Increased LDL Cholesterol and Atherosclerosis in LDL Receptor–Deficient Mice With Attenuated Expression of Scavenger Receptor B1

Dennis Huszar, Mariet Lee Varban, Franz Rinninger, Roslyn Feeley, Takeshi Arai, Victoria Fairchild-Huntress, Michael J. Donovan, Alan R. Tall

Abstract—Scavenger receptor BI (SR-BI) is a multiligand cell-surface receptor that plays a central role in high density lipoprotein homeostasis in rodents. To investigate a role for SR-BI in atherosclerosis, mice with attenuated SR-BI expression were crossed with low density lipoprotein (LDL) receptor–deficient mice. Compound-homozygous mutants showed increased plasma cholesterol, surprisingly due primarily to increased LDL cholesterol and apolipoprotein B levels. LDL turnover studies showed that this resulted from increased LDL cholesterol production rather than decreased LDL catabolism. Atherosclerotic lesion size was significantly increased in male compound-mutant mice relative to LDL receptor–deficient controls (93 4276 16 079 versus 34 4486 5 331 mm², respectively; P=0.003). The proatherogenic effect of attenuated SR-BI expression may in part be due to increased LDL cholesterol levels. These findings suggest that upregulation of the receptor could have therapeutic potential for the treatment of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2000;20:1068-1073.)

Key Words: scavenger receptor BI ■ atherosclerosis ■ HDL ■ cholesterol ■ mouse

The risk of developing atherosclerosis and coronary heart disease is inversely proportional to the plasma concentrations of HDL cholesterol and directly related to the levels of LDL cholesterol. The regulation of plasma LDL cholesterol levels via receptor-mediated clearance is a well-defined process involving endocytosis and degradation of the entire LDL particle. In contrast, it has long been known that clearance of plasma HDL cholesterol occurs in part by the fundamentally different process of selective lipid uptake, in which cholesteryl ester (CE) is selectively extracted from HDL particles without concomitant degradation of apoproteins. It is only recently that the receptor mediating this process, scavenger receptor BI (SR-BI), has been identified. SR-BI is a cell-surface glycoprotein that has been shown to bind HDL with high affinity and to mediate selective lipid uptake in transfected cells. As expected for an HDL receptor, SR-BI is primarily expressed in those tissues (liver, adrenal gland, ovary, testis) that are the principal sites of selective uptake in vivo.

Definitive evidence for a physiological role of SR-BI in mediating HDL cholesterol clearance in vivo has been recently provided by mouse models. Hepatic overexpression of SR-BI results in depletation of plasma HDL cholesterol, increased hepatic selective uptake of HDL cholesterol, and elevated biliary cholesterol. In contrast, reduction of SR-BI expression via gene targeting results in mice with elevated plasma HDL cholesterol levels and decreased hepatic selective uptake of HDL cholesterol.

The importance of SR-BI in HDL homeostasis suggests a role for the receptor in determining susceptibility to atherosclerosis. An antiatherogenic effect of hepatic SR-BI overexpression has been reported in LDL receptor (LDLr)–deficient mice, but these observations are based on SR-BI expression levels that are nonphysiological. To evaluate the consequences of reduced SR-BI expression on atherogenesis, SR-BI att mice, carrying a promoter mutation that reduces hepatic expression of SR-BI and selective uptake of HDL cholesterol by ~50%, were crossed with mice lacking the LDLr (LDLr-0 mice). Deficiency of the LDLr results in a substantial increase in LDL cholesterol, as well as the development of large aortic lesions, when mice are fed a high-fat and cholesterol-containing (Western-type) diet. We have found that attenuation of SR-BI activity in LDLr-0 mice results in a further increase in plasma concentrations of LDL particles due to increased LDL production. Measurements of aortic root lesion area in these mice showed a significant increase in atherosclerosis associated with reduced expression of SR-BI.

