Department of Molecular Medicine and Surgery

Nutritional and dysmetabolic factors with potential impact on type 2 diabetes: epidemiological and molecular studies

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ABSTRACT

Diabetes is a group of diseases characterized by hyperglycaemia. Type 2 diabetes encompasses 85-95% of all diabetes with a prevalence that is expected to increase worldwide.

In search of nutritional and dysmetabolic factors with potential impact on type 2 diabetes this thesis focused on the risk of type 2 diabetes and prediabetes and association with wholegrain intake as well as effects of hyperglycaemia and dyslipidaemia on the function and survival of insulin secreting cells. We found in a population-based prospective study (Stockholm Diabetes Prevention Program) that low consumption of wholegrain was associated with an increased risk of deteriorating glucose tolerance. The strongest association was seen for individuals who at baseline had normal glucose tolerance (NGT) and at follow-up (8-10 years later) had progressed to prediabetes. Furthermore we confirmed effect modifications by polymorphisms of the TCF7L2 gene.

An in vivo study of hyperglycaemic effects on beta cell mitochondrial morphology revealed that moderate hyperglycaemia induced larger, fewer and swollen mitochondria. These morphological effects on mitochondria could partially be inhibited by treatment with a K\textsubscript{ATP}-opener. The morphological effects on mitochondria were reproduced in vitro and were linked to dysfunctional oxidative metabolism.

Since diabetes is often accompanied by dyslipidaemia we aimed to study the effects of increased uptake of fatty acids and low-density lipoprotein (LDL) in insulin secreting cells. By overexpressing CD36 in an insulin secreting cell line (INS-1) we found that CD36 increased uptake of fatty acids. Overexpression of CD36 reduced the acute potentiating effect of fatty acids on glucose induced insulin secretion. Moreover modest effects on fatty acid oxidation and on the activity of carnitine palmitoyl transferase 1 (CPT1) activity were found. CD36 overexpression also enhanced the uptake of oxidatively modified LDL (oxLDL) whereas the uptake of native LDL was not influenced. OxLDL dose-dependently decreased viability, however independently of CD36 overexpression. The result suggest that efficient cholesterol efflux counteracts potential toxicity by uptake of the lipoprotein and that extracellular signalling mediates the negative effects on viability by oxLDL.

Keywords: Type 2 diabetes, wholegrain, hyperglycaemia, dyslipidaemia

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