Diazoxide pre-treatment prevents glucotoxicity-induced beta-cell dysfunction and death in isolated human islets

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Background

Islet transplantation is a promising approach for the treatment of type 1 diabetes patients. However, the procedure is not as effective as expected due to the early exposure of the islets to a high glucose environment, inflammation, ischemia, and ultimately cell death. Diazoxide not only inhibits insulin secretion, leading to "beta-cell rest" but has also anti-apoptotic and anti-ischemic properties. Here, we hypothesise that diazoxide is able to prevent beta-cell dysfunction and death in human islets exposed to the glucotoxic environment present in type 1 diabetes patients after islet transplantation.

Methods

Human pancreatic islets were incubated with or without 325 µmol/l diazoxide for 24h, washed for 24h without drug, and later exposed to high glucose (20 mM) for 96h and 24h. Islets were analysed for cell viability (Annexin staining as an apoptotic marker), insulin function (glucose-stimulated insulin secretion) and gene expression (qPCR).

Results

Preliminary data suggests that diazoxide pre-treatment improves insulin secretion of 96h glucotoxicity-exposed human islets (stimulation index treated vs. control, 0.9X ± 0.5 vs. 0.4x ± 0.1, n=3). In addition, islets pre-treated with diazoxide showed 8% reduction in the percentage of Annexin$^+$ cells as compared to islets exposed to glucotoxicity alone (24.4% vs. 32.4%, n=2). Diazoxide pre-treatment prevented the increased expression of the oxidative stress marker TXNIP both in 24h and 96h of high glucose (fold expression relative to control from treated vs. glucotoxicity, 1.3X vs. 5X and 3.9X vs. 8X, respectively, n=2). Moreover, diazoxide pre-treatment also prevented the increased expression of ER-stress markers ATF3 (5.4X vs. 7.6X to control, n=1), and XBP1s/XBP1u (0,6X vs. 2.2X, to control n=1) in islets exposed to high glucose for 96h.

Conclusions

We propose that diazoxide preincubation prevents beta-cell secretory dysfunction and death in glucotoxicity by preventing the increased expression of ER-stress related markers.