Methods

Mice

“SR-BI att” indicates mice homozygous for the SR-BI–targeted promoter mutation described previously. These mice, on a mixed
129/Sv–BALB/c background, were crossed with C57BL/6 LDLr-deficient mice purchased from Jackson Labs (Bar Harbor, Me). F1 progeny were backcrossed to LDLr-deficient mice, and the resulting offspring were then intercrossed to generate compound-homozygous mutant SR-BI att/LDLr-0 and control LDLr-0 mice. Mice were maintained on a 12-hour light/dark cycle and were fed either PMI 5021 chow containing 9% fat (PMI Feeds) or a high-fat, Western-type diet (0.15% cholesterol, 21% saturated fat; TD 88137 diet, Harlan Teklad) as indicated. Hepatic SR-BI expression in double-mutant and control mice was quantified by densitometry of Western blots as described.

**Plasma Lipoprotein Analysis**
Mice were bled after a 5- to 8-hour fast. Total plasma cholesterol and triglycerides were determined by using commercial enzymatic assays. Plasma HDL cholesterol was quantified after dextran sulfate–Mg precipitation of apoB-containing lipoproteins, and non-HDL cholesterol was determined by subtraction of this value from total plasma cholesterol. Plasma apoB levels were measured by ELISA immunoassay. Fast protein liquid chromatography (FPLC) was performed on 200 µL of pooled plasma samples by using 2 Superose 6 columns connected in series (Pharmacia Biotech). For SDS–polyacrylamide gel electrophoresis (PAGE), VLDL+IDL (d=1.006 to 1.019 g/mL), LDL (d=1.019 to 1.055 g/mL), and HDL (d=1.055 to 1.21 g/mL) were separated by sequential preparative ultracentrifugation of pooled mouse plasma; denaturing polyacrylamide gel analysis was performed with 4% to 20% gradient gels (Bio-Rad) stained with Coomassie Brilliant Blue R.

**LDL Turnover Studies**
LDL was prepared in the density range 1.020 to 1.045 g/mL from plasma of LDLr-0 and SR-BI att/LDLr-0 mice, dialyzed against PBS containing 0.3 mmol/L EDTA and 0.02% NaN3, and radiolabeled in the protein moiety with [125I]–methyl-tyramine cellobiose ([125I]–methyl-tyramine cellobiose (125I–methyl-tyramine cellobiose) and thereafter with [14C]cholesterol oleyl ether ([14C]cholesterol oleyl ether ([14C]Et). Determination of the plasma decay of both LDL tracers and their tissue sites of uptake was carried out as described. Food was removed 4 hours before tracer injection from those mice that had been maintained on a high-fat diet. Animals were fasted for the entire 24-hour study period but had free access to water. Doubly radiolabeled LDL was injected at 10 AM into an i.v. vein, and blood samples were drawn from the tail vein of each animal at 0.08, 0.5, 2.0, 5.0, 9.0, and 24.0 hours after injection. Plasma samples were directly radioassayed for 125I and analyzed for tritium after lipid extraction. Twent-ty-four hours after tracer injection, the animals were anesthetized and perfused with saline (50 mL per animal), and their organs were collected, weighed, homogenized, and radioassayed. Tissue content of 125I radioactivity was directly assayed and that of tritium was analyzed after lipid extraction. Based on the plasma decay of both LDL tracers, plasma fractional catabolic rates (FCRs) were calculated by using a 2-compartment model. Organ FCRs, the fraction of the plasma pool of the traced LDL component cleared per hour by an organ, were calculated as the plasma FCR fraction of the total tracer (in percent) recovered in a specific organ.

**Analysis of Atherosclerotic Lesions**
At 10 weeks of age, 10 LDLr-0 mice and 15 SR-BI att/LDLr-0 mice fed the high-fat diet were killed under anesthesia (Avertin: 0.15 mL of 2% solution per gram of body weight, injected IP) and perfused with 4% paraformaldehyde in PBS. The basal aspect of the heart was embedded in OCT compound (Tissue-Tek), snap-frozen in isopentane cooled with LN2, and stored at −80°C until sectioning. Serial sections (10 µm thick) were collected, starting at the aortic sinus, for a length of 300 µm. Every other section was collected, stained with oil red O to identify lipid and counterstained with hematoxylin. Quantitative analysis was performed on 5 oil red O-stained sections from comparable levels of the aorta from each mouse by using digitized photomicroscopy and reported as the mean lesion area (µm2 per aortic root per mouse).

