stress.

Other ways in which adiponectin improves metabolic homeostasis include an ability to enhance lipid oxidation and insulin sensitivity (765). Indeed, Liu *et al*. (410) found that transplantation of BAT improved insulin sensitivity and decreased circulating levels of cholesterol, low-density lipoproteins and triglycerides. Furthermore, this was concomitant with an increase in whole-body energy expenditure, perhaps suggesting that increased lipid clearance served to activate endogenous BAT and thus promote thermogenesis. With respect to this, UCP1 expression was augmented within endogenous iBAT. Interestingly, the administration of exogenous adiponectin into *ob/ob* mice recapitulates the effects of BAT transplantation observed by Liu *et al*. (410), in that BAT thermogenic activity was increased, whilst bodyweight, and serum glucose and lipid levels were decreased (551). This might therefore suggest that adiponectin released from transplanted BAT is capable of inducing the observed metabolic changes, in part by stimulating endogenous BAT activity. However, in the study by Liu *et al*. (410) levels of adiponectin mRNA remained unchanged within

transplanted BAT, endogenous iBAT, subcutaneous WAT and epididymal WAT. Therefore, it would seem more likely that transplanted BAT secretes factors which stimulate the endogenous production of adiponectin from adipose tissue; perhaps more so from visceral WAT than the aforementioned adipose tissue depots. In turn, the increase in circulating adiponectin would be expected to exert numerous metabolic benefits, including activation of endogenous BAT, enhanced lipid oxidation and improved insulin sensitivity. Given that dyslipidemia, insulin insensitivity and excess adiposity all contribute to the development of hypertension (384, 590, 786), the metabolic benefits imparted by BAT transplantation and the consequential increase in circulating endogenous adiponectin would be expected to improve blood pressure indirectly. Such indirect benefits would act in concert with the direct vasorelaxant effect of adiponectin upon the vasculature.

In addition to the above, adiponectin polarises macrophages towards an anti-inflammatory M2 (alternatively-activated) state (290, 511), and accordingly suppresses both the production of TNFα and ROS (511, 779). Elevated circulating adiponectin levels, as observed post-BAT transplantation, would therefore be expected to exert widespread anti-inflammatory effects, which may serve to reduce adipose tissue inflammation and subsequently protect against obesity-associated hypertension. Whilst increasing the levels of circulating adiponectin would undoubtedly be beneficial, Hui *et al*. (290) have demonstrated that local elevations of adiponectin within the SAT of cold-exposed mice are indispensable for the cold-induced beiging of adipose tissue, via promoting the proliferation of anti-inflammatory M2 macrophages within adipose tissue. This was in spite of the fact that cold-exposed mice possessed moderately, but significantly, diminished serum levels of adiponectin. Similarly, Imai *et al*. (295) found that 24-hour cold-exposure also reduced serum adiponectin. However, in their study, adiponectin gene expression within mesenteric PVAT (as well as epididymal and subcutaneous WAT) was decreased in response to cold-exposure, exhibiting an apparent inverse correlation with *Ucp1* expression, which was augmented within these adipose tissues. Such a finding could therefore suggest that cold-induced beiging might inhibit the anti-contractile effect of mesenteric PVAT through reducing the local bioavailability of adiponectin. With respect to this, Hui *et al*. (290) found that adiponectin gene expression is elevated 6 hours after the onset of cold-exposure, which along with adiponectin protein expression becomes more pronounced with prolonged cold-exposure up to a period of at least one month. Accordingly, Jankovic *et al*. (303) have shown that adiponectin expression within the retroperitoneal WAT of rats is reduced after a single day of *in vivo* cold-exposure, but becomes elevated from 3 to 21 days after the onset of cooling. As such, it is possible that the observations of Imai *et al*. (295) are the result of an initial, transient stressor effect, and that longer-term cold-exposure confers greater metabolic benefits which may improve anti-contractile function. However, whilst Hui *et al*. (290) found adiponectin expression to be elevated within SAT in response to cold-exposure, there was no change within anatomically deeper adipose tissue depots, such as epididymal WAT and interscapular BAT, even after one month of continuous *in vivo* cooling. Moreover, low serum adiponectin persisted. As such, compared with continuous long-term cold-exposure, intermittent cold-exposure (see section 12.1) may be a more appropriate and feasible therapeutic approach in patients.

Taken together, the above findings from BAT transplantation and cold-induced adipose tissue beiging studies suggest that the consequent enhancement of paracrine adiponectin signalling appears to be sufficient for alleviating adipose tissue inflammation, via the ability of adiponectin to stimulate the proliferation of M2 macrophages within adipose tissue. Interestingly, Hui *et al*. (290) found that cold-exposure did not change the number of pro-inflammatory M1 macrophages within adipose tissue, indicating that increasing the population of M2 macrophages alone within inflamed adipose tissue can be protective by effectively reducing the percentage of M1 macrophages within the total adipose tissue macrophage population. In this respect, given that M1 macrophages are pro-inflammatory and that adiponectin is capable of inducing the secretion of pro-inflammatory cytokines, such as TNFα and IL-6 from them (706) the shift towards a predominantly M2 phenotype increases the likelihood that adiponectin will exert anti-inflammatory effects through

stimulating the secretion of anti-inflammatory factors such as IL-10 from M2 macrophages (706). Notably, in healthy adipose tissue M2 macrophages are more abundant than M1 macrophages (422), the latter being the main source of TNFα (698).

In recent years, the mechanisms by which inflammatory and immune cells regulate adipose tissue beiging and metabolic homeostasis have begun to be elucidated, revealing that M2 macrophages appear to be central to the maintenance and induction of beige adipocytes, and thus the establishment of a healthy metabolic phenotype (290, 409, 498). Whilst elevated circulating adiponectin levels post-cold-exposure contribute to adipose tissue beiging via promoting the proliferation of M2 macrophages (290), cold-exposure also induces the secretion of other anti-inflammatory factors from adipose tissue which are implicated in the beiging process. These factors include meteorin-like (Metrnl) (559) and IL-33 (509). Interestingly, Min *et al*. (463) have also demonstrated that cultured human adipocytes induced into a beige phenotype with forskolin express increased levels of both IL-33 mRNA and protein compared with non-beiged adipocytes. The implantation of beige adipocytes, as conducted by Min *et al*. (463), may therefore promote the secretion of IL-33 into the circulation or local endogenous adipose tissue, whereupon it reduces adipose tissue inflammation and initiates beiging. However, Min *et al*. (463) did not detect IL-33 in the circulation of mice which had been implanted with beige cells.

