Increased High Density Lipoprotein (HDL), Defective Hepatic Catabolism of ApoA-I and ApoA-II, and Decreased ApoA-I mRNA in ob/ob Mice

POSSIBLE ROLE OF LEPTIN IN STIMULATION OF HDL TURNOVER*

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David L. Silver, Xian-cheng Jiang, and Alan R. Tall†‡

From the Division of Molecular Medicine, Department of Medicine, Columbia University, New York, New York 10032

Abnormalities of plasma high density lipoprotein (HDL) levels commonly reflect altered metabolism of the major HDL apolipoproteins, apoA-I and apoA-II, but the regulation of apolipoprotein metabolism is poorly understood. Two mouse models of obesity, ob/ob and db/db, have markedly increased plasma HDL cholesterol levels. The purpose of this study was to evaluate mechanisms responsible for increased HDL in ob/ob mice and to assess potential reversibility by leptin administration. ob/ob mice were found to have increased HDL cholesterol (2-fold), apoA-I (1.3-fold), and apoA-II (4-fold). ApoA-I mRNA was markedly decreased (to 25% of wild-type) and apoA-II mRNA was unchanged, suggesting a defect in HDL catabolism. HDL apoprotein turnover studies using nondegradable radiolabels confirmed a decrease in catabolism of apoA-I and apoA-II and a 4-fold decrease in hepatic uptake in ob/ob mice compared with wild-type, but similar renal uptake. Low dose leptin treatment markedly lowered HDL cholesterol and apoA-I and apoA-II levels in both ob/ob mice and in lean wild-type mice, and it restored apoA-I mRNA to normal levels in ob/ob mice. These changes occurred without significant alteration in body weight. Moreover, ob/ob neuropeptide Y+/− mice, despite marked attenuation of diabetes and obesity phenotypes, showed no change in HDL cholesterol levels relative to ob/ob mice. Thus, increased HDL levels in ob/ob mice reflect a marked hepatic catabolic defect for apoA-I and apoA-II. In the case of apoA-I, this is offset by decreased apoA-I mRNA, resulting in apoA-II-rich HDL particles. The studies reveal a specific HDL particle catabolic pathway that is downregulated in ob/ob mice and suggest that HDL apolipoprotein turnover may be regulated by obesity and/or leptin signaling.

In general, HDL levels are inversely related to atherosclerosis susceptibility in humans and mice (1, 2). The protective properties of HDL may be due to its role in reverse cholesterol transport and to antioxidant and anti-inflammatory effects in the arterial wall (3). In humans, low HDL cholesterol levels may be associated with defects in synthesis or catabolism of the major HDL apolipoprotein, apoA-I, with catabolic defects being more common (4, 5). Low HDL is often accompanied by hypertriglyceridemia, obesity, and insulin resistance, and obese subjects characteristically have accelerated catabolism of HDL apolipoproteins (4). A common belief is that low HDL cholesterol reflects increased core lipid exchange between HDL and triglyceride-rich lipoproteins, leading to modifications of HDL composition and size that result in increased catabolism of HDL particles (6). HDL from hypertriglyceridemic subjects with low HDL is smaller and more susceptible to renal filtration and degradation (7).

However, the liver is one of the principal organs of HDL apolipoprotein degradation, and it is unclear how the hepatic catabolism of the major HDL apoproteins is regulated or mediated (8, 9). Recently, an authentic HDL receptor, scavenger receptor B-I (SR-BI), was identified (10). SR-BI mediates the selective uptake of HDL cholesteryl esters in the liver and steroidogenic tissues; however, SR-BI mice do not have defects in catabolism of HDL apoproteins (11, 12), indicating that this receptor is unlikely to mediate hepatic uptake of apoA-I and apoA-II.

