# A novel role for small molecule glycomimetics in the protection against lipid-induced endothelial dysfunction

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subjects. Proteomic data, filtered for FC >2, detected 2051 spots with 1899 (92.5%) being equally oxidised between NT and HT. In addition, oxidation of 57 (2.9%) spots was increased, while 95 (4.6%) were decreased in HT. Candidate proteins exhibiting consistent changes across three experimental replicates included β-actin (FC = –2.86), annexin A1 (–2.23), galectin-1 (–1.67), FK506 binding protein (–2.35) and polymerase I and transcript release factor (PTRF, –1.92). Stimulation with AngII altered the redox status in 2–3% of proteins, both in HT and NT. However, vimentin was the only target changing consistently across the replicates (FC = 2.48). Our findings indicate that pro-hypertensive agents may not impact significantly on irreversible protein and PTP oxidation in health and disease, but may have effects on reversible oxidation. Our proteomic data, in agreement with our previous rat studies, support decreased reversible thiol oxidation in hypertension.

## 42 GLYCATION AND VASCULAR CALCIFICATION: DEVELOPING AN ANTI-CALCIFICATION STRATEGY

[1]R Weston, [1]GP Sidgwick, [1]N Ahmed, [1]N Nazhad, [2,3]A Schiro, [1,2,3]F Serracino Inglott, [1]FL Wilkinson, [1,2]MY Alexander. *[1]Healthcare Science Research Centre, Manchester Metropolitan University, Chester Street, Manchester, M1 5GD, UK; [2]Cardiovascular Research Institute, University of Manchester, Grafton St, Manchester, UK; [3]Vascular Unit, Central Manchester NHS Trust, Manchester Academic Health Science Centre, Manchester, UK*

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It is well established that vascular calcification is a common complication in diabetes and recent studies suggest that glycation may play a pathogenic role in this process. The aim of this study was to investigate the role of glycation in the induction of calcification in vascular smooth muscle cells (SMCs), and the potential inhibitory effects of the anti-diabetic agent, Momordica Charantia. Vascular SMCs were incubated with native or glycated LDL in the presence of osteogenic media and mineral deposition was determined using alizarin red staining and alkaline phosphatase (ALP) activity. We found that SMCs incubated in osteogenic media exhibited mineralisation after 7 days. This calcification was significantly increased following treatment with glycated-LDL, but not by native LDL. Furthermore, we found that ALP activity was significantly elevated at day 4 in glycated-LDL treated cells, compared to those incubated in native LDL. The vascular SMCs were exposed to increasing concentrations of Momordica Charantia extract in the presence of osteogenic media. ALP activity was reduced in treated cells, compared to osteogenic controls. Furthermore, we found that Momordica Charantia reduced gene expression of a range of biomarkers linked with vascular calcification after 4 days in a dose-dependent manner, including osteocalcin and BMP-2. In conclusion, we have shown that glycated LDL promotes osteogenic differentiation of vascular SMCs. Momordica Charantia extract shows promise as a potential therapeutic agent to reduce vascular calcification. Future work will identify the active ingredient responsible for calcification inhibitory effects, and establish whether it links to the pathological glycation-induced osteogenesis.

## 43 A NOVEL ROLE FOR SMALL MOLECULE GLYCOMIMETICS IN THE PROTECTION AGAINST LIPID-INDUCED ENDOTHELIAL DYSFUNCTION

[1,2]Ayman M Mahmoud, [1]Fiona L Wilkinson, [3]Alan M Jones, [4]James A Wilkinson, [5]Miguel Romero, [5]Juan Duarte, [1]M Yvonne Alexander. *[1]Cardiovascular Research Group, Healthcare Science Research Centre; [2]Physiology Division, Department of Zoology, Faculty of Science, Beni-Suef University, Egypt; [3]Division of Chemistry and Environmental Science, Faculty of Science and Engineering, Manchester Metropolitan University, and Manchester Academic Health Science Centre, UK; [4]Centre for Molecular Drug Design, University of Salford, UK; [5]Department of Pharmacology, School of Pharmacy, University of Granada, and Instituto de Investigación Biosanitaria de Granada (Ibs. GRANADA), Spain*

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Glycomimetics are molecules that mimic the structure of carbohydrates involved in important biological processes. Small molecule glycomimetics are an untapped source of novel therapies for endothelial dysfunction, a hallmark of cardiovascular complications associated with diabetes. The current study aims to investigate the possible protective effects of newly synthesised small molecule glycomimetics against lipid-induced endothelial dysfunction, with an emphasis on nitric oxide (NO) and induced oxidative stress. Glycomimetics were synthesised by the stepwise transformation of 2,5-dihydroxybenzoic acid to a range of 2,5-substituted benzoic acid derivatives incorporating the key sulfate groups to mimic the interactions of heparan sulfate. Acetylcholine-induced endothelium-dependent relaxation in mouse thoracic aortic rings was measured using wire myography, and human umbilical vein endothelial cells (HUVECs) function was assessed in the presence or absence of palmitate, with or without the test glycomimetics. NO and reactive oxygen species (ROS) production was measured using DAF-2 and H2DCF-DA, respectively. Colorimetric assays were used to determine lipid peroxidation and activity of the antioxidant enzymes. Expression of Akt, eNOS, Nrf-2, NQO-1 and HO-1 were assessed using RT-PCR and western blotting. At 1 μM concentration, the synthesised glycomimetics significantly improved endothelium-dependent relaxation *ex vivo* and protected HUVECs against palmitate-induced oxidative stress and reduced NO production. Pre-incubation of HUVECs with all compounds upregulated Akt/eNOS signalling, activated Nrf2/ARE pathway, and suppressed ROS-induced lipid peroxidation. In conclusion, our newly synthesised small molecule glycomimetics protect against lipid-induced endothelial dysfunction. These novel cytoprotective effects open the door to a new class of therapeutic drugs to target endothelial dysfunction.

## 44 ASK-1 INHIBITION PREVENTS HYPOXIA-INDUCED PULMONARY ARTERY FIBROBLAST PROLIFERATION AND MIGRATION IN AN *IN VITRO* CELLULAR MODEL OF PULMONARY HYPERTENSION

[1]KS Wilson, [1]K Suveizdyte, [2]J Liles, [2]GR Budas, [1]AJ Peacock, [1]DJ Welsh. *[1]Scottish Pulmonary Vascular Unit, Glasgow, UK; [2]Gilead Sciences Inc., Foster City, CA, USA*

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