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Autonomic nerves and perivascular fat: Interactive mechanisms

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ABSTRACT

The evidence describing the autonomic innervation of body fat is reviewed with a particular focus on the role of the sympathetic neurotransmitters. In compiling the evidence, a strong case emerges for the interaction between autonomic nerves and perivascular adipose tissue (PVAT). Adipocytes have been shown to express receptors for neurotransmitters released from nearby sympathetic varicosities such as adrenoceptors (ARs), purinoceptors and receptors for neuropeptide Y (NPY). Noradrenaline can modulate both lipolysis (via α_2- and β_3-ARs) and lipogenesis (via α_1- and β_3-ARs). ATP can inhibit lipolysis (via P_1 purinoceptors) or stimulate lipolysis (via P_{2y} purinoceptors). NPY, which can be produced by adipocytes and sympathetic nerves, inhibits lipolysis. Thus the sympathetic triad of transmitters can influence adipocyte free fatty acid (FFA) content. Substance P (SP) released from sensory nerves has also been shown to promote lipolysis. Therefore, we propose a mechanism whereby sympathetic neurotransmission can simultaneously activate smooth muscle cells in the tunica media to cause vasoconstriction and alter FFA content and release from adjacent adipocytes in PVAT. The released FFA can influence endothelial function. Adipocytes also release a range of vasoactive substances, both relaxing and contractile factors, including adiponectin and reactive oxygen species. The action of adipokines (such as adiponectin) and reactive oxygen species (ROS) on cells of the vascular adventitia and nerves has yet to be fully elucidated. We hypothesise a strong link between PVAT and autonomic fibres and suggest that this poorly understood relationship is extremely important for normal vascular function and warrants a detailed study.

Contents

Abbreviations: 4HNE, lipid peroxidation by product 4-hydroxy-2-nonenal; ACE, angiotensin converting enzyme; ADRF/ADCF/ADHF, adipose-derived relaxing factor/adipose-derived constricting factor/adipose-derived hyperpolarising factor; AGT, angiotensinogen; Ang II, angiotensin II; ANS, autonomic nervous system; ARs, adrenoceptors; BAT, brown adipose tissue; BMI, Body mass index; CABG, coronary artery bypass graft surgery; CAMP, cyclic adenosine monophosphate; CGRP, calcitonin gene-related peptide; EC, endothelial cell; EFS, electrical field stimulation; ENOS, endothelial-derived nitric oxide synthase; FFA, free fatty acid; IL-6, interleukin 6; INOS, inducible nitric oxide synthase; IP3, inositol trisphosphate (or inositol 1,4,5-trisphosphate); KO, knockout; MCH, melanin concentrating hormone; MEJ, myoendothelial junctions; NA/NE, noradrenaline/norepinephrine; NADPH, nicotinamide adenine dinucleotide phosphate; NEFA, non-esterified fatty acid; NMJ, neuromuscular junctions; NNOS, neuronal nitric oxide synthase; NO, nitric oxide; NPY, neuropeptide Y; O_2^-, superoxide anion radical; OH, obesity hypertension; PACAP, pituitary adenylate cyclase activating polypeptide; PAI-1, plasminogen activator inhibitor-1; Pmch, prohormone precursor of MCH; PPAR γ, peroxisome proliferator-activated receptor gamma; PVAT, perivascular adipose tissue; PVRF/PVCF, perivascular-derived relaxing factor/perivascular-derived constricting factor; ROS, reactive oxygen species; SHR, spontaneous hypertensive rat; SMC, smooth muscle cell; SNS, sympathetic nervous system; SP, substance P; STZ, streptozotocin (induced diabetic model); TNF α, tumour necrosis factor alpha; TRP, transient receptor potential; UCP, uncoupling protein thermogenin; VACht, vesicular acetylcholine transferase; VIP, vasoactive intestinal polypeptide; WAT, white adipose tissue.

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1. Introduction

The modulatory role of perivascular adipose tissue (PVAT) has attracted much attention in the past few years. This interest has been paralleled by the growing acceptance of the whole body adipocyte population as an endocrine organ (Coelho et al., 2013) and the recognition that total body fat is now seen as a key factor in the development of metabolic syndrome leading to cardiovascular disease. PVAT is also now regarded as a powerful paracrine influence on vascular responsiveness (Szasz et al., 2013). This establishes an important link between body fat and the cardiovascular system. The fat itself has a rich vascular supply and conversely many blood vessels have their own unique PVAT. The blood supply and innervation of visceral and subcutaneous fat have been well described. However, the innervation of PVAT (Fig. 1) and the functional interactions in the adventitial-adipose region have yet to be studied in any detail. In this review we shall make the case for a reciprocal modulation between autonomic fibres and PVAT. (See Table 1.)

