

Perivascular adipose tissue as a regulator of vascular disease pathogenesis:

Identifying novel therapeutic targets

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Abstract

Adipose tissue (AT) is an active endocrine organ with the ability to dynamically secrete a wide range of adipocytokines. Importantly, its secretory profile is altered in various cardiovascular disease states. AT surrounding vessels, or perivascular AT tissue (PVAT), is recognized in particular as an important local regulator of vascular function and dysfunction. Specifically, PVAT has the ability to sense vascular paracrine signals and respond by secreting a variety of vasoactive adipocytokines. Due to PVAT's crucial role in regulating many aspects of vascular biology, it may constitute a novel therapeutic target for the prevention and treatment of vascular disease pathogenesis. Signalling axes in PVAT, such as those including adiponectin, hydrogen sulfide (H₂S), glucagon-like peptide 1 (GLP-1) and pro-inflammatory cytokines, are among the potential novel pharmacological therapeutic targets of PVAT.

Key words: Perivascular adipose tissue, adipocytokines, vascular disease, oxidative stress

Table of Links

TARGETS	LIGANDS
Enzymes^a	
DPP4	Adiponectin
eNOS	IL6
CSE	H₂S
CBS	Aldosterone
MST	AngII
ACE	H₂O₂
Nuclear hormone receptors^b	Leptin
PPARγ	NADPH
Mineralocorticoid Receptors	MCP1
G protein-coupled receptors^c	GLP1
Angiotensin Receptors	
Other protein targets^d	
TNF	
TLR4	
GLP1R	

These Tables of Links list key protein targets and ligands in this article and are hyperlinked* to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 (^{a,b,c,d}Alexander *et al.*, 2015a,b,c,d).

Abbreviations

O₂^{•-}: superoxide anion; CAD: Coronary artery disease; NADPH: Nicotinamide adenine dinucleotide phosphate; eNOS: Endothelial nitric oxide synthase; VSMCs: Vascular smooth muscle cells; AT: Adipose tissue; PVAT: Perivascular adipose tissue; EpAT: Epicardial adipose tissue; TNF: Tumour necrosis factor; ADRF: Adipocyte-derived relaxing factor; H₂S: Hydrogen sulfide; NO: Nitric oxide; MCP-1: Monocyte chemoattractant protein-1; IL-6: Interleukin-6; JNK: c-Jun N-terminal kinase; PPAR γ : Peroxisome proliferator-activated receptor gamma; 4-HNE: 4-hydroxynonenal; TZD: thiazolidinediones; CSE: Cystathionine γ -lyase; CBS: Cystathionine β -synthase; MST: 3-Mercaptopyruvate sulfurtransferase; EDRF: Endothelium-derived relaxing factor; EDHF: Endothelium-derived hyperpolarizing factor; HMG-CoA: Hydroxyl-methyl-glutaryl coenzyme A; TLR4: Toll-like receptor 4; GLP-1: Glucagon-like peptide 1; GLP-1R: Glucagon-like peptide 1 receptor; DPP4: Dipeptidyl peptidase IV; RAAS: Renin-angiotensin-aldosterone system; AngII: Angiotensin II; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MR: Mineralocorticoid receptor; O₂: Oxygen

Introduction

Increased vascular inflammation and oxidative stress are critical features in atherogenesis. Indeed, it has long been established that atherosclerotic lesions are characterised by the activation of NADPH oxidases, enzymes dedicated to superoxide ($O_2^{\cdot-}$) production, as well as by increased uncoupling of endothelial nitric oxide synthases (eNOS) resulting in further increases in vascular $O_2^{\cdot-}$ generation (Li *et al.*, 2014). Vascular inflammation is triggered through redox-sensitive pro-inflammatory signalling pathways, and can, in turn, stimulate further production of reactive oxygen species (Biswas, 2016). Such stimuli induce migration of vascular smooth muscle cells (VSMCs), which is an important element of atherosclerotic lesion progression eventually propagating plaque rupture (Bennett *et al.*, 2016). Therefore, the combination of vascular oxidative stress and inflammation creates a vicious cycle that is further supported by a variety of metabolic and genetic risk factors leading to atherogenesis (Libby *et al.*, 2002).

Until recently, adipose tissue (AT) was believed to be a passive reservoir for energy storage along with supportive and thermoregulatory properties. However, during the last decade, it has become clear that AT is a dynamic endocrine organ (Kershaw *et al.*, 2004), the quantity and (more importantly) the biological behaviour and anatomical variability of which are implicated in the pathogenesis of metabolic syndrome, insulin resistance, and cardiovascular disease (Berg *et al.*, 2005; Hajer *et al.*, 2008). Indeed, visceral AT, the AT depot that surrounds most organs, has been revealed as a metabolically active AT depot which is expanded in cases of central obesity and secretes pro-inflammatory cytokines in the circulation, being consistently linked with the development of systemic insulin resistance and vascular disease (Alexopoulos *et al.*, 2014). On the contrary, lower body adiposity is not related with cardiometabolic disease, whereas some reports even identify a possibly protective role for gluteal AT (Karpe *et al.*, 2015). In consistency with this, subcutaneous AT mass of the gluteal

region has been suggested to act as a buffering system for excess nutrient and fat accumulation (Snijder *et al.*, 2005), and is positively correlated with the plasma levels of adiponectin, an adipokine with beneficial cardiovascular and metabolic effects (Antonopoulos *et al.*, 2011; Buemann *et al.*, 2006). This regional variability of AT biology highlights its complex role in vascular disease pathogenesis and suggests that it is the quality, the biological function and the regional variability, rather than the quantity of AT that determine its net effects on the vascular wall.

Perivascular AT (PVAT) consists of fat directly attached to the outer vascular wall. Initially believed to provide structural support to the underlying vessels, PVAT is now recognised as a unique AT depot that actively regulates vascular function, due to its proximity to the vascular wall as well as its ability to produce a wide range of molecules collectively known as adipocytokines, which exert paracrine vascular effects (Rajsheker *et al.*, 2010; Van de Voorde *et al.*, 2014). Recent evidence suggests that the cross-talk between PVAT and the vascular wall is actually bidirectional, allowing for PVAT to act as a sensor of vascular oxidative stress and inflammation and to subsequently respond by altering its secretory behaviour and therefore its paracrine effects on the vascular wall (Margaritis *et al.*, 2013).

In this review, we discuss the biological roles of PVAT in vascular disease, and we focus on its potential as a target for therapeutic intervention.

PVAT: Overview of structure & function

PVAT is a layer of AT surrounding the wall of most human vessels, with no clear anatomical barrier between the two (Siegel-Axel *et al.*, 2016). Despite being an important element of the vascular wall, PVAT in total comprises no more than approximately 3% of total body AT mass (Lee *et al.*, 2013). Microscopically, PVAT contains adipocytes as well as stromal cells (mainly fibroblasts and monocytes) and vasa vasorum (Szasz *et al.*, 2013). The

composition of PVAT often varies between vascular beds, possibly to accommodate its distinct, tissue-specific roles (Gil-Ortega *et al.*, 2015). PVAT volume also differs depending on local regulatory mechanisms, as evidenced by studies linking the expansion of PVAT around the human coronaries with coronary atherosclerosis (Siegel-Axel *et al.*, 2016).

PVAT often simulates characteristics of brown adipose tissue (BAT) (Gu *et al.*, 2013), namely the presence of abundant vasculature as well as of adipocytes with multiple small lipid droplets and ample mitochondria (Saely *et al.*, 2012). This is in contrast with most other AT depots in adults that belong to the white adipose tissue (WAT) type, containing lipid-rich adipocytes with single lipid droplets (Saely *et al.*, 2012). BAT utilises energy for heat production, in contrast with WAT which predominantly stores energy in the form of fatty acids; BAT may also secrete biologically active molecules (Saely *et al.*, 2012; Wang *et al.*, 2015). The similarity of PVAT to BAT suggests that PVAT may be involved in local energy utilization, while its rich vasculature may facilitate adipogenesis via the local effect of endothelium-derived growth factors (Gu *et al.*, 2013). Furthermore, PVAT apparently loses its BAT-like properties in obesity and this may play an important role in obesity-related cardiovascular disease (Gu *et al.*, 2013). The biological implications of PVAT's similarity with BAT require further investigation.

From a functional point of view, the unique anatomy of PVAT distinguishes it from other AT depots in the sense that it allows for its continuous paracrine interaction with the vascular wall that may be independent of systemic factors. A variety of adipocytokines are secreted by PVAT, and are able to exert both paracrine and endocrine roles (Table 1). Such adipocytokines include molecules originating from adipocytes (e.g., adiponectin, leptin, omentin) as well as cytokines mainly coming from inflammatory cells of the stromal component of PVAT, including T lymphocytes and macrophages (e.g. TNF) (Lee *et al.*, 2013). In addition, PVAT expresses a variety of enzymatic systems regulating redox state (Gao *et al.*,

2007), thus being potentially able to convey local redox-sensitive signals to the vascular wall. The secretome of PVAT is influenced by metabolic stimuli such as inflammation, obesity and insulin resistance, which affect the differentiation status of adipocytes as well as the degree and polarization of its infiltrating inflammatory cells (Siegel-Axel *et al.*, 2016); PVAT's secretome is also being uniquely dependent upon its local interactions with the vascular wall (Gu *et al.*, 2013). Consequently, unravelling the potential biological roles of PVAT's secretome in cardiovascular disease is extremely challenging.

