Atherosclerosis and Lipoproteins

Niacin, but Not Gemfibrozil, Selectively Increases LP-AI, a Cardioprotective Subfraction of HDL, in Patients With Low HDL Cholesterol

Takaaki Sakai, Vaijinath S. Kamanna, Moti L. Kashyap

Abstract—Evidence indicates that the high density lipoprotein (HDL) subfraction containing apolipoprotein A-I without apolipoprotein AI (LP-AI) is more antiatherogenic than HDL particles containing apolipoprotein A-I and apolipoprotein A-II (LP-AI+AI). This study examined the effect of extended-release niacin (niacin-ER) and gemfibrozil on LP-AI and LP-AI+AI particles in patients with low levels of HDL cholesterol (HDL-C). Mechanisms by which these agents modulate HDL particles were investigated by in vitro studies using human hepatoblastoma (Hep G2) cells. A total of 139 patients with low HDL-C (≤40 mg/dL) were randomized to niacin-ER or gemfibrozil in a multicenter double-blind trial. Patients were dose-escalated with once-nightly niacin-ER (1 to 2 g) or gemfibrozil (1.2 g) for 19 weeks. Niacin-ER had a greater effect in raising HDL-C and apolipoprotein A-I levels than did gemfibrozil. Niacin-ER at 1- and 2-g doses increased LP-AI levels by 8.7±4.0% (P=0.033) and 24.0±4.4% (P<0.001), respectively. Gemfibrozil had no consistent effect on LP-AI levels. LP-AI+AI levels increased 5% to 8% by both agents. In vitro studies showed that niacin, but not gemfibrozil, selectively decreased the uptake of 125I-labeled LP-AI holoparticles by Hep G2 cells. The uptake of [3H]cholesterol ester was ≈75% greater from LP-AI versus LP-AI+AI particles, but neither niacin nor gemfibrozil affected cholesterol ester uptake. These data indicate that unlike gemfibrozil, niacin selectively increases LP-AI compared with LP-AI+AI particle concentration in patients with low HDL-C levels. The mechanism of action of increased LP-AI concentration appears to be mediated by decreased hepatic removal of LP-AI particles, which are more efficient in reverse cholesterol transport, thus suggesting an additional mechanism by which niacin mediates its antiatherogenic properties. (Arterioscler Thromb Vasc Biol. 2001;21:1783-1789.)

Key Words: lipoproteins ▪ drugs ▪ atherosclerosis ▪ apolipoproteins

Niacin is a commonly used antidyslipidemic agent that effectively decreases total plasma levels of cholesterol, triglycerides (TGs), and LDL cholesterol (LDL-C) and increases HDL cholesterol (HDL-C). Niacin also lowers plasma levels of Lp(a). Treatment of patients with niacin has been shown to decrease myocardial infarction and stroke and, in combination with bile acid–binding regimen, to prevent progression and cause regression of coronary atherosclerosis. Although the use of niacin has been associated with adverse effects (eg, flushing and hepatic toxicity), recent studies have indicated that a once-nightly extended-release niacin (niacin-ER) formulation (Niaspan, Kos Pharmaceuticals) has shown reduced flushing with minimal to no hepatic toxicity with comparable effects on plasma lipid profile. Gemfibrozil is another widely used lipid-regulating agent and has been shown to reduce plasma cholesterol, TGs, VLDL, and LDL and to elevate HDL; in a primary prevention study, it significantly reduced coronary events.
and apoA-II). Furthermore, studies have shown that LP-AI particles are more efficient donors of cholesterol esters (CEs) than are LP-AI+AIi particles. Clinical studies have indicated that the increased levels of LP-AI particles are associated negatively with the degree of arteriographically defined coronary disease. Premenopausal women have higher levels of LP-AI, suggesting that this may have a beneficial effect in reducing cardiovascular risk in these subjects. Oral estrogen replacement therapy in postmenopausal women was shown to increase LP-AI levels. Using human hepatoblastoma cells, we have shown that estradiol selectively stimulates the synthesis of LP-AI particles.

