RESEARCH GROUP:

Diabetes

Project Title:

Discovering the role of kisspeptin related peptides in pancreatic beta-cell function and survival, and possible therapeutic implications for diabetes

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Level:

PhD

Background to the project :

Kisspeptin (also called metastin), is a 54 amino acid hypothalamic peptide hormone that activates the G protein-coupled KISS1 receptors [Matsui & Asami 2014]. However, the physiological function of kisspeptin is not confined to the hypothalamus, as the hormone and its receptor are abundantly expressed in various tissues, including the pancreas [Hauge-Evans et al. 2006]. Moreover, KISS1 receptor expression appears to be confined exclusively to the endocrine pancreas, where it is thought to influence beta-cell function [Hauge-Evans et al. 2006]. Encouragingly, kisspeptin has been shown to stimulate glucose-dependent insulin secretion from beta-cells [Bowe et al. 2009; 2012], akin to the actions of the type 2 diabetes clinically approved incretin class of drugs [Irwin & Flatt 2015]. However, others suggest have suggested that kisspeptin may actually inhibit insulin secretion [Silvestre et al. 2008]. Thus, there is considerable controversy over the direct beta-cell effects of kisspeptin, which need to be resolved in order to determine full therapeutic utility for diabetes. Further to this, there is knowledge that kisspeptin can affect cell survival and proliferation [Golzar & Javanmard 2015]. Whether this extends to survival and proliferation of pancreatic beta-cells, with obvious beneficial effects for diabetes [Irwin & Flatt 2015], still remains to be fully elucidated.

Kisspeptin is a 54 amino acid peptide hormone, proteolytically processed into several smaller fragments that have been isolated in humans composed of 10, 13 and 14 amino acids [Thompson et al. 2004]. Each of these fragments has a conserved C-terminal region, highlighting this as an important part of the molecule for receptor binding and biological actions [Oakley et al. 2009]. Indeed, all four peptides, kisspeptin 10, 13, 14 and 54, possess the same affinity for the KISS1 receptor [Oakley et al. 2009], and have been shown to be biologically active [Muir et al. 2001]. This is particularly encouraging, as smaller peptides are easier to synthesise, less expensive and more favourable drug candidates. Taken together, uncovering the mechanisms involved in kisspeptin degradation, the direct effect of kisspeptin and related fragments on beta-cell function and survival and possible synthesis of long-acting kisspeptin related peptides could help reveal, an as yet untapped, therapeutic strategy for the treatment of diabetes.

Objectives of the research project :

The core objectives of this research project are:

- Determine the full degradation profile of kisspeptin and enzymes involved

- Design, purify and characterise novel stable and long-acting kisspeptin and kisspeptin fragment based peptides
- Assess the *in vitro* enzymatic stability and biological actions of novel peptides in rodent and human insulin-releasing cell lines (INS1, BRIN-BD11 and 1.1B4) and isolated mouse islets
- Determine effects of kisspeptin peptides on human and rodent pancreatic beta-cell proliferation and apoptosis
- Establish in vivo gluco-regulatory and insulin secretory actions of novel kisspeptin peptides
- Determine in vivo biological duration of action / toxicity of long-acting kisspeptin peptides
- Assess beneficial effects of novel peptides alone, and in combination with established anti-diabetic drugs, in animal models with different aetiologies of type 2 diabetes.

Methods to be used :

A wide range of methods are required for this study including peptide synthesis, HPLC purification of peptides, mass-spectrometry, *in vitro* insulin secretion studies using rodent BRIN-BD11 and human 1.1B4 beta-cells and isolated islets, PCR and Western blot, longer term *in vitro* culturing, assessment of markers of proliferation and apoptosis, *in vitro* radio-receptor binding studies, animal studies in normal rodents as well as rodent models of obesity-diabetes, tissue gene expression studies, blood biochemistry assessments, DXA scanning and measurement of body fat, indirect calorimetry measurements, behavioural analysis and use of assays including ELISA and RIA technologies. This will provide excellent training in a wide variety of important research techniques.

Skills required of applicant :

The applicant should ideally have good practical laboratory, computer and communication skills and show enthusiasm and commitment to work diligently on all aspects the research project to completion under the leadership of his/her supervisors. A background degree in biomedical sciences, pharmacology or a related subject would be desirable.

References :

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