Pro-contractile effects of perivascular fat in health and disease

Ramirez JG, O’Malley EJ, Ho WSV.

Vascular Biology Research Centre, St George’s University of London, Cranmer Terrace, London SW17 0RE, UK

Abstract

Perivascular adipose tissue (PVAT) is now recognised as an active player in vascular homeostasis. Expansion of PVAT in obesity and the possible role of PVAT in vascular dysfunction has attracted much interest. In terms of the regulation of vascular tone and blood pressure, PVAT has been shown to release vasoactive mediators, for instance angiotensin peptides, reactive oxygen species, chemokines and cytokines. The secretory profile of PVAT is altered by obesity, hypertension and other cardiovascular diseases, leading to imbalance between its pro-contractile and anti-contractile effects. PVAT adipocytes represent an important source of the mediators, but infiltrating immune cells may become more important under conditions of hypoxia and inflammation. This review describes recent advances on the effects of PVAT on vascular tone regulation, highlighting the evidence for a pro-contractile action in health and disease. The role of the endothelium, vascular smooth muscle, immune cells and probably perivascular nerves in PVAT function is also discussed.

<table>
<thead>
<tr>
<th>TARGETS</th>
<th>LIGANDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPCRs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Adiponectin</td>
</tr>
<tr>
<td>adrenoceptor</td>
<td>Ang 1-7</td>
</tr>
<tr>
<td>AT&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Ang II</td>
</tr>
<tr>
<td>ChemR23</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>ET&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Chemerin</td>
</tr>
<tr>
<td>Ion channels&lt;sup&gt;b&lt;/sup&gt;</td>
<td>cGMP</td>
</tr>
<tr>
<td>BK&lt;sub&gt;Ca&lt;/sub&gt;</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>K&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>Nuclear hormone receptors&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hydrogen sulphide</td>
</tr>
<tr>
<td>PPAR&lt;sub&gt;γ&lt;/sub&gt;</td>
<td>IL-6</td>
</tr>
<tr>
<td>Enzymes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Rho kinase</td>
</tr>
<tr>
<td>ACE</td>
<td>PKC</td>
</tr>
<tr>
<td>Akt</td>
<td>mTOR</td>
</tr>
<tr>
<td>AMPK</td>
<td>PPARγ</td>
</tr>
<tr>
<td>COX</td>
<td>Rho kinase</td>
</tr>
<tr>
<td>eNOS</td>
<td>PKC</td>
</tr>
<tr>
<td>ERK</td>
<td>mTOR</td>
</tr>
<tr>
<td>NO</td>
<td>RANTES</td>
</tr>
<tr>
<td>IL-10</td>
<td>TNFα</td>
</tr>
<tr>
<td>Insulin</td>
<td>PGE&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Leptin</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>MCP-1</td>
<td>RANTES</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>TNFα</td>
</tr>
<tr>
<td>IL-6</td>
<td>TXA&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
</tr>
</tbody>
</table>
These Tables of Links list key protein targets and ligands in this article that 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 (2, Alexander et al., 2015a,b,c,d).

**Abbreviations**

ACE, angiotensin-converting enzyme; ADFC, adipocyte-derived contractile factor; ADRF, adipocyte-derived relaxing factor; ADV, adventitia; Ang, angiotensin, COX, cyclooxygenase; DOCA, deoxycorticosterone acetate; EC, endothelium; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET1, endothelin-1; ETa, endothelin ETa receptor; H2S, hydrogen sulphide; MCP-1, monocyte-chemoattractant protein-1; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PGE2, prostaglandin E2; PKC, protein kinase C; PVAT, perivascular adipose tissue; RANTES, regulated on activation, normal T Cell expressed and secreted; ROS, reactive oxygen species; SHRS, stroke-prone spontaneously hypertensive rat; SM, smooth muscle; thromboxane A2, TXA2; TNFa, tumour necrosis factor-α; mTOR, mechanistic target of rapamycin

**Introduction**

Perivascular adipose tissues (PVAT) were originally thought to only provide structural support and thus routinely removed in vessel contractility studies. However, the growing prevalence of obesity, characterised by excessive adipose tissues, and the realisation that adipose tissues act as a complex paracrine and endocrine organ (Gustafson et al., 2007; Ahima & Flier, 2000) has drawn attention to a functional role of PVAT, which might also provide a mechanistic link between obesity and vascular dysfunction. PVAT is now recognised as a specialised fat depot around most blood vessels, releasing diffusible factors that modulate local vascular reactivity and inflammatory status and, as a result, may contribute to pathophysiological changes seen in cardiovascular diseases, diabetes and obesity (reviewed in, Szasz et al., 2013; Yudkin et al., 2015; Gil-Ortega et al., 2015; Fernandez Alfonso et al., 2017). Indeed, the Framingham Heart Study shows that a higher volume of PVAT around thoracic aorta is associated with metabolic risk factors and higher prevalence of cardiovascular disease in volunteers (Lehman et al., 2010; Britton et al., 2012). Numerous mechanisms have been suggested to underlie the cross talk between PVAT and vascular cells, but the regulation of PVAT function, particularly the balance between its beneficial and deleterious effects remains poorly defined. In 1991, Soltis and Cassis reported that, in rat aorta, PVAT potentiated contractions to a sympathomimetic but reduces that to noradrenaline due to reuptake by adrenergic nerves in PVAT. Subsequently, PVAT was also found to reduce responses to other vasoconstrictors, leading to the proposal of PVAT-derived (PVRFs) or adipocyte-derived relaxing factors (ADRFs). Much of the research has since focused on identifying these relaxing factors and establishing their vascular actions (see Gollasch, 2012 and Withers et al., 2014 for reviews). However, there is also evidence for the production of contractile factors from PVAT, which were initially termed perivascular adipocyte-derived contractile factors (PVCFs; Gao, 2007) and later adipocyte-derived contractile factors (ADCFs;
Meyer et al., 2013). This adds to a complex scenario of anti-contractile vs pro-contractile properties of PVAT. In this review, we intend to provide an update on the balance between relaxant and contractile effects of PVAT, highlighting a potential shift from an anti-contractile action of PVAT in health to a pro-contractile action in obesity and related cardiovascular diseases.

