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The role of AMP-activated protein kinase in perivascular adipose tissue modulates vascular function

Perivascular adipose tissue (PVAT) is an active endocrine and paracrine organ surrounding most blood vessels. It has anti-contractile and anti-inflammatory effects on the underlying blood vessels and secretes a large number of adipocyte-derived biologically active molecules, with physiological and pathophysiological vasoactive effects. In pathophysiological conditions, such as obesity, hypertension and type 2 diabetes mellitus (T2DM), however, PVAT secretion becomes altered and favours chronic low-grade inflammation, which is associated with insulin resistance and cardiovascular diseases (CVD). Therefore, PVAT may implicated in pathophysiology of cardiovascular diseases (CVD). AMP-activated protein kinase (AMPK) is a key regulator of metabolism, vascular function, and inflammation. AMPK is a heterotrimer of an α catalytic subunit and β and γ regulatory subunits. Isoforms (α1, α2, β1, β2, γ1, γ2, γ3) of AMPK are expressed in a tissue-specific manner. The profile of AMPK isoform levels and activities within adipose/adipocytes, and their role in PVAT has not been fully characterized. We therefore characterized AMPK isoform levels and activities within rodent and human adipose/adipocytes, and investigated the role of AMPK in PVAT on endothelium-denuded aortae, using AMPKα1 knockout mice (KO) and their wild type (WT) littermates by wire myography. In addition, the effect of AMPK α1 ablation on the secretion of the adipokine adiponectin by PVAT was investigated by ELISA. All data are expressed as mean ± SEM. We demonstrate that, in the 3T3-L1 adipocyte cell line, mouse mesenteric, mouse epididymal, rat mesenteric and epididymal adipocytes and human subcutaneous adipose tissue, the predominant AMPKα catalytic subunit isoform was α1 (82.6±12.5, 80.1±10.1, 70±6.5, 91±4.0, 96.3±1, and 79.7±4.0 % total AMPK activity respectively), whereas the predominant AMPKβ subunit isoform was β2 (85±7.3, 82.5±0.89, 80±3.1, 84.6±0.5, 85.3±3.0, and 79.4±3.3, % total AMPK activity respectively, n= 3-11). PVAT enhanced relaxation to the K+ channel opener cromakalim from WT mice (59.0 ± 12.3%, n=7; $p<0.001$) and this effect was impaired in KO mice (21.6 ± 1.6% (n=7). Exogenous PVAT from WT mice enhanced relaxation in KO aortic rings (46.29 ± 10.85%, n=6) but PVAT from KO mice had no effect in aortic rings from WT mice. Deletion of AMPKα1 significantly attenuated adiponectin secretion from PVAT by 44%, n=6 and addition of globular adiponectin to either KO or WT endothelium-denuded aortic rings without PVAT augmented relaxation to cromakalim to the same degree (58.2 ± 9.9%, (n=5) and 58.6 ± 12.5% (n = 6) respectively). Finally, an adiponectin receptor blocker significantly reduced relaxation in PVAT intact WT endothelium-denuded aortic rings but not KO rings (65.6 ± 14.2% to 39.9 ± 11.6%; n=6). In conclusion, our data demonstrate that AMPK α1 and β2 are the predominant α and β AMPK subunit isoforms in adipocytes. Furthermore, AMPKα1 plays a key role in PVAT modulation of vascular function in endothelium-denuded vessels and may be through AMPK-mediated stimulation of adiponectin secretion and sensitivity.