**Background / Aims**

Congenital Hyperinsulinism (HI) is principally a disorder of islet β-cell function and is the most common cause of severe and recurrent hypoglycaemia in childhood. Pancreatic polypeptide (PP) cells represent a minor component of the islet endocrine cell population. PP causes satiety, decreases gastrointestinal tract motility and suppresses glucagon release. On the basis that inappropriate PP expression may contribute to the loss of glucagon-mediated counter-regulatory responses to hypoglycaemia in HI and the problems associated with appetite regulation and feeding, we have now investigated the relationship between hormone expression and PP cells in CHI tissue.

**Methods**

Our study is based upon 28 subjects with HI originating from a single specialised treatment centre using established diagnostic criteria including clinical and genotype profiling, and where appropriate 18F-DOPA PET-CT scanning. All patients were positive for defects in the K_\text{ATP}, channel genes, ABCG8 (n=26/28 patients) or KCNJ11 (n=2/28). Seventeen patients were diagnosed with focal CHI and 11 with diffuse disease. In all cases pancreatic surgery was performed for alleviation of sustained hypoglycaemia. Expression of PP was investigated using gene- (transcriptome arrays) and protein (immunohistochemistry, electron microscopy)-based assays.

**Results**

**Clinical studies:** All patients experienced feeding problems during early stages of diagnosis and treatment. These were defined as difficulty with sucking, swallowing, vomiting, and food refusal (or a combination). In 82% of focal CHI cases feeding problems ameliorated within 4-8 weeks following surgery, by contrast 80% of patients with diffuse CHI continued to experience feeding difficulties for more than 2 years after surgery.

**Tissue studies:** Enhanced expression of the PP gene (PPY) was found in focal lesions but not in the diffuse CHI pancreas, Figure 1. PPY was consistently and significantly enhanced in focal lesions (A,B n=6, P=0.02) even when normalised to other islet hormone gene expression, C (**p=0.004, ***p=0.0007, ****p=0.0001). Tissue expression of PP revealed that the hormone was enhanced in focal lesions but not in diffuse CHI islets, Figure 2A. When quantified, all (100%) islet-like structures in focal CHI tissue (n=7 cases, n=193 islets) expressed PP, Panel B, but only 33% and 37% of islets in diffuse and control tissues, respectively P<0.0001. The fraction of cells within islets or islet-like structures expressing PP was increased from <1% in diffuse and control islets to >20% of cells in focal lesions P=0.0001, respectively, Panel C.

**Summary**

Focal CHI is associated with significant increases in PP gene and hormone expression with increased numbers of PP-cells when compared to control pancreatic tissue, and tissue from diffuse CHI patients. In addition to known roles in attenuating secretion of glucagon and thus preventing normal physiological responses to hypoglycaemia, PP may also contribute to feeding problems in infants with CHI-F.