Intriguingly, two monogenic mouse obesity models, ob/ob and db/db, have greatly increased plasma HDL cholesterol levels (13). This contrasts with obese humans with low HDL and other mouse models of obesity and diabetes, such as lethal yellow mice, tubby mice, and the brown adipose-ablated transgenic mouse UCP-DTA, all of which have normal HDL levels (13, 14). ob/ob mice were found to have a nonsense mutation in the leptin gene (15), and db/db mice were shown to have a splicing defect in the gene encoding the leptin receptor (16), resulting in defective leptin production and signaling, respectively. Because ob/ob and db/db represent specific mutations in leptin and its receptor, these findings suggested to us that leptin might play a role in the regulation of HDL apoprotein metabolism. As an initial step in investigating this hypothesis, we have characterized HDL apolipoprotein metabolism in ob/ob and db/db mice, and determined whether leptin deficiency is responsible for the high HDL levels.

EXPERIMENTAL PROCEDURES

Animals—All mice used in these studies were female wild-type, ob/ob, and db/db mice of the pure inbred strain C57BL/6J (purchased from The Jackson Laboratory, Bar Harbor, ME). Mice were between the ages of 8 and 13 weeks old. All mice were fed chow diet. All mice were fasted for 4 h before plasma collections.

Lipoprotein Analysis—Native gel electrophoresis was carried out on plasma from mice fasted for 4 h and separated on a 4–20% polyacrylamide gel (Lipo-Gel, Zaxis) and stained with Sudan Black. HDL size

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† To whom correspondence should be addressed: Div. of Molecular Medicine, Department of Medicine, Columbia University, New York, NY 10032. Tel.: 212-305-5789; Fax: 212-305-5052; E-mail: dls51@columbia.edu.

‡ To whom correspondence should be addressed: Div. of Molecular Medicine, Department of Medicine, Columbia University, New York, NY 10032. Tel.: 212-305-5789; Fax: 212-305-5052; E-mail: dls51@columbia.edu.
was determined using a high molecular weight calibration kit (Amer-
sham Pharmacia Biotech). HDL fractions (1.063 < ρ < 1.21) were
isolated from fasted mice by buoyant density ultracentrifugation,
and apolipoproteins were separated through a 4–20% SDS-polyacryl-
amide gel. Coomassie Blue-stained SDS-polyacrylamide gel electrophoresis
gels were destained, and proteins were quantified using scanning den-
sitometry. Isolation of HDL by chemical precipitation (HDL reagent,
Sigma) and enzymatic measurements (Wako Pure Chemical Industries,
Ltd.) was carried out according to the manufacturers’ instructions.

Catabolic Assay—HDL was radiolabeled with 125I-N-methyl tyra-
mine cellobiose (500 cpm/ng), and 10 μg was injected into the femoral
vein. Asialoglycoprotein (Sigma) was conventionally labeled with 125I
(600 cpm/ng), and 5 μg was injected in the femoral vein. Fractional
catabolic rate was calculated by fitting a least squares multiplexponential
curve to each set of turnover data as previously described (17).

Leptin Treatment—ob/ob, db/db, and lean wild-type mice were in-
jected once daily with either 0.5 μg/g of body weight of leptin (R&D
Systems) or 1.0 μg/g of body weight. Control groups of ob/ob, db/db,
and lean wild-type mice were injected once daily with saline. All mice
were 8 weeks of age at the beginning of the experiments. Saline-injected
mice were pair-fed along with the leptin-injected mice of the same
genotype.

Northern Blot Analysis—10 μg of total liver RNA was hybridized with
radiolabeled cDNAs of mouse apoA-I, apoA-II, and a 28 S oligonu-
cleotide. ApoA-I and ApoA-II signal levels are reported under “Results”
as ApoA-I or ApoA-II signal/28 S RNA signal. 2.5 μg of liver poly(A)+
RNA was hybridized with radiolabeled cDNAs of mouse SR-BI or LDL
receptor. Both signal levels were standardized with a radiolabeled
mouse B-actin cDNA. PhosphorImager analysis was used for all quan-
tifications. Data were reported for all Northern blots as mean ± S.D.
(‘arbitrary units’).

Western Blot Analysis—SR-BI protein levels in 50 μg of mouse liver
membranes were detected using polyclonal antibodies against mouse
SR-BI as described previously (18). SR-BI signals on x-ray film
were quantified by scanning laser densitometry.

