Zinc ions in the pancreas – with special emphasis on β-cells and diabetes

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ABSTRACT

This PhD dissertation was carried out at the Institute of Anatomy, at the University of Aarhus. The purpose was to explore the localisation, existence and trafficking of free zinc ions in the β-cells using zinc sulphide autometallography (ZnS^{AMG}). ZnS^{AMG} is a histochemical method that allows detection of zinc ions chemically bound to sulphide visualized by silver amplification.

Zinc is an essential micronutrient directly involved in insulin physiology. It plays a fundamental role in the storage and regulation of in vivo insulin action; however, the interrelationship between zinc, β-cells and diabetes seems to be complex.

First of all we optimized the in vivo ZnS^{AMG} method for the visualization of zinc ions in the pancreas both at light- and electron microscopical levels. We found that zinc ions were located in the secretory vesicles of both α- and β-cells as well as in the zymogen vesicles of the acinar cells.

The in vivo ZnS^{AMG} method was applied to type 2 diabetic rats as well as obese, insulin resistant rats, in order to compare the zinc ion distribution with controls. No difference in the localisation of ZnS^{AMG} detectable zinc ions was found for any of the two groups, suggesting that the ultrastructural localisation of zinc ions is unaffected of the development of type 2 diabetes in rats in a steady state of glycaemia.

The effect of acute and chronic exposure to different glucose concentrations on ZnS^{AMG} detectable zinc was studied in a β-cell culture. We demonstrated that intra-vesicular zinc ions respond to changes in the extra-cellular glucose concentration, especially during chronic high glucose concentrations, when the content of vesicular zinc ions decreases. Furthermore, the presence of two zinc transporters, ZnT1 and ZnT4, was also examined and found to be present in the cytoplasm of the β-cells.

Finally, the effect of subclinical zinc deficiency in rats on ZnS^{AMG} detectable zinc in the pancreas, as well as on insulin- and glucose levels, was tested. Subclinical zinc-deficiency in rats led to a slightly impaired glucose metabolism without any changes in serum insulin levels, insulin resistance, or β-cell function. No difference in the amount of zinc ions in the islets of pancreas was found, but the acinar cells of the exocrine pancreas were depleted of zinc ions. This suggests that the endocrine pancreas is able to compensate for the zinc deficiency in order to maintain an adequate zinc ion level, whereas the exocrine pancreas does not possess this ability.

We conclude that the results gained in this thesis support the idea that some gluco-homeostatic problems could be explained by a defect zinc transport regulation. Therefore, future studies on the expression of the various zinc transporters in both manipulated β-cells and animal models of diabetes are warranted.