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Rosuvastatin selectively stimulates apolipoprotein A-I but not apolipoprotein A-II synthesis in Hep G2 cells

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Abstract

Hydroxymethylglutaryl–coenzyme A reductase inhibitors (statins) are extensively used to regulate dyslipidemia and to reduce atherosclerotic cardiovascular disease. In addition to effectively lowering cholesterol and low-density lipoprotein levels, rosuvastatin and certain other statins can also increase plasma high-density lipoprotein (HDL) cholesterol modestly. However, the mechanism of action of rosuvastatin on HDL metabolic processes is not understood. Using cultured human hepatoblastoma cells (Hep G2) as an in vitro model system, we assessed the effect of rosuvastatin on apolipoprotein (apo) A-I and apo A-II (the major proteins of HDL) synthesis and HDL catabolic processes. Rosuvastatin dose-dependently increased messenger RNA expression and de novo synthesis of apo A-I but not apo A-II. Rosuvastatin selectively increased the synthesis of HDL particles containing only apo A-I (LP A-I) but not particles containing both apo A-I and A-II (LP A-I + A-II). The HDL_3-protein or HDL_3-cholesterol ester uptake by Hep G2 cells was not affected by rosuvastatin. The apo A-I–containing particles secreted by rosuvastatin-treated Hep G2 significantly increased cholesterol efflux from fibroblasts. The data indicate that rosuvastatin increases hepatic apo A-I but not apo A-II messenger RNA transcription, thereby selectively increasing the synthesis of functionally active apo A-I–containing HDL particles, which mediate cholesterol efflux from peripheral tissues. We suggest that this mechanism of action of rosuvastatin to increase apo A-I production without apo A-I/HDL removal may result in increased apo A-I turnover that results in accelerated reverse cholesterol transport.
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1. Introduction

Rosuvastatin (Crestor, AstraZeneca Pharmaceuticals, Wilmington, DE) is a synthetic hydroxymethylglutaryl–coenzyme A (HMG-CoA) reductase inhibitor with distinctive pharmacologic and pharmacokinetic properties. In comparison with other statins, rosuvastatin exhibits greater number of binding interactions with HMG-CoA reductase, high affinity for the active site of the enzyme, and potent inhibition of cholesterol synthesis in hepatocytes [1]. In addition, rosuvastatin is relatively hydrophilic and is substantially taken up by hepatic cells [1,2]. In a broad spectrum of adult patients with dyslipidemias, several clinical studies have shown that rosuvastatin (10 to 40 mg/d) effectively reduced total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and non–high-density lipoprotein cholesterol (non–HDL-C), and increased apolipoprotein (apo) A-I and HDL-C [3-9]. Compared with other statins, rosuvastatin is the most potent statin to significantly increase apo A-I by 8.8% [4]. Furthermore, rosuvastatin was significantly more effective at milligram equivalent dosages than other statins (atorvastatin, pravastatin, and simvastatin) in improving the overall lipid profiles of patients with hypercholesterolemia [4,6,10]. Rosuvastatin was shown to be more effective than other statins in allowing patients to reach the National Cholesterol Education Program Adult Treatment Panel III and Joint European Societies LDL cholesterol goals.

In addition to effectively reducing plasma cholesterol and LDL levels, a considerable clinical interest has been developed with rosuvastatin for its ability to increase apo

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A-I and HDL-C levels. It is well established that HDL bears an inverse relationship to the development of atherosclerotic coronary heart disease [11]. The recently reported Veterans Affairs HDL Intervention Trial clearly showed for the first time that increasing HDL-C without altering LDL-C in patients treated with gemfibrozil resulted in significant reductions in the risk of major cardiovascular events [12]. The cardioprotective effects of HDL have been largely attributed to the ability of apo A-I (major protein of HDL)–containing HDL particles to initiate cholesterol efflux and thereby facilitate the removal of excess cholesterol from peripheral tissues and its delivery to the liver for elimination through the reverse cholesterol transport pathway [13,14]. The general consensus is that LP A-I particles (a subfraction of HDL particles containing apo A-I without apo A-II) are more potent in effluxing cellular cholesterol than are LP A-I + A-II particles (HDL particles containing apo A-I and apo A-II) [15]. Furthermore, we and others have shown that LP A-I particles are more efficient donors of cholesterol esters than LP A-I + A-II particles [16,17]. Although previously apo A-II was shown to be proatherogenic in animal models [18], recent studies indicated that apo A-II transgenic animals exhibited decreased susceptibility to diet-induced atherosclerosis [19]. In a large prospective study, apo A-II was shown to be inversely associated with the risk of future coronary artery disease [20].