Hepatic Lipase and Phospholipid Transfer Protein (PLTP) Assays—
Both assays were performed as described previously (19, 20). Hepatic
lipase assays and PLTP assays were performed on plasma from n = 5
and n = 10 (for each genotype) mice, respectively.

Statistical Analysis—Probability values were calculated for each
experiment using the Student t test.

RESULTS

Apolipoprotein Composition and apoA-I and apoA-II mRNA
Levels in ob/ob Mice—Previous studies employed nonspecific
precipitation methods to show increased HDL cholesterol in
ob/ob and db/db mice (13). Fractionation of plasma lipopro-
teins from ob/ob mice by fast protein liquid chromatography
confirmed a marked increase in the main peak of HDL relative
to plasma from wild-type mice, as well as a shoulder in the
region where a large subclass of HDL (HDL<sub>1</sub>) and LDL elute
(Fig. 1A). Native gel electrophoresis of plasma from ob/ob and
wild-type mice showed that ob/ob mice have an increased
amount and size of HDL (mean increase in diameter, 0.4 nm)
and increased HDL<sub>1</sub>, as well as decreased size, but an
unchanged amount of LDL (Fig. 1B). Thus, the hypercholesterol-
emia of ob/ob mice is due to a marked increase in HDL and
HDL<sub>1</sub>.

The apoprotein composition of HDL was next determined in
ob/ob and db/db mice. ApoA-II levels were 4-fold (ob/ob) and
3-fold (db/db) increased relative to wild-type mice (Fig. 1C, wt,
286 ± 26; ob/ob, 1136 ± 156; db/db, 788 ± 88 (mean ± S.D.);
p < 0.005; n = 6 for wt and ob/ob, n = 3 for db/db (arbitrary units)). A
more modest elevation in apoA-I was also observed (Fig. 1C; 1.3- and
1.2-fold, respectively; p < 0.005). The marked
increase in apoA-II correlates well with increased HDL chole-
terol, as apoA-II levels are an important determinant of HDL
cholesterol levels in mice (21). The increased plasma apoA-I
and apoA-II protein levels in ob/ob mice were not due to
increased expression of their respective genes (Fig. 1D); hepatic
apoA-II mRNA abundance was similar to that of wild-type
mice, and surprisingly, apoA-I mRNA levels were reduced
4-fold in ob/ob livers (Fig. 1D, wt, 0.047 ± 0.017; ob/ob, 0.01 ±
0.001 (mean ± S.D., arbitrary units); p < 0.05; n = 6 for each
genotype).

HDL Apolipoprotein Clearance in ob/ob Mice—The greatly
increased plasma levels of apoA-II and, to a lesser extent,
apoA-I with no change or an opposite change in their mRNA
levels suggested that the increase in HDL is due to a catabolic
defect of HDL apoproteins. To test this idea, the proteins of
intact HDL particles from ob/ob mice were conjugated to a
radioiodinated nondegradable tracer, N-methyl-tyramine cello-
biose (22), and injected into groups of ob/ob and wild-type mice.
Fig. 2A shows that the removal of the plasma HDL tracer in
ob/ob mice was slower than in wild-type mice. The HDL pro-
tein fractional catabolic rate (17) was significantly decreased
relative to wild-type mice (0.138 ± 0.029 and 0.067 ± 0.011
pools/h, respectively; p < 0.01). Moreover, the initial (0–4 h)
plasma decay of both apoA-I and ApoA-II was markedly re-
duced, with apoA-I levels decaying at a slower rate than apoA-II in
ob/ob mice (Fig. 2B). The level of the HDL protein
tracer in livers of ob/ob mice at the 24-h time point was
profoundly reduced (4.3-fold) relative to wild-type livers (Fig.
2C). No significant difference in the HDL tracer levels were
seen in kidneys of ob/ob and wild-type mice, suggesting that
ob/ob mice have a HDL protein catabolic defect specific for the
liver. The livers of ob/ob mice are moderately enlarged as a
result of increased fat deposition (23). To eliminate the possibil-
ity that ob/ob mice have a general defect in liver function
resulting from increased liver weight, the activity of the well charac-
terized hepatic receptor for asialoligocytrophin was examined (24).
Radiodinated asialoglycoprotein was in-
jected into ob/ob and wild-type mice. Fig. 2D shows that the
plasma clearance of asialoglycoprotein was slightly faster in
ob/ob mice relative to wild-type mice, with similar fractional
catabolic rates (0.29 ± 0.04 and 0.21 ± 0.11, respectively).
Taken together, these data indicate that ob/ob mice have a liver-specific defect in HDL protein catabolism.