Apart from their direct, local paracrine effects, adipocytokines originating from PVAT may also diffuse into the lumen of the underlying vessels, reaching adjacent vascular segments that are outside their paracrine range. This has been described as a “vasocrine” effect of PVAT, and it highlights its unique ability to locally regulate the homeostasis of individual vascular beds (Yudkin *et al.*, 2005). This vasocrine signalling may be crucial for the handling of blood glucose and the development of systemic insulin resistance and type 2 diabetes mellitus by regulating perfusion of organs such as skeletal muscle; it also serves as an elegant example of the *in vivo* cross-talk between metabolic disease and vascular dysfunction (Yudkin *et al.*, 2005).

Epicardial AT (EpAT) is often regarded as a distinct type of PVAT due to its close proximity to the large coronary arterial branches (Ouwens *et al.*, 2010). EpAT is expanded and assumes a pro-inflammatory phenotype in coronary artery disease (CAD) (Iacobellis, 2015). Given this possible role in the development of CAD, EpAT may be considered a promising therapeutic target in cardiovascular diseases (Gu *et al.*, 2013; Mazurek *et al.*, 2015; Payne *et al.*, 2012). Interestingly, while many clinical studies perceive EpAT as one entity, often synonymous with pericoronary AT or the fat surrounding the coronaries (Aydin *et al.*, 2015; Picard *et al.*, 2014), a recent meta-analysis strongly correlates only EpAT volume at the left atrioventricular groove with CAD (Wu *et al.*, 2014). This suggests that the effects of EpAT may vary depending on its proximity with the coronaries, further implying that pericoronary

AT may have distinct properties compared to the rest of EpAT (non-pericoronary EpAT). Furthermore, recent work has shown that EpAT can also interact not only with the coronaries, but also with the myocardium in a bidirectional paracrine way (Antonopoulos *et al.*, 2016a). Considering that coronary and myocardial function are interrelated, unravelling the spectrum of the interactions between EpAT and both the coronaries and the myocardium, and ultimately its role in the context of cardiovascular disease, is extremely challenging.

The role of PVAT in metabolic and vascular disease

Effects on vascular contractility

It has gradually been recognised that PVAT may be able to influence a variety of physiological biological processes in the vasculature, such as vascular contractility. Indeed, *in vitro* as well as *ex vivo* animal studies have revealed the ability of PVAT to influence vascular contractile responses, presumably by secreting an adipocyte-derived relaxing factor (ADRF) which is able to elicit vasorelaxation (Dubrovskaya *et al.*, 2004; Zavaritskaya *et al.*, 2013). Although the presence of such a factor is now widely accepted, it is still unclear if ADRF is actually a novel, unidentified factor or a known signalling molecule, or even a combination of molecules, of which this particular vasorelaxant role on the cross-talk between PVAT and the vascular wall has not yet been described.

Adiponectin, nitric oxide (NO), hydrogen sulfide (H₂S) and palmitic acid methyl ester (PAME) have all been proposed as being ADRFs (Fernandez-Alfonso *et al.*, 2013; Siegel-Axel *et al.*, 2016). Evidence suggests that the anti-contractile effect of ADRF is mediated by the voltage-gated K_v potassium channels of VSMCs, which may identify this channel family as a potential therapeutic target (Tano *et al.*, 2014). This ability of PVAT to regulate vascular tone and endothelial function is abolished in hypertension and obesity (Lu *et al.*, 2011; Oriowo,

2015). The loss of this vasodilatory effect of PVAT in cases of obesity may also be partially due to the secretion of inflammatory cytokines produced by the increased number of infiltrating macrophages (Oriowo, 2015).

Roles in local inflammation and VSMC migration

Evidence suggests that PVAT's secretome is altered in disease states such as obesity and atherosclerosis (Lee *et al.*, 2013; Verhagen *et al.*, 2011). Many studies have demonstrated increased infiltration of PVAT by macrophages in obesity and atherosclerosis in animal models (Szasz *et al.*, 2013) and humans (Henrichot *et al.*, 2005). The expression and secretion of pro-inflammatory cytokines such as MCP-1 and IL-6 in humans is higher in PVAT compared to other AT depots (Chatterjee *et al.*, 2009), implying that PVAT may exert a net pro-atherogenic effect on the vascular wall, although this concept is highly controversial (Verhagen *et al.*, 2011). PVAT also stimulated proliferation of VSMCs in a rat model (Barandier *et al.*, 2005), and such an effect may be mediated by leptin (Gil-Ortega *et al.*, 2015). By regulating the proliferation of VSMCs, PVAT is potentially able to regulate vascular angiogenic responses to a variety of stimuli, an effect with pathophysiological implications (Bennett *et al.*, 2016). In addition, PVAT may influence endothelial cell activation and migration of VSMCs, indicating that it may regulate a variety of vascular responses in health and disease (Van de Voorde *et al.*, 2014).

Effects on endothelial function and vascular redox state

A number of mechanistic studies have provided insight into the mechanisms by which PVAT affects vascular redox state and NO bioavailability. Recently, *ex vivo* studies of vasorelaxation in vascular rings revealed that diet-induced obesity in mice results in impaired endothelial NO bioavailability through deficiency of eNOS substrate L-arginine and eNOS

uncoupling (Xia *et al.*, 2016). This difference was solely attributed to PVAT, as isolated vascular segments (after removal of PVAT) did not differ between obese and non-obese mice (Xia *et al.*, 2016). The relationship of PVAT with NO bioavailability has also been confirmed in pre-diabetic patients in an *in vivo* setting, where MRI-assessed PVAT volume was inversely correlated with flow-mediated dilatation of the brachial artery (Rittig *et al.*, 2008). PVAT may also secrete paracrine factors that reduce NO bioavailability via caveolin-1 mediated events (Lee *et al.*, 2014).

Obesity has also been associated with reduced phosphorylation of eNOS at its activation site, Ser1177, and has been associated with impaired endothelial function in *ex vivo* models of animal and human vessels; this latter effect was abolished after separation of the vascular wall from its surrounding PVAT or after incubation with superoxide dismutase (SOD) as a means to scavenge $O_2^{\cdot -}$ (Greenstein *et al.*, 2009). PVAT has also been shown to produce $O_2^{\cdot -}$ and hydrogen peroxide (H_2O_2), which induce vasoconstriction and vascular oxidative stress (Gao *et al.*, 2007; Lobato *et al.*, 2012; Wang *et al.*, 2014). These findings highlight the importance of oxidative stress from the PVAT, indicating that PVAT in obese subjects may also increase oxidative stress in the underlying vascular wall.

PVAT is also believed to contribute to the development of vascular insulin resistance in the presence of obesity. Indeed, *ex vivo* insulin-mediated vasorelaxation was impaired in diabetic mice in the presence of PVAT as compared to vascular segments separated from their PVAT (Meijer *et al.*, 2013). These mice also exhibit an increase in PVAT mass with a change in PVAT's secretory profile (reduced adiponectin); in addition, inhibition of c-Jun N-terminal kinase (JNK) in this fat depot seems to restore endothelial function in vascular segments, suggesting that PVAT may induce vascular insulin resistance via JNK activation (Meijer *et al.*, 2013).

Collectively, the previously mentioned experimental findings suggest that PVAT is a vital regulator of endothelial function, NO bioavailability and vascular redox state. In cases of obesity, in particular, PVAT loses its vasoprotective effects and may contribute to oxidative stress and endothelial dysfunction, as well as local inflammation via the production of pro-inflammatory adipocytokines (Verhagen *et al.*, 2011; Virdis, 2016). Furthermore, PVAT may influence insulin signalling at the vascular level, thus providing a potential link between systemic and vascular insulin resistance, events that are hallmarks of obesity-related vascular disease.

Clinical aspects of the relationship between PVAT and vascular disease

As mentioned earlier, multiple clinical studies have linked obesity, especially visceral AT volume, with cardiovascular risk, while also highlighting the significance of the regional variability in AT function. Furthermore, PVAT has been identified as a potentially significant regulator of vascular biology, and such findings have been confirmed in humans by several translational studies (Aghamohammadzadeh *et al.*, 2012). On the other hand, findings are rather inconclusive regarding the overall association of PVAT with cardiovascular risk. Indeed, EpAT and pericoronary AT thickness have been associated clinically with coronary calcification and cardiovascular risk factors such as plasma cholesterol and intima-media thickness (Greif *et al.*, 2009; Sinha *et al.*, 2016). However, most of these associations are driven by the overall visceral AT content, as confirmed by the Framingham Heart study which revealed that the associations of EpAT and PVAT around the thoracic aorta with cardiovascular disease risk were dependent upon visceral AT, the only independent predictor of cardiovascular risk (Britton *et al.*, 2013). On the other hand, EpAT thickness has been independently associated with coronary calcification as well as with atherosclerotic plaque burden and vulnerability (Liu *et al.*, 2010; Park *et al.*, 2013). Interestingly, EpAT volume has also been

independently associated with the risk of atrial fibrillation and left atrial volume (Fitzgibbons *et al.*, 2014), suggesting that the interaction of EpAT with the myocardium may be clinically more relevant than the one with the coronaries. In light of this, pericoronary AT may prove to be a more sensitive biomarker of CAD, but better imaging tools are required for its accurate characterisation.

