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Themed Section: Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets?

REVIEW ARTICLE

Comparisons between perivascular adipose tissue and the endothelium in their modulation of vascular tone

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The endothelium is an established modulator of vascular tone; however, the recent discovery of the anti-contractile nature of perivascular adipose tissue (PVAT) suggests that the fat, which surrounds many blood vessels, can also modulate vascular tone. Both the endothelium and PVAT secrete vasoactive substances, which regulate vascular function. Many of these factors are common to both the endothelium and PVAT; therefore, this review will highlight the potential shared mechanisms in the modulation of vascular tone. Endothelial dysfunction is a hallmark of many vascular diseases, including hypertension and obesity. Moreover, PVAT dysfunction is now being reported in several cardio-metabolic disorders. Thus, this review will also discuss the mechanistic insights into endothelial and PVAT dysfunction in order to evaluate whether PVAT modulation of vascular contractility is similar to that of the endothelium in health and disease.

LINKED ARTICLES

This article is part of a themed section on Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets? To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.20/issuetoc

Abbreviations

BAT, brown adipose tissue; CSE, cystathionine γ-lyase; CVD, cardiovascular disease; H_2O_2, Hydrogen peroxide; H_2S, hydrogen sulphide; MLC, myosin light chain; O_2^-, superoxide; PVAT, perivascular adipose tissue; PVRFs, PVAT-derived relaxant factors; VSM, vascular smooth muscle; WAT, white adipose tissue

DOI:10.1111/bph.13648

Tables of Links

TARGETS	
Other protein targets[a]	**Enzymes**[e]
TNF-α	Adenylate cyclase
GPCRs[b]	AMPK
IP receptor	COX-1
Voltage-gated ion channels[c]	COX-2
K_V channels	CSE
Ligand-gated ion channels[d]	eNOS
BK_{Ca} channel	Guanylyl cyclase
IK_{Ca} channel	NOS
K_{Ca} channel	PKA
K_{ATP} ($K_{ir}6.1$) channel	PKG
SK_{Ca} channel	

LIGANDS	
5-HT	L-arginine
Adiponectin	MCP-1 (CCL2)
ATP	NO
cAMP	Noradrenaline
cGMP	PGD_2
GTP	PGE_2
H_2O_2	$PGF_{2\alpha}$
IL-6	PGI_2
Indomethacin	TXA_2

These Tables 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 ([a,b,c,d,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

Blood vessels are composed of three layers: tunica adventitia, tunica media and tunica intima, and many blood vessels are surrounded by perivascular adipose tissue (PVAT). The adventitia mainly contains connective tissue, while the tunica media (especially in arteries) consists mainly of vascular smooth muscle (VSM). The endothelium, the inner layer of all blood vessels, consists of a thin layer of squamous endothelial cells. Vascular contractility is primarily regulated by the level of contraction of the VSM that can be influenced by the endothelium. The recent discovery of the anti-contractile nature of PVAT suggests that the fat around blood vessels can also modulate vascular contractility rather than merely providing a structural support. The principal role of VSM is regulation of blood vessel tone/diameter and blood pressure (Owens *et al.*, 2004). VSM contraction may be modulated by vasoconstrictive hormones, vasodilating agents as well as electrical and mechanical stimuli. Some vasoconstricting agonists can activate the RhoA/Rho-kinase pathway, which sensitizes the VSM contractile machinery to Ca^{2+} inducing greater contraction at lower intracellular Ca^{2+} levels; mechanistically this is achieved via inhibition of dephosphorylation of the MLC by myosin light chain phosphatase (Fukata *et al.*, 2001). Increasing $[Ca^{2+}]_i$ also activates potassium (K^+) channels, which results in VSM hyperpolarisation and subsequent vasodilatation (Eichhorn and Dobrev, 2007).

