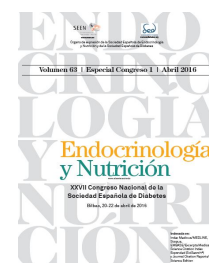




# Endocrinología y Nutrición



## O-007. - 4-PHENYLBUTYRATE ADMINISTRATION AMELIORATES BETA-CELL FUNCTION AND AMYLOID FORMATION IN MICE OVEREXPRESSING HUMAN ISLET AMYLOID POLYPEPTIDE

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### Resumen

**Introduction and objectives:** Human islet amyloid polypeptide (hIAPP) is the major component of amyloid deposits in pancreatic islets of patients with type 2 diabetes. The process of hIAPP misfolding and aggregation is one of the factors that may lead to beta-cell dysfunction and death. We have previously shown that chemical chaperone 4-phenylbutyrate (PBA) relieves endoplasmic reticulum stress and ameliorates beta-cell function *in vitro*. Here, we aim to determine whether *in vivo* administration of PBA is able to counteract hIAPP-induced beta-cell dysfunction and amyloid formation in hIAPP expressing transgenic mice.

**Material and methods:** hIAPP-expressing islets were cultured with 16 mM glucose and 400  $\mu$ M palmitate and treated with chemical chaperones taurine conjugated ursodeoxycholic (TUDCA) or PBA. Islet function was determined by glucose-stimulated insulin secretion. Apoptosis was determined by caspase 3 staining and amyloid formation was analyzed by ThioS staining. Wild type and hIAPP Tg mice were treated with 300 mg/ml of PBA dissolved in water. Glucose tolerance tests were performed at 0, 6 and 12 weeks after treatment. Serum parameters, gene expression levels and morphologic studies were determined at sacrifice.

**Results:** hIAPP-Tg islets exposed to high glucose and palmitate showed a decrease in insulin output and increased apoptosis. Treatment with chemical chaperones TUDCA or PBA ameliorated beta-cell function by decreasing apoptosis and increasing insulin secretion upon stimulation with 16 mM glucose. When hIAPP Tg islets were cultured for 7 days at 16 mM glucose, amyloid plaques were formed throughout the islet engaging  $18.2 \pm 2.3\%$  of the insulin positive area. TUDCA and PBA treatment was able to diminish amyloid formation of hIAPP Tg islets to  $5.3 \pm 0.9\%$  and  $1.2 \pm 0.4\%$  respectively. Next, hIAPP Tg mice were administered PBA in water for 12 weeks. PBA treatment completely counteracted impaired glucose homeostasis after a glucose tolerance test. Further, PBA decreased expression of inflammatory genes, insulin levels and beta-cell area. These results indicate that PBA may play an important role in preventing beta-cell dysfunction and amyloid formation associated to T2D.

**Conclusions:** PBA administration increased insulin secretion and diminished amyloid formation in a mouse model of type 2 diabetes. This innovative *in vivo* approach could reveal a new therapeutic target and aid in the development and evaluation of strategies to diminish ER stress and limit the

damaging amyloid observed in type 2 diabetic patients.