PVAT as a recipient of vascular signals: Novel aspects of the cross-talk between PVAT and vascular wall

The ability of PVAT to affect vascular biology in a paracrine, outside-to-inside manner (from the PVAT to the vascular wall) is now widely accepted. However, recent work from our group has introduced the concept of inside-to-outside signals (from the vascular wall to the PVAT), suggesting that the secretory profile of PVAT is largely driven by paracrine signals from the adjacent vessel (Antonopoulos *et al.*, 2015). We have recently revealed that circulating levels of adiponectin are driven by AT depots remote to the vascular wall (such as subcutaneous AT) and the systemic effects of adiponectin improve vascular redox state and NO bioavailability in patients undergoing coronary artery bypass graft surgery (CABG) (Margaritis *et al.*, 2013). Conversely, we also found that the expression of adiponectin in PVAT is positively correlated with O_2^- production from the underlying vessel (Margaritis *et al.*, 2013). These findings imply that adiponectin expression is differentially regulated in various AT depots, and that local mechanisms may override the effect of systemic factors in the regulation of the secretome of PVAT.

Attempting to explain the positive association between PVAT-derived adiponectin and O_2^- production in the underlying artery, we demonstrated that vascular oxidative stress leads to the release of oxidation products such as 4-hydroxynonenal (4-HNE) from the vascular wall, that could diffuse to the surrounding PVAT serving as an inside-to-outside messenger able to

activate peroxisome proliferator-activated receptor gamma (PPAR γ) signalling, a well-known regulator of adiponectin expression, in PVAT (Margaritis *et al.*, 2013). Therefore, apart from the more established outside-to-inside signalling, PVAT is also subject to inside-to-outside signals with the human vascular wall. This allows PVAT to act as a “sensor” of vascular pathology, thus being able to adjust its own secretome appropriately, as a local defence mechanism against cardiovascular disease. However, this cross-talk may be impaired in conditions such as insulin resistance or diabetes, partly explaining the increased vascular oxidative stress observed in these disease states. As this atheroprotective mechanism has been discovered in atherosclerosis-free vessels (such as the internal mammary arteries), it is possible it contributes to the well-established resistance of these arteries to atherosclerosis. It is still unknown whether the same mechanism is also present in PVAT surrounding diseased arteries such as the coronaries.

Prospects and challenges in pharmacological targeting of PVAT

Lifestyle changes have long been proposed as a means of weight loss and concomitant reduction of obesity-associated disease risk; these include diet, physical activity and behavioural therapy for maintenance of weight control (Wadden *et al.*, 2012). Such measures are easily applicable at a large scale for primary and secondary prevention in cardiovascular disease. Even more importantly, physical activity has been associated with a reduction of inflammation in AT and better cardiovascular function in insulin-resistant rats (Crissey *et al.*, 2014), and with decreased EpAT thickness in obese humans (Kim *et al.*, 2009).

On the other hand, the long-term benefit of lifestyle changes on cardiovascular disease progression is controversial (Huerta *et al.*, 2004; Thompson *et al.*, 2012), as moderate obesity has been associated with improved cardiovascular outcomes in secondary prevention, an observation called “obesity paradox”(Antonopoulos *et al.*, 2016b). This reflects the distinction

between obesity as a phenotype and AT biology, and reflects a lack of understanding regarding the interactions between AT and the cardiovascular system in humans, highlighting the need for more translational studies which will identify the right therapeutic targets for the prevention and treatment of vascular disease in obesity. Lifestyle changes such as physical activity, albeit still being viable options for treatment of obesity, should be integrated in a broader understanding of AT biology. The new concept that PVAT behaves as a dynamic sensor of vascular biology modifying its secretory profile accordingly, suggests that targeting of individual AT depots would be beneficial over targeting overall AT mass reduction. It also suggests that if we were able to control the PVAT-vessel interactions, we may be able to enhance the vasoprotective potential of PVAT, using it against vascular disease pathogenesis.

It is now widely accepted that PVAT, just as any other AT depot, secretes a wide variety of adipocytokines with both beneficial (e.g., adiponectin, H₂S, omentin) and detrimental (e.g., TNF, IL6, resistin) effects on the vasculature (Rajsheker *et al.*, 2010). Even more importantly, the net cardiovascular effect of PVAT's secretome depends upon the underlying disease context (Lee *et al.*, 2013). However, every single one of the aforementioned adipocytokines has a variety of wide-reaching systemic effects, making their universal targeting challenging. Also, since there is little consensus in defining those PVAT characteristics with beneficial or detrimental cardiovascular effects under different disease states, targeting PVAT and its secretory profile is quite difficult (Fasshauer *et al.*, 2015). Furthermore, it is unclear whether one should better aim to potentiate actions of presumably anti-atherogenic adipocytokines such as adiponectin or inhibit the actions of pro-atherogenic adipocytokines such as resistin, or both (Andrade-Oliveira *et al.*, 2015). It is also unclear which cell type within the AT needs to be targeted or which key transcriptional pathways need to be modified to improve its overall secretory profile.

Identifying novel therapeutic targets in PVAT

PPAR γ & Adiponectin axis

At present, adiponectin is one of the most thoroughly studied adipocytokines. Vast literature has identified a plethora of anti-inflammatory, insulin-sensitising, and anti-oxidant roles for adiponectin. Indeed, adiponectin induces phosphorylation-mediated activation of AMPK, whereas it may be able to inhibit serine phosphorylation of IRS1, thereby improving insulin sensitivity and overall insulin signalling in a variety of tissues (Ruan *et al.*, 2016). In addition, adiponectin has direct anti-oxidant roles in the human vascular wall (Antonopoulos *et al.*, 2015; Margaritis *et al.*, 2013). Additionally, adiponectin induces M2 macrophage polarization while inhibiting inflammatory infiltration and reducing lipid content in AT (Ruan *et al.*, 2016).

Despite these roles, its usefulness as a therapeutic target at a clinical level has not been adequately explored. The half-life of adiponectin, estimated to be approximately 75 minutes (Halberg *et al.*, 2009), adds practical complexity to the pharmacological regulation of its circulating levels. A way to bypass direct targeting of adiponectin while still intervening in adiponectin signalling would be to target adiponectin receptors (AdipoR1, AdipoR2). Recently, an oral adiponectin receptor agonist improved insulin sensitivity and glucose tolerance in mice, suggesting that *in vivo* signalling of adiponectin may be beneficial, but its significance in vascular disease remains to be evaluated (Okada-Iwabu *et al.*, 2015).

An upstream regulator of adiponectin expression and secretion from AT is PPAR γ (Antonopoulos *et al.*, 2014), which facilitates the beneficial effects of this adipocytokine. PPAR γ is an important regulator of adipocyte function, with diverse effects on whole body glucose and lipid metabolism. Activation of PPAR γ in a variety of tissues such as the liver and skeletal muscle ameliorates insulin resistance (Hevener *et al.*, 2003). Additionally, PPAR γ

improves insulin sensitivity and prevents lipotoxicity in AT (Lehrke *et al.*, 2005; Medina-Gomez *et al.*, 2007). Pharmacological PPAR γ agonists such as thiazolidinediones (TZDs), have long been used in type 2 diabetes as a means of insulin sensitisation. However, despite their lipid- and glucose-lowering effects, these agents have a variety of adverse effects including a reportedly elevated risk for heart failure (Ciudin *et al.*, 2012). This highlights the need for better understanding of the tissue-specific effects of PPAR γ , in order to target its signalling more effectively. The pharmacological regulation of PPAR γ /adiponectin signalling is illustrated in Figure 1.

Endogenous H₂S

H₂S has recently emerged as an important signalling molecule in the cardiovascular system, endogenously synthesised by enzymes such as cystathionine γ -lyase (CSE), cystathionine β -synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (MST), and is now believed to cross plasma membranes, allowing it to not only have autocrine but paracrine and endocrine effects as well (Polhemus *et al.*, 2014; Wallace *et al.*, 2015).

In particular, H₂S has been shown to have significant pro-angiogenic (Papapetropoulos *et al.*, 2009), anti-atherosclerotic (Xie *et al.*, 2016), and anti-oxidant (Wallace *et al.*, 2015) roles in the vasculature. It has also been shown to have anti-inflammatory (Zanardo *et al.*, 2006) and vasodilatory effects (Mustafa *et al.*, 2011), but these effects are still controversial with different experimental settings often yielding distinct effects (Li *et al.*, 2011; Polhemus *et al.*, 2014). Despite these known and sometimes controversial effects on the vasculature, little is known about H₂S's effects on vascular function in humans *in vivo*. A recent observational study indicated that plasma H₂S is elevated in vascular disease in men (Peter *et al.*, 2013), while there is a clinical trial (Phase I) suggesting that H₂S may lead to cardiovascular benefits by increasing NO bioavailability *in vivo* (Polhemus *et al.*, 2015) (NCT01989208; NCT02278276). However,

there is no clinical trial to date examining and identifying the effects of H₂S on vascular clinical endpoints, though such studies are crucially needed.

H₂S is also produced by AT (Feng *et al.*, 2009), and H₂S levels in vessels, AT, and circulation are altered in the presence of obesity or increased weight, suggesting that obesity-related changes in AT's secretory profile may affect the production and levels of H₂S (Candela *et al.*, 2016). Indeed, studies have further shown a disparity in H₂S production by PVAT in acute versus chronic obesity (Beltowski, 2013). Thus, while systemic changes in H₂S may affect the vasculature, PVAT-derived H₂S may have particular importance in obesity-related vascular disease, especially as PVAT-derived H₂S has direct paracrine, vasodilatory effects on the vascular wall (Fang *et al.*, 2009). The mechanisms behind these paracrine, vascular effects of H₂S may include changes in NO production from NOSs (Polhemus *et al.*, 2014) or direct S-sulfhydration or persulfidation of key cysteine residues on membrane ion channels (Paul *et al.*, 2012) but further human studies are needed.