In 2008, almost a quarter of adults in England were classified as obese of whom nearly half had recorded high blood pressure and were at risk of cardiovascular disease (CVD, NHS, 2010). Underlying mechanisms in the generation of obesity-related illnesses, such as hypertension, are complex and include endocrine, paracrine and neural influences. Increased white adipose tissue (WAT), resulting from increased adipocyte number is evident (Lambert et al., 2010).

Elevated sympathetic nervous activity is associated with higher visceral adiposity with suggestions that this increase in sympathetic activity contributes to the development of hypertension in the obese state. However, examination of firing patterns of sympathetic nerves in obese and non-obese hypertensive patients suggests a complex relationship between sympathetic activity, obesity and hypertension (Lambert et al., 2007). Therefore, it is not simply the case that obesity leads to increased sympathetic activity and this in turn promotes hypertension. It may even be that increased sympathetic activity could lead to obesity since elevated plasma noradrenaline levels have been identified as a predictor of weight gain (Masuo et al., 2003). If such a mechanism were active at a local level, it is fascinating to speculate that increased activity of vascular sympathetic nerves may be a driver for increasing PVAT. A common vascular dysfunction in obesity and hypertension exists at the level of the endothelium. Since reducing sympathetic activity (with moxonidine) in obese hypertensives can restore endothelial function it is possible that a direct link between nerve and endothelium may exist. We postulate a complex interaction between PVAT, sympathetic nerves and endothelial function (Fig. 2a & b); all of which may be influenced by obesity and/or hypertension. Here we review the possible interaction between adipokines and sympathetic neurotransmission in modulating vascular function. We examine each of the co-transmitters released from sympathetic nerves and consider their influence on adipocyte activation and interactions or synergies which may exist.

Organisms have self-defence mechanisms to protect the muscle from substrate over-supply by creating local fat depositions with specialist vasoregulatory function (Yudkin et al., 2005). However a prolonged and excessive fat accumulation results in a dysfunctional response exhibited by abnormal production of the adipokines (overproduction of some of the atherogenic adipokines whilst the anti-atherogenic adiponectin is hyposecreted). Around the vascular wall, the PVAT could thus promote inflammation, atherosclerosis and smooth muscle proliferation associated with cardiovascular disease (Rajsheker et al., 2010). The location of the PVAT around the adventitial layers of blood vessels permits a complex crosstalk where adipokines with chemotactic properties could promote accumulation of lymphocytes and monocytes at the vascular endothelium (Rajsheker et al., 2010). PVAT is now regarded as a powerful endocrine influence on vascular responsiveness with contributions from adipokines including 'anti-contractile' perivascular adipocyte-derived relaxation factors (PVRF or ADRF) and constricting factors (PVCF or ADCF) (Gao, 2007). The identification of factors released from PVAT is an ongoing process with increasing lists of different

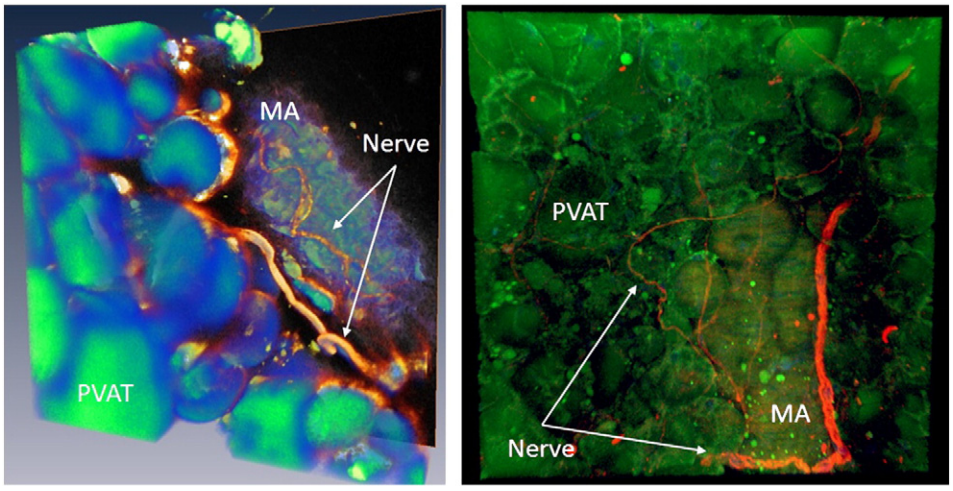

Fig. 1. Innervation of PVAT. Left; The image shows a mouse mesenteric artery (MA) running under its surrounding PVAT (half of which has been cleared for visualisation). Nerves running on the vessel surface also appear to innervate the PVAT. The nerves appear red/orange as a result of binding BODIPY-TMR CGP12177 (1 μM), a fluorescent β-adrenoceptor ligand. Right; The mesenteric artery (MA) has been incubated BODIPY FL-Prazosin (1 uM), a green fluorescent α-adrenoceptor ligand and a red fluorescent nerve-specific antibody (PGP 9.5). In both panels, data was collected using a confocal microscope and re-constructed using AMRIA (left) or IMARIS (right) software.