Although niacin is the most potent clinically used agent for elevating HDL-C and apoA-I levels in dyslipidemic patients (see review), the effect of niacin on plasma levels of LP-AI and LP-AI+AIi is not established. In the present study, using a multicenter double-blind randomized design, we have examined the effect of niacin-ER versus gemfibrozil on plasma levels of LP-AI and LP-AI+AIi particles in patients with low HDL-C. Previously, we have shown that niacin, by inhibiting the uptake/removal of HDL–apoA-I (without influencing apoA-I synthesis), increased the accumulation of apoA-I in the culture media. In the present study, we hypothesized that the increase in LP-AI particles in niacin-ER–treated patients may be due to decreased hepatic removal/uptake of LP-AI particles. To address this issue and to understand the mechanism by which niacin or gemfibrozil modulates these HDL subfractions, in vitro studies examining the uptake of these particles by human hepatoblastoma (Hep G2) cells were carried out. The data in the present study indicate that niacin, but not gemfibrozil, selectively increases LP-AI particles in these patients. The in vitro experiments show that niacin selectively decreases the uptake of LP-AI by cultured Hep G2 cells, whereas gemfibrozil does not, indicating the cellular site of action of niacin on these particles. Uptake of CE is greater from LP-AI than LP-AI+AIi particles, but neither agent affected CE uptake, thus defining the mechanism by which niacin increases LP-AI and reverse cholesterol transport.

Methods

Study Design and Patient Selection

A total of 139 patients were randomized to receive either niacin-ER or gemfibrozil. These patients were a subset of the original study from 11 participating institutions detailed previously. The protocols were approved by the institutional review boards of the participating institutions, and written informed consent was obtained from each patient. All lipid-lowering medications were withdrawn, and patients were counseled on a National Cholesterol Education Program Step I diet for a 4-week lead-in period. Baseline mean lipid profile was obtained from consecutive blood samples taken 7 to 10 days apart from the dietary lead-in period. The eligibility criteria for patients to be included in the study were as follows: HDL-C ≤40 mg/dL, TGs ≤400 mg/dL, and LDL-C ≤160 mg/dL or <130 mg/dL with documented coronary disease. Patients with gallbladder or peptic ulcer disease, active gout, clinically significant hyperuricemia, renal or hepatic disease, cardiac arrhythmias, or other serious cardiac abnormalities were excluded. Diabetic patients were excluded, but non–insulin-requiring diabetic patients with hemoglobin A1c within the normal range and fasting glucose ≤120 mg/dL were included in the study.

In the double-blind, placebo-controlled treatment phase, patients were randomly assigned to receive either niacin-ER (n=72) or gemfibrozil (n=67). Niacin-ER was administered as a once-a-night dose at bedtime after a low-fat snack. During an initial 3-week titration period, niacin-ER was given initially at 375 mg and was increased at weekly intervals to 500 mg and then to 750 mg. The dose of niacin-ER was subsequently escalated to 1000 mg for the next 4 weeks, 1500 mg for 4 weeks, and then 2000 mg for 8 weeks. Gemfibrozil was given a dose of 600 mg twice daily, 30 minutes before the morning and evening meals for the entire 19-week period.

Measurement of Plasma Lipid Profile, ApoA-I, LP-AI, and LP-AI+AIi Particles

Blood samples were collected after a 12-hour fast. Plasma cholesterol, TGs, HDL-C, and LDL-C concentrations were analyzed at the Lipid Research Laboratory, Washington University, St. Louis, Mo, which is certified by the Lipid Standardization Program of the Centers for Disease Control. Plasma concentrations of apoA-I, apoB, and Lp(a) were measured by previously described procedures at the Northwest Lipid Research Laboratory.

Plasma concentrations of LP-AI particles were measured by the Hydregal LPAI kit (No. 4055, Sebia, Inc) according to the manufacturer’s instructions. In brief, LP-AI particles were quantified in serum by the electroimmunodiffusion method on agarose gels containing monospecific anti–apoA-I and excess anti–apoA-II antibodies. After electrophoretic migration, the resulting rockets were stained with acid violet solution, and excess stain was removed with an acid-alcohol mixture. The Sebia gel kit uses excess anti–apoA-II incorporated into the agarose gels to block the migration of LP-AI+AIi particles. The LP-AI particles continue to migrate and react with anti–apoA-I antibodies, and the height of the resulting immunoprecipitation rocket is proportional to the LP-AI concentration. Serum LP-AI concentrations were calculated by measuring the rocket heights and were compared with the calibration curve generated with the LP-AI standard serum pool. Plasma concentrations of LP-AI+AIi particles were derived by subtracting LP-AI values from the total serum apoA-I concentration (as measured by radioimmunoassay). The within-day and between-day coefficient of variation for LP-AI assay was 4.2% and 5.4%, respectively.