The endothelium functions as a semi-selective barrier between the circulating blood in the lumen and the tissues of the vessel wall and extracellular compartment. Fluid and solutes easily pass across the endothelial layer, and white blood cells may also pass into and out of the blood stream. The endothelium is an important endocrine and paracrine organ that plays a key role in the regulation of vascular tone by releasing factors that modulate VSM contractility (Edwards *et al.*, 2010). Furchgott and Zawadzki (1980) were the first to observe a role for the endothelium in the control of vascular contractility when they demonstrated the release of a diffusible factor, an endothelium-derived relaxing factor, which promoted vasorelaxation (Furchgott and Zawadzki, 1980). Numerous research studies have shown that the endothelium releases both vasodilating (such as endothelium-derived hyperpolarising factors, the prostaglandin PGI_2 and NO) and vasoconstricting agents (such as endothelin-1, TXA_2 and angiotensin II) and, in the healthy individual, controls vascular tone by balancing their release (see Feletou and Vanhoutte, 2006). The endothelium can modulate VSM contraction via myo-endothelial gap junctions, which permit ions and polar molecules to pass from cell to cell via an aqueous central pore (Fleming, 2000). It is well known that the endothelium plays a key role in the control of vascular function as its dysfunction is a major factor in the pathogenesis of many cardiovascular diseases (CVD) including hypertension and atherosclerosis (Shaul, 2002; Gollasch and Dubrovska, 2004; Nagata *et al.*, 2004; Boily *et al.*, 2008; Horman *et al.*, 2008; Malinowski *et al.*, 2008; Maenhaut and Van de Voorde, 2011). Endothelial cell dysfunction is also associated with diabetes and metabolic syndrome (Kim *et al.*, 2006; Avogaro *et al.*, 2011).

Although the importance of the endothelium in the regulation of vascular tone is undisputed, it is now clear that it is not the only significant regulator of arterial tone. PVAT surrounds many blood vessels in the body; it is very abundant around the aorta and mesenteric arteries, but it is absent in the cerebral vasculature and microvasculature (Horman *et al.*, 2008; Miao and Li, 2012). At first it was thought to provide mechanical support. However, since the original publication by Soltis and Cassis in 1991 (Soltis and Cassis, 1991), a number of groups have demonstrated that PVAT can significantly influence vascular contractility; these include Lohn's

observations on the existence of a adipocyte derived relaxing factor (ADRF) in 2002 (Lohn *et al.,* 2002). PVAT is composed of both white (WAT) and brown adipose tissue (BAT). WAT serves mainly as an energy store (Miao and Li, 2012), whereas BAT is mainly associated with thermogenesis, is more vascularized and is highly active metabolically (Smith and Roberts, 1964). The ratio of WAT/BAT is not constant across vascular beds; for example, PVAT in rats and mice surrounding the abdominal aorta and mesenteric vessels is mainly composed of WAT, while PVAT associated with the thoracic aorta is predominantly BAT (Frontini and Cinti, 2010; Cinti, 2011; Miao and Li, 2012). Interestingly, recently it has been proposed that adipocytes can undergo 'browning' (Young *et al.,* 1984), a process whereby WAT transforms into BAT via activation of the PI3K/Akt and AMPK signalling pathways (Than *et al.,* 2015).

PVAT consists of a variety of cells, including adipocytes, macrophages, lymphocytes, endothelial cells, fibroblasts and adipocyte stem/progenitor cells. PVAT is an endocrine organ that releases free fatty acids/non-esterified fatty acids by lipolysis and also secretes a number of bioactive proteins, called adipokines. These adipokines have autocrine, paracrine and endocrine functions, and they can modulate vascular function under normal physiological conditions. Some adipokines including adiponectin, nesfatin, vaspin, chemerin and omentin may be involved in the regulation of cardiovascular function; however, the mechanisms are still unclear and, for some, their expression in PVAT has not been conclusively demonstrated (Yamawaki, 2011).

PVAT has also been shown to modulate vascular contractility through the release of PVAT-derived relaxant factors (PVRFs) (Chang *et al.,* 2013). Although it is still unclear how PVRFs exert their anti-contractile effects, a number of potential PVRFs have been suggested including hydrogen sulphide H_2S (Wojcicka *et al.,* 2011), NO (Gao *et al.,* 2007) and angiotensin 1–7 (Lee *et al.,* 2009). Data from a number of groups suggest that this PVAT-induced vasodilatation is not species or vessel subtype specific (Soltis and Cassis, 1991; Dubrovska *et al.,* 2004; Gollasch and Dubrovska, 2004; Guzik *et al.,* 2007; Greenstein *et al.,* 2009). In addition to endothelial dysfunction, it has also been demonstrated that PVAT dysfunction is evident in many cardio-metabolic diseases, including hypertension and obesity (Greenstein *et al.,* 2009; Zou *et al.,* 2016).