As local H₂S originating from AT depots such as PVAT could be responsible for paracrine effects on the vasculature, H₂S may be an interesting therapeutic target for vascular disease. Modulating local levels of H₂S via donors may be one approach but these donors have limitations: the half-life of free H₂S is minutes and likely will need to be replenished to maintain bioavailability, especially as H₂S can be oxidized in biological systems (Wallace *et al.*, 2015). Targeting H₂S's enzymatic sources CSE and CBS may also pose challenges as these enzymes belong to an evolutionarily conserved pathway, the reverse trans-sulfuration pathway (Wallace *et al.*, 2015); thus influencing these enzymes' activity in humans, even with selective inhibitors, may have unintended side-effects, such as affecting substrate homocysteine levels which is associated with cardiovascular disease risk (Paul *et al.*, 2012).

Nonetheless, it is already known that some current drugs (e.g. non-steroid anti-inflammatory drugs (NSAIDs), sulfhydrated angiotensin converting enzyme inhibitors (ACEi)

and phosphodiesterase 5 inhibitors (PDE5) may mediate part of their effects through H₂S and furthermore some drugs like atorvastatin specifically increase PVAT-derived H₂S (Beltowski, 2015), corroborating H₂S's therapeutic potential. On the other hand, the sulfide prodrug resveratrol has only displayed limited cardiovascular benefit in clinical studies (Gliemann *et al.*, 2016), implying that its effects may depend upon the underlying disease state or pharmacokinetic limitations. As such, further research into modulating AT-derived H₂S provides an exciting avenue to explore novel, pharmacological targets against vascular disease pathogenesis (Figure 1).

Insulin resistance, GLP-1, and DPP4

There is a close relationship between insulin resistance and AT biology such that identifying ways to target peripheral insulin resistance in the vascular wall and AT may convey additional benefits beyond modulating systemic insulin resistance status. In particular, regulation of PVAT biology may ameliorate microvascular dysfunction and improve overall insulin sensitivity (Karaca *et al.*, 2014) as drugs that are currently used as insulin sensitizers (e.g. metformin) have been shown to influence the biology of PVAT as illustrated in Figure 1. Indeed, treatment of fructose-fed rats with metformin restored the dysregulated adipocytokine expression profile of PVAT and attenuated the loss of endothelium-dependent, acetylcholine-mediated vasorelaxation *ex vivo* (Sun *et al.*, 2014). On the other hand, PPAR γ agonists, having been previously described as important regulators of AT function in terms of lipid storage, adipocytokine secretion, differentiation and inflammation, partly exert their biological effects by improving insulin sensitivity of AT (Wahli *et al.*, 2012). These findings suggest that PVAT function may be influenced by local insulin resistance, detrimentally affecting vascular biology; thus, efficient targeting of insulin signalling in PVAT may be beneficial over holistic targeting of systemic insulin resistance (Figure 1).

Glucagon-like peptide 1 (GLP-1) has recently emerged as an exciting multi-layered signalling molecule with a variety of potential target tissues and a wide range of receptor-mediated as well as non-receptor-mediated cellular effects (Cantini *et al.*, 2016). GLP-1 as well as a variety of GLP-1 receptor (GLP-1R) analogues are believed to have anti-inflammatory and antioxidant effects in the vasculature, inhibiting NADPH-oxidase activity and stimulating AMPK and eNOS activation (Cantini *et al.*, 2016). Recent findings of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial have confirmed the beneficial role of GLP-1 signalling by demonstrating favourable cardiovascular outcomes in diabetic patients who were treated with the GLP-1R analogue liraglutide (Marso *et al.*, 2016). Regarding GLP-1's potential role in AT biology, it is unclear whether AT is able to secrete GLP-1, or if it expresses GLP-1 receptors (GLP-1R). However, GLP-1 and analogues apparently have a variety of direct effects on AT biology, ranging from reduced lipid accumulation (Meier, 2012) to stimulation of adipogenesis (Challa *et al.*, 2012). Additionally, GLP-1 analogues upregulate adiponectin expression (Kim Chung le *et al.*, 2009) and promote M2 macrophage polarization (Shiraishi *et al.*, 2012). The specific effects of these agents on PVAT and whether they can be involved in paracrine cross-talk loops between PVAT and the vascular wall are still questioned.

The enzyme responsible for cleavage of circulating GLP-1, Dipeptidyl peptidase 4 (DPP4), has been targeted with inhibitors (DPP4 inhibitors) to promote anti-hyperglycaemic actions (Pratley *et al.*, 2007) and it is reasonable to assume, consequently, that the effects of DPP4 inhibitors on AT and cardiovascular disease will derive from the concomitant potentiation of GLP-1 actions. While this may be true, recent evidence suggests that DPP4 inhibitors may also have a variety of direct effects on AT and the vasculature independently of GLP-1 signalling. Indeed, DPP4 has recently been revealed as a novel adipocytokine, the expression of which is elevated in visceral fat of obese patients, and is positively correlated

with subcutaneous and visceral adipocyte size (Lamers *et al.*, 2011), thus providing a novel link between AT biology and metabolic syndrome. As DPP4 inhibitors have displayed various beneficial antioxidant and anti-inflammatory effects on the vasculature as well (Fadini *et al.*, 2011), targeting of DPP4 may be a crucial regulator of the cross-talk between PVAT and the vascular wall (Figure 1).

Pro-inflammatory cytokines

Pro-inflammatory cytokines are a key feature of vascular disease pathogenesis. Such cytokines are abundantly produced in inflamed PVAT, potentially facilitating the establishment of local inflammation and disease progression (Rajsheker *et al.*, 2010). Consequently, efficient targeting of PVAT-derived pro-inflammatory adipocytokines may have a significant vasoprotective potential.

Currently, there is no established effective way to directly target local inflammation within PVAT, as existing anti-inflammatory strategies (such as anti-TNF monoclonal antibodies Infliximab and Etanercept) exert mainly systemic vascular effects (Booth *et al.*, 2004), partially via elevation of circulating adiponectin levels (Nishida *et al.*, 2008). Nanotechnology has now emerged as a novel scientific field utilising a variety of nanoparticles to offer targeted drug delivery options (Psarros *et al.*, 2012), and as such it could allow for direct targeting of PVAT. Indeed, peptide-conjugated nanoparticles have recently been revealed as a successful means of specifically targeting AT (Xue *et al.*, 2016). Although it is unclear whether similar methods could be applied specifically on PVAT, they certainly comprise promising potential tools for efficient and specific therapeutic interventions.

Some drugs that are already frequently used in the treatment of cardiovascular disease exert pleiotropic, anti-inflammatory effects and may target AT in exerting their effects. Apart from their roles in H₂S signalling as described above, statins have also been shown to decrease

AT inflammation (Tousoulis *et al.*, 2014), potentially by inhibiting activation of macrophages via toll-like receptor 4 (TLR4) downstream events (Abe *et al.*, 2008) (Figure 1). While the direct effects of statins on PVAT's inflammatory secretome are unknown, these findings suggest further exploration of such accepted drugs to establish potential, new ways to target local inflammation within PVAT (Antonopoulos *et al.*, 2012).

Effects of common cardiovascular drugs on PVAT

Several drugs routinely prescribed for the management of cardiovascular disease are able to influence AT biology. Indeed, AT is an important activator of the renin-angiotensin-aldosterone system (RAAS) via secretion of angiotensinogen, which increases the production of angiotensin II (AngII) (Sowers, 2013). Obesity has also been associated with increased plasma levels of aldosterone (Whaley-Connell *et al.*, 2011), and both AngII and aldosterone may inhibit physiological insulin signalling and promote local inflammation via activation of T cells and macrophages (Ohshima *et al.*, 2012; Wei *et al.*, 2009). Consequently, targeting of AT and the consequent blockade of the RAAS system may be significant components of the beneficial metabolic and cardiovascular effects of RAAS inhibitors such as angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and aldosterone inhibitors such as spironolactone (Sowers, 2013). Some ARBs are also able to act as partial PPAR γ agonists, upregulating adiponectin expression (Watanabe *et al.*, 2006). The effects of ACEi, ARB and aldosterone inhibitors are summarised in Figure 1.

Recent evidence suggests that aldosterone and mineralocorticoid receptor (MR) antagonists such as eplerenone may have beneficial effects on vascular function, which could be mediated by their direct effects on AT biology. MR antagonists have revealed beneficial effects in terms of vascular redox state, systemic insulin sensitivity, vascular remodelling, endothelial function and AT inflammation (Briones *et al.*, 2012; Guo *et al.*, 2008; Nguyen Dinh

Cat *et al.*, 2011; Silva *et al.*, 2015). Interestingly, adipocytes have been revealed to express both aldosterone and MR, which would in the case of PVAT allow for both autocrine and paracrine (towards the neighbouring blood vessels) aldosterone signalling to occur (Briones *et al.*, 2012). On the other hand, aldosterone has detrimental direct effects on the vasculature (Briet *et al.*, 2013); therefore, the beneficial effects of MR antagonists observed in the previous experimental settings could, in theory, originate from the blockade of aldosterone signalling either in the vasculature or in adipose tissue (or both). Recent work has addressed this issue by utilising an adipose tissue-specific MR-overexpressing mouse model; the direct action of aldosterone on adipose tissue was associated with metabolic syndrome, insulin resistance, a pro-inflammatory phenotype of the adipose tissue and paracrine effects of PVAT on the vasculature (Nguyen Dinh Cat *et al.*, 2016). These findings identify aldosterone as a link between AT and vascular biology. On the other hand, not all studies have demonstrated beneficial effects for MR antagonist treatment on cardiovascular disease prognosis (Parviz *et al.*, 2015), warranting further investigation.