Composition of PVAT

Adipose tissue surrounding blood vessels is not physically separated from the vascular wall by a fascial layer, providing access for its paracrine effects. In general, brown adipocytes are larger in size, with smaller oil droplets and larger numbers of mitochondria than white adipocytes, which store triglycerides. Morphological and gene expression analysis indicate that whilst perivascular adipocytes often resemble white adipocytes, they are distinct from visceral and subcutaneous fat and display characteristics of both white and brown adipocytes; sometimes referred to as beige adipocytes. For instance, perivascular adipocytes of human coronary arteries are smaller and irregularly shaped, with fewer differentiation markers but higher expression of some brown adipocyte-related genes, when compared to subcutaneous adipocytes (Chatterjee et al., 2009). The precise phenotype appears to depend on the vascular region and species (Szasz et al., 2013; Gil-Ortega et al., 2015). Adipocytes around thoracic aorta are more similar to brown adipocytes, at least in rodents (Gálvez-Prieto et al., 2008a; Padilla et al., 2013). However, adipocytes from abdominal aorta and mesenteric arteries are closer to white adipocytes in both rodents and humans (Henrichot et al., 2005; Police et al., 2009; Padilla et al., 2013).

Importantly, adipose tissues are dynamically regulated, showing cellular and metabolic plasticity. Sustained obesity is associated with increases in size and/or number of PVAT white adipocytes (Marchesi et al., 2009; Ketonen et al., 2010; Ma et al., 2010; Greenstein et al., 2009). These are accompanied by functional changes, including altered secretion pattern of PVAT (Greenstein et al., 2009; Chatterjee et al., 2009; Ketonen et al., 2010). On the other hand, increased proportion of brown to white adipocytes (browning of adipose tissues) promotes thermogenesis and might represent a protective mechanism against metabolic diseases (Pellegrinelli et al., 2016), and perhaps improve vascular function in obesity and atherosclerosis (Fitzgibbons et al., 2011; Chang et al., 2012).

In addition to adipocytes, PVAT contains other important cell types such as macrophages, T-lymphocytes and fibroblasts, which may also contribute to PVAT function. Indeed, infiltration of immune cells in PVAT is characteristic of disease states associated with vascular inflammation (Omar et al., 2014; Pellegrinelli et al., 2016). Expansion of PVAT also likely involves generation of pre-adipocytes from resident mesenchymal stem cells and maturation of pre-adipocytes (Pellegrinelli et al., 2016). Moreover, PVAT is also innervated by sympathetic nerves (Bulloch and Daly, 2014; Darios et al., 2016), which could stimulate the browning of PVAT. Nonetheless, the interactions among perivascular adipocytes, immune cells and nerves in vascular regulation remain poorly defined. Adipocytes, which are the main cellular component of PVAT, are known to release vasoactive substances (e.g. ADRF and ADCF), but immune cells and sympathetic nerves might serve as additional sources (e.g. Gao et al., 2006; Lumeng et al., 2007; Dashwood and Loesche, 2011; Nguyen
et al., 2011). Where possible, we will highlight the likely cellular source(s) of vasoactive substances within PVAT.

**Evidence for contractile factors from PVAT**

Similar to adipocytes in other anatomical locations, increasing evidence suggests that PVAT secretes bioactive molecules, including adipokines and other cytokines that regulate cardiovascular function. A number of these diffusible factors can induce direct vasocontraction, and maybe referred to as PVAT-derived or adipocyte-derived contract factors (denoted ADCFs herein), which are highlighted in Table 1. Much of the evidence comes from contractility studies using isolated arteries with and without PVAT, combined with isolated PVAT and its conditioned media under physiological conditions.

Adipocytes are known to express a local renin-angiotensin-aldosterone system (RAAS), including angiotensinogen and angiotensin converting enzyme for synthesis of the potent vasoconstrictor, angiotensin II (Ang II; Cassis et al., 2008; Karlsson et al., 1998). The expression of RAAS components can vary depending on the composition and location of adipose tissues (Cassis et al., 1988; Engeli et al., 1999; Galvez-Prieto et al., 2008a; Riedel et al., 2016). PVAT is thought to express all components of RAAS and that PVAT-derived Ang II promotes contractions through AT1 receptor activation in rat mesenteric arteries (Lu et al., 2010). Gao and co-workers proposed that Ang II acts indirectly by stimulating superoxide radical production from NADPH oxidase in PVAT adipocytes or the vascular wall itself (Gao et al., 2006; Lu et al., 2008). Ang II has also been shown to play a role in local inflammation associated with hypertension and obesity, stimulating infiltration of immune cells including T-lymphocytes and macrophages in PVAT and production of reactive oxygen species (Police et al., 2009; Guzik et al., 2007; Mikolajczyk et al., 2016). However, the importance of PVAT as a source of Ang II in the control of vascular tone and blood pressure, particular in hypertension and obesity, remains to be established. Moreover, it is likely that the production and function of PVAT-derived Ang II show regional heterogeneity (Galvez-Prieto et al., 2008a). Ang II can also further exacerbate PVAT dysfunction, since AT1 receptor activation has been shown to reduce browning of adipose tissue, and promote adipocyte hypertrophy, insulin resistance and weight gain in high fat-induced obesity in mice (Graus-Nunes et al., 2017).