The endothelium is a well-established modulator of vascular tone; however, more recently, PVAT has also been shown to control arterial contractility. Both the endothelium and PVAT play a part in the pathogenesis of many vascular diseases. Therefore, this review will focus on the control of vascular tone by PVAT and its similarities in the control of contractility by the endothelium.

Anti-contractile effects

Both the endothelium and PVAT release vasodilators and vasoconstrictors with the net effect in a healthy individual tending towards vasodilatation. The landmark discovery of NO (Palmer *et al.,* 1987), which has subsequently been demonstrated to be the main vasodilator released by the endothelium, established its key role in the endothelium-dependent modulation of vascular contractility. More recently, PVAT has been similarly shown to have the ability to reduce vascular contractility through the release of PVRFs (Lohn *et al.,* 2002). The mechanisms by which PVAT exerts this anti-contractile effect are not as well established as the control of vascular contractility by the endothelium; however, a number of studies have noted that the endothelium and PVAT release many common vasoactive factors that modulate vascular tone, and these are discussed below.

Nitric oxide

NO is a free-radical, endogenous gas that is involved in many physiological and pathophysiological processes of the cardiovascular system. In the endothelium, NO is synthesized from endothelial NOS (eNOS), which is sensitive to changes in $[Ca^{2+}_i]$ concentration. eNOS catalyses the oxidation of L-arginine into NO and L-citrulline, a reaction requiring the presence of cofactors such as calmodulin, flavin mononucleotide, flavin adenine dinucleotide and nicotinamide adenine dinucleotide phosphate. eNOS is regulated by phosphorylation at two major sites with opposing effects; Ser^{1177} phosphorylation leads to its activation while Thr^{495} phosphorylation decreases its activity (Dudzinski and Michel, 2007).

Palmer *et al.* showed that endothelial cells are able to generate NO that is responsible for the vasodilating properties of the endothelium-derived relaxing factor (Palmer *et al.,* 1987) described 7 years earlier (Furchgott and Zawadzki, 1980). NO regulates basal vascular tone and causes relaxation of VSM by stimulation of soluble GC to produce cGMP (Murad, 1986). Increased cGMP levels activate calcium sensitive potassium channels (K_{Ca} channels) and K_{ATP} channels leading to a decreased $[Ca^{2+}]_i$ concentration and subsequent relaxation of VSM (Warner *et al.,* 1994). NO can also directly activate K_{Ca} channels (Bolotina *et al.,* 1994).

eNOS is expressed in adipocytes (Ribiere *et al.,* 1996) and has now also been demonstrated in PVAT (Gao *et al.,* 2007). The anti-contractile effect of PVAT in various vascular beds – including rat aorta (Gao *et al.,* 2007), mouse mesenteric arteries (Lynch *et al.,* 2013), rat mesenteric artery (Bussey *et al.,* 2016; Zaborska *et al.,* 2016) and human subcutaneous arteries – has been shown to be abolished by NOS inhibition (Greenstein *et al.,* 2009; Aghamohammadzadeh *et al.,* 2015). NO leads to increased cGMP levels and subsequent protein kinase G activation (Rapoport and Murad, 1983). The anti-contractile effect of PVAT is also lost in mesenteric arteries from protein kinase G knockout mice (Withers *et al.,* 2014).

To summarize, inhibition of NOS has been shown to modulate the effects of both the endothelium and PVAT on vascular tone suggesting that NO is an important vasodilator, which is synthesized and released from both the endothelium and PVAT.