Although rosuvastatin was shown to increase apo A-I and HDL, the hepatocellular mechanisms by which rosuvastatin raises apo A-I and HDL concentrations are not clearly understood. In this study, we examined the effect of rosuvastatin on apo A-I and apo A-II de novo synthesis, messenger RNA (mRNA) expression, and LP A-I and LP A-I + A-II HDL particle synthesis in human hepatoblastoma cells (Hep G2). Additional studies were performed to examine the effect of rosuvastatin on HDL–apo A-I/cholesterol ester uptake by Hep G2 cells to determine whether it had any effect on hepatocyte HDL catabolism.

2. Methods

2.1. Materials

Tissue culture materials, media, and fetal bovine serum (FBS) were obtained from Sigma Chemical (St Louis, MO). L-[4,5-^{3}H]Leucine and [^{3}H]cholesterol were purchased from Amersham (Arlington Heights, IL). The Hep G2 cells and fibroblasts were obtained from American Type Culture Collection (Manassas, VA). The polyclonal antibody for human apo A-I and apo A-II was purchased from Boehringer Mannheim Biochemicals (Ridgefield, CT). All other chemicals used were of analytical grade.

2.2. Studies on de novo synthesis of apo A-I and apo A-II

The Hep G2 cells were grown in 60-mm Petri dishes in high-glucose Dulbecco modified Eagle medium (DMEM) (containing 10% FBS, 1% glutamine-penicillin-streptomycin, and 1% fungizone) and grown for 3 to 4 days until they attained 75% to 80% confluence. Studies examining the effect of rosuvastatin on the de novo synthesis of apo A-I and apo A-II by Hep G2 cells were performed by measuring the incorporation of radiolabeled leucine into apoprotein secreted into the media, as described previously [21]. The Hep G2 cells were incubated with varying concentrations of rosuvastatin (0-5 μmol/L) in DMEM containing 10% FBS for 48 hours at 37°C in a humidified incubator. After the incubation, the medium was replaced with leucine-poor DMEM (5% leucine of normal media) without FBS containing the corresponding amounts of rosuvastatin and [^{3}H]leucine (5 μCi/mL) and incubated for 18 hours at 37°C. At the end of the incubation, the medium was collected and used for immunoprecipitation. The incorporation of radiolabeled leucine into apo A-I or apo A-II was measured by immunoprecipitation using monospecific antibodies for apo A-I or apo A-II. The incorporation of [^{3}H]leucine into apo A-I and apo A-II was expressed as counts per minute per milligram cellular protein.

2.3. Reverse transcriptase–polymerase chain reaction analysis for apo A-I and apo A-II mRNA expression

The Hep G2 cells were incubated with various amounts of rosuvastatin (0-2.5 μmol/L) at 37°C for 48 hours. At the termination of the incubation, culture medium was removed; and the cell monolayer was washed with phosphate-buffered saline (PBS) and collected for total RNA isolation. Cells were collected by trypsinization, and total RNAs were extracted using RNeasy minikit (Qiagen, Valencia, CA). Complementary DNA was synthesized from 900 ng of total RNA in 20 μL using random hexamers and murine Moloney leukemia virus reverse transcriptase (Life Technologies, Gaithersburg, MD). The apo A-I primers used were as follows: sense, 5'-ATG AAA GCT GCG GTG CTG ACC-3' and antisense, 5'-GGA GCT CTA CCG CCA GAA GGT G-3'. The apo A-II primers used were as follows: sense, 5'-CGC AGC AAC TGT GCT ACT CCT-3' and antisense, 5'-GCA AAG AGT GGG TAG GGA CA-3'. Semiquantitative reverse transcriptase–polymerase chain reaction (RT-PCR) analysis was performed starting with first-strand complementary DNA from reverse transcription with 150 nmol/L of sense and antisense primer in a final volume of 50 μL. Sense and antisense primers for β-actin (150 nmol/L) were also included in the reaction mixture. The PCR amplification products at different cycles were separated on 1.2% agarose gel and were visualized with ethidium bromide. The band intensity was measured using Eagle Sight (La Jolla, CA) gel documentation system.