Examination of Factors Known to Affect HDL Turnover—
Next, we examined the possibility that factors known to alter HDL catabolism might be altered in ob/ob mice. First, the level of the HDL receptor SR-BI was evaluated by Western blot analysis and found to be unchanged (Fig. 3A, ob/ob, 174 ± 55; wt, 151 ± 8 densitometric units; n = 6 for each genotype); SR-BI mRNA levels were also unchanged (Fig. 3B, wt, 1.9 ± 0.6; ob/ob, 1.9 ± 0.3 arbitrary units; n = 6 for each genotype). Second, the LDL receptor is known to catabolize large apolipoprotein E (apoE)-containing HDL particles (25). However, LDL receptor mRNA levels were found to be unchanged (Fig. 3A, wt, 0.38 ± 0.045; ob/ob, 0.39 ± 0.046 arbitrary units; n = 6 for each genotype). Third, the activity of hepatic lipase, an enzyme shown to promote the uptake of HDL by cultured hepatocytes (25), was found to be normal (wt, 3685 ± 311 cpm transferred/μl of plasma/h; ob/ob, 4284 ± 339 cpm transferred/μl of plasma/h). Fourth, the activities of PLTP, which circulates bound to HDL and mediates the transfer and exchange of phospholipids between different lipoproteins (19), was found to be increased (wt, 203 ± 8 cpm transferred/μl of plasma/h; ob/ob, 397 ± 65 cpm transferred/μl of plasma/h; p < 0.001). However, PLTP mRNA levels in the liver of ob/ob mice were unchanged (data not shown). The increased PLTP activity, with no increase in PLTP mRNA, suggests that the increased activity is secondary to increased concentration of HDL particles. These data indicated that it is unlikely that these factors account for the high HDL level in ob/ob mice.

Leptin Treatment of ob/ob and Lean Wild-type Mice—These experiments indicate major defects in HDL metabolism in ob/ob mice: both decreased synthesis of apoA-I, as implied by decreased apoA-I mRNA, and decreased catabolism of apoA-I and apoA-II. To determine whether abnormalities of HDL were reversible with leptin treatment, low doses of leptin were injected into ob/ob and wild-type mice. Doses of leptin that are suboptimal for weight reduction were used throughout these studies so that no major effects of leptin on adiposity occurred, as measured by body weight. Fig. 4A shows that mice injected with leptin or saline (and pair-fed) had similar body weights as measured by body weight. Fig. 4A, ob/ob, 174 ± 55; wt, 151 ± 8 densitometric units; n = 6 for each genotype); SR-BI mRNA levels detected in poly(A) RNA from individual mice of each genotype injected with saline or leptin for 14 days (S, saline; L, leptin). Three mice treated with leptin or saline (shown in Fig. 4D) were examined for SR-BI and LDL receptor mRNA levels.
mice (Fig. 4B). After cessation of injections, HDL cholesterol rebounded to saline-injected levels. There was no decrease in plasma HDL cholesterol levels in leptin and saline-injected wild-type mice (Fig. 4B), nor in db/db mice injected with leptin (day 0, 90 ± 17 mg/dl; day 14, 86 ± 17 mg/dl). However, injection of 3-fold more leptin into wild-type and ob/ob mice resulted in a 25% decrease in HDL cholesterol in both groups (Fig. 4D), without a decrease in body weight in wild-type mice (Fig. 4C). Once again, db/db mice injected with leptin showed no decrease in plasma HDL cholesterol levels (day 0, 89 ± 4.2
mg/dl; day 14, 90 ± 7.3 mg/dl). At both lower (Fig. 4E) and higher (Fig. 4G) doses of leptin, the decrease in plasma HDL cholesterol in ob/ob mice was associated with a 50–60% decrease in HDL apoA-II levels, with no decrease in apoA-II in saline-injected ob/ob mice. Similarly, apoA-II levels were decreased by 45–50% in leptin-injected wild-type mice (Fig. 4, F and H). Leptin did not change steady state HDL apoA-I levels in ob/ob or wild-type mice (Fig. 4, E–H). These results indicate a substantial reversal of the increased HDL cholesterol and apoA-II by low dose leptin in ob/ob mice. Moreover, a parallel process occurred in wild-type mice at a 3-fold higher leptin dosage. That more leptin was necessary to cause a decrease in plasma HDL cholesterol in wild-type mice indicates that wild-type mice are less sensitive to the effects of leptin than are ob/ob mice, as previous reports suggested for body weight changes and as noted here (26–28). In addition, leptin treatment did not alter levels of either SR-BI or LDL receptor mRNA in livers of ob/ob and wild-type mice (Fig. 3B).

