Heterogeneous Vascular Responses to 2-Arachidonylglycerol in Zucker Diabetic Fatty Rats

Amanda Wheal\textsuperscript{1,2}, Michael Randall\textsuperscript{1}, Saoirse O'Sullivan\textsuperscript{2}

\textsuperscript{1}School of Biomedical Sciences, University of Nottingham, Nottingham, NG7 2UH, United Kingdom, \textsuperscript{2}School of Graduate Entry Medicine & Health, University of Nottingham, Derby, NG22 3DT, United Kingdom

Type 2 diabetes is a multisystem disorder, which may be associated with cardiovascular complications such as hypertension and endothelial dysfunction. The endocannabinoids anandamide and 2-arachidonylglycerol (2-AG) have been shown to have vasodilator actions in normal rat arteries through a variety of mechanisms (Randall et al. 2004; Ho & Randall, 2007). Here we aimed to investigate possible alterations of the \textit{in vitro} actions of the endocannabinoid 2-AG in a model of type 2 diabetes, Zucker Diabetic Fatty rats.

Mesenteric arterial beds were taken from male, Zucker Diabetic Fatty rats (319 – 360g) and their lean controls (275 – 311g). Blood glucose was measured immediately after cervical dislocation. Third-order branches from the superior mesenteric artery, and sections of femoral artery, were set to 4.9mN of tension in a wire myograph, whilst segments of thoracic aortae were started at a basal tension of 9.8mN. Once equilibrated, vessels were contracted with methoxamine, and concentration-response curves to 2-AG (10nM–100μM) were constructed.

Blood glucose levels of the diabetic rats (17.3 ± 1.9 mM, n=6, mean ± s.e.mean) were significantly higher than those of the controls (6.60 ± 0.34 mM, n=6; P<0.001, Student’s t-test). In both diabetic rats and their lean controls, 2-AG caused concentration-dependent vasorelaxation in third-order mesenteric arteries ($pEC_{50\%}$ Lean = 4.97 ± 0.33, n=5; Diabetic = 4.85 ± 0.24, n=5). 2-AG had no effect on preconstricted thoracic aortic rings from control rats, but vasoconstriction was observed in the diabetic preparations. In femoral arteries from both strains 2-AG caused vasoconstriction, which was enhanced in the diabetic rats (percentage increase in tone: Lean = 20.6 ± 2.8 %, n=6; Diabetic = 39.5 ± 12.6 %, n=6; P<0.05, 2-way ANOVA lean vs. diabetic).

In summary, the vasculature of these diabetic rats has demonstrated heterogeneous responses to 2-AG in this model of type 2 diabetes. Furthermore, alterations of the endocannabinoid system may contribute to vascular dysfunction in this strain.

This work was funded by Diabetes UK.
