

Zinc transporters in the pathophysiology of diabetes

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ABSTRACT

This PhD thesis originates from the Department of Pharmacology, Aarhus University, Denmark. It is based on three published studies.

Background: In diabetes, inadequate insulin secretion causes chronic hyperglycaemia. The insulin deficiency may be caused by disturbed β -cell function with normal insulin sensitivity, by a relative deficiency with high insulin resistance, related to obesity, or by an absolute lack of β -cells as seen in autoimmune diabetes. In adipose tissue and β -cells alike, a number of vital processes depend on the regulation of zinc across membranes, be it cell membranes or intracellular membranes. In adipose tissue the secretion of leptin, among others, depends on zinc, and in insulin-producing β -cells a number of processes require a tightly regulated zinc metabolism. Transport of zinc across membranes is mediated by two different solute-linked carrier families, cation diffusion facilitator/zinc transporters (CDF/ZnT or SLC30A) and ZRT/IRT-related proteins (ZIP or SLC39A). ZnTs are responsible for the efflux of zinc from the cytoplasm into cellular compartments or to the extracellular matrix. ZIPs facilitate transport in the opposite direction.

Aim: The main purpose of this thesis was to explore the role and/or regulation of zinc transporters in the pathogenesis of diabetes. We hypothesised that zinc transporter gene expression is regulated in response to different conditions related to diabetes with special focus on adipose tissue and β -cells.

Methods/results: We examined the expression of zinc transporters in subcutaneous and visceral fat from lean and obese women. We found that most of the examined zinc transporters have higher expression levels in lean women. Furthermore, the majority of the examined zinc transporters had higher expression levels in subcutaneous tissue compared to visceral tissue.

In INS-1E cells we found that the expression of zinc transporter 3 and 8, ZnT-3 and ZnT-8, is up- (ZnT-3) and down- (ZnT-8) regulated by high glucose concentrations and stimulation with 100 μ M DEDTC, a zinc chelator. Both conditions lead to cell death in the INS-1E cells. 44% knock-down of ZnT-3 by siRNA transfection in INS-1E cells decreased insulin expression and secretion. Streptozotocin-treated mice had higher plasma-glucose levels after in vivo ZnT-3 knock-out, particularly in overt diabetic animals.

Conclusion: This thesis supports the idea that zinc transporters are regulated differentially in unhealthy environments compared to healthy environments and that zinc transporters have an impact on in vitro and in vivo glucose metabolism. Therefore, we conclude that adipose tissue and β -cell zinc metabolism is emerging as yet another important system in understanding the pathophysiology of type 2 diabetes.