Prostacyclin

Prostaglandins were one of the first vasoactive substances produced by the vasculature to be identified (Moncada *et al.,* 1977). They are synthesized from arachidonic acid by two

COX enzymes (COX1 and COX2). The five primary prostaglandins include PGE_2, prostacyclin (PGI_2), PGD_2, $PGF_{2\alpha}$ and TXA_2. These species modulate vascular contractility by activation of specific PG receptors either inducing vasoconstriction ($PGF_{2\alpha}$; TXA_2) or vasodilatation (PGD_2; PGI_2) or both (PGE_2). PGI_2 is the most abundant prostaglandin produced by the endothelium (Moncada *et al.,* 1977) and is an important endogenous vasodilator that binds to IP receptors on the VSM. Via stimulation of the G_S subunit, activation of adenylate cyclase promotes cAMP production and subsequent VSMC relaxation (Alfranca *et al.,* 2006). This prostacyclin-mediated vasorelaxation is associated with the opening/activation of potassium channels in the VSM cells, including ATP-sensitive potassium channels (K_{ATP}) and delayed-rectifier potassium channels (K_{dr}); both subtypes are sensitive to the increasing intracellular cAMP levels (Li *et al.,* 1997).

Both COX1 and COX2 are also expressed in adipocytes (Bolduc *et al.,* 2004), endothelial cells (Hla and Neilson, 1992) and macrophages (Fels *et al.,* 1986); all of which are present in PVAT. Adipocytes also serve as a major source of PGs induced by catecholamine stimulation (Shaw and Ramwell, 1968) suggesting PVAT has the ability to produce and release prostaglandins and that these PGs may be involved in the mediation of the anti-contractile effect of PVAT on the vascular tone. Experimentally, the data are inconsistent; the early work by Lohn *et al.* (2002) suggested that COX is not an ADRF, as PVAT still exerted an anti-contractile effect in response to 5-HT stimulation, in the presence of a non-specific COX inhibitor, indomethacin, in the rat aorta (Lohn *et al.,* 2002), while others have determined that COX does contribute to the noradrenaline-induced anti-contractile effect of PVAT in mouse mesenteric artery (Lynch *et al.,* 2013) and human saphenous vein (Ozen *et al.,* 2013). The latter data suggests that prostaglandins (specifically PGE_2 and PGI_2) only mediate noradrenaline-induced vasodilatation by PVAT (Ozen *et al.,* 2013) (i.e. the involvement of products of COX enzymic activity is agonist-dependent). PGI_2 has also been shown to be responsible for the PVAT-mediated endothelium-dependent vasodilatation in mouse carotid artery (Chang *et al.,* 2012). TXA_2 release from mouse aortic PVAT is increased in obesity in response to 5-HT stimulation (Meyer *et al.,* 2013).

To summarize, both the endothelium and PVAT modulate vascular contractility by releasing a variety of prostaglandins.

Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is a ROS produced in the endothelium (Breton-Romero and Lamas, 2014) either by spontaneous dismutation of superoxide (O_2^-) or dismutation of O_2^- by superoxide dismutases. It is clear from the literature that H_2O_2 significantly alters vascular tone; however, the data are inconsistent as some studies report vasodilatation (Matoba *et al.,* 2000; Matoba *et al.,* 2002; Shimokawa and Matoba, 2004; Liu *et al.,* 2011) while others vasoconstriction (Gao and Lee, 2005; Mills *et al.,* 2009; Suvorava and Kojda, 2009). H_2O_2 has been shown to vasodilate mouse and human mesenteric arteries (Matoba *et al.,* 2000; Matoba *et al.,* 2002); these vasodilator effects of H_2O_2 may be mediated by activation of large conductance calcium-activated potassium channels (BK_{Ca}) on the VSM cells (Liu *et al.,* 2011) and activation of endothelial NO production (Drummond *et al.,* 2000).

H_2O_2 has also been shown to be produced in adipocytes (Luoma *et al.,* 1998) and has been proposed as a PVRF. PVAT-intact rat aortae incubated with catalase (a H_2O_2 scavenger) show enhanced vessel contraction (Gao *et al.,* 2007) suggesting that H_2O_2 may play a role in the anti-contractile effect of PVAT. This PVAT-derived H_2O_2 exerts vasodilatation through activation of soluble guanylyl cyclase within VSMC (Gao *et al.,* 2007).