2.4. Separation of LP A-I and LP A-I/A-II particles

The experimental protocol was the same as described above in the "de novo synthesis of apo A-I and apo A-II" studies. The medium was collected and used to isolate LP A-I and LP A-I/A-II particles by immunoaffinity column chromatography as described earlier [22]. In brief, affinity

columns specific for apo A-I or apo A-II were prepared by coupling polyclonal antibodies for human apo A-I or apo A-II to CNBr-activated Sepharose 4B (Pharmacia, Ramsey, MN) according to the procedure described in the instruction manual. Aliquots of culture medium (250 μL) were loaded onto the apo A-I affinity column and incubated at 4°C for 16 to 18 hours to allow binding of apolipoprotein particles to specific antibody. The affinity column was then washed with 0.5 mol/L NaCl; and retained apo A-I–containing particles were eluted with 3 mol/L NaSCN, pH 6.0. An aliquot of eluted fraction was counted for radioactivity and represents LP A-I with and without A-II particles. Similarly, another aliquot (250 μL) of culture medium was subjected to apo A-II–specific immunoaffinity column chromatography; and an aliquot of NaSCN-eluted retained fraction was counted for radioactivity. This retained fraction on apo A-II–specific affinity column represents the contribution of apo A-II in LP A-I + A-II particles. Quantitative analysis of the incorporation of [^{3}H] leucine into LP A-I particles (without A-II) was attained by the difference in radioactivity between retained fractions on apo A-I affinity column and apo A-II affinity column.

2.5. Studies on the uptake of HDL-protein

Studies examining the uptake by Hep G2 cells were performed by using radiolabeled HDL–total protein or apo A-I–HDL, according to the procedures described previously [21]. Radio iodination of HDL–total protein was carried out by incubating freshly isolated HDL_3 with carrier-free ^{125}I as described earlier [21]. After the iodination, unreacted ^{125}I was removed by gel filtration followed by exhaustive dialysis against PBS. Uptake studies were initiated by preincubating Hep G2 cells with varying concentrations of rosuvastatin (0-5 μmol/L) for 48 hours at 37°C. The medium was replaced with fresh DMEM containing fetal bovine albumin (FBA) (5 mg/mL) and ^{125}I-HDL (50 μg protein). After 8 hours of incubation at 37°C, cell monolayers were washed thoroughly and digested with 1 N sodium hydroxide solution. An aliquot was used for radioactivity measurement. The uptake of radiolabeled HDL-protein by Hep G2 cells was expressed in terms of cellular protein.

2.6. Uptake of [^{3}H]cholesterol esters labeled HDL

For these studies, radiolabeled HDL–cholesterol ester (HDL-CE) was prepared by incubating 4 μCi of [1a,2a (n)-^{3}H]cholesterol with the serum HDL fraction for 18 hours at 37°C (through lecithin:cholesterol acyltransferase [LCAT] enzyme reaction–mediated cholesterol-ester formation [21]). The [^{3}H]cholesterol ester–HDL was isolated by ultracentrifugation at d = 1.210 g/mL and dialyzed extensively against 0.15 mol/L NaCl. Uptake studies were performed by preincubating Hep G2 cells with rosuvastatin (0-5 μmol/L) for 48 hours. Medium was removed, and fresh DMEM containing 5 mg/mL FBA (fatty acid free) and [^{3}H] cholesterol ester–labeled HDL (50 μg HDL-protein per milliliter) was added. Cells were harvested 6 hours later, washed thoroughly, and digested with 1 mL of 1 N NaOH. Radioactivity was measured and expressed as counts per minute per milligram cellular protein.