Importantly, Metrnl and IL-33 appear to be involved in initiating the anti-inflammatory axis which drives adipose tissue beiging in response to cold-exposure and helminth infection (248). In this regard, helminths (199) and cold-exposure (392, 509) promote a type 2 immune response through stimulating the production of IL-33 and Metrnl, which act upon type 2 innate lymphoid cells (ILC2s) and eosinophils respectively (392, 559). In turn, ILC2s secrete IL-13 and eotaxin, the latter of which promotes localised eosinophil accumulation (507). Eosinophils are the main source of IL-4 in the WAT of mice (752), and both IL-4 and IL-13 stimulate beiging of subcutaneous WAT in mice housed at thermoneutrality (392). Indeed, these type 2 cytokines have been found to induce the proliferation of bipotent platelet-derived growth factor receptor-α^+ adipocyte precursor cells and subsequently drive them towards committing to a beige adipocyte fate via IL-4Rα receptor-mediated signalling (392). Furthermore, eosinophil-derived IL-4 and ILC2-derived IL-13 promote the alternative activation of macrophages (440, 498, 553, 752), which secrete catecholamines that further contribute to the upregulation of thermogenic genes and the beiging of surrounding adipose tissue (498, 553). However, a recent study by Fischer *et al*. (200) disputes the role of M2 macrophage-derived catecholamines in adipose tissue beiging, and so IL-4 and IL-13 mediated beiging may be of greater significance. Notably, we have recently demonstrated that eosinophils within mesenteric PVAT are capable of constitutively secreting catecholamines (744), and so eosinophil-derived catecholamines may participate in maintaining a healthy adipose tissue phenotype, perhaps by ensuring a baseline level of adipose tissue "beigeness". In this regard, the constitutive presence of catecholamines within adipose tissue may serve to mediate metabolic homeostasis and protect against the development of excess adiposity through maintaining basal levels of lipolysis in WAT, and thermogenesis in the UCP1-expressing adipocytes of BAT and beige adipose tissue. Nonetheless, M2 macrophages play a key part in beiging, as ablation of macrophages impairs the thermogenic response to cold-exposure, and IL-4 induced beiging has been shown to be dependent upon macrophages (498). Additionally, intraperitoneal injection of M2 macrophages into diet-induced obese mice has been demonstrated to ignite beiging of WAT, reduce inflammation and improve insulin sensitivity (409).

Interestingly, anti-inflammatory cytokines may be key in connecting adipose tissue beiging to the regulation of blood pressure, as high-salt diets are associated with the development of hypertension, and high-salt intake has been shown to reduce IL-4 and IL-13- induced alternative activation of macrophages (62), upon which the beiging of adipose tissue is dependent. Furthermore, IL-4 and IL-10, another anti-inflammatory cytokine, are dysregulated in pre-eclampsia, the condition of pregnancy-associated hypertension, and treatment with these cytokines restores blood pressure and ameliorates endothelial

dysfunction (115). Moreover, cold-exposure has been found to increase the gene expression of IL-4 and IL-10 within mesenteric PVAT and results in macrophage infiltration. (707)As such, it could be possible that IL-4- and IL-10-mediated beiging of PVAT influences systemic blood pressure.

See Figure 8 for a summary of mechanisms by which beiging occurs and the therapeutic potential of BAT activation.

13. Summary

High calorie diets and low physical activity are the most common causes of obesity, resulting in an increased need for energy storage in the form of adipose tissue. The clear link between obesity and vascular diseases such as hypertension and T2D is increased adiposity. The ability of adipose tissues to recruit new adipocytes is limited, resulting in hypertrophy of existing cells. Adipocyte size rather than number is an independent marker for metabolic disease, and hypertrophy is associated with local hypoxia, FFA spill over, and inflammation.

Adipose tissue is a highly metabolically active organ which has a variety of functions in health through the vasoactive adipokines it secretes. In addition to a systemic contribution of adipokines released into circulation, PVAT will exert a local effect on modulating blood pressure and nutrient delivery. Therefore, over the past 28 years PVAT has become an increasingly attractive research area. PVAT exerts anti- and pro-contractile effects on the vasculature, and there is significant interest in identifying these factors in the search for novel targets in obesity-related vascular diseases. A number of adipokines have been identified, although their relative importance in comparison to one another in modulating the PVAT effect is not yet clear. In addition, the importance of the local PVAT effect vs the endocrine effect of adipokines from all adipose tissue depots has not yet been compared.

In recent years, more focus has turned to the mechanism of release of these vasoactive factors; in particular the role of sympathetic nerves. Interest in these studies arose from the clear role of catecholamines in adipocyte metabolism, and changes to autonomic activity in obesity. In particular, our group has found the PVAT anti-contractile effect in small mesenteric resistance arteries is dependent on sympathetic nerves, and as well as finding a link between sympathetic stimulation and release of the vasodilator adiponectin, we uncovered a novel “sponging effect” of PVAT, whereby some of the sympathetic nerve derived NE is sequestered by adipocytes; thus reducing the concentration available to elicit contraction. Others have indicated that PVAT specific adipocytes have a unique ability to store this NE. Further study of the implications of this sponging effect is vital considering that plasma NE is increased in obesity. Moreover, studies are required to compare the relative importance *in vivo* of the sponging effect to the local release of anti-contractile factors from PVAT.

In obesity, the PVAT anti-contractile effect is lost. This is likely due to an alteration in the adipokine secretory profile. Dysfunction in PVAT will result in increased vascular tone, increased vessel stiffness, and an increase in the activity of the RAAS; all of which will contribute to hypertension. In addition, adipokine dysregulation will reduce muscle perfusion, insulin sensitivity and metabolism, and will induce inflammation of the liver; all resulting in a diabetic phenotype. Understanding these mechanistic links is critical in order to guide future therapeutics in obesity. So far, there has been some success in pharmacologically manipulating the bioavailability of some adipokines in obesity; in particular NO and H_2S. In obese rodent models, increasing production of NO or H_2S *in vivo* has been shown to restore the PVAT anti-contractile effect in isolated arteries. However, there have been no studies examining the correlation between this restoration using these compounds and hypertension or T2D. Further developing these studies will be vital in proving the clinical efficacy of pharmacologically targeting adipokines.