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**TABLE 1. Plasma Lipid Levels in Mice Fed a High-Fat Diet**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDLr-0</td>
<td>SR-BI att/LDLr-0</td>
</tr>
<tr>
<td>TC</td>
<td>946±373</td>
<td>1613±105*</td>
</tr>
<tr>
<td>TG</td>
<td>924±625</td>
<td>1698±333*</td>
</tr>
<tr>
<td>HDLc</td>
<td>46±6</td>
<td>59±5†</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>899±374</td>
<td>1554±110†</td>
</tr>
<tr>
<td>ApoB</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND indicates not determined. The values are expressed as mg/dL for total cholesterol (TC), triglyceride (TG), and HDL cholesterol (HDLc) and as µg/mL for apoB. The data are shown as mean±SD, n=5 mice, except for apoB (n=10, 5 of which were bled after fasting and 5 that were not fasted).

*P<0.05, †P<0.01, relative to LDLr-0 control value.

**Statistical Analysis**
Statistical analyses were performed by 2-tailed Student’s t test for unpaired data.

**Results**
**Compound-Mutant Mice**
SR-BI att mice were bred with mice lacking the LDLr to produce compound-homozygous mutant SR-BI att/LDLr-0 mice and control LDLr-0 littermates. Because att is a promoter mutation potentially subject to strain-specific background effects, hepatic SR-BI protein expression was measured in the progeny mice. As observed in previous analyses, the att mutation reduced hepatic expression of SR-BI by 50% (1386±477 arbitrary units for SR-BI att/ LDLr-0, n=6, versus 2786±326 arbitrary units for LDLr-0, n=6; P=0.038).

**Plasma Cholesterol and Lipid Profiles**
To determine the consequences of reduced SR-BI expression on plasma cholesterol levels in LDLr-0 mice, blood was collected from SR-BI att/LDLr-0 and LDLr-0 mice maintained on a high-fat diet. As in LDLr +/+ mice with attenuated SR-BI expression, total plasma cholesterol was increased (70% for males, 40% for females) in compound-mutant mice relative to LDLr-0 controls (Table 1). However, in contrast to mice expressing the LDLr, the increased cholesterol in LDLr-0 mice was primarily in non-HDL lipoproteins (Table 1). In males there was a small (28%), significant increase in HDL cholesterol, but the majority of elevated cholesterol resulting from decreased SR-BI expression was in the non-HDL lipoproteins. In females, the increased cholesterol also resided almost exclusively in non-HDL lipoproteins, with a proportionate increase in plasma apoB levels, and there was a small (25%), nonsignificant increase in HDL cholesterol. FPLC showed that the elevated non-HDL cholesterol in males was primarily in the LDL cholesterol portion (Figure 1A). Characterization of apoprotein composition by denaturing gel electrophoresis indicated that increased LDL cholesterol in double-mutant males was associated with elevated levels of apoB100 and apoE, relative to corresponding levels in LDLr-0 controls (Figure 1B).
expression (Figure 1C), with corresponding increases in apoB100, apoB48, and apoE (Figure 1D).

**Effect of a Chow Diet**

The minimal increase in HDL cholesterol levels in LDLr-0 mice with reduced SR-BI expression was unexpected, given earlier observations of 50% to 70% increases in HDL cholesterol in otherwise wild-type mice with reduced SR-BI activity.10,11 Because SR-BI has been shown to bind VLDL and LDL as well as HDL particles,19–21 it is possible that the abundant VLDL and LDL particles in LDLr-0, relative to wild-type, mice may compete with HDL for binding to SR-BI. Thus, a decrease in SR-BI expression would primarily affect non-HDL cholesterol levels in LDLr-0 mice. To assess whether a reduction of non-HDL cholesterol levels would unmask a significant effect of the SR-BI mutation on plasma HDL cholesterol levels in female LDLr-0 mice, SR-BI att/LDLr-0 and control LDLr-0 mice were switched from a high-fat diet to chow for 2 weeks, and blood was subsequently collected. On a chow diet, the plasma concentrations of non-HDL cholesterol were markedly reduced (Figure 2). The only significant effect of the SR-BI mutation in female mice on the chow diet was an elevation of HDL cholesterol (44%), whereas, as also noted above, on the high-fat diet the only significant effect was elevation of non-HDL cholesterol (Table 1).