2.7. Measurement of cholesterol efflux

The Hep G2 cells were incubated with various amounts of rosuvastatin (0-5 μmol/L) at 37°C for 48 hours. At the termination of the incubation, culture medium was removed; and the cell monolayer was washed with PBS and collected for cellular protein measurement. The medium collected was used for cholesterol efflux measurements as described in our earlier publications [22,23]. An aliquot of culture medium (5 mL) was concentrated to 1 mL by lyophilization and dialyzed against DMEM to remove excess salt present in the concentrated sample. The ability of the media (containing

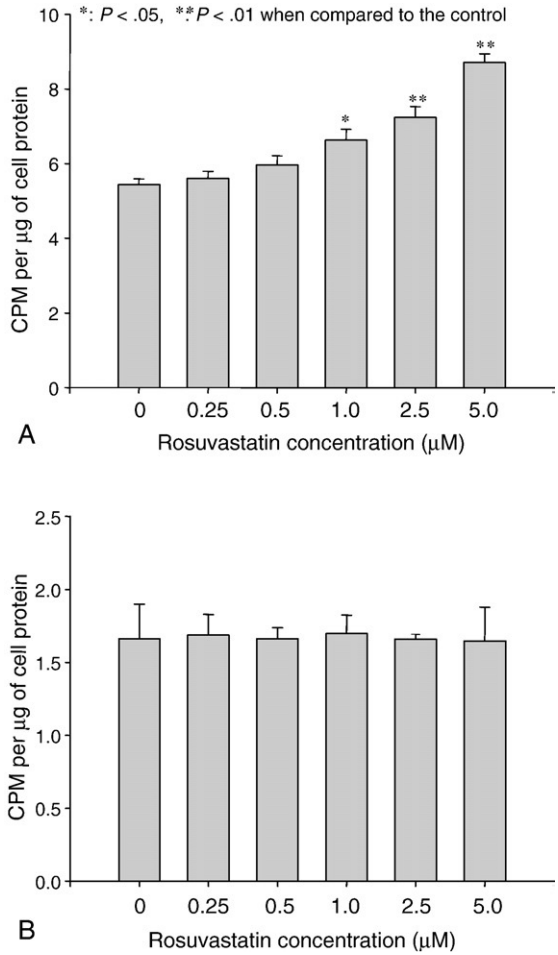


Fig. 1. Effect of rosuvastatin on the incorporation of [^{3}H]leucine into newly synthesized apo A-I (A) and apo A-II (B) by Hep G2 cells. Cells were incubated with varying concentrations of rosuvastatin (0 to 5 μmol/L) for 48 hours. Medium was then changed to fresh FBS-free leucine-poor DMEM with the respective concentrations of rosuvastatin containing 5 μCi/mL of [^{3}H]leucine and incubated for 18 hours. At the end of the incubation, culture media were assayed for radiolabeled apo A-I or apo A-II by immunoprecipitation; and results were expressed in terms of total cellular protein. Statistical significance was compared with results of control. Data are mean ± SE of 3 experiments done in duplicate.

secreted apo A-I lipoprotein particles) to efflux free cholesterol was measured using [^{3}H]cholesterol-labeled human fibroblasts. Cholesterol efflux assay was initiated by incubating concentrated culture medium with [^{3}H] cholesterol-labeled fibroblasts for 20 hours as described previously [22,23]. Quantitative analysis of the ability of Hep G2 cell culture medium (in the presence or absence of rosuvastatin) to efflux cholesterol was performed by measuring the [^{3}H]cholesterol radioactivity appearing in the medium per milliliter of incubation medium per milligram of fibroblast cellular protein.