In the initial study by Soltis and Cassis (1991), PVAT greatly enhanced contractions to electrical field stimulation or the indirect sympathomimetic tyramine in rat aorta, suggesting a role for sympathetic nerve activity in PVAT. Sympathetic nerves have been reported in PVAT of human saphenous veins (Dashwood and Loesche, 2011). The role for sympathetic innervation in the regulation of vascular tone and blood pressure is well established. Elevated sympathetic activity is also associated with hypertension, including obesity-associated hypertension (Thalmann and Meier, 2007), however the interaction between PVAT and local sympathetic activity in healthy and disease conditions has not been scrutinised. Sympathetic activity and subsequent release of catecholamines are known to regulate lipolysis, and proliferation and differentiation of adipocytes activation through α- and β-adrenoceptors. Recent evidence has also suggested that adipocytes and alternatively activated macrophages in adipose tissues may synthesize and release noradrenaline and adrenaline (Vargovic et al., 2011; Nguyen et al., 2011). In thoracic aorta and superior mesenteric arteries, where PVAT enhances contraction via α1-adrenoceptors, noradrenaline and its synthetic
enzymes are detected in PVAT adipocytes (Ayala-Lopez et al., 2014). PVAT-dependent contractions to the sympathomimetic tyramine have also been reported in the same large arteries (Soltis and Cassis, 1991; Ayala-Lopez et al., 2014). Tyramine is traditionally used to release catecholamines from sympathetic nerve endings, but the possibility of an action on adipocytes or immune cells in PVAT cannot be excluded.

Another factor that may contribute to the contractile effects of PVAT is the adipokine, chemerin (Table 1). Chemerin, in particular chemerin-9, evokes direct vasoconstriction and enhances agonist-induced contractions via its G-protein-coupled receptor, ChemR23 in rat and human arteries. Moreover, these effects are exaggerated in thoracic aorta and mesenteric arteries with reduced endothelium-dependent relaxation, a phenomenon often found in hypertension and obesity (Watts et al., 2013). A follow-up study by the same group (Darios et al., 2016) has also shown that PVAT-derived chemerin potentiates sympathetic contraction through ChemR23, which is co-localised with tyrosine hydrolase in sympathetic nerves of rat superior mesenteric artery. Direct application of chemerin to isolated aorta or mesenteric artery also augments agonist-induced contraction in a manner dependent on endothelin ETα receptor and ERK activation (Lobato et al., 2012), and increases systolic blood pressure in mice (Kunimoto et al., 2015). Thus, chemerin might play a particularly important role in some forms of hypertension and obesity.

In addition to chemerin, cytokines derived from PVAT might also increase vascular tone. For instance, tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6) are known to enhance contractions, probably via upregulation of endothelin signalling or reduced nitric oxide (NO) production and endothelium-dependent relaxation, especially in obese patients (Greenberg et al., 1985; Orshal and Khalil, 2004; Virdis et al., 2015). High-fat diet has also been shown to promote IL-6 expression in human coronary PVAT (Chatterjee et al., 2009).

Aortic and small mesenteric PVAT also release contractile cyclooxygenase (COX) products, including thromboxane A₂ (TXA₂) and PGE₂ (Meyer et al., 2013; Mendizabal et al., 2013). In the same vascular regions, contraction to prostanoids and their receptor expression are enhanced in obese mice (Traupe et al., 2002) or diabetic rats (Ishida et al., 2012). Interestingly, however, a significant amount of PVAT-derived TXA₂ and PGE₂ are also detected in healthy controls suggesting a possible physiological role (Meyer et al., 2013). Prostanoids might also mediate PVAT-induced endothelial dysfunction in both normotensive and hypertensive rats (Mendizabal et al., 2013), contributing to a pro-contractile effect of PVAT. It remains to be clarified how the secretory pattern of various prostanoids is altered in pathophysiological conditions.

Taken together, PVAT is capable of releasing multiple contractile factors, which elicit direct vasoconstriction, or enhance nerve- or agonist-mediated contractions by acting on the vascular smooth muscle. These factors appear, at least partly, active in healthy conditions especially in larger arteries. Previous studies have reported elevated systemic levels of angiotensin II, superoxide, catecholamines, contractile prostanoids, TNFα, chemerin and leptin in hypertension, diabetes or obesity (Brunner et al., 2005; Gu et al., 2015), but PVAT is yet to be established as a major source of these mediators. There is however evidence pointing to increased responsiveness to chemerin, TNFα and prostanoids in aorta and resistance arteries (Watts et al., 2013; Meyer et al., 2013; Traupe et al., 2002; Ishida et al., 2012; Virdis et al., 2015). In addition to acute vasoconstriction, sustained elevation of some of the ADCF, such as superoxide, Ang II and TNFα, might stimulate vascular smooth muscle growth and arterial stiffness (Fleenor et al., 2014; Almabrouk et al., 2014; Kunimoto
et al., 2015; Noblet et al., 2016; also reviewed by Miao & Li, 2012, Aroor et al., 2013 and Villacorta & Chang, 2015), commonly found in atherosclerosis, hypertension and ageing. In line with this, PVAT expression of chemerin is positively correlated with atherosclerosis in human aorta and coronary artery (Spiroglou et al., 2010). The vascular remodelling effect of PVAT is also associated with endothelial dysfunction, a hallmark of cardiovascular diseases. For vascular tone regulation, a reduction in endothelium-dependent relaxation would exaggerate the pro-contractile effects of PVAT and will be further explored in the following section.

Evidence for PVAT-induced endothelial dysfunction

The vascular endothelium is critical for maintaining cardiovascular homeostasis, and its dysfunction is considered an early sign or predictor of cardiovascular diseases, including those associated with obesity and diabetes (Brunner et al., 2005). Endothelial dysfunction can manifest, for example, as reduced endothelium-dependent relaxation, endothelium-dependent contraction, leukocyte adhesion and reduced anti-coagulation properties. In Table 2, we highlight some of the studies demonstrating the inhibitory effect of PVAT on responses to endothelium-dependent relaxants, which could enhance vasocontraction and might be particularly relevant to hypertension linked to obesity and diabetes. Where possible, the specific PVAT-derived mediators and disease conditions involved are also indicated in Table 2.