**LDL Clearance**

To examine whether the increase in plasma LDL cholesterol in double-mutant mice maintained on a high-fat diet reflects altered catabolism of LDL particles, female mice were injected with LDL radiolabeled with tracers that are not degraded in the plasma or tissue compartments: [3H]CEt to label LDL CE and 125I-NMTC for labeling of the protein moiety. Plasma decay curves showed no differences in the clearance of 125I-NMTC–labeled protein or [3H]CEt between SR-BI att/LDLr-0 and control LDLr-0 mice over a 24-hour period (Figure 3). Because labeling of LDL protein introduces the tracer into both apoB and apoE, the plasma decay of each apoprotein was also quantified separately. No differences in clearance were observed between double-mutant and control mice (Table 2). Plasma FCRs calculated from the plasma decay curves similarly showed no alterations in clearance of the lipid or protein tracers in double-mutant mice (Table 3). Furthermore, no selective uptake of CE from plasma LDL, calculated as the difference between CE and protein FCRs, was detected in either SR-BI att/LDLr-0 or LDLr-0 mice (Table 2).

SR-BI is highly expressed in the liver, which is the primary site of HDL catabolism in rodents.3,4 Quantification of hepatic tracer uptake and calculation of liver FCRs showed no effect of the SR-BI att mutation on LDL CE or protein catabolism in LDLr-0 mice (Figure 4). Consistent with the

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**Figure 1.** FPLC cholesterol profiles and SDS-PAGE of isolated lipoproteins in SR-BI att/LDLr-0 and LDLr-0 mice. The pooled (n=5) plasma samples of male (A) and female (C) mice on a high-fat diet were analyzed by FPLC, and the cholesterol content of the fractions was determined. Open symbols represent SR-BI att/LDLr-0 mice and the closed symbols, LDLr-0 mice. Lipoproteins were fractionated by ultracentrifugation of pooled plasma, and samples corresponding to 1 μL of plasma (VLDL/IDL) or 4 μL of plasma (LDL and HDL) in B and 6 μL of plasma in D were analyzed on 4% to 20% denaturing gradient gels.

**Figure 2.** Plasma lipid levels of female mice on high-fat (left) and chow (right) diets. Plasma was taken from mice (n=5) fed a high-fat diet and again 2 weeks after the same mice had been switched to a chow diet. HDL cholesterol was quantified after precipitation of apoB-containing lipoproteins, and non-HDL cholesterol was determined by subtraction of this value from the level of total plasma cholesterol. Asterisks indicate statistical significance (P<0.05) relative to LDLr-0 controls. Numbers within or directly above the columns indicate mean values.
plasma data, there was also no evidence of selective uptake of labeled CEt from LDL in LDLr-0 mice (Figure 4).

**Atherosclerosis in SR-BI att/LDLr-0 Mice**

As described above, male mice lacking the LDLr have a large increase in plasma LDL cholesterol and a lesser increase in plasma HDL cholesterol as a result of reduced SR-BI expression. To evaluate the consequences of this lipoprotein profile on atherogenesis, males maintained on the Western diet were examined for the extent of atherosclerosis in serial sections of the aortic root at 10 weeks of age. As shown in Figure 5, LDLr-0 mice characteristically showed small lesions composed predominantly of foamy macrophages. Double-mutant mice with reduced SR-BI expression exhibited larger, more advanced, raised plaques composed of foam cells and abundant extracellular lipid, suggesting macrophage cellular lysis. There was a significant (170%) increase in mean atherosclerotic lesion size of SR-BI att/LDLr-0 mice relative to LDLr-0 controls (93 427±16 079 μm² for SR-BI att/LDLr-0 versus 34 448±5331 μm² for LDLr-0 mice; P=0.003; Figure 6). The increased lesion area of mice carrying the SR-BI mutation was significant, even when the 4 highest SR-BI att/ LDLr-0 data points were excluded from analysis (58 384±5415 μm² for SR-BI att/LDLr-0 versus 34 448±5331 μm² for LDLr-0 mice; P=0.005).