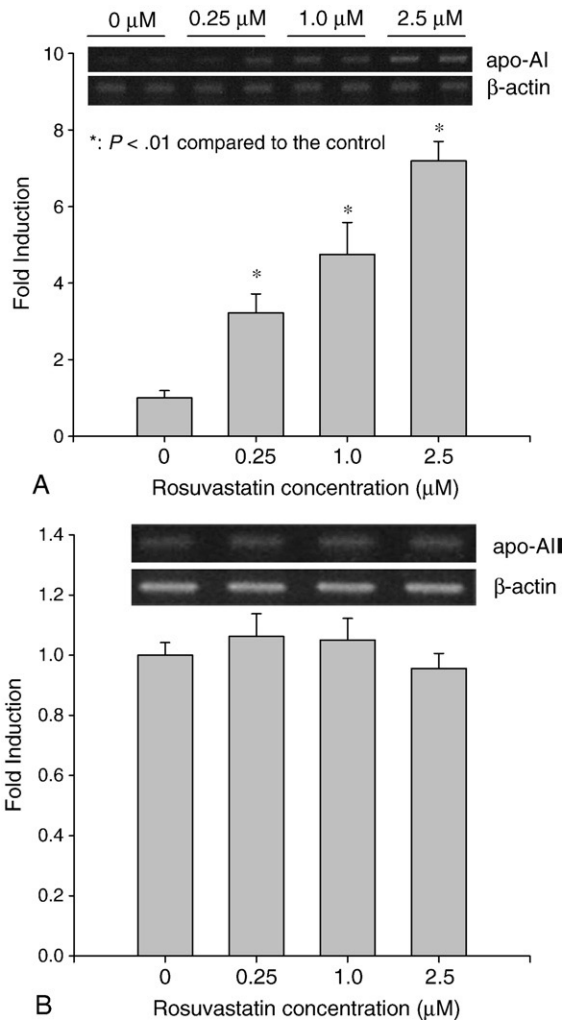


Fig. 2. Effect of rosuvastatin on apo A-I and apo A-II mRNA expression in Hep G2 cells. Cells were incubated with varying concentrations of rosuvastatin (0 to 2.5 μmol/L) for 48 hours. Total RNA was isolated as described in Methods, and the RNA was subjected to semiquantitative RT-PCR analysis. After 19, 22, 25, and 30 cycles, samples were collected and run on a 1.2% agarose gel. Quantitative analysis of apo A-I and apo A-II mRNA expression was performed by measuring the band intensity of the mRNA message at 19 cycles of the amplification (linear phase) and normalizing with the internal standard β-actin using Eagle Sight software. A, Representative mRNA expression blot for apo A-I (upper panel); quantitative data on the fold induction of apo A-I mRNA expression over control (lower panel). Data are mean ± SE of 3 experiments. B, Representative mRNA expression blot for apo A-II (upper panel); quantitative data on the fold induction of apo A-II mRNA expression over control (lower panel). Data are mean ± SE of 3 experiments.

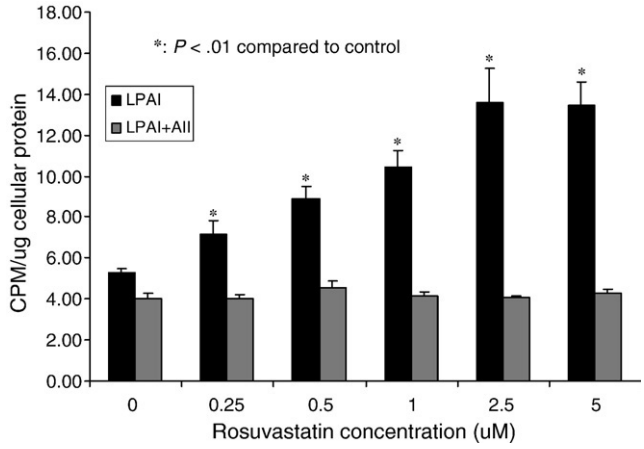


Fig. 3. Effect of rosuvastatin on the incorporation of [^{3}H]leucine into newly synthesized LP A-I and LP A-I + A-II particles by Hep G2 cells. Experimental protocol was the same as noted in Fig. 1 legend and in Methods. Culture media were used to isolate LP A-I and LP A-I + A-II particles by immunoaffinity chromatography, as described in Methods. Radiolabeled leucine incorporated into LPs was measured and expressed in terms of total cellular protein. Statistical significance was compared with results of control. Data are mean ± SE of 3 experiments.

2.8. Statistical analysis

Data presented are the mean ± SE of 3 separate experiments. Statistical significance was calculated by using the Student t test, and a value of $P < .05$ was considered significant.