There is a clear link between the inflammasome in PVAT and vascular disease. The diverse and highly plastic immune cell population in PVAT presents an exciting route by which we may be able to improve cardiovascular and metabolic outcomes in obesity. Multiple studies have indicated that exercise has beneficial effects on inflammation, and of course weight loss. However, exercise relies on a degree of effort from patients. An interesting path to take may be to target the immune cell population using parasitic infection. Helminth infection has shown benefits on glucose metabolism in obesity, and it would be interesting to study the specific effects of helminth infection on PVAT tissue function. We hypothesise that helminth infection will increase eosinophil number in PVAT (which is diminished in obesity), and will restore function. Whilst this is of great interest in our field, suggesting deliberate parasitic infection to human patients may be lacking in appeal. Instead, once a clear beneficial role of eosinophilia in obesity is established, we can begin to explore other mechanisms of increasing eosinophil number.

Another attractive therapeutic target is beiging of adipose tissue. Studies in both rodents and humans have indicated that activation of BAT has metabolic benefits, in particular on glucose metabolism. Obesity is associated with an expansion of WAT. There is growing interest in the field of beiging, and multiple studies have indicated that via adrenergic stimulation (through cold exposure, exercise, or pharmacological activation), WAT can be stimulated into becoming beige adipocytes, which may be able to confer the metabolic benefits of BAT. This area is still in its infancy; nonetheless it presents a promising strategy by which to alleviate metabolic and vascular diseases in obesity.

14. References

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Table 1: Summary of adipokines. **BP:** blood pressure; **ET-1:** endothelin-1; **eNOS:** endothelial nitric oxide synthase; **H_2O_2:** hydrogen peroxide; **H_2S:** hydrogen sulphide; **iNOS:** inducible nitric oxide synthase; **KO:** knockout; **NADPH:** Nicotinamide adenine dinucleotide phosphate; **RAAS:** renin-angiotensin-aldosterone-system; **SHR:** spontaneously hypertensive rat.

Adipokine	Vasoconstrictor or Vasodilator	Pro- or Anti-inflammatory	Expression in obesity	Evidence of role in blood pressure modulation	Evidence of role in blood glucose regulation
Adiponectin	Vasodilator	Anti-	Decreased	Adiponectin KO mouse hypertensive. Overexpression in obese mouse normalises BP.	Overexpression in diabetic *ob/ob* mouse normalises blood glucose. Improves insulin sensitivity. Increases glucose uptake.
Leptin	Vasodilator (Can act as vasoconstrictor through ET-1 when chronically elevated).	Pro-	Increased	Leptin injections in sympathectomised rats cause hypotension.	Leptin deficient *ob/ob* mouse diabetic.
Nitric Oxide	Vasodilator	Anti- (at physiological levels) Pro- (when elevated)	Increased early in obesity. Decreased in chronic obesity.	eNOS and iNOS KO mice hypertensive.	Increases insulin-stimulated glucose uptake. eNOS KO mouse diabetic.
Apelin	Unclear: Possibly vasodilator in small arteries and	Anti-	Increased	Apelin-13 injections increase BP. Apelin-12 and apelin-17 injections reduce BP.	Increases glucose utilization.

	vasoconstrictor in vein. May depend on fragment.				
Visfatin	Vasoconstrictor	Pro-	Increased	Elevated in both normal weight and obese hypertensive patients.	Insulin mimetic in cultured adipocytes. Visfatin deficient mouse has elevated blood glucose.
Omentin	Vasodilator	Anti-	Decreased	Omentin injections reduce BP.	Enhances insulin stimulated glucose uptake in adipocytes.
Hydrogen Sulphide	Vasodilator	Anti- (at physiological levels) Pro- (when elevated)	Decreased	Administration of H_2S donor to SHR reduces BP.	Reduces insulin-stimulated glucose transport into adipocytes.
Hydrogen Peroxide	Vasodilator	Pro-	Increased	NADPH inhibitor reduces H_2O_2 expression in obesity and reduces BP.	NADPH inhibitor reduces H_2O_2 expression in obesity and improved insulin resistance. Prolonged exposure of adipocytes to H_2O_2 induces insulin

					insensitivity.
Palmitic acid methyl ester	Vasodilator	Pro-	Decreased	Expression and vasodilator effect reduced in SHR.	Reduces glucose transport.
Angiotensin 1-7	Vasodilator	Anti-	Decreased	Known component of RAAS.	Enhances insulin signalling pathway.
Chemerin	Vasoconstrictor	Pro-	Increased	Chronic treatment of mice with chemerin increases BP.	Reduces glucose uptake and insulin secretion.
Resistin	Vasoconstrictor	Pro-	Increased	Elevated in human hypertensive patients and mouse models of hypertension.	Impairs insulin stimulated glucose transport. Treatment with resistin antibodies in obese model reduces blood glucose.