To summarize, H_2O_2 modulates vascular contractility. Endothelium-derived H_2O_2 can induce either vasoconstriction or vasodilatation depending on the concentration, species and vessel type. However, PVAT-derived H_2O_2 has only been shown to contribute to the anti-contractile effect through activation of soluble GC in VSM.

Hydrogen sulphide

H_2S is a gaseous transmitter synthesized from L-cysteine by the enzyme cystathionine γ-lyase (CSE) (Kimura, 2011). Endothelium-dependent relaxation has been shown to be impaired in $CSE^{-/-}$ knockout mice (Mustafa *et al.,* 2011), suggesting that H_2S is a vasorelaxant produced/released by the endothelium. Additionally, CSE expression has been demonstrated in mouse endothelial cells, where it is activated by Ca^{2+}/calmodulin (Yang *et al.,* 2008). H_2S induces relaxation by activating endothelial SK_{Ca} and IK_{Ca} channels; it has also been shown to activate K_{ATP} channels in VSM cells (Zhao *et al.,* 2001; Mustafa *et al.,* 2011). CSE expression has also been demonstrated in rat aortic PVAT where it has been proposed to be responsible for the anti-contractile effects of PVAT (Kohn *et al.,* 2012). It has also been suggested that H_2S mediates the anti-contractile effect of PVAT via opening of K_V channels (Schleifenbaum *et al.,* 2010). However, the minutiae of how this gas acts within the cell to promote vasodilatation are yet to be fully elucidated.

To summarize, H_2S is a gaseous relaxant that activates K^+ channels when released from the endothelium. It may contribute to the anti-contractile effect of PVAT, although the mechanism is currently unknown.

Potassium channels

VSM membrane potential is the major determinant of vascular tone due to its influence on voltage-gated Ca^{2+} channels, which permit Ca^{2+} entry into the cell and subsequent constriction. K^+ channels are key regulators of the membrane potential, their activation leads to K^+ efflux and closure of voltage-dependent Ca^{2+} channels, which results in vasodilatation. However, K^+ channel inhibition results in depolarisation and subsequently contraction. SK_{Ca} and IK_{Ca} channels are expressed in endothelial cells (Marchenko and Sage, 1996; Burnham *et al.,* 2002) and were proposed to modulate VSM contraction via endothelial hyperpolarization that can be transmitted to VSM through myo-endothelial gap junctions (Marrelli *et al.,* 2003; Gluais *et al.,* 2005). Activation of these channels also results in an increase in extracellular K^+, which promotes hyperpolarization of VSM through

activation of Na^+/K^+-ATPase or inwardly rectifying K^+ channels (K_{ir}) (Weston *et al.,* 2002).

Experimentally, an increase in extracellular K^+ concentration (60 mM KCl) abolishes the anti-contractile effect of PVAT, suggesting that K^+ channels are involved in the modulation of vascular tone by PVAT [since a high extracellular K^+ concentration attenuates the effects of K^+ channels by reducing the K^+ gradient across the cell membrane (Lohn *et al.,* 2002)]. In addition to this, PVAT also hyperpolarises the membrane potential in rat mesenteric (Verlohren *et al.,* 2004; Weston *et al.,* 2013) and gracillis muscle arteries (Zavaritskaya *et al.,* 2013) further supporting the role of K^+ in the anti-contractile capacity of PVAT. Moreover, BK_{Ca} and K_V channels have also been proposed to modulate the effect of PVAT on vascular contractility (Verlohren *et al.,* 2004; Galvez *et al.,* 2006; Schleifenbaum *et al.,* 2010; Lynch *et al.,* 2013) in numerous vascular beds.

To summarize, activation of K^+ channels may be involved in the anti-contractile effects of both PVAT and the endothelium on vascular contractility.

Endothelial/PVAT dysfunction

Resistance artery dysfunction observed in obesity can arise from, and contribute to, hypertension (de Jongh *et al.,* 2004; Frisbee, 2005) leading to a 'vicious cycle' in which the resistance vasculature maintains or even augments the initial rise in blood pressure (Levy *et al.,* 2001). Obesity has detrimental effects on health; it can lead to insulin resistance, the metabolic syndrome, Type 2 diabetes mellitus and increased blood pressure, all being major risk factors for CVD.

