Islet amyloid polypeptide (IAPP; 4kD) is cosecreted with insulin from pancreatic beta-cells. In type 2 diabetes, impaired processing of proIAPP (8kD), the IAPP precursor, may initiate amyloid formation and lead to beta cell death due to accumulation of IAPP-derived peptides, in particular a COOH-terminally processed, NH₂-terminally extended human proIAPP intermediate (6kD).

**Aim:** Determine the effect of elevated glucose and fatty acids on proIAPP synthesis, processing and secretion.

INS-1 beta cells were pre-cultured for 24 h in 2 or 22 mM glucose prior to addition of the saturated fatty acid palmitate for a further 24 h. Brefeldin A was added to block constitutive release. Cells were labelled for 30-60 min with ³H-Leu and chased for 0-180 min. A secretagogue mixture was added to the final chase medium to induce secretion. Chase medium and cell lysates were immunoprecipitated with an IAPP antibody prior to gel electrophoresis and fluorography.

Culture in 22 mM glucose led to elevated levels of 8kD-proIAPP and decreased mature 4kD-IAPP in cell lysates, suggesting that high glucose leads to impaired proIAPP processing. Culture in 100 µM palmitate resulted in increased synthesis of proIAPP and elevated constitutive secretion of proIAPP; an effect blocked by brefeldin A treatment. Palmitate had no detectable impact on proIAPP processing.

Exposure of beta-cells to high glucose leads to impaired proIAPP processing whereas palmitate impairs IAPP sorting to the regulated secretory pathway. We speculate that hyperglycemia and hyperlipidemia in type 2 diabetes may contribute to islet amyloid formation by inducing impairments in proIAPP processing and/or sorting.