In contrast to aldosterone antagonists, thiazide diuretics have reportedly detrimental effects on glucose and lipid metabolism, worsening insulin sensitivity, a process which may be at least partially dependent upon activation of the RAAS system (Raheja *et al.*, 2012). Therefore, a combination of thiazide diuretics with inhibitors of the RAAS system such as ARBs may be beneficial in the management of cardiovascular disease in diabetic patients, in order to preserve insulin sensitivity (Sowers *et al.*, 2010). However, the extent to which thiazide diuretics directly affect AT depots and their secretome is not adequately explored. It has been suggested that chlorothiazide downregulates expression of adiponectin in 3T3-L1 adipocytes (Brody *et al.*, 2009), an effect with potentially detrimental cardiovascular effects (Figure 1). Further knowledge of the direct effects of thiazide diuretics on AT, as well as the systemic consequences of these effects is needed to optimise the administration of these agents.

Beta-blockers are another class of drugs that, although used extensively in a variety of cardiovascular diseases, have been associated with a variety of metabolic side effects such as obesity and insulin resistance (Pischon *et al.*, 2001). Non-selective alpha-adrenergic blockade, which results in inhibition of lipase activity, has been implicated in such effects (Cruickshank, 2000). On the other hand, beta-blockers also have the ability to suppress excessive sympathetic activity and stimulation of the RAAS system, an effect which would be beneficial in terms of inflammation and insulin resistance (Sowers, 2013). It seems that the overall metabolic effects of beta-blockers depend on the specific characteristics of individual members of this heterogeneous drug class, with third generation beta-blockers being associated with anti-oxidant properties and fewer non-selective side effects (Ozyildiz *et al.*, 2016). Although there is evidence that beta-blockers exert direct metabolic effects on AT, ranging from stimulation of mitochondrial biogenesis to induction of adipogenesis (Huang *et al.*, 2013; Wong *et al.*, 2012), the extent to which these drugs are able to modulate the secretome of distinct AT depots *in vivo* is unknown.

Conclusion

Recent progress in our understanding of AT biology in health and disease has revealed that AT is, in fact, an active endocrine organ subject to complex regulatory mechanisms and able to affect vascular biology in many direct and indirect ways. PVAT in particular, due to its anatomical proximity to the wall of most arteries, is now believed to be of unique functional significance for vascular physiology and pathophysiology, with its paracrine roles being crucial. Vast literature has identified the ability of PVAT to regulate vascular tone as well as other aspects of vascular function via its secretome. These abilities are altered in states of obesity and vascular disease, where the quantity and functional phenotype of PVAT differ, potentially resulting in a net pre-atherogenic secretome inducing inflammation,

vasoconstriction, endothelial dysfunction and proliferation and migration of VSMCs, thus propagating vascular disease. Importantly, PVAT may also act as a recipient of a variety of signals such as oxidation products from the vascular wall, allowing it to dynamically “sense” alterations of vascular biology and modify its secretome appropriately. Such paracrine feedback loops that provide intrinsic rescue mechanisms may be dysregulated in vascular disease, and may thus comprise potentially novel and attractive therapeutic targets for pharmacological intervention. However, at present, increased understanding of the underlying mechanisms is needed to allow the development of new therapeutic strategies for the prevention and treatment of cardiovascular disease, by targeting PVAT.

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References

Abe M, Matsuda M, Kobayashi H, Miyata Y, Nakayama Y, Komuro R, *et al.* (2008). Effects of statins on adipose tissue inflammation: their inhibitory effect on MyD88-independent IRF3/IFN-beta pathway in macrophages. *Arterioscler Thromb Vasc Biol* 28: 871-877.

Aghamohammadzadeh R, Withers S, Lynch F, Greenstein A, Malik R, & Heagerty A (2012). Perivascular adipose tissue from human systemic and coronary vessels: the emergence of a new pharmacotherapeutic target. *Br J Pharmacol* 165: 670-682.

Alexopoulos N, Katritsis D, & Raggi P (2014). Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. *Atherosclerosis* 233: 104-112.

Anand K, Mooss AN, Hee TT, & Mohiuddin SM (2006). Meta-analysis: inhibition of renin-angiotensin system prevents new-onset atrial fibrillation. *Am Heart J* 152: 217-222.

Andrade-Oliveira V, Camara NO, & Moraes-Vieira PM (2015). Adipokines as drug targets in diabetes and underlying disturbances. *J Diabetes Res* 2015: 681612.

Antonopoulos AS, Lee R, Margaritis M, & Antoniades C (2011). Adiponectin as a regulator of vascular redox state: therapeutic implications. *Recent Pat Cardiovasc Drug Discov* 6: 78-88.

Antonopoulos AS, Margaritis M, Coutinho P, Digby J, Patel R, Psarros C, *et al.* (2014). Reciprocal effects of systemic inflammation and brain natriuretic peptide on adiponectin biosynthesis in adipose tissue of patients with ischemic heart disease. *Arterioscler Thromb Vasc Biol* 34: 2151-2159.

Antonopoulos AS, Margaritis M, Coutinho P, Shirodaria C, Psarros C, Herdman L, *et al.* (2015). Adiponectin as a link between type 2 diabetes and vascular NADPH oxidase activity in the human arterial wall: the regulatory role of perivascular adipose tissue. *Diabetes* 64: 2207-2219.

Antonopoulos AS, Margaritis M, Shirodaria C, & Antoniades C (2012). Translating the effects of statins: from redox regulation to suppression of vascular wall inflammation. *Thromb Haemost* 108: 840-848.

Antonopoulos AS, Margaritis M, Verheule S, Recalde A, Sanna F, Herdman L, *et al.* (2016a). Mutual Regulation of Epicardial Adipose Tissue and Myocardial Redox State by PPAR-gamma/Adiponectin Signalling. *Circ Res* 118: 842-855.

Antonopoulos AS, Oikonomou EK, Antoniades C, & Tousoulis D (2016b). From the BMI paradox to the obesity paradox: the obesity-mortality association in coronary heart disease. *Obes Rev.*

Araki K, Masaki T, Katsuragi I, Tanaka K, Kakuma T, & Yoshimatsu H (2006). Telmisartan prevents obesity and increases the expression of uncoupling protein 1 in diet-induced obese mice. *Hypertension* 48: 51-57.

Aydin AM, Kayali A, Poyraz AK, & Aydin K (2015). The relationship between coronary artery disease and pericoronary epicardial adipose tissue thickness. *J Int Med Res* 43: 17-25.

Barandier C, Montani JP, & Yang Z (2005). Mature adipocytes and perivascular adipose tissue stimulate vascular smooth muscle cell proliferation: effects of aging and obesity. *Am J Physiol Heart Circ Physiol* 289: H1807-1813.

Beltowski J (2013). Endogenous hydrogen sulfide in perivascular adipose tissue: role in the regulation of vascular tone in physiology and pathology. *Can J Physiol Pharmacol* 91: 889-898.

Beltowski J (2015). Hydrogen sulfide in pharmacology and medicine--An update. *Pharmacol Rep* 67: 647-658.

Bennett MR, Sinha S, & Owens GK (2016). Vascular Smooth Muscle Cells in Atherosclerosis. *Circ Res* 118: 692-702.

Berg AH, & Scherer PE (2005). Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 96: 939-949.

Biswas SK (2016). Does the Interdependence between Oxidative Stress and Inflammation Explain the Antioxidant Paradox? *Oxid Med Cell Longev* 2016: 5698931.

Booth AD, Jayne DR, Kharbanda RK, McEniery CM, Mackenzie IS, Brown J, *et al.* (2004). Infliximab improves endothelial dysfunction in systemic vasculitis: a model of vascular inflammation. *Circulation* 109: 1718-1723.

Briet M, & Schiffrin EL (2013). Vascular actions of aldosterone. *J Vasc Res* 50: 89-99.

Briones AM, Nguyen Dinh Cat A, Callera GE, Yogi A, Burger D, He Y, *et al.* (2012). Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: implications in diabetes mellitus-associated obesity and vascular dysfunction. *Hypertension* 59: 1069-1078.

Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, & Fox CS (2013). Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. *J Am Coll Cardiol* 62: 921-925.

Brody R, Peleg E, Grossman E, & Sharabi Y (2009). Production and secretion of adiponectin from 3T3-L1 adipocytes: comparison of antihypertensive drugs. *Am J Hypertens* 22: 1126-1129.

Buemann B, Astrup A, Pedersen O, Black E, Holst C, Toubro S, *et al.* (2006). Possible role of adiponectin and insulin sensitivity in mediating the favorable effects of lower body fat mass on blood lipids. *J Clin Endocrinol Metab* 91: 1698-1704.

Candela J, Velmurugan GV, & White C (2016). Hydrogen sulfide depletion contributes to microvascular remodeling in obesity. *Am J Physiol Heart Circ Physiol* 310: H1071-1080.

Cantini G, Mannucci E, & Luconi M (2016). Perspectives in GLP-1 Research: New Targets, New Receptors. *Trends Endocrinol Metab* 27: 427-438.

