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).

SBFSEM 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.

Results

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.

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.