Insulin promotes the degradation of HDL Generation-Related Functional Protein ABCA1 through IRS/Pi3K/Akt signaling pathway in 3T3-L1 adipocytes

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Objectives: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of human death. Dyslipidemia is one of the most important risk factors for atherosclerosis. Although the early intensive statin therapy is closely associated with the improved survival in patients with coronary heart disease (CHD), cardiovascular residual risk still exists. Hyperinsulinemia/insulin resistance is the major risk factor for ASCVD. And decreased high-density lipoprotein (HDL) levels are usually the main changes of blood lipid spectrum of the hyperinsulinemia/insulin resistance. But the exact mechanism is not fully clearly understood. This study is aimed to discuss effects of high insulin environment on HDL generation-related functional protein ATP binding cassette transporter A1 (ABCA1), and explore mechanisms of its specific signaling pathway to provide a new basic medical evidence for the intervention of residual cardiovascular risks.

Methods: In this experiment, 3T3-L1 adipocytes were induced to differentiation and maturation. Mature 3T3-L1 adipocytes were taken as the objects and stimulated by different concentrations of insulin (0 mmol/L, 10 mmol/L, 100 mmol/L) for 12 hours. The expression of HDL-related genes were detected by quantitative PCR. Effects of insulin on HDL-related gene expression in 3T3-L1 adipocytes and related mechanisms determined by Western Blot.

Results: (1) Insulin could inhibit cholesterol efflux from 3T3-L1 adipocytes in a dose and time-dependent manner (both P<0.05); (2) Different concentrations of insulin had no effect on the regulation of ABCA1 mRNA (P>0.05); (3) Insulin could down-regulate ABCA1 protein expression in a dose and time-dependent manner (both P<0.05); (4) Insulin promoted ABCA1 protein degradation by calpain and proteasome pathway; (5) Insulin could promote insulin receptor phosphorylation in a concentration-dependent manner (P<0.01) and selective inhibitor LY294002 of PI3K/Akt signaling pathway could inhibit the role of insulin in promoting ABCA1 protein degradation, whereas the selective inhibitor Rap1 inhib 1 of MAPK signaling pathway could not.

Conclusions: We demonstrate for the first time that insulin promotes the ABCA1 protein degradation by IRS/Pi3K/Akt signaling pathway, which is not consistent with ABCA1-mediated cholesterol efflux and nascent HDL generation in 3T3-L1 adipocytes.

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