A primary mechanism of action for PVAT is reduced NO production or bioavailability, although NO-independent signalling pathways may also be compromised. Given the physical distance between PVAT and the endothelium particularly in conduit arteries, it is thought that mediators released by PVAT are involved. They include NADPH oxidase-derived reactive oxygen species (superoxide, hydrogen peroxide) and pro-inflammatory cytokines (leptin, TNFα, IL-6, resistin, visfatin) (Payne et al., 2010; Ketonen et al., 2010; Marchesi et al., 2009; Greenstein et al., 2009; Vallejo et al., 2011; Aghamohammadzadeh et al., 2016). Importantly, targeting dysregulation of these PVAT factors, which accompanies adipocyte hypertrophy in obesity and metabolic syndrome can improve endothelial function (Marchesi et al., 2009; Aghamohammadzadeh et al., 2016). Circulating visfatin levels may also predict the extent of endothelium-dependent, flow-mediated dilation in patients with atherosclerosis and diabetes (Romacho et al., 2013). These findings support the clinical relevance of PVAT dysfunction in vascular health. Indeed, oxidative stress and increased production of pro-inflammatory cytokines, as well as endothelial dysfunction, have been closely linked to the pathophysiology of obesity, hypertension, atherosclerosis, and insulin resistance.

On the other hand, PVAT can also reduce endothelium-independent relaxation. In many studies, the presence of PVAT has no significant effect on relaxation to NO donors (Payne et al., 2008; Ma et al., 2010; Vallejo et al., 2011; Lee et al., 2014). However, Tune and co-workers (Owen et al., 2013; Noblet et al., 2015) have shown that PVAT inhibits distinct subtypes of K+ channels in coronary smooth muscle of lean versus diet-induced obese pigs. Another adipokine, nesfatin-1 has also been shown to reduce smooth muscle cGMP production in mesenteric arteries, and increase arterial blood pressure in rats (Yamawaki et al., 2012).
Evidence for relaxant factors from PVAT

In contrast to the aforementioned (pro)contractile actions, numerous PVAT-derived mediators are vasorelaxants and therefore exert anti-contractile effects, which have been the focus of a number of excellent reviews (e.g. Gollasch, 2012 and Withers et al., 2014). PVAT relaxants include adiponectin, omentin, leptin, angiotensin 1-7 (Ang 1-7), NO, hydrogen peroxide and hydrogen sulphide (H₂S) (Dubrovská et al., 2004; Gao et al., 2007; Lee et al., 2009; Payne et al., 2010; Gil-Ortega et al., 2010; Schleifenbaum et al., 2010). Again, isolated tension recording and bioassay experiments have been instrumental in establishing an anti-contractile action of PVAT in arteries from rodents and humans. Of note, the presence of PVAT reduces contraction to some, but not all, vasoconstrictors (Solitis and Cassis, 1991; Lohn et al., 2002; Verlohren et al. 2004; Gao et al., 2005b; Malinowski et al., 2008; Greenstein et al., 2009). Under physiological conditions, adipocytes are thought to be the main cellular source of these factors, which are sometimes referred to as ADRFs (Solitis and Cassis, 1991; Lohn et al., 2002; Verlohren et al., 2004).

Diverse signalling mechanisms have been proposed, including endothelial NO release, cGMP generation, reactive oxygen species, and opening of various K⁺ channel subtypes, but independent of COX products or sympathetic nerves (Gollasch, 2012 and Withers et al., 2014). Accumulating evidence suggests that the anti-contractile effect of PVAT relies on smooth muscle K⁺ channels. Specifically, activation of voltage-gated K⁺ channels (Kᵥ7) and Ca²⁺-activated K⁺ channels (BKᵥ7) through endothelium-independent and -dependent pathways respectively. Interestingly, in healthy rat coronary septal arteries, increases in PVAT mass also reduces Rho kinase-dependent Ca²⁺ sensitivity in vascular smooth muscle (Aalbaek et al., 2015). This contrasts the observation that PVAT from pig coronary artery enhances vasoconstriction via Rho kinase (Owen et al., 2013).

As for a pathological role, a loss or reduced relaxant effect of PVAT is often reported in disease states. In spontaneously hypertensive rats, there is a loss of anti-contractile effect in mesenteric arteries possibly due to downregulation of Kᵥ7 channels in vascular smooth muscle or reduced PVAT production of Ang 1-7, one of the ADRF candidates (Galvez et al., 2006; Galvez-Prieto et al., 2008b; Li et al., 2013). In experimental models of obesity and metabolic syndrome, increases in PVAT-derived leptin (Gill-Ortega et al., 2009), superoxide, hydrogen peroxide (Gao et al., 2005a; Rebolledo et al., 2010; Ketonen et al., 2010; Aghamohammazadeh et al., 2016) or free fatty acid level (Sun et al., 2013) also play a role in aorta, mesenteric or subcutaneous arteries. Although PVAT produce the vasorelaxants adiponectin and NO, obesity is associated with reduced PVAT adiponectin and reduced endothelial NO release and bioavailability, partly due to oxidative stress (c.f. Figure 2). For example, in rodent mesenteric arteries, this can be rescued by superoxide dismutase and catalase, which remove superoxide and hydrogen peroxide respectively, or anti-oxidants (Marchesi et al., 2009; Aghamohammazadeh et al., 2016). Despite an upregulation of leptin, there is an impairment of leptin-induced NO release from the endothelium in hypertension and obesity models (Beltowski et al., 2003; Rahmouni et al., 2005; Galvez-Prieto et al., 2012). This implicates PVAT in vascular leptin-resistance, which exacerbates the cardiovascular complications associated with obesity.