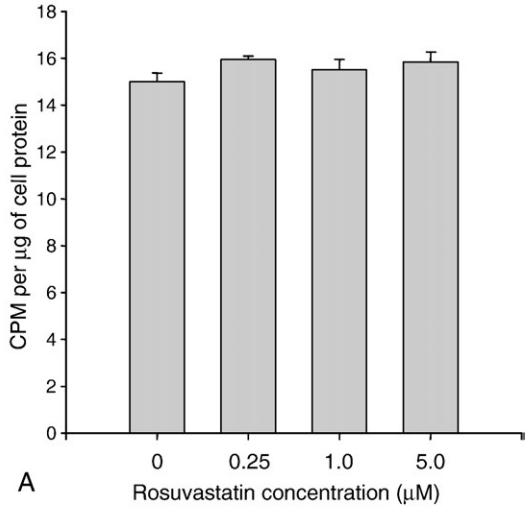
3. Results

3.1. Effect of rosuvastatin on apo A-I and apo A-II de novo synthesis in Hep G2 cells

De novo synthesis of apo A-I or apo A-II was assessed by measuring the incorporation of [^{3}H]leucine into newly synthesized apo A-I or apo A-II secreted into the medium. Data from these studies show that the incorporation of radiolabeled leucine into apo A-I increased in a dose-dependent manner by Hep G2 cells incubated with rosuvastatin (Fig. 1A). Rosuvastatin as low as 1 μmol/L significantly increased apo A-I de novo synthesis, and the maximum effect was observed at 5 μmol/L rosuvastatin (Fig. 1A). Incubation of Hep G2 cells with rosuvastatin did not alter the de novo synthesis of apo A-II (Fig. 1B). Similar studies examining the de novo synthesis of albumin showed that the incubation of rosuvastatin (0-5 μmol/L) with Hep G2 cells did not alter the de novo synthesis of albumin, as measured by the incorporation of radiolabeled leucine into immunoprecipitable albumin in the culture medium (data not shown).

3.2. Effect of rosuvastatin on apo A-I and apo A-II mRNA expression

As shown in representative RT-PCR blot, the incubation of varying amounts of rosuvastatin with Hep G2 cells induced dose-dependently the mRNA expression of apo A-I (Fig. 2A, top panel). Quantitative analysis of apo A-I mRNA message, as measured by densitometric scanning of blots and normalization with β-actin as an internal control, indicated that the treatment of Hep G2 cells with rosuvastatin as low as 0.25 μmol/L concentration significantly stimulated apo A-I mRNA levels and rosuvastatin at 2.5 μmol/L dose increased apo A-I mRNA by about 7-fold (Fig. 2A, lower panel). In contrast to apo A-I mRNA expression, rosuvastatin did not affect the mRNA expression of apo A-II (Fig. 2B).



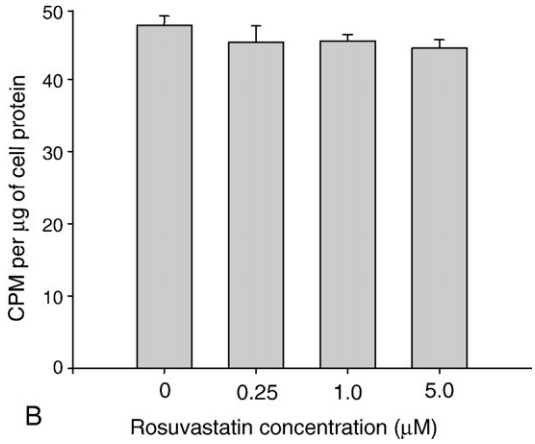


Fig. 4. Effect of rosuvastatin on ^{125}I-HDL$_3$–protein and [^{3}H]CE-labeled HDL uptake by Hep G2 cells. Cells were preincubated with varying concentrations of rosuvastatin (0 to 5 μmol/L) for 48 hours. A, Fresh DMEM containing 5 mg/mL FBA, rosuvastatin, and ^{125}I-HDL–protein (100 μg protein per milliliter) was added. Cells were harvested 16 hours later, washed thoroughly with PBS, and digested with 1 N NaOH. Radioactivity was measured, and the HDL-protein uptake was expressed as counts per minute per microgram of cellular protein. Data are mean ± SE of 3 experiments. B, Fresh DMEM containing 5 mg/mL FBA, rosuvastatin, and [^{3}H]CE-labeled HDL (100 μg protein per milliliter) was added. Cells were harvested 6 hours later, washed thoroughly with PBS, and digested with 1 N NaOH. Radioactivity was measured and expressed as counts per minute per microgram of cellular protein. Data are mean ± SE of 3 experiments.