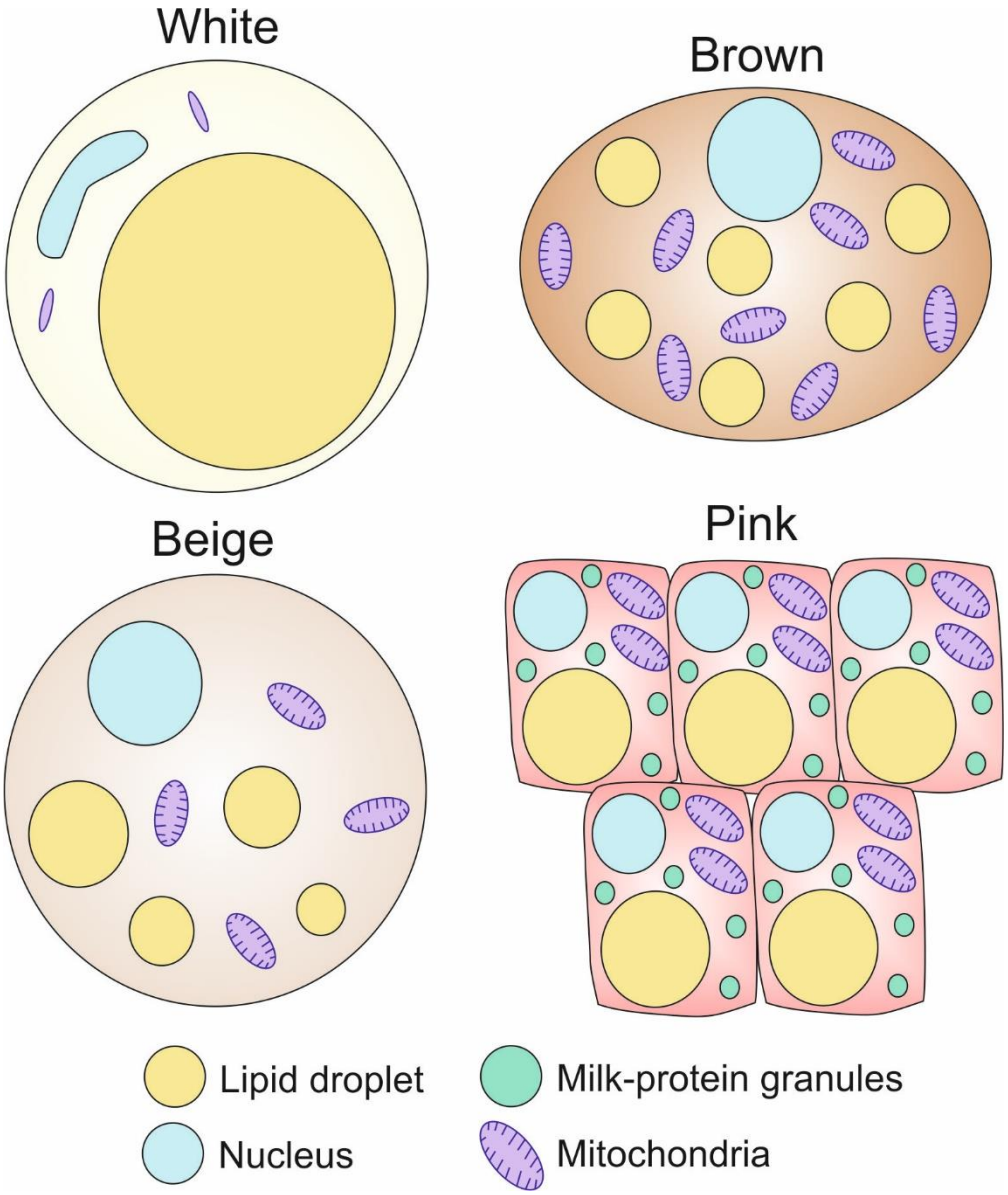

Figure 1: ***Adipocyte morphology varies with function*****:** White adipocytes play an important role in energy storage in the form of free fatty acids, therefore lipids in these adipocytes are located in a large single droplet. Brown adipocytes on the other hand are important in thermogenesis, requiring a large number of mitochondria for energy production. Recently, evidence has emerged that white adipocytes can be stimulated to become beige adipocytes, which bear resemblance to brown adipocytes and are capable of thermogenesis. Pink adipocytes are located only in mammary tissue. During pregnancy and lactation, white adipocytes differentiate into lobulo-alveolar glandular structures which can secrete milk, but still contain large amounts of lipids. These cells have been termed pink adipocytes, and they revert back to white adipocytes once lactation has ended.