In Vitro Studies on the Uptake of LP-AI and LP-AI+AIi Particles by Hep G2 Cells

In these studies, the isolation of LP-AI and LP-AI+AIi particles from normal serum, radiolabeling, and their uptake by Hep G2 cells were performed by the following procedures.

LP-AI and LP-AI+AIi particles from normal human serum were isolated by immunoaffinity column chromatography with the use of anti–apoA-I and anti–apoA-II columns according to modified previously described methods. In brief, affinity columns specific for apoA-I or apoA-II were prepared by coupling polyclonal antibodies for human apoA-I or apoA-II to CNBr-activated Sepharose 4B (Pharmacia) according to the procedures described in the instruction manual. Serum samples were loaded onto the apoA-II affinity column and incubated at 4°C for 16 to 18 hours to allow binding of apolipoprotein particles to the specific antibody. The unretained fraction was collected. The retained fraction on the anti–apoA-II column was eluted with 3 mol/L NaSCN, pH 6.0, to obtain apoA-II–containing particles (ie, LP-AI+AIi). The unretained fraction from the anti–apoA-II column was washed through the anti–apoA-I column, and the retained particles were eluted with 3 mol/L NaSCN, pH 6.0, to obtain LP-AI particles. After elution, the contact of HDL subfractions with NaSCN was minimized by immediate passage through the Sephadex G-25 columns and dialysis against PBS. During initial standardization, we have established that the unretained washing fractions from anti–apoA-I and anti–apoA-II affinity columns were devoid of apo-A-I and apoA-II (as measured by ELISA), respectively, suggesting that the amount of plasma used for immunoaffinity separation did not exceed the column capacity. We have previously validated the specificity of these immunoaffinity procedures for the isolation of LP-AI and LP-AI+AIi particles.

We have established that the LP-AI subfraction did not contain apoA-II.

Radioiodination of LP-AI and LP-AI+AIi particles was carried out by incubating freshly isolated particles with carrier-free 125I, as described earlier by McFarlane. After radioiodination, unreacted 125I was removed by gel filtration, followed by exhaustive dialysis.
TABLE 1. Plasma Lipid and Apolipoprotein Values at Baseline and During Treatment With Niacin-ER and Gemfibrozil

<table>
<thead>
<tr>
<th></th>
<th>Niacin-ER</th>
<th></th>
<th>Gemfibrozil</th>
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<tbody>
<tr>
<td></td>
<td>0 wk</td>
<td>7 wk</td>
<td>11 wk</td>
<td>19 wk</td>
</tr>
<tr>
<td>n</td>
<td>72</td>
<td>71</td>
<td>70</td>
<td>69</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>190.4±3.1</td>
<td>189.1±4.0</td>
<td>187.2±4.0</td>
<td>183.9±3.8†</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>194.4±9.6</td>
<td>159.0±8.8*</td>
<td>140.3±8.9*</td>
<td>135.5±8.5*</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>30.7±0.6</td>
<td>34.9±0.7*</td>
<td>36.8±0.7*</td>
<td>38.3±0.8*</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>120.5±2.8</td>
<td>122.7±3.5</td>
<td>122.3±3.6</td>
<td>118.6±3.2</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>63.9±0.21</td>
<td>56.1±0.18*</td>
<td>52.2±0.15*</td>
<td>4.97±0.16*</td>
</tr>
<tr>
<td>ApoA-I, mg/dL</td>
<td>105.1±1.7</td>
<td>110.6±1.9*</td>
<td>113.7±1.8*</td>
<td>115.9±2.0*</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>106.2±2.1</td>
<td>102.2±2.8†</td>
<td>100.6±3.0*</td>
<td>97.4±2.6*</td>
</tr>
</tbody>
</table>

n indicates number of patients. Values are expressed as mean±SEM.

†P<0.01 and *P<0.05 vs week 0.

