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Review

Human perivascular adipose tissue dysfunction as a cause of vascular disease: Focus on vascular tone and wall remodeling

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ABSTRACT

Obesity is one of the major risk factors for the development of cardiovascular diseases. It is characterized by excessive or abnormal accumulation of adipose tissue, including depots which surround the blood vessels named perivascular adipose tissue (PVAT). PVAT plays endocrine and paracrine roles by producing large numbers of metabolically vasoactive adipokines. The present review outlines our current understanding of the beneficial roles of PVAT in vascular tone and remodeling in healthy subjects supported by clinical studies, highlighting different factors or mechanisms that could mediate protective effects of PVAT on vascular function. Most studies in humans show that adiponectin is the best candidate for the advantageous effect of PVAT. However, in pathological conditions especially obesity-related cardiovascular diseases, the beneficial effects of PVAT on vascular functions are impaired and transform into detrimental roles. This change is defined as PVAT dysfunction. In the current review, the contribution of PVAT dysfunction to obesity-related cardiovascular diseases has been discussed with a focus on possible mechanisms including an imbalance between beneficial and detrimental adipokines (commonly described as decreased levels of adiponectin and increased levels of leptin or tumor necrosis factor-alpha (TNFα)), increased quantity of adipose tissue, inflammation, cell proliferation and endothelial dysfunction. Finally, novel pharmacotherapeutic targets for the treatment of cardiovascular and metabolic disorders are addressed.

Contents

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1. Introduction

Obesity is one of the biggest epidemic health problems in the world and has been considered as a major risk factor for cardiovascular diseases. However, mechanisms of metabolic syndrome, diabetes mellitus and coronary artery disease in obese individuals are still under discussion. Obesity is characterized by excessive or abnormal accumulation of adipose tissue which is an active endocrine organ, secreting and producing many bioactive substances called adipokines (Boydens et al. 2012). It is well known that obesity-related cardiovascular diseases are accompanied by endothelial dysfunction which is characterized by a decrease in endothelium-dependent vasodilatatory factors such as nitric oxide (NO), prostacyclin (PGI_2) and an augmentation of endothelium-derived contractile factors (Hadi et al., 2005). Recent studies have proposed that not only endothelial dysfunction but also adipose tissue dysfunction has a potent role in the pathogenesis of obesity-related cardiovascular diseases. Maintenance of healthy adipose tissue function might become as important as preservation of endothelial integrity for prevention of vascular diseases (Gollasch, 2012; Gu and Xu, 2013).

Almost every blood vessel apart from cerebral artery and pulmonary vessels are surrounded by various quantities of perivascular adipose tissue (PVAT) (Szasz et al., 2013). It is now well established that PVAT not only provides mechanical protection for blood vessels, but also secretes vasoactive adipokines such as adiponectin, leptin, resistin, visfatin or other bioactive mediators (Oriowo, 2015). These mediators secreted from PVAT could easily reach the adjacent blood vessel wall since there is no anatomical barrier between PVAT and adventitia. They play important roles in regulation of the vascular tone and wall remodeling via their paracrine or endocrine effects. In this review, we aim to discuss these roles of PVAT on vascular functions in both physiologic and pathological conditions.

2. Release of adipokines from PVAT

Adipokines released from PVAT have been shown to have a more inflammatory, proliferative and angiogenic profile compared to other adipose depots such as subcutaneous or visceral adipose tissues in humans (Mazurek et al., 2003; Chatterjee et al., 2009; Rittig et al., 2012; Schlich et al., 2013).

Recent studies have focused on modulation of adipokines release depending on pathological conditions. In humans, most studies for determinating the role of adipose tissue in cardiovascular diseases have been performed in epicardial adipose tissue (EAT). EAT is the adipose tissue around the heart reaching from the myocardium to the pericardium. PVAT around coronary artery is a part of EAT. There is no obvious anatomical separation between coronary PVAT and EAT; however, PVAT releases greater levels of monocyte chemotactic protein-1 (MCP-1) than EAT (Chatterjee et al., 2009; Verhagen and Visseren, 2011). In coronary artery disease, inflammatory and proliferative adipokine expression or release such as interleukin-6 (IL-6), resistin, interleukin-1 beta (IL-1ß), MCP-1, chemerin, plasminogen activator inhibitor 1, tumor necrosis factor-alpha (TNFα), visfatin and leptin are increased, whereas adipokines with anti-inflammatory, anti-proliferative and vasodilatator properties (Terata et al., 2000; Xi et al., 2005) such as adiponectin or adrenomedullin are decreased in human EAT or PVAT surrounding coronary artery (Table 1). This imbalance between beneficial and detrimental adipokines may play a major role in cardiovascular diseases such as atherosclerosis, restenosis and hypertension by increasing vascular tone, inflammatory processes and vascular smooth muscle cell (VSMC) proliferation or migration.