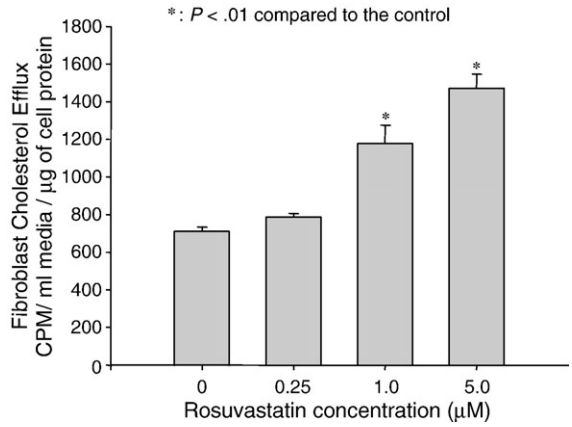


Fig. 5. Effect of rosuvastatin-induced apo A-I–containing particles from Hep G2 cells on cholesterol efflux from fibroblasts. The Hep G2 cells were incubated with varying concentrations of rosuvastatin (0 to 5 μmol/L) for 48 hours. After the incubation, an aliquot of medium was concentrated and added to [^{3}H]cholesterol-labeled fibroblast cultures to measure its ability to efflux cholesterol, as described in Methods. Radioactivity appearing in the culture medium (as a measure of cholesterol efflux) was expressed in terms of cellular protein. Data are mean ± SE of 3 experiments.

3.3. Effect of rosuvastatin on the synthesis of LP A-I and LP A-I + A-II HDL particles

To examine the effect of rosuvastatin on the de novo synthesis of LP A-I and LP A-I + A-II–containing HDL particles in Hep G2 cells, aliquots of medium from de novo synthesis experiments were fractionated into LP A-I and LP A-II particles by immunoaffinity column chromatography. Results from these experiments revealed that the incubation of rosuvastatin with Hep G2 cells selectively increased, in a dose-dependent manner, the secretion of LP A-I but not LP A-I + A-II HDL particles into the medium (Fig. 3).

3.4. Effect of rosuvastatin on HDL-protein and HDL-cholesterol uptake

Additional studies were performed to assess the effect of rosuvastatin on uptake of HDL and its components by Hep G2 cells. The uptake of HDL-protein and HDL-CE by Hep G2 cells was measured by incubating with [^{3}H]CE-HDL and ^{125}I-HDL$_3$, respectively. As shown in Fig. 4, the preincubation of Hep G2 cells with rosuvastatin at varying concentrations (0-5 μmol/L) did not alter the uptake of either HDL-protein (Fig. 4A) or HDL-CE (Fig. 4B).

3.5. Effect of secreted HDL particles from Hep G2 cells on cholesterol efflux by human fibroblasts

The ability of rosuvastatin-induced apo A-I–containing lipoprotein particles to efflux cholesterol was examined by using [^{3}H]cholesterol-labeled fibroblasts. Cholesterol efflux

studies using conditioned medium obtained from Hep G2 cells treated with varying amounts of rosuvastatin (0-5 μmol/L) showed a dose-dependent increase in cholesterol efflux, as measured by the release of [^{3}H]cholesterol from fibroblasts into the culture medium (Fig. 5).

4. Discussion

In this study, using Hep G2 cell system, we have delineated the effect of rosuvastatin on cellular processes involved in HDL synthesis and catabolism that in turn determine the overall concentrations of apo A-I and HDL. We have shown that rosuvastatin increases apo A-I mRNA expression and de novo synthesis of apo A-I and LP A-I HDL particles in Hep G2 cells. Because HDL catabolic processes also regulate apo A-I and HDL levels, we performed additional studies to examine the effect of rosuvastatin on HDL-protein and HDL-CE uptake/removal by Hep G2 cells. The results indicate that rosuvastatin had no effect on HDL uptake/removal by Hep G2 cells. The data indicate that rosuvastatin by increasing apo A-I mRNA levels increased the de novo synthesis of apo A-I particles without affecting HDL catabolic processes in Hep G2 cells. In addition, we have shown that the apo A-I–containing lipoprotein particles secreted in the culture medium of Hep G2 cells treated with rosuvastatin were able to significantly increase cholesterol efflux from fibroblasts, suggesting that these particles are functionally active in initiating reverse cholesterol transport. However, because the findings of this study were derived from in vitro studies using HepG2 cells, real limitations exist in extrapolating in vitro findings of this study to in vivo conditions in humans.