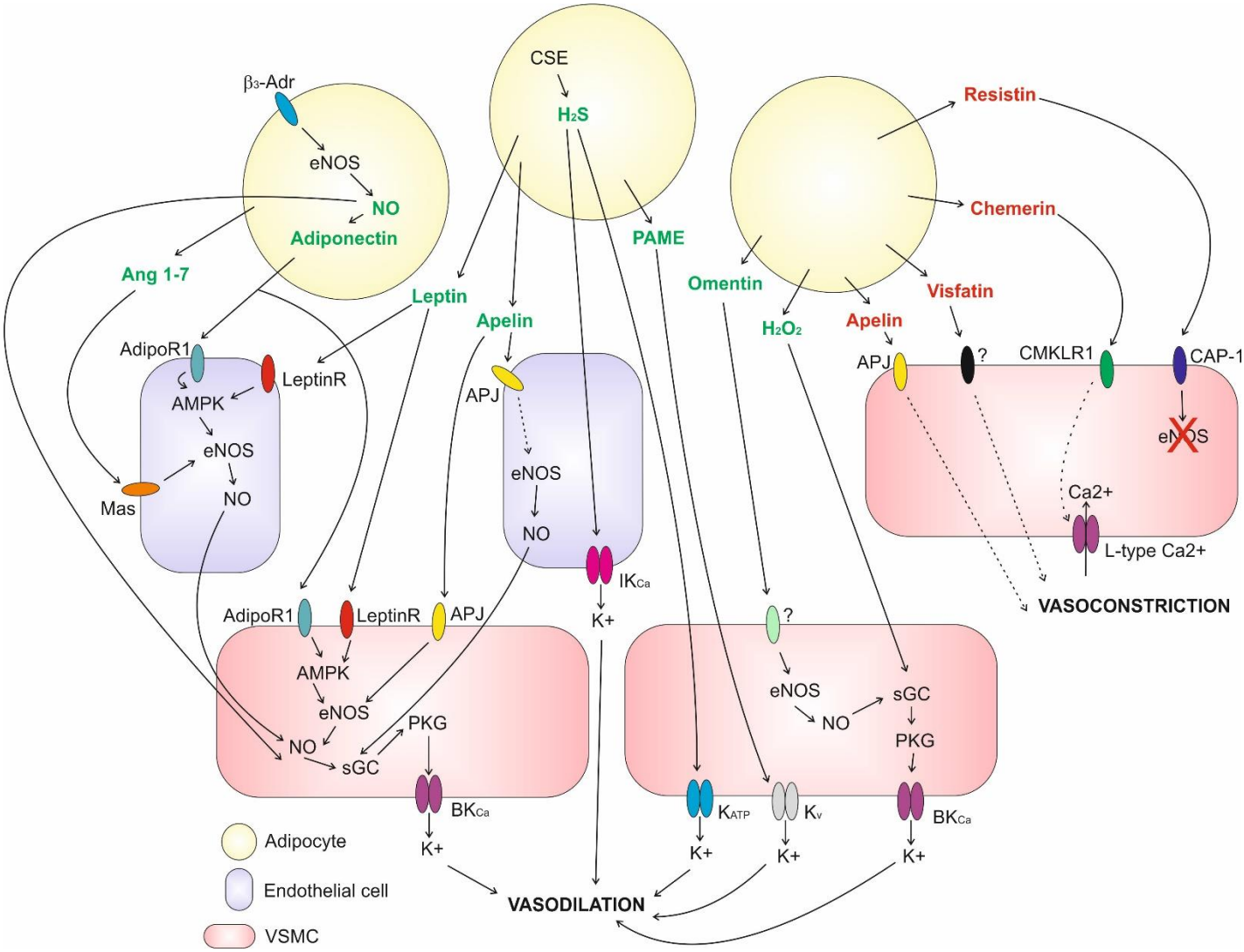

Figure 2: ***Adipocytes secrete adipokines which modulate vascular tone*****:** Adipocytes release a variety of vasoactive factors; those labelled in green are vasodilators, and those in red are vasoconstrictors. The majority of the vasodilator adipokines exert their effects via increasing phosphorylation of endothelial nitric oxide synthase (eNOS) either directly in the vascular smooth muscle cells (VSMCs) or the endothelium. Phosphorylation of eNOS increases production of nitric oxide (NO), activating soluble guanylate cyclase (sGC) and increasing protein kinase G (PKG), which will increase opening of large conductance Ca^{2+} sensitive K^+ channels (BK_{Ca}). Hydrogen sulphide (H_2S) and palmitic acid methyl ester (PAME) have direct effects on various K^+ channels, and hydrogen peroxide (H_2O_2), similar to NO directly activates sGC. Resistin, chemerin, and visfatin are vasoconstrictors. Resistin inhibits phosphorylation of eNOS, whereas chemerin activates L-type Ca^{2+} channels via an unknown mechanism. The mechanism by which visfatin induces vasoconstriction is unknown. Apelin can act as a vasodilator or vasoconstrictor depending on which form is present. The vasodilator mechanism is via eNOS, but the vasoconstrictor mechanism is unknown.

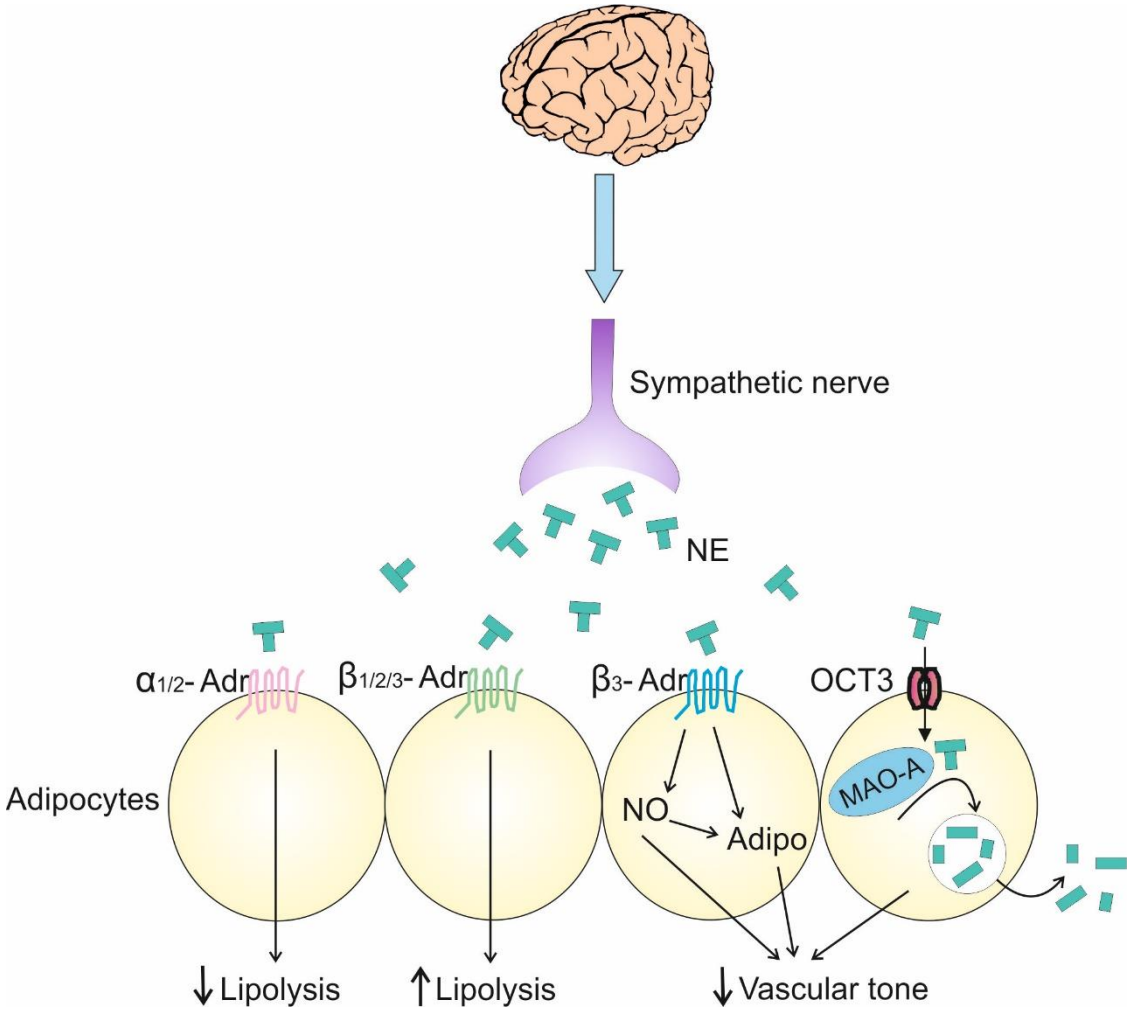

Figure 3: ***The adrenergic system in adipose tissue***: Sympathetic nerves supplying adipose tissue originate from the general central nervous system outflow and release norepinephrine (NE). All adrenoceptor subtypes are present on adipocytes. The α-adrenoceptors ($\alpha_{1/2}$-Adr) have an inhibitory effect on lipolysis whereas β-adrenoceptors ($\beta_{1/2/3}$-Adr) have a stimulatory effect. Adipocyte β_3-adrenoceptor activation has been shown to reduce vascular tone through release of the vasodilators nitric oxide (NO) and adiponectin (Adipo). Also present on adipocytes is the NE transporter organic cation transporter 3 (OCT3). Recently we have shown that OCT3 plays a role in modulating vascular tone by transporting NE into the adipocyte where it is broken down by monoamine oxidase A (MAO-A), thereby preventing the NE from reaching the blood vessel and eliciting contraction.