Endothelial dysfunction refers to the inability of the endothelium to maintain vascular homeostasis resulting from an imbalance in the production of vasodilating and vasoconstricting factors from the endothelium. This dysfunction results in a shift towards the production of vasoconstricting factors, thus increasing peripheral resistance and consequently blood pressure (Drexler, 1998). This impairment in endothelial function is observed early in the progression of CVD; hence, endothelial dysfunction is an early predictor of future CVD, hypertension and atherosclerosis (Schachinger *et al.,* 2000). A blunted endothelium-dependent response to vasodilating agents (such as acetylcholine) has been reported in studies on hypertension and obesity (Aalkjaer *et al.,* 1987; Izzard *et al.,* 1996; Jonk *et al.,* 2007).

PVAT dysfunction is also now becoming evident in disease states. Age, environmental conditions and nutritional status also change the percentage of the cellular subtypes within PVAT. Normal adipose tissue tends to be in a non-inflammatory state, while obesity results in abnormal adipokine production, oxidative stress, hypoxia and inflammation of the adipose tissue (Achike *et al.,* 2011). PVAT dysfunction is also associated with an up-regulation of vasoconstricting factors (Almabrouk *et al.,* 2014) and has been implicated in obesity (Greenstein *et al.,* 2009; Meijer *et al.,* 2015) and hypertension (Aghamohammadzadeh *et al.,* 2015). PVAT dysfunction has been shown to contribute to the obesity-related endothelial dysfunction (Ketonen *et al.,* 2010) and smooth muscle cell dysfunction (Greenstein *et al.,* 2009).

Obesity-related hypertension is associated with endothelial (de Jongh *et al.,* 2004) and PVAT dysfunction (Aghamohammadzadeh *et al.,* 2015), and several factors have been proposed to play a role and are discussed in more detail below.

Endothelial/PVAT dysfunction – nitric oxide

The endothelial dysfunction observed in obesity is associated with reduced NO bioavailability due to increased production of ROS (Bakker *et al.,* 2000). eNOS uncoupling leads to the production of O_2^- (Kalinowski and Malinski, 2004) instead of NO. O_2^- can cause vasoconstriction directly due to the production of peryoxynitrate (from O_2^- + NO), which in turn increases the production of vasoconstricting prostaglandins by interacting with prostaglandin endoperoxide synthase (Goodwin *et al.,* 1999); O_2^- can also cause vasoconstriction indirectly by reducing NO bioavailability. In obesity, endothelial dysfunction is associated with the decreased NO bioavailability due to eNOS uncoupling (Lobato *et al.,* 2011).

Similarly, obesity-linked PVAT dysfunction is also associated with reduced NO bioavailability from PVAT (Bussey *et al.,* 2016), which is responsible for the reduced anti-contractile effect observed in obesity. Uncoupling of eNOS and increased O_2^- production were also proposed to contribute to the PVAT-induced endothelial dysfunction in obese mice (Xia *et al.,* 2016).

Endothelial/PVAT dysfunction – prostanoids

Another mechanism involved in endothelial and PVAT dysfunction in obesity is the impairment of prostaglandin release. Both COX1 and COX2 activities are increased in the endothelium from obese rats; however, in lean rats, COX2 does not influence the endothelial function, suggesting that the shift in COX2 activity observed in obesity contributes to the endothelial dysfunction (Sanchez *et al.,* 2010). Indeed the increased production of the TXA_2 and reduced PGI_2 release observed in obesity were attributed to the increased prostaglandin production from arachidonic acid by COX2, induced by inflammation (Lobato *et al.,* 2011).

Obesity is also associated with increased activity of both COX1 and COX2 in adipose tissue (Hsieh *et al.,* 2010; Farb *et al.,* 2014). Recently, Meyer *et al.* (2013) reported that obesity is associated with increased COX activity that leads to the release of a pro-contractile factor (TXA_2) from PVAT, suggesting that COX activity may play a part in obesity-induced PVAT dysfunction (Meyer *et al.,* 2013).