Contrary to apo A-I synthesis, rosuvastatin had no effect on the synthesis of either apo A-II or apo A-II–containing LP A-I + A-II particles in Hep G2 cells. Because apo A-I and apo A-II exhibit differential atherogenic properties, our data suggest that rosuvastatin selectively increases cardioprotective LP A-I HDL particles. Several studies suggested the beneficial role of LP A-I HDL particles in coronary disease. Previously, it was shown that transgenic mice producing human apo A-I have significantly less atherosclerosis than those producing both apo A-I and apo A-II when fed an atherogenic diet [18,24,25]. Clinical studies have indicated that the increased levels of LP A-I particles are associated negatively with the degree of arteriographically defined coronary disease [26,27]. Premenopausal women have higher levels of LP A-I, suggesting that this may have beneficial effect in reducing cardiovascular risk in these subjects [28]. Oral estrogen replacement therapy in postmenopausal women was shown to increase LP A-I levels [29]. In Hep G2 cells, we have shown that estradiol selectively stimulates the synthesis of LP A-I particles [22]. The potential cardioprotective effects of LP A-I particles may, at least in part, be attributed to their enhanced cholesterol-effluxing properties [15]. Furthermore, LP A-I particles are more significantly efficient donors of cholesterol esters than LP A-I + A-II particles in cultured Hep G2 cells [16,17]. However, recently, apo A-II has also been shown to have protective effects against atherosclerosis in animals [19] and inverse relationship with future coronary artery disease in humans [20]. Further studies are warranted to precisely define the role of apo A-II–containing particles in atherosclerosis and cardiovascular disease. We suggest that rosuvastatin, by selectively increasing hepatocyte LP A-I particles, may enhance the removal of excess cholesterol from peripheral tissues (including arteries) and play a significant role in cardioprotection beyond its conventional role as cholesterol- and LDL-lowering drug.

Statins (eg, cerivastatin and pitavastatin) were previously shown to increase apo A-I mRNA levels in Hep G2 cells, and this effect was mediated by inducing apo A-I promoter activity by these statins [30]. These studies also indicated that the addition of mevalonate blocked apo A-I mRNA expression induced by statins, suggesting HMG-CoA reductase as the relevant target of statins to increase apo A-I. Additional mechanistic studies indicated that statin-induced inhibition of Rho-signaling pathway mediates peroxisome proliferator-activated receptor α activation and subsequent apo A-I mRNA transcription by statins [30]. Our data showing the ability of rosuvastatin to increase apo A-I mRNA expression are consistent with cerivastatin and pitavastatin, and likely to use HMG-CoA reductase as the mechanistic target to increase apo A-I transcription. Our data also indicate that the increase in apo A-I mRNA was higher than the rise from control in apo A-I mass. This suggests that, in our system, there may be posttranslational degradation of apo A-I and other unclear mechanisms needing further research. Studies are also warranted regarding the possible participation of peroxisome proliferator-activated receptor–mediated events and/or other signaling pathways in rosuvastatin-mediated effects on apo A-I mRNA expression in HepG2 cells. The effects of rosuvastatin or other statins to modulate apo A-II levels are not clearly understood. We have shown that rosuvastatin had no effect on apo A-II mRNA expression in Hep G2 cells, suggesting that HMG-CoA reductase may not be one of the regulatory sites for apo A-II transcription.

In summary, these data suggest that rosuvastatin increases hepatic apo A-I but not apo A-II mRNA transcription, thereby selectively increasing the production of functionally active apo A-I–containing HDL particles, which mediate cholesterol efflux from peripheral tissues. We suggest that this mechanism of action of rosuvastatin to increase apo A-I production without apo A-I/HDL removal may result in increased apo A-I turnover that in turn accelerates reverse cholesterol transport.

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