This article is protected by copyright. All rights reserved.
Other data suggest that, in obesity and diabetes, downregulation of PVAT-derived adiponectin might lead to upregulation of superoxide and TNFα, and reduced endothelial NO production and relaxation (c.f. Table 2; Virdis et al., 2015; Hou et al., 2016; Nacci et al., 2016). It is often unclear why PVAT-derived relaxants are downregulated in disease states, but hypoxia in PVAT might be a contributing factor (Withers et al., 2011). A local reduction of PVAT adiponectin (Virdis et al., 2015; Aghamohammadzadeh et al., 2016) without concomitant changes in its circulatory levels is also evident in human obesity (Dreier et al., 2016). Of particular relevance to insulin resistance and diabetes, adiponectin is known to activate AMP-activated protein kinase (AMPK), a key intracellular energy sensor that improves insulin sensitivity and modulate adipocyte metabolism and inflammation (see Almabrouk et al., 2014 for review). AMPK in endothelium and vascular smooth muscle also regulates vascular tone and remodelling (Ma et al., 2010; Meijer et al., 2013; Almabrouk et al., 2014), and probably contribute to the cardiovascular benefits of the anti-diabetic drugs, glitazones which are Peroxisome Proliferator-Activated Receptor gamma (PPARγ) agonists and AMPK activators. Interestingly, a recent study suggests that AMPK in PVAT is required for the secretion of adiponectin in mouse aorta (Almabrouk et al., 2016), providing a molecular mechanism for cross-talks with hypoxia and other PVAT-derived vasoactive substances that activate or inhibit AMPK (Almabrouk et al., 2014; Virdis et al., 2015).

Anti-contractile versus pro-contractile effects of PVAT

The co-existence of pro-contractile and anti-contractile actions of PVAT may seem contradictory but such dual effects have also been demonstrated in the same arteries and within the same studies (Soltis and Cassis, 1991; Lohn et al., 2002; Ketonen et al., 2010; Li et al., 2013; Aalbaek et al., 2015). Indeed, some of the PVAT-derived factors such as leptin, TNFα, IL-6 and hydrogen peroxide are known to have both contractile and relaxant properties (Brian and Faraci, 1998; Orshal and Khalil, 2004; Thakali et al., 2006; Virdis et al., 2015). Upregulation or downregulation of these factors can also compromise endothelial function (c.f. Table 2). It is therefore not surprising that the balance between pro-contractile and anti-contractile function, and how it is altered in disease conditions is under increasingly intense investigations.

Both relaxant and contractile actions of PVAT effects are detectable in healthy conditions, at least in thoracic aorta, mesenteric and coronary artery (Soltis and Cassis, 1991; Dubrovskova et al., 2004; Verlohren et al., 2004; Payne et al., 2010). Many studies have proposed a predominantly anti-contractile action in health, although it is possible that the net effect on vascular tone depends on the anatomical location and experimental conditions used. As discussed in the previous section, systemic arteries (including mesenteric artery, thoracic and abdominal aorta) and coronary arteries often show a reduced production or responsiveness to PVAT-derived relaxants or other vasorelaxants in hypertension, obesity and diabetes. This, together with an underlying contraction induced by PVAT, which can also be enhanced in some forms of hypertension and obesity (c.f. Table 1), would promote a net contractile action of PVAT (Figure 1). This may result in sustained vasoconstriction. Indeed, PVAT dysfunction is correlated with raised arterial blood pressure in obese rats (Aghamohammadzadeh et al., 2016). Genetic deletion of PPARγ in mouse perivascular adipocytes during development results in the absence of PVAT and hypotension, pointing to a key role for PVAT in blood pressure regulation (Chang et al., 2012). However, we are yet to fully understand how PVAT function transitions from health to disease, and how best to reverse the
adverse effects of PVAT. In the case of obesity, weight loss through bariatric surgery or caloric restriction might reduce PVAT inflammation and improve NO bioavailability, resulting in normalised blood pressure (Aghamohammadzadeh et al., 2013; Bussey et al., 2016).

**Interactions between adipocytes and immune cells in PVAT**

Aside from vascular reactivity, many of the PVAT-derived mediators are also critical players in vascular inflammation. Evidence suggests that a pro-inflammatory phenotype of PVAT is a common feature of hypertension, obesity, insulin resistance and atherosclerosis (Chatterjee et al., 2009; Omar et al., 2014; Almabrouk et al., 2014; Mikolajczyk et al., 2016). Adipocytes are the main component in PVAT, but immune cells such as macrophages and T-lymphocytes also play an important role in regulating PVAT function, and provide an alternative source of vasoactive mediators. As part of the pathological remodelling of adipose tissues, obese rodents and humans have a higher PVAT mass and adipocyte hypertrophy (Marchesi et al., 2009; Ma et al., 2010; Greenstein et al., 2009). The hypertrophied PVAT likely exceeds the diffusion limit of oxygen and suffers from hypoperfusion, leading to local hypoxia (Hosogai et al., 2007; Greenstein et al., 2009). The hypoxic state is linked to increased expression of the chemokine MCP-1 in PVAT, which in turn promotes recruitment and infiltration of macrophages, which act as a major source of TNFα (see Gustafsson et al., 2007 for review; Ketonen et al., 2010). Through upregulation of the other chemokines IL-8 and RANTES in PVAT and superoxide in PVAT and vascular cells (Table 2), PVAT also stimulates recruitment of monocytes and lymphocytes in arteries from models of obesity, hypertension or metabolic syndrome (Henrichot et al., 2005; Marchesi et al., 2009; Mikolajczyk et al., 2016). Figure 2 illustrates how dysregulation of PVAT-derived factors might occur in these disease states.

At the same time, there is an upregulation of pro-inflammatory mediators (e.g. TNFα and IL-6) and a downregulation of anti-inflammatory mediators (e.g. adiponectin and IL-10), from adipocytes and macrophages (Greenstein et al., 2009; Chatterjee et al., 2009; Lumeng et al., 2007). The resultant pro-inflammatory phenotype has been linked to the loss of PVAT-induced relaxation and this deficit may be partially reversed by TNFα antagonists or IL-6 antibodies (Greenstein et al., 2009; Ozen et al., 2015; Aghamohammadzadeh et al., 2016). Endothelium-dependent relaxation is also likely compromised by PVAT-derived TNFα and reactive oxygen species (Virdis et al., 2015). In macrophage-deficient mice, the ability of hypoxia to inhibit PVAT relaxation is greatly reduced, supporting a key role for PVAT macrophages (Withers et al., 2011). In addition, there is an accumulation of leukocytes in PVAT, so much so that deficiency in P-selectin glycoprotein ligand-1 (Psgl-1), a ligand essential for leukocyte attachment and rolling at the endothelium, prevents endothelial dysfunction and inflammation induced by PVAT in obese mice (Wang et al., 2012).

