

P008 The Role of EGFR in hyperglycaemia-induced endothelial cell dysfunction

Sioned M Griffiths¹, Mariam H Yousif², Ibrahim F Benter²,
Saghir Akhtar¹

1. Centre for Genome Based Therapeutics (CGT), The Welsh School of Pharmacy, Cardiff University, Cardiff CF10 3XF

2. Department of Pharmacology, Faculty of Medicine, Kuwait University, Kuwait

Diabetes leads to the development of micro- and macrovascular disease but the underlying molecular mechanisms involved remain unclear. We hypothesized that the Epidermal Growth Factor Receptor (EGFR) plays an important role in mediating vascular dysfunction. Initial work on streptozotocin (STZ) diabetic rats showed higher levels of phosphorylated (p) EGFR compared to non-diabetic controls. We also showed that impairment in vasoconstriction response to noradrenaline observed in the STZ-diabetic rats could be normalized by both genistein (receptor tyrosine kinase inhibitor) and AG1478 (EGFR inhibitor). Parallel studies in the endothelial-like ECV-304 cell line grown in high (25.5mM) glucose media also showed alterations in EGFR signalling. Changes in pEGFR levels by glucose were accompanied by alterations in upstream and downstream signalling proteins such as TGF β , c-Src, HB-EGF, ADAM10, Ras, P38MAPK and Akt. These results suggest an important role of EGFR signalling in mediating diabetes-induced vascular dysfunction and as such inhibition of this pathway may represent a novel therapeutic strategy for the treatment of diabetes-induced vascular dysfunction.