Challa TD, Beaton N, Arnold M, Rudofsky G, Langhans W, & Wolfrum C (2012). Regulation of adipocyte formation by GLP-1/GLP-1R signaling. *J Biol Chem* 287: 6421-6430.

Chatterjee TK, Stoll LL, Denning GM, Harrelson A, Blomkalns AL, Idelman G, *et al.* (2009). Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ Res* 104: 541-549.

Ciudin A, Hernandez C, & Simo R (2012). Update on cardiovascular safety of PPARgamma agonists and relevance to medicinal chemistry and clinical pharmacology. *Curr Top Med Chem* 12: 585-604.

Crissey JM, Jenkins NT, Lansford KA, Thorne PK, Bayless DS, Vieira-Potter VJ, *et al.* (2014). Adipose tissue and vascular phenotypic modulation by voluntary physical activity and dietary

restriction in obese insulin-resistant OLETF rats. *Am J Physiol Regul Integr Comp Physiol* 306: R596-606.

Cruickshank JM (2000). Beta-blockers continue to surprise us. *Eur Heart J* 21: 354-364.

Doulton TW, He FJ, & MacGregor GA (2005). Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. *Hypertension* 45: 880-886.

Dubrovskaya G, Verlohren S, Luft FC, & Gollasch M (2004). Mechanisms of ADRF release from rat aortic adventitial adipose tissue. *Am J Physiol Heart Circ Physiol* 286: H1107-1113.

Fadini GP, & Avogaro A (2011). Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. *Vascul Pharmacol* 55: 10-16.

Fang L, Zhao J, Chen Y, Ma T, Xu G, Tang C, *et al.* (2009). Hydrogen sulfide derived from periaortic adipose tissue is a vasodilator. *J Hypertens* 27: 2174-2185.

Fasshauer M, & Bluher M (2015). Adipokines in health and disease. *Trends Pharmacol Sci* 36: 461-470.

Feng X, Chen Y, Zhao J, Tang C, Jiang Z, & Geng B (2009). Hydrogen sulfide from adipose tissue is a novel insulin resistance regulator. *Biochem Biophys Res Commun* 380: 153-159.

Fernandez-Alfonso MS, Gil-Ortega M, Garcia-Prieto CF, Aranguez I, Ruiz-Gayo M, & Somoza B (2013). Mechanisms of perivascular adipose tissue dysfunction in obesity. *Int J Endocrinol* 2013: 402053.

Fitzgibbons TP, & Czech MP (2014). Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. *J Am Heart Assoc* 3: e000582.

Fukuda K, Matsumura T, Senokuchi T, Ishii N, Kinoshita H, Yamada S, *et al.* (2015). Statins mediate anti-atherosclerotic action in smooth muscle cells by peroxisome proliferator-activated receptor-gamma activation. *Biochem Biophys Res Commun* 457: 23-30.

Gao YJ, Lu C, Su LY, Sharma AM, & Lee RM (2007). Modulation of vascular function by perivascular adipose tissue: the role of endothelium and hydrogen peroxide. *Br J Pharmacol* 151: 323-331.

Gil-Ortega M, Somoza B, Huang Y, Gollasch M, & Fernandez-Alfonso MS (2015). Regional differences in perivascular adipose tissue impacting vascular homeostasis. *Trends Endocrinol Metab* 26: 367-375.

Gliemann L, Nyberg M, & Hellsten Y (2016). Effects of exercise training and resveratrol on vascular health in aging. *Free Radic Biol Med* 98: 165-176.

Greenstein AS, Khavandi K, Withers SB, Sonoyama K, Clancy O, Jeziorska M, *et al.* (2009).

Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. *Circulation* 119: 1661-1670.

Greif M, Becker A, von Ziegler F, Lebherz C, Lehrke M, Broedl UC, *et al.* (2009). Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 29: 781-786.

Gu P, & Xu A (2013). Interplay between adipose tissue and blood vessels in obesity and vascular dysfunction. *Rev Endocr Metab Disord* 14: 49-58.

Guo C, Ricchiuti V, Lian BQ, Yao TM, Coutinho P, Romero JR, *et al.* (2008). Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation* 117: 2253-2261.

Hajer GR, van Haeften TW, & Visseren FL (2008). Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 29: 2959-2971.

Halberg N, Schraw TD, Wang ZV, Kim JY, Yi J, Hamilton MP, *et al.* (2009). Systemic fate of the adipocyte-derived factor adiponectin. *Diabetes* 58: 1961-1970.

Henrichot E, Juge-Aubry CE, Pernin A, Pache JC, Velebit V, Dayer JM, *et al.* (2005). Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? *Arterioscler Thromb Vasc Biol* 25: 2594-2599.

Hevener AL, He W, Barak Y, Le J, Bandyopadhyay G, Olson P, *et al.* (2003). Muscle-specific Pparg deletion causes insulin resistance. *Nat Med* 9: 1491-1497.

Hu WL, Qiao SB, & Li JJ (2007). Decreased C-reactive protein-induced resistin production in human monocytes by simvastatin. *Cytokine* 40: 201-206.

Huang C, Chen D, Xie Q, Yang Y, & Shen W (2013). Nebivolol stimulates mitochondrial biogenesis in 3T3-L1 adipocytes. *Biochem Biophys Res Commun* 438: 211-217.

Huerta JM, Gonzalez S, Fernandez S, Patterson AM, & Lasheras C (2004). No evidence for oxidative stress as a mechanism of action of hyperhomocysteinemia in humans. *Free Radic Res* 38: 1215-1221.

Iacobellis G (2015). Local and systemic effects of the multifaceted epicardial adipose tissue depot. *Nat Rev Endocrinol* 11: 363-371.

Iwaki M, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, *et al.* (2003). Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. *Diabetes* 52: 1655-1663.

Karaca U, Schram MT, Houben AJ, Muris DM, & Stehouwer CD (2014). Microvascular dysfunction as a link between obesity, insulin resistance and hypertension. *Diabetes Res Clin Pract* 103: 382-387.

Karpe F, & Pinnick KE (2015). Biology of upper-body and lower-body adipose tissue--link to whole-body phenotypes. *Nat Rev Endocrinol* 11: 90-100.

Kershaw EE, & Flier JS (2004). Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 89: 2548-2556.

Kim Chung le T, Hosaka T, Yoshida M, Harada N, Sakaue H, Sakai T, *et al.* (2009). Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression. *Biochem Biophys Res Commun* 390: 613-618.

Kim MK, Tomita T, Kim MJ, Sasai H, Maeda S, & Tanaka K (2009). Aerobic exercise training reduces epicardial fat in obese men. *J Appl Physiol* (1985) 106: 5-11.

Kortekaas KE, Meijer CA, Hinnen JW, Dalman RL, Xu B, Hamming JF, *et al.* (2014). ACE inhibitors potently reduce vascular inflammation, results of an open proof-of-concept study in the abdominal aortic aneurysm. *PLoS One* 9: e111952.

Lamers D, Famulla S, Wronkowitz N, Hartwig S, Lehr S, Ouwens DM, *et al.* (2011). Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes* 60: 1917-1925.

Lee HY, Despres JP, & Koh KK (2013). Perivascular adipose tissue in the pathogenesis of cardiovascular disease. *Atherosclerosis* 230: 177-184.

Lee MH, Chen SJ, Tsao CM, & Wu CC (2014). Perivascular adipose tissue inhibits endothelial function of rat aortas via caveolin-1. *PLoS One* 9: e99947.

Lehrke M, & Lazar MA (2005). The many faces of PPARgamma. *Cell* 123: 993-999.

Li H, Horke S, & Forstermann U (2014). Vascular oxidative stress, nitric oxide and atherosclerosis. *Atherosclerosis* 237: 208-219.

Libby P, Ridker PM, & Maseri A (2002). Inflammation and atherosclerosis. *Circulation* 105: 1135-1143.

Liu J, Fox CS, Hickson D, Sarpong D, Ekunwe L, May WD, *et al.* (2010). Pericardial adipose tissue, atherosclerosis, and cardiovascular disease risk factors: the Jackson heart study. *Diabetes Care* 33: 1635-1639.

Lobato NS, Filgueira FP, Akamine EH, Tostes RC, Carvalho MH, & Fortes ZB (2012). Mechanisms of endothelial dysfunction in obesity-associated hypertension. *Braz J Med Biol Res* 45: 392-400.

Lu C, Su LY, Lee RM, & Gao YJ (2011). Alterations in perivascular adipose tissue structure and function in hypertension. *Eur J Pharmacol* 656: 68-73.

Maenhaut N, & Van de Voorde J (2011). Regulation of vascular tone by adipocytes. *BMC Med* 9: 25.

Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, *et al.* (2013). Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. *Circulation* 127: 2209-2221.

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, *et al.* (2016). Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 375: 311-322.

Mazurek T, & Opolski G (2015). Pericoronary adipose tissue: a novel therapeutic target in obesity-related coronary atherosclerosis. *J Am Coll Nutr* 34: 244-254.

Medina-Gomez G, Gray SL, Yetukuri L, Shimomura K, Virtue S, Campbell M, *et al.* (2007). PPAR gamma 2 prevents lipotoxicity by controlling adipose tissue expandability and peripheral lipid metabolism. *PLoS Genet* 3: e64.

Meier JJ (2012). GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 8: 728-742.

Meijer RI, Bakker W, Alta CL, Sipkema P, Yudkin JS, Viollet B, *et al.* (2013). Perivascular adipose tissue control of insulin-induced vasoreactivity in muscle is impaired in db/db mice. *Diabetes* 62: 590-598.

