# Evidence that Hyperinsulinemia, known to Accelerate Diabetes Progression, may also Contribute to Dyslipidemia via Impairing ApoA1/ABCA1-Mediated Cholesterol Efflux

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## Abstract

Low levels of plasma high-density lipoprotein cholesterol (HDL-C) are associated with insulin resistance and type 2 diabetes (T2D). As it is well appreciated that hyperinsulinemia contributes to the progression/worsening of insulin resistance, we tested here if this key metabolic derangement impaired cellular mechanisms of HDL-C generation. An initial event in this process is the binding of apolipoprotein A1 (ApoA1) to the plasma membrane (PM)-localized ATP-binding cassette cholesterol transporter protein ABCA1. Subcellular fractionation analyses revealed that 3T3-L1 adipocytes exposed to chronic insulin (12h, 5nM) displayed a 25% decrease ($P<0.05$) in PM ABCA1 content and a reciprocal increase in endosomal ABCA1 content. These insulin-induced changes in cellular ABCA1 distribution occurred concomitantly with a decrease in ApoA1-mediated cellular cholesterol efflux. Consistent with endosomal/cytosolic cycling of the small molecular GTPase Rab8 playing a functional role in ABCA1 vesicle trafficking, we found a 50% increase ($P<0.05$) in endosomal Rab8 content and a 30% decrease ($P<0.05$) in cytosolic Rab8 content. New data shows that increased HBP activity increases cholesterol biosynthesis and increased endosomal cholesterol content inhibits the functional cycling of Rab proteins. In line with these observations, we found that cells treated with the cholesterol-lowering agent methyl-β-cyclodextrin were protected against insulin-induced defects in ABCA1/Rab8 vesicle trafficking and PM cholesterol accrual. These data are consistent with the concept that the coexistence of low plasma HDL-C with insulin resistance and T2D may reflect a negative influence of hyperinsulinemia on Rab8-mediated trafficking of ABCA1 to the PM for ApoA1-mediated cholesterol efflux.