Hepatic Low Density Lipoprotein Receptor-Related Protein (LRP-1) and HDL Metabolism

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Cholesterol is essential to life as a major component of cell membranes and a precursor for steroidal hormone biosynthesis. However, elevated plasma cholesterol is a major risk factor for pathological conditions such as atherosclerosis. The receptor LRP-1 has been shown to have many roles in lipid metabolism and signal transduction, most of which are related to its binding to triglyceride-rich lipoproteins. Its contribution to regulation of reverse cholesterol transport and HDL metabolism has not been explored. In this study, we crossbred *Lrp1*$^{flox/flox}$ mice with liver-specific *cre* transgenic mice to generate liver-specific LRP-1 knockout mice to examine the role of hepatic LRP1 in HDL metabolism. Plasma total- and HDL-cholesterol levels in male age matched wild type and hepatic LRP1 KO mice were compared. Metabolite levels and lipoprotein profiles were determined. Circulating levels of apolipoprotein E and AI and LCAT were quantified. Components of HDL metabolism including plasma LCAT activity, plasma-mediated cholesterol efflux from lipid-loaded macrophages, and plasma HDL clearance were assayed. Hepatic LRP1 KO mice had lower fasting total cholesterol as compared to wild type (WT=112mg/dL, KO=74mg/dL , $P \leq 0.01$) while plasma glucose, non-esterified fatty acids, and triglyceride levels were equivalent. The lower total plasma cholesterol levels observed in hLRP1 KO mice were the result of decreased HDL cholesterol. Circulating apolipoprotein E and LCAT levels were decreased in hLRP1 KO (30% and 15%, respectively) with no difference in plasma level of the major HDL protein apolipoprotein AI. In addition, hLRP1 KO mice displayed a decrease in LCAT activity (ratio of 360:490 WT=5.97, KO=5.08, $P \leq 0.05$). However, cholesterol efflux from lipid-loaded macrophages to plasma of WT and hLRP1 KO mice were similar. Intravenously injected HDL containing [^{3}H]cholesterol ester was cleared from circulation more rapidly in hLRP1 KO mice compared to that observed in WT mice. Therefore, the lower total- and HDL-cholesterol levels observed in hLRP1 KO mice are most likely due to the more rapid HDL-cholesterol clearance rate. The decrease in LCAT protein and activity may also prevent the maturation of HDL particles, thus contributing to the accelerated clearance of smaller HDL. In conclusion, liver LRP1 participates in HDL cholesterol metabolism by accelerating its clearance from circulation. This study was supported in part by NIH grants T35 DK 60444 and RO1 DK74632.