**Discussion**

In this study, we have examined the effects of reduced SR-BI expression on plasma cholesterol levels and atherosclerotic lesion formation in an atherosclerosis-susceptible mouse model. The SR-BI att mutation, which reduces hepatic SR-BI expression by 50%, was found to increase plasma cholesterol levels by 40% to 70% when crossed onto a background of LDLr deficiency. This increase was almost entirely attributable to elevation of non-HDL lipoproteins, predominantly LDL, in both males and females, with only a slight increase in HDL cholesterol levels. The elevation of non-HDL lipoproteins was accompanied by a significant increase in atherosclerosis in male mice: the mean aortic lesion area of mice with reduced expression of SR-BI was increased 2.5 fold relative to LDLr-0 controls. Female double-mutant mice might also show the same tendency, but the effect may be less pronounced due to their lower absolute levels of non-HDL cholesterol relative to male mice.

The minimal effect of attenuated SR-BI expression on HDL cholesterol levels in LDLr-0 mice is notable. In wild-type mice, in which virtually all of the plasma cholesterol is carried within HDL particles, a 50% reduction of SR-BI expression results in a 50% to 70% increase in HDL cholesterol levels10,11 and a concomitant decrease in hepatic selective uptake of HDL CE from the plasma.11 In LDLr-0 mice fed a Western diet, there is an abundance of non-HDL lipoproteins, and only a minority of the plasma cholesterol is found within HDL particles. It is possible that under these conditions, there is sufficient competition for binding to SR-BI by non-HDL lipoproteins such that binding of HDL is largely outcompeted. This concept is consistent with evidence for SR-BI binding of VLDL and LDL19–21 and also with our findings that in female mice switched to a chow diet, which substantially reduces plasma concentrations of non-HDL cholesterol, the only significant increase in plasma cholesterol between SR-BI att/LDLr-0 and control LDLr-0 mice occurred exclusively in HDL cholesterol. It should be noted that Acton et al15 found that native LDL had little competitive effect on HDL’s association with the SR-BI in vitro. However, in vivo characteristics of LDL and its binding to SR-BI may well differ; furthermore, competition between VLDL/ remnants and HDL for SR-BI binding sites has not been assessed. Alternatively, other mechanisms could be involved.

**TABLE 2. Plasma Decay of Radiolabeled ApoB and ApoE**

<table>
<thead>
<tr>
<th></th>
<th>10 min</th>
<th>30 min</th>
<th>2 h</th>
<th>5 h</th>
<th>9 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLr-0</td>
<td>100%</td>
<td>106±1</td>
<td>99±14</td>
<td>82±10</td>
<td>67±7</td>
<td>39±5</td>
</tr>
<tr>
<td>SR-BI att/LDLr-0</td>
<td>100%</td>
<td>105±5</td>
<td>102±23</td>
<td>77±8</td>
<td>60±9</td>
<td>34±4</td>
</tr>
<tr>
<td>ApoE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLr-0</td>
<td>100%</td>
<td>108±12</td>
<td>91±15</td>
<td>68±9</td>
<td>49±7</td>
<td>27±4</td>
</tr>
<tr>
<td>SR-BI att/LDLr-0</td>
<td>100%</td>
<td>105±10</td>
<td>95±20</td>
<td>64±11</td>
<td>43±9</td>
<td>23±4</td>
</tr>
</tbody>
</table>

Radiolabeled apoB and apoE were quantified after separation on denaturing gradient gels. The values represent percentages of counts detected 10 minutes after intravenous injection of the tracer and are shown as mean±SD.
For example, alternative HDL clearance pathways (eg, apoE-dependant clearance) could become relevant on a high-fat diet.

