RESEARCH GROUP: Diabetes

Project Title: Mechanistic investigation into the actions of taurine on beta cells and potential therapeutic actions in diabetes

Supervisor(s): Professor NH McClenaghan, Dr Abdel-Wahab

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Level: PhD

Background to the project:

Taurine (2-aminoethanesulphonic acid) is a semi-essential amino acid, which is not incorporated into proteins. In mammalian tissues, taurine is ubiquitous and is the most abundant free amino acid in the heart, retina, skeletal muscle, brain, and leukocytes, exhibiting multiple functions and tissue-protective effects in many models of oxidant-induced injury [1,2]. This sulphur-containing amino acid may be derived from the diet or biosynthesized as an end-product of methionine and cysteine metabolism. Although a considerable amount of taurine has long been known to be localized in the pancreas and has recently been shown to influence the secretion of insulin [3-5]. Several reports also postulate that taurine may exhibit antidiabetic activity perhaps through promoting beta cell defense and enhanced islet function [6-8]. Taurine, like the insulinotropic amino acids alanine and proline, is co-transported with Na⁺ as a prerequisite for its uptake. Indeed, a Na⁺-dependent beta-amino acid transport mechanism shared by beta-alanine and taurine, has been described in retinal, synaptosomal, hepatic, sacrolemmal, renal and other cells. Although the pancreatic transport system for, or actions of, taurine have not been fully characterized, preliminary studies in our laboratory suggest that taurine uptake evokes pleiotropic effects in beta cells. While the exact mechanisms underlying these effects remain uncertain, our primary observations suggest that taurine is an important insulin-releasing signal recognition factor and potential therapeutic agent to help counter type 2 diabetes [9,10].

Objectives of the research project:

This project will examine functional aspects of taurine and related sulphydryl amino acids in the modulation of pancreatic beta cell signal transduction and insulin secretion in vitro and in vivo. These studies will be coupled with investigations into the possible role of taurine in pancreatic beta cell cytoprotection. The aims of this project are to: (a) determine pancreatic beta cell taurine uptake and metabolism and the expression and function of taurine transporters; (b) examine the impact of acute and long-term exposure to taurine on the regulation of pancreatic beta cell function, gene expression and insulin-releasing actions of established secretagogues; (c) evaluate the effects of taurine on beta cell Na⁺ handling, cellular membrane potential, ionic flux and beta signal transduction elements (G-proteins, adenylate cyclase/cAMP, tyrosine and protein kinases); (d) determine possible protective effects of taurine against established pancreatic beta cell cytotoxins (cytokines, hydrogen peroxide, nitric oxide and reactive oxygen species); (f) examine the hypoglycaemic and insulin-releasing effects of taurine alone and in combination with established antidiabetic drugs in normal and animal models of diabetes. These proposed studies will advance understanding of pancreatic beta cell function and evaluate possible insulin-releasing and cytoprotective actions of taurine, which may be of importance to understanding the aetiology and pathogenesis of the diabetic state.

Our hypothesis is that taurine is an important but hitherto unrecognised physiological stimulator of beta cell function, acting through pathways which might be exploitable for the treatment of type 2 diabetes.

Methods to be used:
Cell and tissue culture techniques; Experimental islet cell biology, electrophysiology and intracellular Ca$^{2+}$ signaling (including Flexstation determination of cellular membrane potential and ionic flux); Acute and dynamic measurement of insulin secretion, insulin content and radioimmunoassay; Nutrient uptake, metabolism and beta cell enzyme activity; Regulation of key beta cell signal transduction elements; Assessment of pancreatic beta cell function, dysfunction and apoptosis particularly Neutral Red, MTT, Comet, acridine orange/ethidium bromide and TUNEL assays; Molecular biology techniques particularly: RNA and DNA purification, gene and protein expression analysis (including Northern and Western blotting), polymerase chain reaction; In vivo assessments of circulating insulin and blood glucose control in animal models.

**Skills required of applicant:**

The applicant should have a sound knowledge in biomedical sciences / pharmacology, ideally with some practical laboratory experience. The applicant must have good computer and communication skills. The applicant must demonstrate enthusiasm and commitment to work diligently on all aspects of the research project to completion under the leadership of the supervisors.

**References:**


