STUDY OF THE DESTRUCTION MECHANISM OF BETA PANCREATIC CELLS DURING THE ONSET OF DIABETES MELLITUS (DM2): SEARCH FOR INHIBITION STRATEGIES OF THIS PROCESS AS WELL AS FOR THE RECOVERY OF INSULAR MASS IN DIFFERENT ANIMAL MODELS

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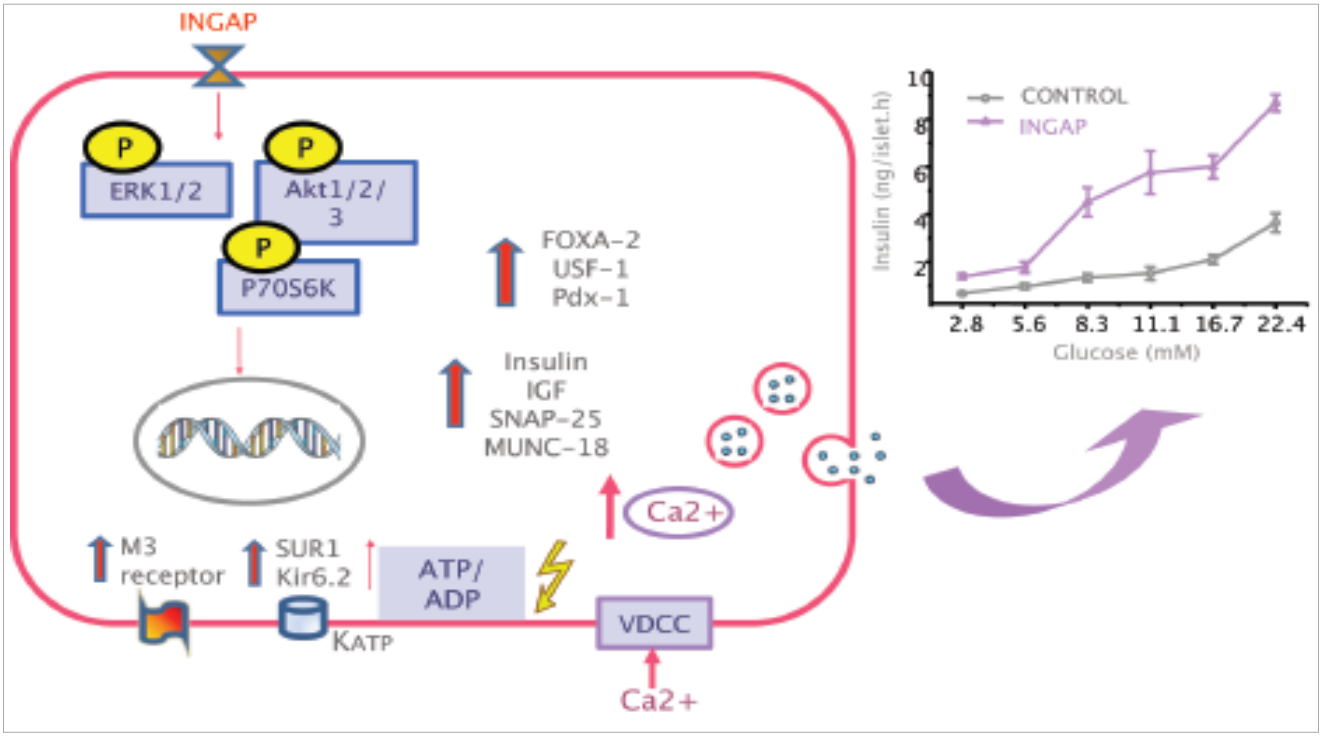

INGAP (islet neogenesis associated protein) is related to islet neogenesis and beta cell mass increase in rodents and dogs. INGAP-PP, the active part of INGAP, promotes maturation and improves insulin secretion in response to glucose in pancreatic islets. The expression of several genes is modulated by INGAP in pancreatic islets of neonatal rats, as well as insulin secretion increases in response to different concentrations of glucose. Beta cell transcription factors, insulin granules extrusion machinery proteins, insulin, insulin-like growth factor, type 3 muscarinic receptor , and KATP channel subunits genes are examples of genes modulated by INGAP in pancreatic

The most frequent Diabetes mellitus (DM) is DM2 which, generally, results from an increase in resistance to the action of insulin followed by the inability of the pancreatic B cells to secrete sufficient quantities of the hormone to compensate for hyperglycemia. It became evident that the presence of an adequate and renewable mass of pancreatic B cells during various stages of life is fundamental for the maintenance of the normoglycemia. The alterations in the mass and sensitivity of the secretory cells of insulin to glucose are commanded by several hormones at different periods in life. In this project we studied the destruction mechanism of the beta cells in several experimental models, *in vivo* and *in vitro*, as well as different strategies for the inhibition of this process and the recovery of insular mass.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Signaling paths of prolactin (PRL) and effects of the "Islet Neogenesis Associated Protein" and of the "Ciliary Neurotrophic Factor" (CNTF) on pancreatic islets

PRL modulated the expression of the CERCA (responsible for the control of Ca^{2+} in the reticule), a mechanism dependent on the STAT3. As the effects of the PRL were antagonized by dexametasone, we suggest that glycocorticoids participate in the readaptation of the endocrine pancreas in the postpartum. PRL also increased the expression of proteins that participate in the extrusion of granules of insulin. Acutely, PRL increased phosphoryrilation/association of proteins implicated in the secretory machinery indicating that the hormone prepares the pancreatic β cells for secretion, probably through the MAPK/PKC path. The chronic treatment of new-born or adult mice islets with INGAP increased the mass of the islets and their secretory capacity in response to different stimulators. The INGAP modified the expression of two hundred genes in islets of new-borns after 4 days' culture. Among those genes, the ones that express proteins forming the KATP (*Sur*1 and *Kir*6.2 and *Fox*A2) channels making the islets more sensitive to glucose, indicating that the INGAP improved secretion through the increase in the number of KATP channels associated with a better handling of the Ca^{2+} by the pancreatic islets. Finally we also showed that in islets of newborn mice treated with CNTF, a decrease occurred in the activation of caspase-3 (which is one of the main caspases effecting and promoting apoptosis). Associated with this, we observed a decrease in the production of NAD(P)H and reduction in the secretion of insulin.

Participation of UCP2 in the process of the insulin secretion

This project involved diabetic mice with "antisense oligonucleotides" to *Ucp*2 and we evaluated the effects of treatment on the secretion and action of insulin. Swiss mice, made obese through a hyperlipidic diet as well as obese mice ob/ob, treated with the above-mentioned antisense showed a significant improvement in the hyperglycemic syndrome. This improvement was due to an increase in the peripheral sensitivity to insulin, associated with a better secretory response to glucose.

MAIN PUBLICATIONS

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