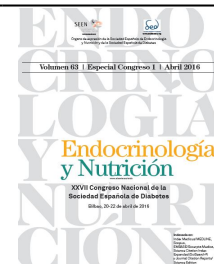




Endocrinología y Nutrición



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

J. Montané, S. de Pablo, C. Castaño, J. Rodríguez, G. Alcarraz-Vizán, J.M. Servitja and A. Novials

Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona.

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 μ 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.