In contrast to the case for obesity, the size of PVAT adipocytes and PVAT mass are often reduced in experimental models of hypertension, including spontaneously hypertensive and DOCA-salt hypertensive rats (Galvez et al., 2006; Ruan et al., 2010). Despite this, a recent study has demonstrated that Ang II-induced hypertension increases PVAT expression of RANTES, resulting in increased T-lymphocyte infiltration and impaired endothelium-dependent relaxation (Mikolajczyk et al., 2016; Figure 2). It should be noted that whilst adipokines such as chemerin, adiponectin and leptin are released from PVAT adipocytes, many of the PVAT-derived chemokines, cytokines and
reactive oxygen species might be produced by multiple cell types within PVAT, including adipocytes and immune cells (see also Szasz et al., 2013 and Pellegrinelli et al., 2016 for reviews). Furthermore, vascular cells produce some of the same pro- or anti-inflammatory mediators from PVAT, and also express receptors for these mediators. Therefore, the interplay among adipocytes, infiltrated immune cells and vascular cells would need to be further explored.

**PVAT dysfunction in humans**

The past ten years have seen growing interests in PVAT dysfunction. Whilst the current data on human PVAT remain limited, they broadly agree with those obtained in animal models. For instance, anti-contractile effects of PVAT is compromised in small arteries of patients with metabolic syndrome or obesity (Greenstein et al., 2009; Aghamohammadzadeh et al., 2013), and that human PVAT shows distinctive expression pattern of pro-inflammatory mediators, including IL-6, MCP-1 and leptin, compared to subcutaneous adipose tissue (Rittig et al., 2012; Mauro et al., 2013). However, the functional significance of various ADCF and ADRFs may differ. For example, adiponectin appears to play a more important role in PVAT relaxation in humans than in rodents (Fesus et al., 2007; Greenstein et al., 2009; Meijer et al., 2013). In patients undergoing coronary bypass surgery, initial experiments suggest that saphenous vein graft with intact adventitia and PVAT, as opposed to a conventional free graft, reduces vasospasm and potentially improves its patency (Dashwood et al., 2009). Thus, it might be concluded that PVAT exerts a predominantly anti-contractile effects in humans. In contrast, individuals with more PVAT in brachial artery has diminished hyperaemic blood flow (Rittig et al., 2008), suggesting a basal contractile influence of PVAT. Further characterisation of PVAT-derived factors from different vascular regions are needed. Thus far, mechanistic studies have been performed on the more accessible vessels from volunteers, namely the internal thoracic artery (Gao et al., 2005a; Malinowski et al., 2008), small arteries in gluteal fat (Greenstein et al., 2009; Aghamohammadzadeh et al., 2013) and saphenous veins (Dashwood et al., 2009).

The Framingham Heart Study reported a correlation between periaortic fat mass and hypertension or diabetes irrespective of the body mass index, but a causal relationship is yet to be established (Lehman et al., 2010; Britton et al., 2012). In addition to reduced body weight, bariatric surgery in severely obese patients has been shown to restore PVAT-induced relaxation, improve inflammatory cytokines profile and NO bioavailability, and reduce macrophage infiltration and systolic blood pressure (Aghamohammadzadeh et al., 2013). More recently, in diet-induced obese rats, calorie restriction and sustained weight loss has similarly been found to reverse PVAT-mediated vascular damage (Bussey et al., 2016). These data support the contribution of PVAT dysfunction to the pathogenesis of obesity and metabolic syndrome. Elevated circulatory level of chemerin also correlates with impaired endothelial function and increased arterial stiffness in hypertensive patients (Gu et al., 2015). The specific role played by PVAT relative to other fat depots merits further investigations, particularly in view of the differential responses to high fat diet in white and brown adipocytes (Fitzgibbons et al., 2011).
When assessing data from animal and human experimental studies, it is also important to consider the effect of ageing, an independent risk factor for cardiovascular diseases. Ageing exacerbates aorta PVAT dysfunction, with increases in oxidative stress and macrophage infiltration, and a pro-inflammatory secretion pattern of cytokines and chemokines (Bailey-Downs et al., 2013; Mauro et al., 2013; Fleenor et al., 2014). This effect is at least partly mimicked by medium conditioned with aged aorta PVAT, and is accompanied by endothelial dysfunction in aorta, especially in diet-induced obese mice (Bailey-Downs et al., 2013). Thus, PVAT may also contribute to the endothelial dysfunction and vascular remodelling seen in ageing. On the other hand, PVAT relaxation is inhibited in ageing mice (Agabiti-Rosei et al., 2017), hinting at an overall pro-contractile action of PVAT during ageing. Further investigations will need to clarify the PVAT function in healthy versus pathological ageing. It is also worth noting that the age of rodent models of obesity vary (Lutz and Woods, 2012) and are generally younger than subjects of clinical studies.

Conclusion

In this review, we have focused on the effects of PVAT on vascular tone regulation. It is apparent that PVAT exerts both contractile and relaxant actions through the release of autocrine/paracrine factors from adipocytes and infiltrating inflammatory cells in PVAT (Figure 1). PVAT is therefore an integral part of vascular function, including cross-talk with the endothelium, smooth muscle, immune cells and perivascular nerves. The balance between pro-contractile and anti-contractile effects maybe tissue-specific but modulation by obesity and hypertension induces a shift towards a pro-contractile, pro-inflammatory and pro-oxidative phenotype (Figure 2). This PVAT dysfunction may also occur in other obesity-related disorders, including metabolic syndrome, diabetes and atherosclerosis. However, despite a much better knowledge on the structure and function of PVAT, there are still many unanswered questions. The molecular mechanisms that regulate PVAT quantity and composition, and secretion of vasoactive factors in health and disease, which likely exist in a continuum, remain elusive. Although there is experimental evidence for PVAT dysfunction in the pathogenesis of hypercontractility in disease states, it is also possible that it has a protective and adaptive role in vascular homeostasis. Moreover, the function of PVAT relative to the systemic influence of visceral and subcutaneous fat remains to be clarified. Given the heterogeneity in PVAT function in different anatomical regions and species, more studies using human tissues are required.