ApoA-I mRNA Levels after Leptin Treatment—Although these findings could result if leptin reverses the catabolic defect of HDL proteins in ob/ob mice, apoA-I levels were unchanged by leptin treatment (Fig. 4, E–H). This may be explained if leptin also increases the low levels of apoA-I mRNA observed in ob/ob livers (Fig. 1D), thereby increasing apoA-I synthesis. Indeed, apoA-I mRNA from ob/ob mice treated with leptin was restored to levels of wild-type mice, whereas apoA-I mRNA levels in ob/ob mice treated with saline and db/db mice treated with leptin remained at a low level, with no change in apoA-II mRNA levels (Fig. 5). Thus, low dose leptin essentially normalized apoA-II levels (Fig. 4, E and G) and apoA-I mRNA (Fig. 5) in ob/ob mice. However, HDL cholesterol levels remained above wild-type levels (Fig. 4, B and D).

HDL Cholesterol Levels in Neuropeptide Y (NPY)−/−, ob/ob Mice—The leptin administration studies showed that HDL abnormalities were partly reversible without changes in body weight. To further examine the relationship between HDL and obesity, we measured HDL levels in ob/ob NPY-deficient mice. Mice deficient in NPY and carrying the NPY−/− mutation (29) show a 51% reduction in adiposity and a marked attenuation of hyperphagia and diabetes-associated phenotypes caused by the ob/ob mutation (29). Therefore, we asked whether decreases in plasma insulin, glucose, and adiposity would have a proportional effect on HDL cholesterol levels in ob/ob mice. Despite the attenuation of obesity in npy−/− ob/ob mice (29), a lack of NPY on the ob/ob background did not reduce plasma HDL levels relative to the ob/ob mice carrying a functional npy gene (Fig. 6). Thus, significant decreases in obesity-related phenotypes do not appear to reduce the high HDL cholesterol levels in ob/ob mice.

**DISCUSSION**

This study has revealed major alterations in the metabolism of apoA-I and apoA-II in ob/ob and db/db mice. In the case of apoA-I, a striking 4-fold decrease in apoA-I mRNA is offset by a comparable decrease in hepatic catabolism, so that plasma levels are only slightly elevated. Low dose leptin administration reversed the decrease in apoA-I mRNA in ob/ob mice, without changing plasma apoA-I levels. These findings, which imply that leptin enhances the turnover of plasma apoA-I, are reminiscent of its stimulation of glucose turnover without significant changes in plasma level (30). In contrast to apoA-I, hepatic apoA-II mRNA was unchanged; thus, a marked hepatic catabolic defect resulted in increased HDL apoA-II levels. In mice, increased plasma apoA-II levels are commonly associated with increased HDL cholesterol (21). Therefore, increased apoA-II may be the predominant factor responsible for increased HDL cholesterol in ob/ob mice. The parallel defects in hepatic catabolism of apoA-I and apoA-II provide novel evidence for a specific liver catabolic process that is down-regulated in ob/ob mice.