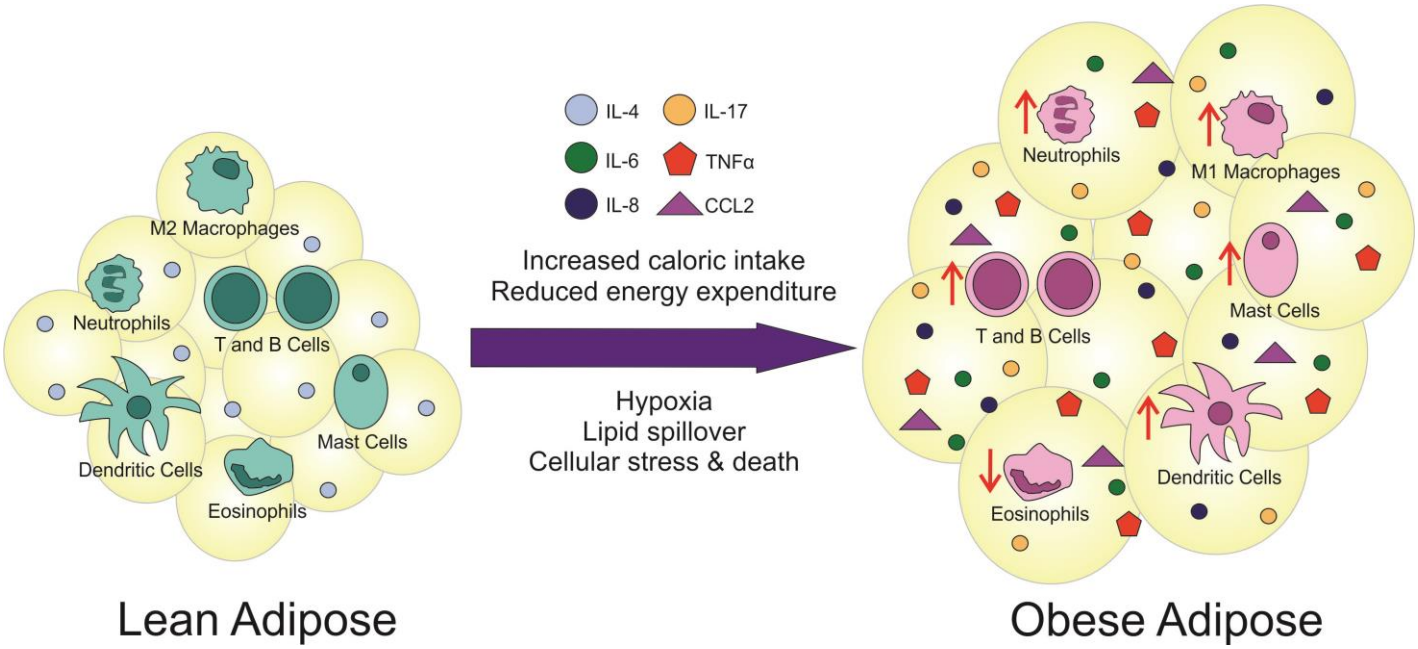

Figure 4: ***The adipose tissue inflammasome***: In health adipose tissue contains a diverse immune cell population. Anti-inflammatory cells including eosinophils and M2 macrophages, and the anti-inflammatory cytokine interleukin-4 (IL-4) are present at high levels, whereas the pro-inflammatory cells; neutrophils, T and B cells, dendritic cells and mast cells are present at low levels. However, in obesity hypoxia, lipid spill over and cellular stress drive an upregulation of these pro-inflammatory cells. The number of eosinophils drastically decreases and M2 macrophages undergo a phenotypic switch to pro-inflammatory M1 macrophages. This results in a high level of tumour necrosis factor α (TNFα) interleukin-6/8/17 (IL-6/8/17) and C-C motif chemokine ligand 2 (CCL2).