Conflict of interest

The authors declare no conflicts of interest.


Superoxide signaling in perivascular adipose tissue promotes age-related artery stiffness. *Aging Cell.* 13: 576–578


Comparative expression analysis of the renin-angiotensin system components between white and brown perivascular adipose tissue. *J Endocrinol.* 197: 55–64.

A reduction in the amount and anti-contractile effect of periadventitial mesenteric adipose tissue precedes hypertension development in spontaneously hypertensive rats. *Hypertens Res.* 31: 1415–1423

Anticontractile effect of perivascular adipose tissue and leptin are reduced in hypertension. *Front Pharmacol.* 3: 103.


Nacci C, Leo V, De Benedictis L, Potenza MA, Sgarra L, De Salvia MA et al (2016). Infliximab therapy restores adiponectin expression in perivascular adipose tissue and improves endothelial nitric oxide-


Table 1. PVAT-derived contractile factors. Studies that demonstrate PVAT production of mediators, which either induce direct contraction or potentiate contractions to other vasoconstrictors, are highlighted.

▲, increase; →, lead to; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; COX, cyclooxygenase; DOCA, deoxycorticosterone acetate; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET1, endothelin-1; ET α, endothelin ET α receptor; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PGE 2, prostaglandin E 2; PVAT, perivascular adipose tissue; SHRSP, stroke-prone spontaneously hypertensive rat; thromboxane A 2, TXA 2; TNF α, tumour necrosis factor-α

<table>
<thead>
<tr>
<th>Contractile factor</th>
<th>PVAT expression</th>
<th>Effect</th>
<th>Vascular bed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang II</td>
<td>Ang II protein; angiotensinogen and ACE mRNA in PVAT adipocytes</td>
<td>▲ Sympathetic contraction</td>
<td>Rat superior mesenteric artery</td>
<td>Lu et al., 2010</td>
</tr>
<tr>
<td></td>
<td>Ang II protein, angiotensinogen, ACE and chymase mRNA</td>
<td></td>
<td>Rat thoracic aorta</td>
<td>Galvez-Prieto et al., 2008a</td>
</tr>
<tr>
<td>Superoxide</td>
<td>Superoxide; NADPH oxidase protein in PVAT adipocytes</td>
<td>▲ Sympathetic contraction (via tyrosine kinase and ERK, but independent of NO)</td>
<td>Rat superior mesenteric artery</td>
<td>Gao et al., 2006</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Noradrenaline and adrenaline in PVAT adipocytes</td>
<td>Contraction</td>
<td>Rat thoracic aorta</td>
<td>Ayala-Lopez et al., 2014</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline from sympathetic nerve endings</td>
<td>Contraction</td>
<td>Rat thoracic aorta</td>
<td>Soltis and Cassis, 1991</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>TXA 2 in PVAT-conditioned buffer; COX-1 and COX-2 mRNA</td>
<td>▲ Agonist-induced contraction (independent of NOS or ET α).</td>
<td>Mouse thoracic aorta (only in monogenic obesity and diet-induced obesity)</td>
<td>Meyer et al., 2013</td>
</tr>
<tr>
<td></td>
<td>PGE 2 in PVAT (or PVAT-conditioned buffer)</td>
<td>Contraction</td>
<td>Rat mesenteric artery</td>
<td>Mendizabal et al., 2013;</td>
</tr>
<tr>
<td>TNFα</td>
<td>TNFα protein in PVAT adipocytes</td>
<td>▲ Contraction to eNOS inhibition</td>
<td>Human small arteries from visceral fat (enhanced in obese patients)</td>
<td>Virdis et al., 2015</td>
</tr>
<tr>
<td>IL-6</td>
<td>IL-6 in PVAT adipocytes</td>
<td>Human coronary artery (enhanced with high fat diet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemerin</td>
<td>Chemerin protein in PVAT adipocytes</td>
<td>Contraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ agonist-induced contraction (enhanced by endothelial removal or NOS inhibition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watts et al., 2013</td>
<td>Rat superior mesenteric artery (enhanced responses in DOCA-salt hypertensive but not diet-induced obese or SHRSP rats)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemerin protein in PVAT adipocytes</td>
<td>Contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ agonist-induced contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watts et al., 2013</td>
<td>Human resistance mesenteric artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemerin protein in PVAT adipocytes</td>
<td>↑ Sympathetic contraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Watts et al., 2013</td>
<td>Rat superior mesenteric artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin (PVAT-conditioned buffer)</td>
<td>↑ Agonist- and depolarisation-induced contraction (via increased voltage-gated Ca^{2+} entry)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owen et al., 2013; Noblet et al., 2016</td>
<td>Pig coronary artery (enhanced in diet-induced obesity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Smooth muscle proliferation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Inhibitory effect of PVAT on endothelium-dependent relaxation. This is often demonstrated by studying the effects of PVAT on responses to endothelium-dependent relaxants that are applied to isolated arteries or isolated vascular cells. Upregulation or downregulation of PVAT-derived factors are thought to exaggerate the reduction in endothelium-dependent relaxation in disease states. However, in some studies the diffusible factors responsible for the inhibitory effects of PVAT on endothelial function are not identified.

