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A comparative study of receptor mediated apelin APJ activation versus incretin mimetic actions for alleviation of metabolic dysfunction in diabetes

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Statement of the problem: Current diabetes therapies often fail to reach target glycaemic control. The adipokine apelin derived from processing of the precursor preproapelin, exists in multiple truncated isoforms. Novel stable apelin-13 peptide analogues acting via their cognate APJ receptor, have shown promising acute antidiabetic effects in high-fat fed diet induced obese (DIO) mice, as well as in supressing appetite and reducing food intake in diet restricted trained healthy mice.

Methodology and theoretical orientation: Various acylated and non-acylated peptide analogues of apelin-13 were produced and tested for anti-diabetic and anti-obesity actions in different models of metabolic disease including high-fat fed DIO mice and leptin receptor-deficient diabetic db/db mice (n=8). Comparative studies were performed using twice daily injections of saline controls, apelin-13 analogues, incretin mimetics exendin-4(1-39) or liraglutide in acute and chronic studies. Progressive changes in glycaemic control, glycated haemoglobin (HbA1c) and plasma insulin were monitored in chronic (21-day) studies. To further examine the positive effects of apelin analogues on pancreatic responses we investigated their potential benefits on islet cell apoptosis, proliferation and transdifferentiation using Ins1Cre/+ ;Rosa26-eYFP transgenic mice following diabetes induction with either streptozotocin or high-fat feeding.

Findings: Apelin and incretin analogue treatment significantly improved both oral and intraperitoneal glucose tolerance, accompanied by enhanced insulin responses compared with saline-treated control db/db mice. Apelin-13 analogues were superior to incretin mimetics in markedly lowering (34% reduction) circulating plasma triglycerides. Immunocytochemistry studies revealed that apelin analogues unlike both incretin mimetics reduced pancreatic α-cell area, however all peptide treatments enhanced pancreatic insulin content. Apelin-13 analogues effectively reduced β- to α-cell transdifferentiation and decreased β-cell apoptosis and α-cell proliferation in both diabetic models.

Conclusion: Overall, apelin-13 analogues, induced similar and sometimes more effective metabolic improvements than incretin mimetics in db/db mice, providing a viable and effective alternative approach for counteracting metabolic dysfunction in diabetes.

Biography

Prof Finbarr O'Harte completed his primary degree in Biochemistry and PhD in Clinical Biochemistry at Queen's University Belfast. He worked in the regulatory peptide research at Creighton University Medical School in Omaha, USA and University College Cork. He has been involved in diabetes research at Ulster University, Coleraine since 1993. His research interests have focused on development of stable peptide analogues of regulatory peptides including GIP, GLP-1, CCK, glucagon and apelin for therapy of Type 2 diabetes and obesity. He has published more than 140 peer-reviewed full papers and reviews. He is serving on current editorial boards for Frontiers in Endocrinology and Peptides.