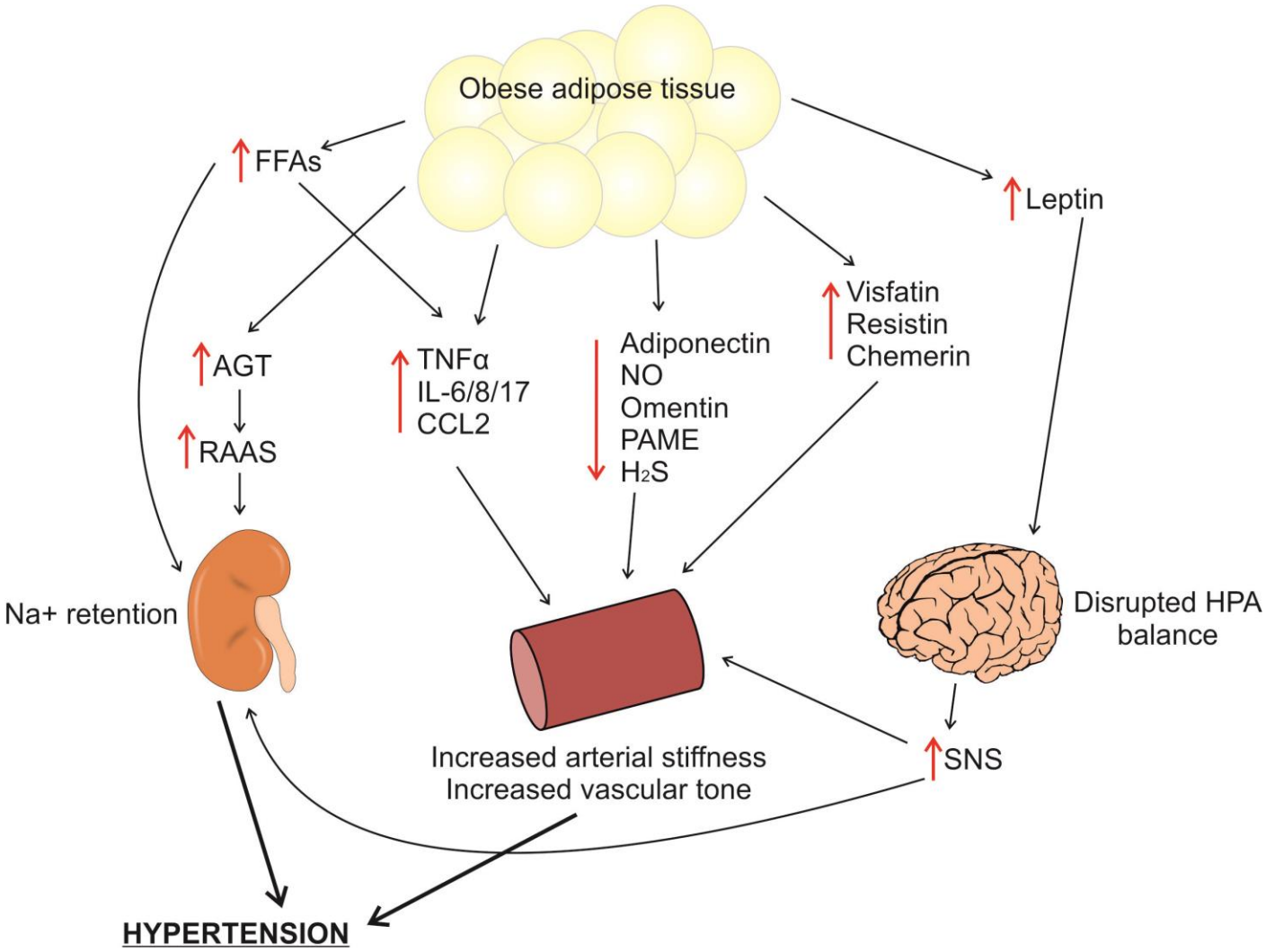

Figure 5: ***The contribution of adipose tissue to hypertension in obesity*****:** There are a number of mechanisms by which adipose tissue may be contributing to hypertension in obesity, which centre around changes in the secretory profile in adipose tissue. Adipocytes secrete a number of adipokines which affect vascular tone. Expression of the vasodilators adiponectin, nitric oxide (NO), omentin, palmitic acid methyl ester (PAME) and hydrogen sulphide (H_2S) are reduced in obesity, whereas expression of the vasoconstrictors visfatin, resistin, and chemerin in increased. This will result in a direct increase in vascular tone, and many of these factors are also thought to influence arterial stiffness. In addition, the adipose tissue becomes inflamed in obesity, and is associated with a higher expression of tumour necrosis factor α (TNFα), interleukin-6 (IL-6), and C-C motif chemokine ligand 2 (CCL2), which will all have direct detrimental effects on the vasculature. Expression of leptin is increased in obesity, which will contribute to disruption of the hypothalamic-pituitary-axis (HPA), resulting in pathological over-activity of the sympathetic nervous system (SNS). Lipid spill over from adipose tissue will increase circulating free fatty acids (FFAs), resulting in increased Na^+ retention in the kidneys. Adipose tissue has it's own renin-angiotensin-aldosterone system (RAAS), and angiotensinogen (AGT) in particular is highly expressed in obese adipose tissue, which will contribute to kidney dysfunction. All of these mechanisms may contribute to development of hypertension.

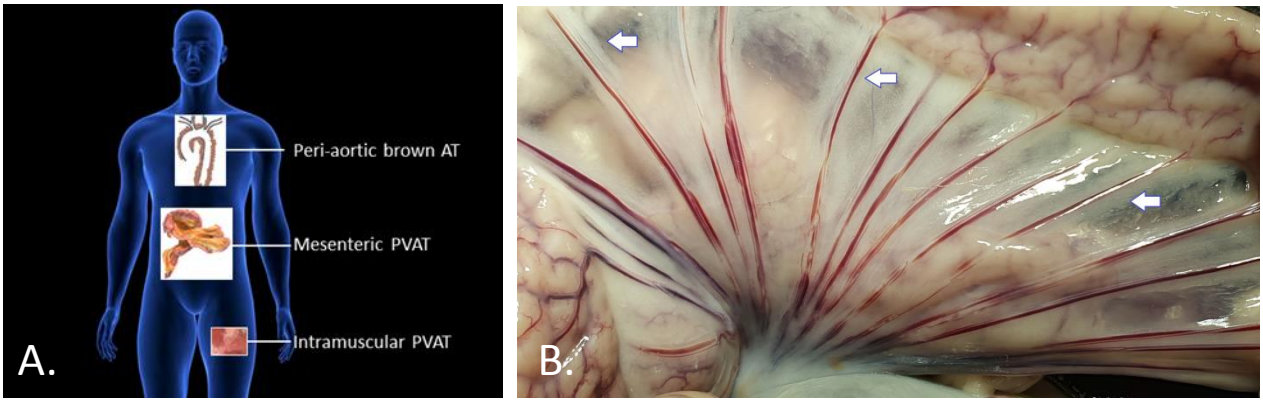

Figure 6: ***Adipose tissue depots contributing to T2D diabetes pathology*****: A:** PVAT around the thoracic aorta, the superior mesenteric artery and the microvascular beds of muscles regulates and contributes to key processes in the pathogenesis of type 2 diabetes, including lipotoxicity, low-grade inflammation and muscle blood flow (AT: adipose tissue). **B:** Mesenteric bed surrounded by PVAT.

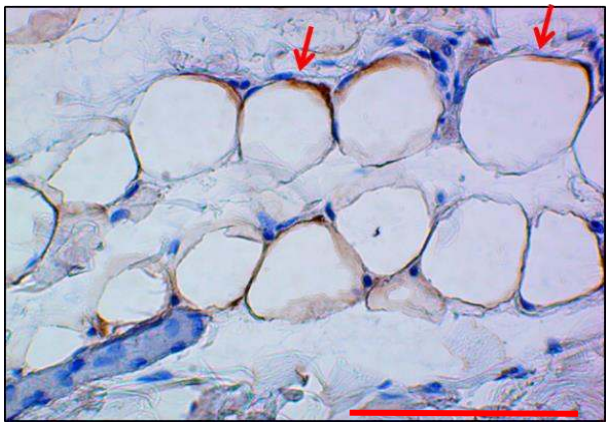

Figure 7. ***Adiponectin expression in human intramuscular PVAT***. 10 µm-thick slices of muscle including PVAT from lean subjects were stained with an anti-adiponectin primary antibody (1:500; Abcam, Cat. No. ab22554), followed by a horse radish peroxidase-coupled secondary antibody (Envision kit; Dako Cytomation; Heverlee, Belgium) and visualisation with DAB solution (1:50, Cat. No. K3468, Dako). Hematoxylin was used as a counterstain. Red arrows indicate adiponectin within adipocytes. Scale bar = 100µm.