↑, increase; ↓, decrease; →, lead to; AMPK, adenosine monophosphate-activated protein kinase; AT1, angiotensin II receptor type 1; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; IRS-1, insulin receptor substrate-1; MCP-1, monocyte chemotactic protein-1; mTOR, mechanistic target of rapamycin; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PVAT, perivascular adipose tissue; TNFα, tumour necrosis factor-α; RANTES, regulated on activation, normal T cell expressed and secreted

<table>
<thead>
<tr>
<th>PVAT-derived factor</th>
<th>Proposed mechanism of inhibition</th>
<th>Endothelium-dependent relaxant affected</th>
<th>Vascular bed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistin</td>
<td>↓ IRS-1 and PI3K activity in endothelium → ↓ eNOS activity</td>
<td>Insulin</td>
<td>Mouse aorta Mouse mesenteric artery</td>
<td>Gentile et al., 2008</td>
</tr>
<tr>
<td></td>
<td>↑ Endothelial superoxide → ↓ eNOS expression</td>
<td>Bradykinin</td>
<td>Pig coronary artery</td>
<td>Kougiias et al., 2005</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>↓ Adiponectin in PVAT → ↓ AMPK and Akt phosphorylation</td>
<td>Insulin</td>
<td>Mouse resistance artery from skeletal muscle (only in genetic model of obesity and Type 2 diabetes)</td>
<td>Meijer et al., 2013</td>
</tr>
<tr>
<td>Unknown</td>
<td>↓ AMPK phosphorylation → ↑ mTOR phosphorylation → ↓ eNOS expression</td>
<td>Acetylcholine</td>
<td>Rat thoracic aorta and mesenteric artery (only in diet-induced obesity)</td>
<td>Ma et al., 2010</td>
</tr>
<tr>
<td>Leptin</td>
<td>↑ Leptin in PVAT and ↑ leptin receptor expression → ↑ PKCβ activity in vascular cells</td>
<td>Bradykinin</td>
<td>Pig coronary artery (only in obesity with metabolic syndrome)</td>
<td>Payne et al., 2010</td>
</tr>
<tr>
<td>Unknown</td>
<td>↑ PKCβ-mediated eNOS phosphorylation → ↓ endothelial NO</td>
<td>Bradykinin</td>
<td>Dog coronary artery</td>
<td>Payne et al., 2008; Payne et al., 2009</td>
</tr>
<tr>
<td>Unknown</td>
<td>↓ Endothelial Ca²⁺ signal</td>
<td>Acetylcholine Methacholine</td>
<td>Rat coronary septal artery</td>
<td>Aalbaek et al., 2015</td>
</tr>
<tr>
<td>Factor</td>
<td>Effect</td>
<td>Exogenous Stimulant</td>
<td>Vessel/Model</td>
<td>Reference</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>---------------------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Unknown (but independent of superoxide, prostanoids, ET-1 and AT₁)</td>
<td>↑ Endothelial caveolin-1 → ↓ NO production</td>
<td>Acetylcholine</td>
<td>Rat thoracic aorta</td>
<td>Lee et al., 2014</td>
</tr>
<tr>
<td>Superoxide, hydrogen peroxide, leptin and MCP-1 in PVAT</td>
<td>↑ Superoxide, hydrogen peroxide, leptin and MCP-1 in PVAT</td>
<td>Acetylcholine</td>
<td>Mouse abdominal aorta (only in diet-induced obesity)</td>
<td>Ketonen et al., 2010</td>
</tr>
<tr>
<td>Visfatin</td>
<td>↑ NADPH oxidase activity in vascular cells → ↓ endothelial NO</td>
<td>Bradykinin or acetylcholine</td>
<td>Rat and human resistance mesenteric arteries</td>
<td>Vallejo et al., 2011</td>
</tr>
<tr>
<td>TNFα, Adiponectin</td>
<td>↑ TNFα and ↓ adiponectin in PVAT → NADPH oxidase activation → ↓ eNOS expression → ↓ basal endothelial NO</td>
<td>Bradykinin or acetylcholine</td>
<td>Human small arteries from visceral fat (enhanced effects in obesity)</td>
<td>Virdis et al., 2015</td>
</tr>
<tr>
<td>RANTES</td>
<td>↑ RANTES → ↑ T-lymphocytes in PVAT but not visceral fat</td>
<td>Acetylcholine</td>
<td>Mouse thoracic and abdominal aorta (enhanced in Ang II-induced hypertension)</td>
<td>Mikolajczyk et al., 2016</td>
</tr>
</tbody>
</table>
Figure 1. Regulation of vascular tone by PVAT in health and disease. (A) PVAT releases a diverse group of bioactive and diffusible substances, including leptin, adiponectin, angiotensin II, angiotensin 1-7, catecholamines, reactive oxygen species, nitric oxide, hydrogen sulphide, cytokines such as tumour necrosis factor-α and interleukin-6, and chemokines such as MCP-1 and RANTES. These mediators modulate vascular tone through a paracrine action on the endothelium, vascular smooth muscle and immune cells. The chemokines and cytokines regulate migration of immune cells into PVAT, and activated macrophages and lymphocytes within PVAT can also release additional cytokines. (B) In healthy conditions, PVAT tends to exert a net anti-contractile effect. Pathophysiological stimuli for example in obesity, hypertension and diabetes alter the secretary pattern of PVAT, leading to increased pro-contractile and decreased anti-contractile actions. This imbalance is characteristic of PVAT dysfunction in disease states. Other changes in PVAT composition and function include adipocyte hypertrophy, infiltration of macrophages and lymphocytes, and inflammation within PVAT and vascular cells.

ADCF, adipocyte-derived contractile factor; ADRF, adipocyte-derived relaxing factor; ADV, adventitia; EC, endothelium; PVAT, perivascular adipose tissue; SM, smooth muscle.
Figure 2. Proposed mechanisms of PVAT dysfunction in obesity, diabetes and hypertension. PVAT dysfunction is characterised by changes in its secretory pattern and increased occurrence of activated macrophages and lymphocytes in PVAT. In addition to adipocytes, activated immune cells within PVAT also release additional cytokines. In obesity and Type 2 diabetes, PVAT dysfunction is likely triggered by adipocyte hypertrophy and increases in PVAT mass. PVAT expansion is not a prerequisite for PVAT dysfunction since the size of adipocytes and overall PVAT mass maybe reduced in some forms of hypertension in the absence of obesity.

Ang 1-7, angiotensin 1-7; Ang II, angiotensin II; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; RANTES, regulated on activation, normal T cell expressed and secreted;