Mustafa AK, Sikka G, Gazi SK, Stepan J, Jung SM, Bhunia AK, *et al.* (2011). Hydrogen sulfide as endothelium-derived hyperpolarizing factor sulfhydrates potassium channels. *Circ Res* 109: 1259-1268.

Nakamura T, Kawachi K, Saito Y, Saito T, Morishita K, Hoshino J, *et al.* (2009). Effects of ARB or ACE-inhibitor administration on plasma levels of aldosterone and adiponectin in hypertension. *Int Heart J* 50: 501-512.

Nguyen Dinh Cat A, Antunes TT, Callera GE, Sanchez A, Tsiropoulou S, Dulak-Lis MG, *et al.* (2016). Adipocyte-Specific Mineralocorticoid Receptor Overexpression in Mice Is Associated With Metabolic Syndrome and Vascular Dysfunction: Role of Redox-Sensitive PKG-1 and Rho Kinase. *Diabetes* 65: 2392-2403.

Nguyen Dinh Cat A, Briones AM, Callera GE, Yogi A, He Y, Montezano AC, *et al.* (2011). Adipocyte-derived factors regulate vascular smooth muscle cells through mineralocorticoid and glucocorticoid receptors. *Hypertension* 58: 479-488.

Nishida K, Okada Y, Nawata M, Saito K, & Tanaka Y (2008). Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-alpha antibody. *Endocr J* 55: 213-216.

Ohshima K, Mogi M, Jing F, Iwanami J, Tsukuda K, Min LJ, *et al.* (2012). Roles of interleukin 17 in angiotensin II type 1 receptor-mediated insulin resistance. *Hypertension* 59: 493-499.

Okada-Iwabu M, Iwabu M, Ueki K, Yamauchi T, & Kadowaki T (2015). Perspective of Small-Molecule AdipoR Agonist for Type 2 Diabetes and Short Life in Obesity. *Diabetes Metab J* 39: 363-372.

Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, *et al.* (2013). A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature* 503: 493-499.

Oriowo MA (2015). Perivascular adipose tissue, vascular reactivity and hypertension. *Med Princ Pract* 24 Suppl 1: 29-37.

Ouwens DM, Sell H, Greulich S, & Eckel J (2010). The role of epicardial and perivascular adipose tissue in the pathophysiology of cardiovascular disease. *J Cell Mol Med* 14: 2223-2234.

Ozyildiz AG, Eroglu S, Bal U, Atar I, Okyay K, & Muderrisoglu H (2016). Effects of Carvedilol Compared to Nebivolol on Insulin Resistance and Lipid Profile in Patients With Essential Hypertension. *J Cardiovasc Pharmacol Ther.*

Papapetropoulos A, Pyriochou A, Altaany Z, Yang G, Marazioti A, Zhou Z, *et al.* (2009). Hydrogen sulfide is an endogenous stimulator of angiogenesis. *Proc Natl Acad Sci U S A* 106: 21972-21977.

Park JS, Choi SY, Zheng M, Yang HM, Lim HS, Choi BJ, *et al.* (2013). Epicardial adipose tissue thickness is a predictor for plaque vulnerability in patients with significant coronary artery disease. *Atherosclerosis* 226: 134-139.

Parviz Y, Iqbal J, Pitt B, Adlam D, Al-Mohammad A, & Zannad F (2015). Emerging cardiovascular indications of mineralocorticoid receptor antagonists. *Trends Endocrinol Metab* 26: 201-211.

Paul BD, & Snyder SH (2012). H(2)S signalling through protein sulfhydration and beyond. *Nat Rev Mol Cell Biol* 13: 499-507.

Payne GA, Kohr MC, & Tune JD (2012). Epicardial perivascular adipose tissue as a therapeutic target in obesity-related coronary artery disease. *Br J Pharmacol* 165: 659-669.

Peter EA, Shen X, Shah SH, Pardue S, Glawe JD, Zhang WW, *et al.* (2013). Plasma free H₂S levels are elevated in patients with cardiovascular disease. *J Am Heart Assoc* 2: e000387.

Picard FA, Gueret P, Laissy JP, Champagne S, Leclercq F, Carrie D, *et al.* (2014). Epicardial adipose tissue thickness correlates with the presence and severity of angiographic coronary artery disease in stable patients with chest pain. *PLoS One* 9: e110005.

Pischon T, & Sharma AM (2001). Use of beta-blockers in obesity hypertension: potential role of weight gain. *Obes Rev* 2: 275-280.

Polhemus DJ, & Lefer DJ (2014). Emergence of hydrogen sulfide as an endogenous gaseous signaling molecule in cardiovascular disease. *Circ Res* 114: 730-737.

Polhemus DJ, Li Z, Pattillo CB, Gojon G, Sr., Gojon G, Jr., Giordano T, *et al.* (2015). A novel hydrogen sulfide prodrug, SG1002, promotes hydrogen sulfide and nitric oxide bioavailability in heart failure patients. *Cardiovasc Ther* 33: 216-226.

Pratley RE, & Salsali A (2007). Inhibition of DPP-4: a new therapeutic approach for the treatment of type 2 diabetes. *Curr Med Res Opin* 23: 919-931.

Psarros C, Lee R, Margaritis M, & Antoniadou C (2012). Nanomedicine for the prevention, treatment and imaging of atherosclerosis. *Nanomedicine* 8 Suppl 1: S59-68.

Raheja P, Price A, Wang Z, Arbique D, Adams-Huet B, Auchus RJ, *et al.* (2012). Spironolactone prevents chlorthalidone-induced sympathetic activation and insulin resistance in hypertensive patients. *Hypertension* 60: 319-325.

Rajshanker S, Manka D, Blomkalns AL, Chatterjee TK, Stoll LL, & Weintraub NL (2010). Crosstalk between perivascular adipose tissue and blood vessels. *Curr Opin Pharmacol* 10: 191-196.

Rittig K, Staib K, Machann J, Bottcher M, Peter A, Schick F, *et al.* (2008). Perivascular fatty tissue at the brachial artery is linked to insulin resistance but not to local endothelial dysfunction. *Diabetologia* 51: 2093-2099.

Ruan H, & Dong LQ (2016). Adiponectin signaling and function in insulin target tissues. *J Mol Cell Biol* 8: 101-109.

Saely CH, Geiger K, & Drexel H (2012). Brown versus white adipose tissue: a mini-review. *Gerontology* 58: 15-23.

Shiraishi D, Fujiwara Y, Komohara Y, Mizuta H, & Takeya M (2012). Glucagon-like peptide-1 (GLP-1) induces M2 polarization of human macrophages via STAT3 activation. *Biochem Biophys Res Commun* 425: 304-308.

Siegel-Axel DI, & Haring HU (2016). Perivascular adipose tissue: An unique fat compartment relevant for the cardiometabolic syndrome. *Rev Endocr Metab Disord* 17: 51-60.

Silva MA, Cau SB, Lopes RA, Manzato CP, Neves KB, Bruder-Nascimento T, *et al.* (2015). Mineralocorticoid receptor blockade prevents vascular remodelling in a rodent model of type 2 diabetes mellitus. *Clin Sci (Lond)* 129: 533-545.

Sinha SK, Thakur R, Jha MJ, Goel A, Kumar V, Kumar A, *et al.* (2016). Epicardial Adipose Tissue Thickness and Its Association With the Presence and Severity of Coronary Artery Disease in Clinical Setting: A Cross-Sectional Observational Study. *J Clin Med Res* 8: 410-419.

Snijder MB, Visser M, Dekker JM, Goodpaster BH, Harris TB, Kritchevsky SB, *et al.* (2005). Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* 48: 301-308.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al.* (2016). The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative

interactions between 1300 protein targets and 6000 ligands. *Nucleic Acids Res* 44: D1054-1068.

Sowers JR (2013). Diabetes mellitus and vascular disease. *Hypertension* 61: 943-947.

Sowers JR, Raij L, Jialal I, Egan BM, Ofili EO, Samuel R, *et al.* (2010). Angiotensin receptor blocker/diuretic combination preserves insulin responses in obese hypertensives. *J Hypertens* 28: 1761-1769.

Sun Y, Li J, Xiao N, Wang M, Kou J, Qi L, *et al.* (2014). Pharmacological activation of AMPK ameliorates perivascular adipose/endothelial dysfunction in a manner interdependent on AMPK and SIRT1. *Pharmacol Res* 89: 19-28.

Szasz T, Bomfim GF, & Webb RC (2013). The influence of perivascular adipose tissue on vascular homeostasis. *Vasc Health Risk Manag* 9: 105-116.

Tano JY, Schleifenbaum J, & Gollasch M (2014). Perivascular adipose tissue, potassium channels, and vascular dysfunction. *Arterioscler Thromb Vasc Biol* 34: 1827-1830.

Thompson D, Karpe F, Lafontan M, & Frayn K (2012). Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol Rev* 92: 157-191.

Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniadis C, & Stefanadis C (2014). Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. *J Am Coll Cardiol* 63: 2491-2502.

Usui I, Fujisaka S, Yamazaki K, Takano A, Murakami S, Yamazaki Y, *et al.* (2007). Telmisartan reduced blood pressure and HOMA-IR with increasing plasma leptin level in hypertensive and type 2 diabetic patients. *Diabetes Res Clin Pract* 77: 210-214.