Endothelial/PVAT dysfunction – K^+ channels

Various potassium channels (such as K_{Ca}, K_{ir} and K_V) have been implicated in the endothelial dysfunction observed in obesity and hypertension (reviewed by (Climent *et al.,* 2014). The diminished anti-contractile effect of PVAT

observed in hypertension can be restored using KCNQ channel openers in rat Gracilis muscle arteries from spontaneously hypertensive rats, suggesting that a dysfunction in K^+ channels activation mediates the altered PVAT regulation of vascular tone (Zavaritskaya *et al.,* 2013).

Endothelial/PVAT dysfunction – inflammation

Obesity also leads to an increased production of the pro-inflammatory cytokines, such as monocyte chemoattractant protein-1 (also known as CCL2), TNF-α and IL-6 by endothelial cells and pre-adipocytes (Wellen and Hotamisligil, 2003). Obesity-linked inflammation contributes to endothelial dysfunction (Ziccardi *et al.,* 2002) by stimulating ROS generation and reducing NO bioavailablity (Virdis *et al.,* 2011). Local inflammation and hypoxia of PVAT observed in obesity were also proposed to attenuate its anti-contractile properties (Greenstein *et al.,* 2009).

In summary, endothelial dysfunction is well recognized as an important predictor of CVD, but more recently, PVAT has also been proposed to play a role. Obesity-linked PVAT and endothelial dysfunction are associated with altered NO and

