THE EFECT AND ROLE OF ATORVASTATIN THERAPY AND UNCOUPLING PROTEIN-2 IN LIPID METABOLISM

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ABSTRACT

The aim of our study was to examine the influence of atorvastatin on lipid parameters, particularly on HDL, and on the activity of LCAT and CETP and how they affect the activity of the HDL-associated antioxidant enzyme paraoxonase. Thirty-three patients with types II.a and II.b primary hyperlipoproteinemia were enrolled into our study. The patients received atorvastatin, 20 mg daily, for 3 months. In addition to the lipid parameters we measured the serum paraoxonase activity and concentration, oxidized LDL, LCAT and CETP activities. Atorvastatin significantly reduced the levels of cholesterol, triglyceride, LDL-C and apoB, while it did not influence the levels of HDL-C and apo A-I. The increases in serum PON-specific activity, PON/HDL ratio and LCAT activity were significant, while oxLDL and CETP activities were significantly decreased. Atorvastatin may influence the composition and function of HDL, thereby possibly increasing the activity of paraoxonase and preventing atherosclerosis.

In the other part of my experiments we studied the role of uncoupling protein-2 (UCP2) in pancreatic β-cells. UCP2 regulates insulin secretion by controlling ATP levels in beta-cells. Although UCP2 deficiency improves glycemic control in mice, increased expression of UCP2 interferes with glucose-stimulated insulin secretion. These observations link UCP2 to beta-cell dysfunction in type 2 diabetes with a perplexing evolutionary role. We found higher residual serum insulin levels and blunted lipid

metabolic responses in fasted *ucp2*$^{-/-}$ mice. In the absence of UCP2, fasting initially promotes peripheral lipolysis and hepatic fat accumulation at less than expected rates but culminates in protracted steatosis, indicating diminished hepatic utilization and clearance of fatty acids. We conclude that UCP2-mediated control of insulin secretion is a physiologically relevant mechanism of the metabolic response to fasting.

Kulcsszavak: koleszterin-észter-transzfer-protein, lecitin-koleszterin-acil-transzferáz, paraoxonáz, uncoupling protein-2

Keywords: cholesteryl ester transfer protein, lecithin:cholesterol acyltransferase, paraoxonase, uncoupling protein-2