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Reversing adrenoceptor dysfunction in obese perivascular adipose tissue using exercise

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Background/Purpose: Healthy perivascular adipose tissue (PVAT) exerts an anti-contractile effect on resistance arteries which is vital in regulating vascular tone. Activation of adipocyte β3-adrenoceptors by sympathetic nerve-derived noradrenaline may be implicated in this effect. In obesity, autonomic dysfunction occurs, which may lead to desensitisation and loss of PVAT function. Accordingly, we investigated sympathetic nerve stimulation within PVAT, and the potential for healthy sympathetic hyper-stimulation by exercise in reversing PVAT dysfunction in obesity.

Methods: Electrical field stimulation (EFS) profiles of murine mesenteric arteries (<250µm, +/-PVAT) from healthy, obese, and exercised obese mice were characterised using wire myography (0.1-30Hz, 20V, 0.2ms pulse, 4s train). To demonstrate the release of an anti-contractile factor, the solution surrounding stimulated exogenous PVAT was transferred to a PVAT denuded vessel. Healthy PVAT was sympathetically denervated using the catecholamine toxin 6-hydroxydopamine (2µM). β3-adrenoceptor function was investigated using the agonist CL-316,243 (10µM) and antagonist SR59203A (100nM). The role of the adipokine, adiponectin, was examined using exogenous adiponectin (5µg/ml) and a blocking peptide for adiponectin receptor 1 (5µg/ml). Immunohistochemistry was used to examine β3-adrenoceptor expression.

Results: During EFS PVAT elicited a reproducible anti-contractile effect, which was lost in obesity. Solution transfer from stimulated exogenous PVAT to a –PVAT vessel significantly reduced contraction, confirming that stimulated healthy PVAT releases a transferable anti-contractile factor. Pharmacological denervation using 6-hydroxydopamine abolished the anti-contractile effect. In health, the β3-adrenoceptor agonist SR59203A reduced the anti-contractile effect; however β3-adrenoceptor agonist CL-316,243 could not restore function in obesity. Using immunohistochemistry, expression of β3-adrenoceptors was reduced in obesity. Exogenous application of adiponectin induced vasodilation of healthy vessels, and a blocking peptide for adiponectin receptor-1 significantly reduced the anti-contractile effect of PVAT in health. However, in obese vessels exogenous adiponectin no longer exerted a vasodilator effect. In obese exercised mice, the PVAT anti-contractile was restored, and the development of hypertension and type-II diabetes was reversed, although the mice remained obese. Exercise increased β3-adrenoceptor expression, and restored the vasodilator effects of adiponectin.

Conclusions: In conclusion, sympathetic nerve stimulation elicits an anti-contractile effect via activation β3-adrenergoreceptors and release of adiponectin. This effect was lost in obesity, which may contribute to development of hypertension and type-II diabetes. Exercise restored PVAT dysfunction in obesity, and normalised glucose, insulin, and blood pressure independent of weight loss.