P1-P549

Enhanced Mitochondrial Densities Associate with the Pathobiology of β-cells in Congenital Hyperinsulinism in Infancy

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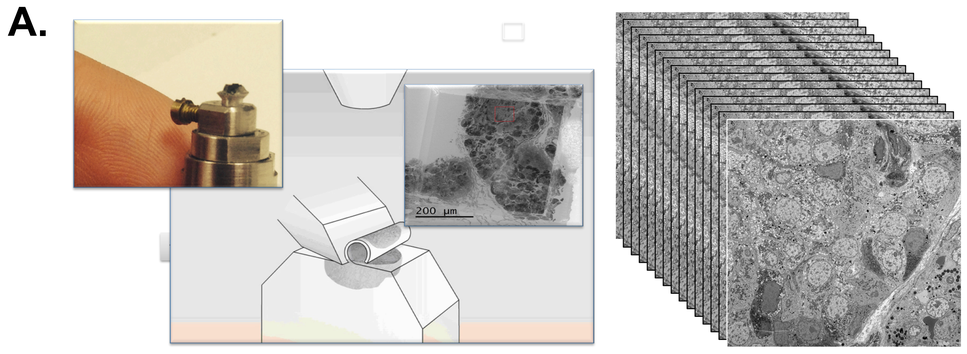
Introduction and Objectives

Background: Congenital Hyperinsulinism in Infancy (CHI) is associated with inappropriate insulin release from β-cells. This is causally linked to defects in the ion channel genes *ABCC8* and *KCNJ11*, but little is known about the metabolic support for sustained insulin exocytosis in the face of hypoglycaemia.

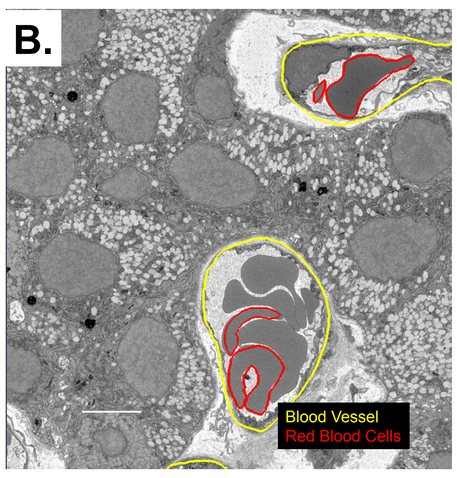
Objective and hypotheses: We hypothesised that inappropriate insulin release in CHI would require sustained ATP generation by enhanced mitochondrial activity. To test this we have quantified total mitochondrial volumes in individual islet β-cells and in glucagon-secreting α-cells from in CHI tissue and compared these with control samples.

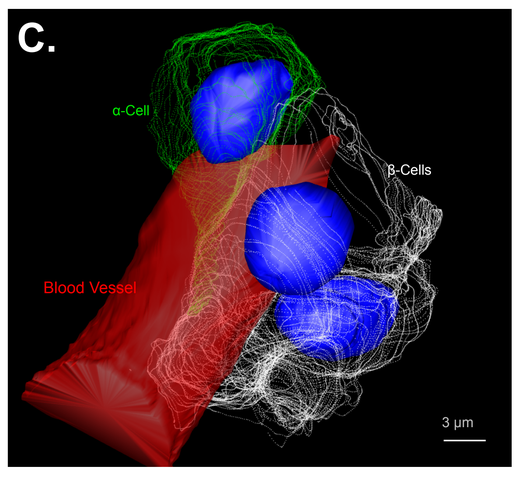
Methods

Pancreatic tissue was obtained (with permission) from six patients with CHI following surgery. All patients were positive for *ABCC8* gene defects and underwent surgery following failure of medical therapy to adequately control hypoglycaemia. Tissue samples were fixed and embedded for use in either transmission electron microscopy (TEM) serial block face-scanning electron microscopy (SBFSEM).



SBFEM was used to generate ultrastructural images of islet cells from serial sections of tissue 100nm thick, Panel A. From these images islet cells were identified and digitized manually using iMOD Software (http://bio3d.colorado.edu/imod/), which was also used in the three-dimensional reconstruction of cells, Panel B. These approaches were used for investigating the spatial organisation of islet cells in CHI tissue (Panel C) and for the quantification of cellular, nuclear and mitochondrial volumes. Mitochondrial density was calculated by expressing mitochondrial volume as a proportion of total cytoplasmic volume for an individual cell.

