NITRIC OXIDE MEDIATES THE ANTICONTRACTILE EFFECT OF PERIVASCULAR ADIPOSE TISSUE

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Objective Perivascular adipose tissue (PVAT) exerts an anticontractile effect. Studies using various vasoconstrictor agents suggest that this may be dependent on adrenergic stimulation and the subsequent release of nitric oxide. Moreover, nitric oxide synthase expression has previously been identified in PVAT isolated from human saphenous vein grafts. This study investigated the role of nitric oxide in the anticontractile action of PVAT.

Design and methods The effect of PVAT on the contractility of isolated rat mesenteric arteries (approx. 250-300 μm internal diameter) was investigated using wire myography. Concentration-response curves to noradrenaline (1×10^{-5} - 3×10^{-9} mol.l^{-1}) were generated following 30 minute incubation with the nitric oxide synthase inhibitor, L-NMMA (100 $\mu\text{mol.l}^{-1}$). In addition, a Griess reagent kit was used to determine NO production from the adipose tissue surrounding the mesenteric artery in response to stimulation with the adrenergic agonists (10 $\mu\text{mol.l}^{-1}$), noradrenaline, phenylephrine or CL-316, 243 +/-L-NMMA (100 $\mu\text{mol.l}^{-1}$). Data were analysed by two-way ANOVA.

Results and conclusions The vasoconstrictor response to noradrenaline was reduced in the presence of PVAT through an endothelium-dependent mechanism (endo: PVAT vs no PVAT $P < 0.05$, $n=5$, no endo: PVAT vs no PVAT $P=0.965$, $n=5$). The presence of L-NMMA produced an increase in the vasoconstrictor action of noradrenaline only in the presence of **both** PVAT and endothelium (PVAT: no L-NMMA vs L-NMMA $P < 0.001$, $n=5$, no PVAT: no L-NMMA vs L-NMMA $P=0.367$, $n=5$) indicating that nitric oxide release from PVAT contributes to its anticontractile effect.

Adrenergic stimulation of adipose tissue (devoid of vessels) with noradrenaline and CL-316,243, but not the α -adrenergic agonist, phenylephrine, was associated with a significant increase in nitric oxide production (noradrenaline and CL-316,243, $P < 0.05$, $n=5$), which was inhibited by the presence of L-NMMA. This confirms that β -adrenergic activation stimulates nitric oxide production by PVAT which may contribute to the anticontractile effect. Moreover, the similarity in response to noradrenaline and CL-316,243 suggests that β_3 -adrenoceptors are the main β -adrenergic subtype mediating this response.

Overall, our data indicate that the anticontractile effect of PVAT is dependent on nitric oxide release following upstream activation of β -adrenoceptors.