3. Role of PVAT quantity in vascular disease

Recent studies have indicated a potential role of PVAT quantity in the development of coronary artery diseases. EAT thickness (Ahn et al., 2008; Demircelik et al., 2014; Eroglu et al., 2009) and also EAT volume (Mihl et al., 2014; Kaya et al., 2014; Mohar et al., 2014; Groves et al., 2014; Kim et al., 2014) were found to be higher in patients with coronary artery diseases. Total quantity of PVAT around coronary artery is strongly related to atherosclerotic plaque (Mahabadi et al., 2010; Maurovich-Horvat et al., 2011). More recently, extra media thickness has been suggested as a novel index of PVAT and associated with an increasing number of cardiovascular risk factors (Haberka and Gasior, 2015). A larger adipocyte size and increased density of differentiating preadipocyte are found in EAT obtained from coronary artery disease patients compared to healthy subjects (Silaghi et al., 2007).

It has been demonstrated that adipose tissue quantity is negatively correlated with microvascular coronary vasodilatation response and also coronary flow hyperemia in humans (Shen et al., 2013). EAT thickness is also negatively correlated with flow-mediated dilatation which has been established as a parameter of endothelial dysfunction (Temiz et al., 2015). Endothelial dysfunction has been indicated to be one of the critical initiating step in the development of atherosclerosis. Consistent with these studies, when there is no PVAT such as the intramyocardial portions of coronary arteries, less atherosclerosis has been observed (Ishikawa et al., 2006; Verhagen and Visseren, 2011).

PVAT surrounding human brachial artery is associated with insulin sensitivity; however, it is not correlated with local endothelial dysfunction (Rittig et al., 2008). Moreover, quantity of PVAT surrounding renal sinus is related to the number of prescribed antihypertensive medications and stage II hypertension (Chughtai et al., 2010). Framingham Heart study has indicated that higher thoracic and abdominal aortic dimensions are associated with PVAT quantity. This result has suggested that PVAT could induce aortic remodeling especially observed in aortic aneurysm (Thanassoulis et al., 2012).

4. Role of PVAT in vascular tone control *in vitro*

Firstly, Soltis and Cassis have shown that PVAT decreases the vascular contractile response to norepinephrine in rat aorta (Soltis and Cassis, 1991). Subsequently, it was confirmed that PVAT reduces vascular reactivity in response to not only norepinephrine but also serotonin, phenylephrine and angiotensin II (Lohn et al., 2002). This vasorelaxant effect of PVAT is mostly observed in animal tissues such as mesenteric arteries of rats/mice (Galvez et al., 2006; Takemori et al., 2007), venous rings of rats (Lu et al., 2011) and coronary arteries of pigs (Bunker and Laughlin, 2010).

The factors mediating the vasorelaxant effect of PVAT are not fully understood. This mediator named adipocyte-derived relaxing factor (ADRF) is abolished in the presence of ATP-dependent K channel blocker, whereas it is not modified by nitric oxide synthase (NOS) or cyclooxygenase (COX) inhibitors in rat aorta preparations (Lohn et al., 2002). However, in rat mesenteric arteries, voltage-dependent K channel blocker inhibits the vasorelaxant effect of PVAT (Galvez et al., 2006). It is suggested that regulation of vascular tone by PVAT is mediated by release of different adipokines from PVAT, depending on anatomic location of the adipose tissue depots and also the species: Hydrogen peroxide (Gao et al., 2007), hydrogen sulfide (H_2S) (Fang et al., 2009), adiponectin (Lynch et al., 2013), leptin (Galvez-Prieto et al., 2012) and methyl palmitate (Lee et al., 2011) have been considered as candidates for the vasorelaxant effect of PVAT in animal tissues. However, this vasorelaxant effect is abolished in several models of pathologies