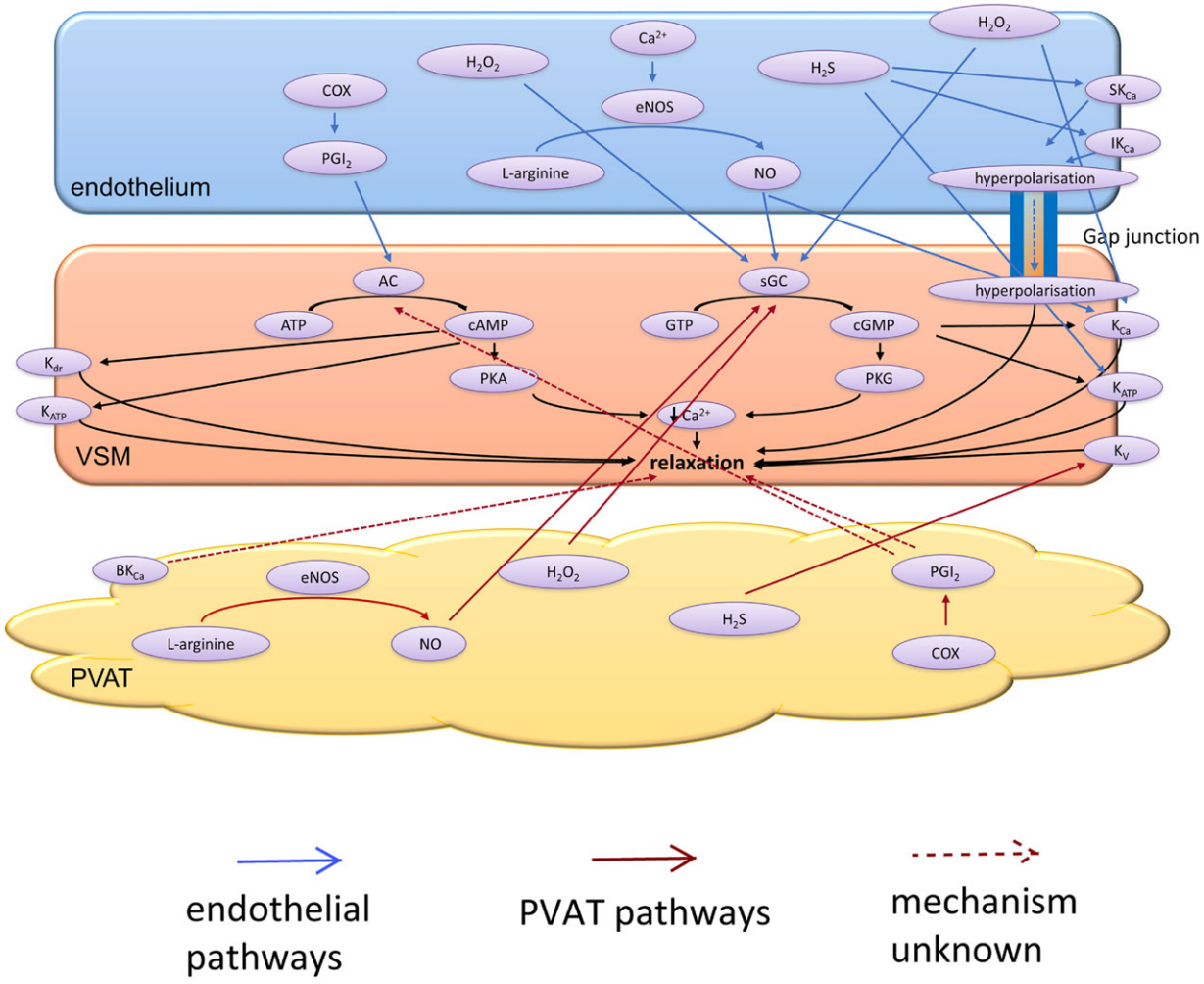

Figure 1

The vasodilating factors released by the endothelium and PVAT. The conversion of L-arginine into NO by endothelial (e) NOS in both the endothelium and PVAT stimulate soluble guanylyl cycles (sGC) in the VSM, which in turn converts GTP into cGMP. PKG activation leads to vasorelaxation. The enzymatic activity of COX leads to PGI_2 production within the endothelium and PVAT. Endothelial PGI_2 stimulates AC, which converts ATP into cAMP. PKA is then activated, which leads to relaxation of the VSM. Increasing levels of cAMP can also activate delayed rectifier potassium channels (K_{dr}) ATP-sensitive potassium channels (K_{ATP}). PVAT-derived PGI_2 causes relaxation of VSM via an unknown mechanism; however, it is most likely to stimulate AC. H_2O_2 is released by both the endothelium and PVAT and exerts its anti-contractile effects via sGC activation within the VSM. Endothelial H_2O_2 can also directly activate K_{Ca} on the VSM. H_2S mediates the anti-contractile effects of PVAT via voltage-gated potassium channels (K_V) on VSM. Within the endothelium, H_2S activates small-conductance (SK_{Ca}) and intermediate-conductance (IK_{Ca}) calcium-activated potassium as well as K_{ATP} channels on VSM. Activation of SK_{Ca} and IK_{Ca} on the endothelium leads to hyperpolarisation, which can spread to VSM via myo-endothelial gap junctions. Large-conductance calcium-activated potassium channels (BK_{Ca}) are also thought to mediate the anti-contractile effect of PVAT.

prostaglandin production, as well as inflammation and impaired K^+ channel activation.

Conclusions

The endothelium and PVAT produce both vasodilating and vasoconstricting factors that have been clearly demonstrated to modulate vascular contractility. There are many common pathways by which the endothelium and PVAT control vascular tone; these include NO, prostaglandins, K^+ channels, H_2O_2 and H_2S (Figure 1). An imbalance in the production of vasodilating and vasoconstricting factors that promotes an increased release of the latter leads to endothelial and PVAT dysfunction. These cellular dysfunctions are observed in both human obesity and animal models of disease, and the mechanisms involved are similar in both the endothelium and PVAT. The role of the endothelium in the control of vascular contractility is well established, more so than for PVAT; however, recent studies have shown that PVAT releases similar vasoactive substances to those released from the endothelium. The ability of PVAT to alter vascular reactivity by the production and release of vasoactive factors would ensure that the perfusion of local blood vessels could be attuned by PVAT to more accurately meet the needs of the tissues. However, more research is needed with regards to the modulation of vascular tone mediated by PVAT, as the mechanisms have yet to be fully elucidated.

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Conflict of interest

The authors declare no conflicts of interest.

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