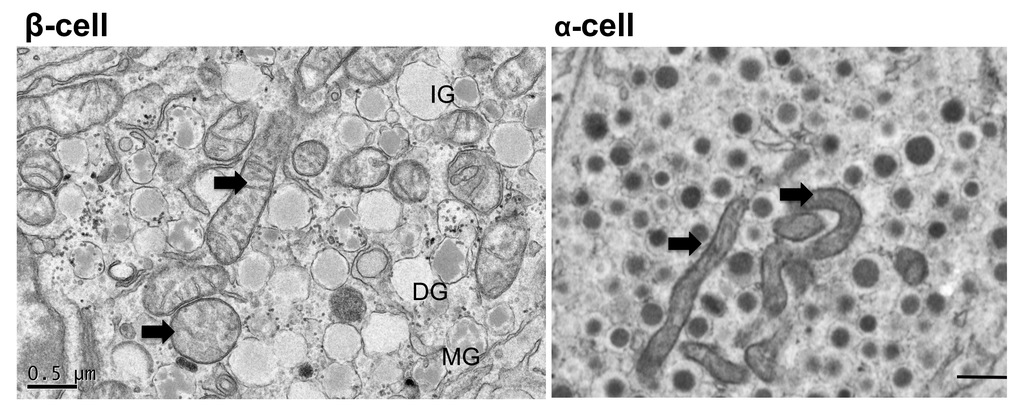




Summary / Implications

In CHI β-cells we found a greater than 2-fold increase in the mitochondrial density compared to controls. There was no difference in mitochondrial densities in α-cells. These data imply that mitochondrial expansion associates with the pathobiology of islet β-cells and provides an enhanced energy capacity to sustain uncontrolled insulin release.

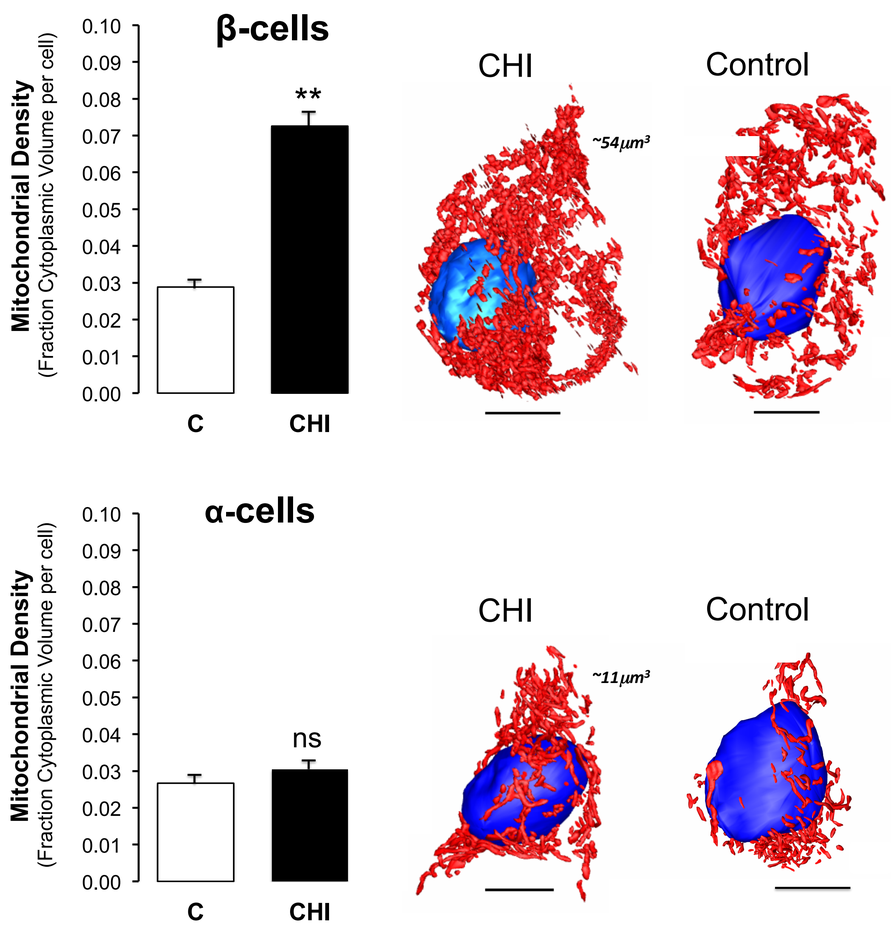
2: Co-Localization of Mitochondria with Secretory Granules



MG: Mature Granule IG: Immature Granule DG: Depleted Granule

TEM images of an β-cell and a α-cell in CHI islets to illustrate the co-localization of mitochondria (arrows) with secretory granules. Note that in β-cells insulin-containing granules have different profiles (see Poster P1-P549). Scale Bar, 0.5µm

3: Enhanced Mitochondria Density in CHI β-cells



Summary of mitochondrial density values in islet β-cell and α-cells from CHI tissue compared to control cells. Average values for total mitochondrial volumes (β-cell; 53.7 ± 10µm^3 (n=6), α-cell: 10.8 ± 1µm^3 (n=3)) have been expressed as a fraction of the cytoplasmic volume (cell volume - nuclear volume). Overall, CHI was associated with a >2.25 fold increase in the mitochondrial density in β-cells but not α-cells. Digital reconstruction of typical cells also imply differences in the profiles of mitochondria since α-cells tended to have elongated mitochondria localized in clusters compated to β-cells. Scale Bar, 10µm.

Support

Supported by the NORCHI Charitable Fund, Central Manchester University Hospitals, The National Institute for Health Research and The Million Dollar Bike Fund (Pilot Award Number: MDBR-16-100-CHI). We are also grateful to research nurses and clinical colleagues at Central Manchester University Hospitals NHS Trust and the Manchester Biomedical Research Centre.