Although altered catabolism of HDL apoproteins commonly underlies variation in HDL cholesterol levels in humans (4, 5, 31), the regulation and molecular mechanisms of apolipoprotein catabolism are obscure. Our findings indicate a catabolic pathway for apoA-I and apoA-II that is liver-specific, down-regulated in ob/ob mice, and possibly regulated by leptin. A variety of factors that could potentially be responsible for these effects were excluded, including SR-BI levels, LDL receptor mRNA, hepatic lipase activity, and PLTP and hepatic PLTP mRNA levels. Other potential pathways include the LDL receptor-related protein (32) and an apoE-proteoglycan pathway.
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(25). However, the phenotype of mice overexpressing the LDL receptor-related protein inhibitor RAP suggests that LDL receptor-related protein is unlikely to represent the major catabolic factor for apoA-I and apoA-II (33). Moreover, apoE accumulation was not particularly prominent in ob/ob or db/db mice (Fig. 1C), suggesting that it may not be the ligand primarily regulating HDL apoprotein metabolism in these animals. ob/ob mice do have increased lipoprotein lipase (LPL) activity when measured relative to the entire adipose mass (34). LPL acts by hydrolyzing triglycerides from apoB-containing particles in plasma (35). However, mice overexpressing LPL do not show increases in HDL apolipoproteins (36). In addition, leptin has recently been shown to increase LPL expression in vivo (37); therefore, in our experiments to decrease HDL cholesterol, it is unlikely that LPL is responsible for the HDL phenotype in ob/ob mice. Thus, the parallel severe defects in apoA-I and apoA-II catabolism in ob/ob mice suggest down-regulation of a novel process, possibly a receptor, mediating HDL particle uptake in the liver.

Increased apoA-I gene expression in transgenic mice is associated with a potent, consistent anti-atherogenic effect in different mouse models (38, 39). The molecular mechanisms of regulation of apoA-I gene expression have been intensively studied, at both the transcriptional and posttranscriptional levels. The proximal 256 base pairs of the human apoA-I gene contain sufficient information to direct high level hepatic expression (40), and a number of transcription factors appear to be active on the proximal promoter, such as apoA-I regulatory protein-I (41), retinoid X receptor α (42), thyroid hormone receptor (43), and early growth response factor I (44). Although a number of pharmacological and dietary factors may signal through these and other transcription factors to affect apoA-I levels, apoA-I gene expression has proven relatively insensitive to physiological change. Some of the states in which there is altered apoA-I gene expression in rodents include experimental hyperthyroidism (1.7–2.5-fold increased apoA-I mRNA) (45), and nephrotic syndrome (2-fold increased apoA-I mRNA) (44). High fat diets are also associated with a 40% increase in apoA-I synthesis, reflecting increased translational efficiency of apoA-I mRNA (46). The finding of a 4-fold decrease in apoA-I mRNA in ob/ob mice that is completely reversed by low dose lepin administration is notable and may indicate that lepin signaling pathways play a major role in vivo in the regulation of apoA-I synthesis.

ob/ob mice have multiple metabolic defects, including obesity, insulin-resistant diabetes, and hypercortisolism (47, 48). Potentially, any of these or other abnormalities in ob/ob mice could be responsible for the metabolic derangement of HDL apoprotein metabolism. Several lines of evidence indicate that the increased HDL levels of ob/ob mice are not solely and simply secondary to obesity or diabetes. First, several other obese diabetic mouse models do not have increased HDL levels (13, 49). Second, in the present study, compound ob/ob mice are not solely and simply secondary to obesity or diabetes. First, several other obese diabetic mouse models do not have increased HDL levels (13, 49). Second, in the present study, compound ob/ob mice do not have increased HDL levels simply secondary to obesity or diabetes. First, several other obese diabetic mouse models do not have increased HDL levels (13, 49). Second, in the present study, compound ob/ob mice do not have increased HDL levels simply secondary to obesity or diabetes. First, several other obese diabetic mouse models do not have increased HDL levels (13, 49). Second, in the present study, compound ob/ob mice do not have increased HDL levels simply secondary to obesity or diabetes.

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David L. Silver, Xian-cheng Jiang and Alan R. Tall

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