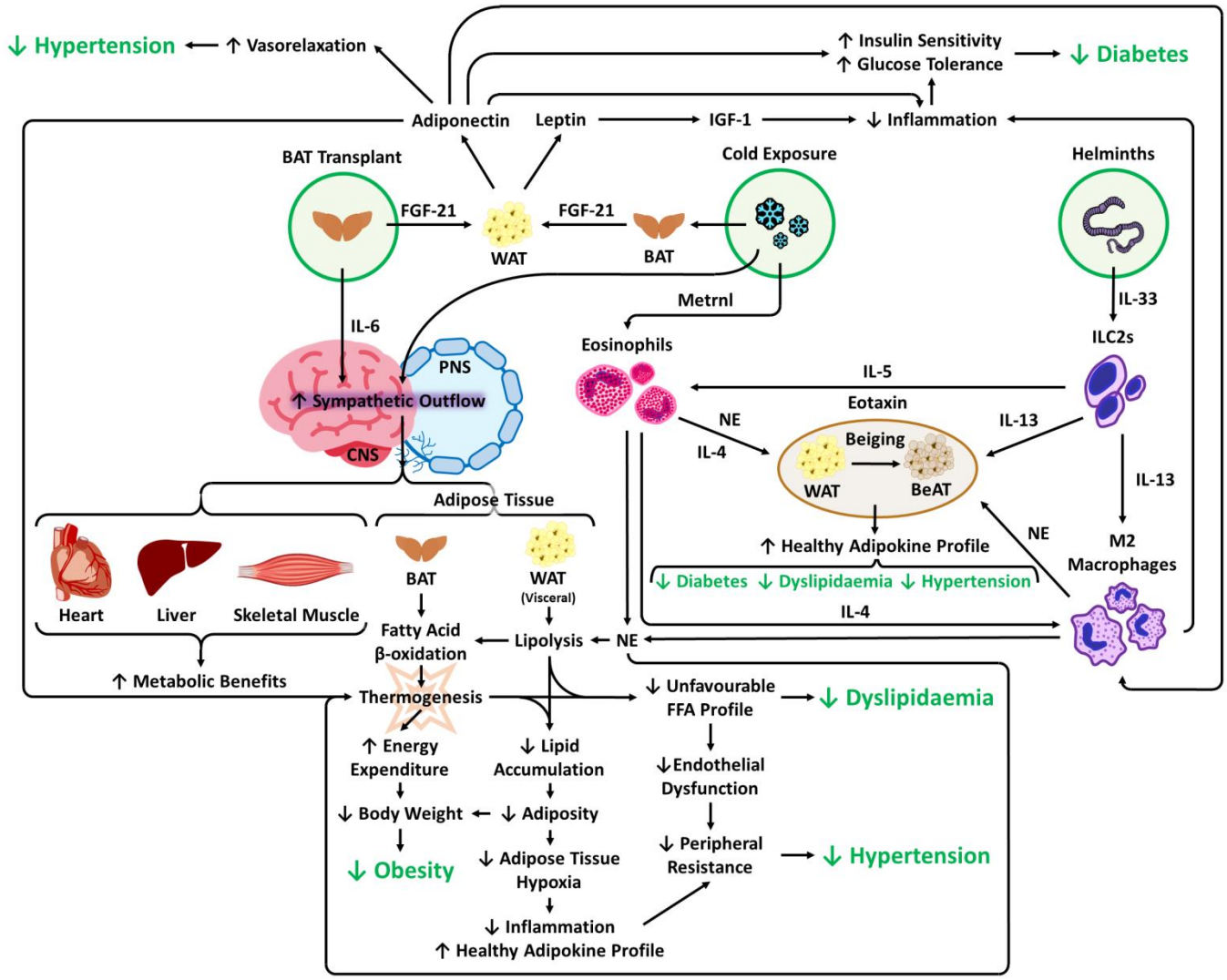

Figure 7: Mechanisms by which potential therapeutic interventions which induce beiging of adipose tissue and/or activate endogenous BAT may improve metabolic health. Cold-exposure and brown adipose tissue (BAT) transplantation increase circulating levels of fibroblast growth factor 21 (FGF-21), which stimulates the release of adiponectin and leptin from white adipose tissue (WAT). Both leptin and adiponectin promote increased insulin sensitivity and glucose tolerance via exerting anti-inflammatory effects, through insulin-like growth factor 1 (IGF-1) and the inducement of M2 macrophages, respectively. Adiponectin also stimulates thermogenesis and directly induces vasorelaxation. Additionally, transplantation of BAT and cold-exposure (as well as pharmacological adrenergic agonism) augment sympathetic outflow to numerous metabolically active tissues (heart, liver, skeletal muscle) including BAT and visceral WAT. Enhanced sympathetic innervation of BAT and WAT increases thermogenesis and lipolysis respectively, which counteracts the lipotoxic effects of the metabolic syndrome. Therapeutic manipulation of the immune system also instigates the beiging of WAT. Cold-exposure and helminth infection induce the production of metrnl, which induces IL-4 secretion from eosinophils, and IL-33, which promotes the activity of type 2 innate lymphoid cells (ILC2s), respectively. Consequently, ILC2s secrete eosinophil attractants, inducing further eosinophil accumulation within adipose tissue. ILC2-derived IL-13 and eosinophil-derived IL-4 induce the polarisation of adipose tissue macrophages towards the anti-inflammatory M2 phenotype and facilitate adipose tissue beiging. In addition, locally elevated levels of norepinephrine secreted from eosinophils and M2 macrophages stimulate lipolysis and thermogenesis and are believed to further contribute to the beiging of WAT. Overall, BAT activation and WAT beiging protect against the hallmarks of the metabolic syndrome (obesity, hypertension, diabetes, dyslipidaemia), in part through imparting a healthy adipose tissue environment and redressing pathologically perturbed adipokine profiles, which would thus restore physiological function of not only adipose tissue but other metabolically important tissues and organs. **Key**: Potential therapeutic interventions which induce beiging and/or activate endogenous BAT (circled in green); Metabolic syndrome-associated pathologies which may be improved (green text). **Additional abbreviations: BeAT**: Beige adipose tissue; **CNS**: Central nervous system; **FFA**: Free fatty acid; **IL-4/5/6/13/33**: Interleukin-4/5/6/13/33; **Metrnl**: Meteorin-like; **NE**: Norepinephrine; **PNS**: Peripheral nervous system