Short- and long-term effects of fatty acids on pancreatic alpha cell function: studies in vitro

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ABSTRACT

Beta cell dysfunction had long been considered the only decisive abnormality in the pathogenesis of diabetes. The bihormonal abnormality hypothesis, however, established the essential additional role of glucagon in this disease. Only limited information is available from alpha cell study. The aim of the present PhD project is to evaluate the short- and long-term impacts of fatty acids on alpha cell function.

We investigated the short-term effects of eleven different fatty acids on glucagon secretion. We evaluated the chronic influence of fatty acids on glucagon secretion, glucagon content, triglyceride accumulation, glucose oxidation and cell proliferation. The impact of addition of etomoxir, insulin and stevioside, respectively, as well as the alterations in gene expressions were investigated in isolated mouse islets or in clonal alpha cells.

Palmitate acutely stimulated glucagon release in a concentration-dependent manner. The longer the chain length of saturated fatty acids, the higher glucagon responses were obtained. Saturated fatty acids were more potent than unsaturated fatty acids in stimulating glucagon secretion. At equimolar concentrations, trans fatty acids were more potent than their cis isomers.

High glucose more markedly inhibited the glucagon release from islets in the presence rather than in the absence of palmitate in 48h. Palmitate induced a relative enhancement in glucagon secretion, an accumulation of triglyceride and a decline in glucose oxidation. Etomoxir was capable of reducing the glucagon secretion in the presence of palmitate. Exogenous insulin failed to restore normal alpha cell responsiveness. Furthermore, palmitate also reduced the mRNA levels of ACC-1 and SREBP-1c.

In alpha cells, fatty acids stimulated glucagon secretion and increased triglyceride accumulation in a time- and concentration-dependent manner. These changes were accompanied by a reduction of alpha cell proliferation and an up-regulation of CPT-1 gene expression. Etomoxir significantly counteracted fatty acid-induced glucagon hypersecretion. Stevioside reduced palmitate-stimulated glucagon release by 22% and 45%, respectively. Stevioside enhanced CPT-1, PPAR gamma and SCD gene expressions in the presence of palmitate.

In conclusion, fatty acids acutely stimulate glucagon secretion from isolated mouse islets and clonal alpha cells. The chain length, spatial configuration, and degree of unsaturation of fatty acids influence the glucagonotropic effect. Long-term exposure to fatty acids causes alpha cell dysfunction, which may be related to the glucose fatty acid cycle. Moreover, stevioside is able to counteract the alpha cell hypersecretion caused by palmitate and enhances the expression of genes involved in fatty acid metabolism. Thus stevioside may turn out to be a promising antidiabetic agent in treatment of type 2 diabetes.