Previous studies have demonstrated that SR-BI can internalize LDL-associated lipids in transfected cells. Interestingly, our studies indicate that in vivo, SR-BI does not mediate selective uptake of CE from LDL and does not appear to play a physiological role in LDL catabolism. Plasma clearance and hepatic uptake of LDL protein and LDL CE were unaffected by a reduction of SR-BI expression in LDLr-0 mice. Thus, the elevation of plasma LDL cholesterol does not reflect impaired LDL catabolism but rather implies increased production of LDL (production rate = pool size × FCR). This event could result from increased secretion of VLDL or decreased VLDL catabolism, leading to increased conversion of VLDL to LDL. Increased VLDL secretion seems unlikely to be the primary defect, since there was no or relatively little increase in the VLDL concentration in double-mutant mice. Preliminary data with double-labeled VLDL have indicated increased conversion of VLDL CE to LDL CE in SR-BI att/LDLr-0 mice relative to control LDLr-0

Figure 4. Uptake of labeled LDL by the liver. Liver FCRs, calculated as described in Methods, are shown for uptake of labeled protein (125I, open bars) and CEt (tritium, solid bars). The dotted bars represent selective CE uptake (tritium minus 125I). The values are mean ± SD.

Figure 5. Histological sections of aortic root. Mice were 10 weeks of age and had been fed a high-fat diet. Cross section (10 μm) of the proximal aorta from a control male LDLr-0 mouse (A) with a mean lesion area of 38 600 μm² and from an SR-BI att/LDLr-0 male mouse (B) with a mean lesion area of 85 400 μm². Dark-staining material represents oil red O-positive, lipid-laden macrophages as well as extracellular lipid within the aortic wall and valve leaflets; magnification ×10. Higher magnification of the aortic wall from an LDLr-0 (C) and an SR-BI att/LDLr-0 (D) mouse; magnification ×20.

Figure 6. Quantitative analysis of atherosclerotic lesion area in the aortic root. Ten-week-old male SR-B1 att/LDLr-0 (n=15) and control LDLr-0 (n=10) mice fed a high-fat diet were analyzed for extent of lesion formation in the aortic root. Serial 10-μm-thick sections were collected and stained with oil red O to determine lipid content and the extent of lesion area. For each mouse, 5 anatomically comparable sections of oil red O-stained sections were quantified, and the mean area was calculated.
mice (F.R. et al, unpublished observations, 1999), thereby supporting a role for SR-BI in the clearance of VLDL remnants. However, analogous to the role of the LDLr-related protein in remnant clearance,22 an impact of SR-BI expression on VLDL or LDL levels only becomes apparent in the context of reduced LDLr activity. Similarly, SR-BI overexpression reduces VLDL and LDL levels in LDLr-deficient mice.12 These findings could indicate a backup function of SR-BI in VLDL remnant metabolism when LDLr activity is low.

Reduction of SR-BI levels in male LDLr-0 mice resulted in a significant increase in the mean atherosclerotic lesion area in the aortic root. Similarly, a proatherogenic effect of the SR-BI-null mutation on the apoE-deficient background was recently reported and appeared to be associated with increased VLDL cholesterol.23 In both models, the increased atherogenicity could be related to the substantial increase in non-HDL cholesterol in double-mutant mice,24 but the effects of SR-BI downregulation on reverse cholesterol transport or local effects in the vessel wall cannot be ruled out. The consequences of the small increase in HDL cholesterol on the atherosclerotic phenotype in our double-mutant mice are not easily assessed. It remains unresolved whether the elevation of HDL cholesterol levels in these mice contributes any atheroprotective effect, or alternatively, promotes increased atherogenesis because it reflects a reduced clearance of HDL. What is clear is that SR-BI underexpression is proatherogenic in atherosclerosis-susceptible mice. This notion is consistent with recent results describing an antiatherogenic effect of hepatic SR-BI overexpression in LDLr-deficient mice.12 Taken together, these data indicate that upregulation of the SR-BI could potentially serve as a useful therapeutic strategy for treatment of atherosclerosis.

Lastly, one could speculate from the data presented here that human SR-BI deficiency states may be characterized by elevated plasma LDL and HDL cholesterol levels and a predisposition to atherosclerosis. Although rare, such kindreds have been observed25 and may, at least in part, result from an underlying defect in SR-BI expression.

Acknowledgments

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