Van de Voorde J, Boydens C, Pauwels B, & Decaluwe K (2014). Perivascular adipose tissue, inflammation and vascular dysfunction in obesity. *Curr Vasc Pharmacol* 12: 403-411.

Verhagen SN, & Visseren FL (2011). Perivascular adipose tissue as a cause of atherosclerosis. *Atherosclerosis* 214: 3-10.

Virdis A (2016). Endothelial Dysfunction in Obesity: Role of Inflammation. *High Blood Press Cardiovasc Prev* 23: 83-85.

Wadden TA, Webb VL, Moran CH, & Bailer BA (2012). Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. *Circulation* 125: 1157-1170.

Wahli W, & Michalik L (2012). PPARs at the crossroads of lipid signaling and inflammation. *Trends Endocrinol Metab* 23: 351-363.

Wallace JL, & Wang R (2015). Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter. *Nat Rev Drug Discov* 14: 329-345.

Wang D, Wang C, Wu X, Zheng W, Sandberg K, Ji H, *et al.* (2014). Endothelial dysfunction and enhanced contractility in microvessels from ovariectomized rats: roles of oxidative stress and perivascular adipose tissue. *Hypertension* 63: 1063-1069.

Wang GX, Zhao XY, & Lin JD (2015). The brown fat secretome: metabolic functions beyond thermogenesis. *Trends Endocrinol Metab* 26: 231-237.

Watanabe S, Okura T, Kurata M, Irita J, Manabe S, Miyoshi K, *et al.* (2006). The effect of losartan and amlodipine on serum adiponectin in Japanese adults with essential hypertension. *Clin Ther* 28: 1677-1685.

Wei Y, Whaley-Connell AT, Habibi J, Rehmer J, Rehmer N, Patel K, *et al.* (2009). Mineralocorticoid receptor antagonism attenuates vascular apoptosis and injury via rescuing protein kinase B activation. *Hypertension* 53: 158-165.

Whaley-Connell A, & Sowers JR (2011). Aldosterone and Risk for Insulin Resistance. *Hypertension* 58: 998-1000.

Wong A, Hardy KL, Kitajewski AM, Shawber CJ, Kitajewski JK, & Wu JK (2012). Propranolol accelerates adipogenesis in hemangioma stem cells and causes apoptosis of hemangioma endothelial cells. *Plast Reconstr Surg* 130: 1012-1021.

Wu FZ, Chou KJ, Huang YL, & Wu MT (2014). The relation of location-specific epicardial adipose tissue thickness and obstructive coronary artery disease: systemic review and meta-analysis of observational studies. *BMC Cardiovasc Disord* 14: 62.

Xia N, Horke S, Habermeier A, Closs EI, Reifenberg G, Gericke A, *et al.* (2016). Uncoupling of Endothelial Nitric Oxide Synthase in Perivascular Adipose Tissue of Diet-Induced Obese Mice. *Arterioscler Thromb Vasc Biol* 36: 78-85.

Xie L, Gu Y, Wen M, Zhao S, Wang W, Ma Y, *et al.* (2016). Hydrogen sulfide induces keap1 S-sulphydration and suppresses diabetes-accelerated atherosclerosis via Nrf2 activation. *Diabetes*.

Xue Y, Xu X, Zhang XQ, Farokhzad OC, & Langer R (2016). Preventing diet-induced obesity in mice by adipose tissue transformation and angiogenesis using targeted nanoparticles. *Proc Natl Acad Sci U S A* 113: 5552-5557.

Yudkin JS, Eringa E, & Stehouwer CD (2005). "Vasocrine" signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 365: 1817-1820.

Zanardo RC, Brancalone V, Distrutti E, Fiorucci S, Cirino G, & Wallace JL (2006). Hydrogen sulfide is an endogenous modulator of leukocyte-mediated inflammation. *FASEB J* 20: 2118-2120.

Zavaritskaya O, Zhuravleva N, Schleifenbaum J, Gloe T, Devermann L, Kluge R, *et al.* (2013). Role of KCNQ channels in skeletal muscle arteries and periadventitial vascular dysfunction. *Hypertension* 61: 151-159.

Table 1: Major adipose tissue products and their main biological roles and pharmacological potential in vascular biology

Adipose tissue product	Functions	Pharmacological targeting
Adiponectin	Insulin-sensitizing, anti-oxidant, and anti-inflammatory properties	PPAR γ agonists and ARBs upregulate adiponectin expression; novel AdipoR agonists may be useful for stimulation of adiponectin signaling (Iwaki <i>et al.</i> , 2003; Nakamura <i>et al.</i> , 2009; Okada-Iwabu <i>et al.</i> , 2013)
Leptin	Hyperleptinaemia and leptin resistance are associated with cardiometabolic disease, but the direct effects of this hormone in different disease settings are controversial	At present there is no efficient targeting option for leptin in the context of cardiovascular disease; commonly used drugs such as ARBs have been shown to increase plasma leptin (Usui <i>et al.</i> , 2007)
Omentin	Insulin-sensitizing and anti-oxidant effects	Omentin is an attractive therapeutic target due to its potential beneficial roles; however, no specific treatments have been proposed yet
Resistin	Promotion of insulin resistance, inflammation, and oxidative stress	Drugs such as statins and ACEi/ARB have been revealed to downregulate expression of resistin in AT and reduce its circulating levels (Araki <i>et al.</i> , 2006; Hu <i>et al.</i> , 2007)
TNF	Wide range of pro-inflammatory effects, induction of oxidative stress & insulin resistance	Anti-TNF treatment is an efficient way of inhibiting TNF, but is associated with significant side effects; several drugs including ACEi and statins have been proposed to suppress TNF expression in some studies (Fukuda <i>et al.</i> , 2015; Kortekaas <i>et al.</i> , 2014)
IL-6	Potent pro-inflammatory properties, induction of oxidative stress	Anti-IL-6 monoclonal antibodies have been developed as therapeutic modalities; their use in cardiovascular disease however is compromised by their non-specific side effects
Angiotensinogen/AngII/Aldosterone	Pro-oxidant and pro-inflammatory roles on the vascular wall	ACEi and ARB are established drugs that potently inhibit the AngII/aldosterone axis and its detrimental effects in a variety of cardiovascular diseases (Anand <i>et al.</i> , 2006; Briones <i>et al.</i> , 2012; Doulton <i>et al.</i> , 2005)
H ₂ S	Pro-angiogenic, anti-atherogenic, anti-oxidant, vasoactive (predominantly vasodilatory), anti-inflammatory (primarily), possible oxygen (O ₂) sensor	Direct targeting of H ₂ S is challenging; H ₂ S donors have had limited usefulness in the treatment of cardiovascular disease thus far and further exploration of endogenous mechanisms regulating H ₂ S production may reveal novel targets (Beltowski, 2015)
ROS & H ₂ O ₂	Mostly pro-oxidant and pro-inflammatory roles resulting in vasoconstriction and endothelial dysfunction; H ₂ O ₂ may have novel signal transduction properties	The biological roles of adipose tissue-derived ROS are well established (Gao <i>et al.</i> , 2007; Maenhaut <i>et al.</i> , 2011); conversely, no efficient antioxidant treatments exist at present, although a variety of medications may interfere with ROS production

TNF: Tumour necrosis factor; AngII: Angiotensin II; O₂: Oxygen; H₂S: Hydrogen sulfide; PPAR γ : Peroxisome proliferator-activated receptor gamma; ARB: Angiotensin receptor blocker; ACEi: Angiotensin converting enzyme inhibitor; AT: Adipose tissue; ROS: Reactive oxygen species; H₂O₂: Hydrogen peroxide

Legend to the figure

Figure 1: Overview of the potential cardiovascular pharmacology of perivascular adipose tissue (PVAT). PVAT secretes adipocytokines originating from adipocytes (e.g., adiponectin, leptin, omentin, H₂S, DPP-IV, aldosterone) or from immune cells such as lymphocytes and macrophages (TNF, IL-6 and other interleukins). These adipocytokines influence vascular redox state (i.e., the production of reactive oxygen species (ROS) such as superoxide (O₂^{•-}), hydrogen peroxide (H₂O₂) and peroxynitrite (ONOO⁻)) as well as the migration and proliferation of VSMCs, regulating vascular injury and atherogenesis. Various pharmacological agents influence the secretome of PVAT. PPAR γ agonists, statins, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) as well as mineralocorticoid receptor antagonists and aldosterone antagonists all upregulate PPAR γ , in contrast with thiazides. PPAR γ in turn stimulates adiponectin secretion from adipocytes, which inhibits oxidative stress and restores the bioavailability of tetrahydrobiopterin (BH₄), a critical co-factor of the endothelial nitric oxide synthase (eNOS), resulting in improved eNOS coupling and increased nitric oxide (NO) bioavailability. Adiponectin expression is also upregulated in response to vascular oxidative injury via novel mediators such as 4-hydroxynonenal (4-HNE), a lipid peroxidation product. ACEi, ARB, and aldosterone inhibitors as well as mineralocorticoid receptor (MR) inhibitors also inhibit the detrimental pro-oxidant effects of AngII and aldosterone signalling. ROS as well as cytokines produced by immune cells of PVAT are also involved in vascular oxidative injury and pro-inflammatory signalling, and these effects are inhibited by statins and possibly DPP4 inhibitors. Statins also upregulate adipocyte production of H₂S, a gas with vasorelaxant and PPAR γ -stimulating roles inflammation, via enzymes such as cystathionine γ lyase. Further investigation of local PVAT-vessel interactions may provide novel therapeutic options for vascular disease.