Effect of Niacin-ER and Gemfibrozil on Lipid Profile

Lipid and apolipoprotein profile analyses of patients in this study showed that niacin-ER significantly decreased total cholesterol (TC, at 19 weeks of treatment), TGs, TC/HDL-C ratio, and apoB compared with baseline values (at 7, 11, and 19 weeks of treatment; Table 1). Niacin-ER significantly increased HDL-C and apoA-I during all treatment periods (Table 1). Patients treated with gemfibrozil showed a significant decrease in TC (at 7 weeks of treatment), in TGs and the TC/HDL-C ratio (at all treatment periods), and in apoB levels (at 7 and 11 weeks, Table 1). Gemfibrozil increased plasma concentrations of HDL-C at all treatment periods and apoA-I at 11 weeks of treatment (Table 1). Comparative analysis between values after niacin-ER versus gemfibrozil treatment compared with the respective baseline values (at the 19-week treatment period) had the following effects on lipid profile: reduction in TGs by 30% versus 45% and TC/HDL-C by 22% versus 13% and increase in HDL-C by 25% versus 13% and apoA-I by 10% versus 2.5%, respectively (P<0.01 for all parameters).

Effect of Niacin-ER and Gemfibrozil on LP-AI and LP-AI+AlI Levels

Measurement of HDL particles without apoA-II (LP-AI) and with apoA-II (LP-AI+AlI) showed that niacin-ER significantly and dose-dependently increased LP-AI particles by...
TABLE 2. Plasma Lp-AI and Lp-AI+All Values at Baseline and During Treatment With Niacin-ER and Gemfibrozil

<table>
<thead>
<tr>
<th></th>
<th>Niacin-ER</th>
<th></th>
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<th>Gemfibrozil</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 wk</td>
<td>7 wk</td>
<td>11 wk</td>
<td>19 wk</td>
<td>0 wk</td>
<td>7 wk</td>
<td>11 wk</td>
</tr>
<tr>
<td>Dose, g/d</td>
<td>0</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
<td>0</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>n</td>
<td>72</td>
<td>71</td>
<td>70</td>
<td>69</td>
<td>67</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>Lp-AI, mg/dL</td>
<td>30.3±0.8</td>
<td>31.9±1.1*</td>
<td>33.0±0.9*</td>
<td>36.2±1.1†</td>
<td>28.1±0.8</td>
<td>24.4±0.9*</td>
<td>26.1±1.0</td>
</tr>
<tr>
<td>Baseline,%</td>
<td>100</td>
<td>108.7±4.0</td>
<td>113.2±3.7</td>
<td>124.0±4.4</td>
<td>100</td>
<td>89.5±3.6</td>
<td>98.3±4.3</td>
</tr>
<tr>
<td>Lp-AI+All, mg/dL</td>
<td>74.8±1.5</td>
<td>78.7±1.8*</td>
<td>81.1±1.7*</td>
<td>79.8±1.7*</td>
<td>77.7±1.5</td>
<td>81.4±1.99</td>
<td>83.6±1.9*</td>
</tr>
<tr>
<td>Baseline,%</td>
<td>100</td>
<td>105.2±1.7</td>
<td>109.5±2.3</td>
<td>108.1±2.31</td>
<td>100</td>
<td>106.0±4.8</td>
<td>108.0±4.7</td>
</tr>
</tbody>
</table>

n indicates number of patients. Values are mean±SEM. Baseline values are calculated as percent change for each sample. *P<0.01 and §P<0.05 vs week 0; †P<0.01 and ‡P<0.05 for niacin-ER vs gemfibrozil at each visit.

8.7% to 24.0%, respectively, during all the treatment periods (between 7 to 19 weeks) compared with the baseline values (Table 2). Niacin-ER also significantly increased LP-AI+All levels by 5.2% to 9.5% compared with the baseline values; however, the effect was less when LP-AI+All levels were compared with LP-AI levels (Table 2). Treatment of patients with gemfibrozil did not consistently increase LP-AI levels compared with the baseline values (Table 2). However, gemfibrozil significantly increased LP-AI+All concentrations by 4.2% to 8.0% compared with their baseline values (Table 2).

Effect of Niacin and Gemfibrozil on the Uptake of LP-AI and LP-AI+All Particles by Hep G2 Cells

The next series of in vitro experiments were performed on the uptake of radiolabeled-LP-AI and LP-AI+All particles by Hep G2 cells to understand the mechanisms by which niacin and gemfibrozil affect LP-AI and LP-AI+All levels. In these in vitro studies, we used optimal concentrations of niacin or gemfibrozil and incubation period based on initial studies and our previous reports.25,29 For example, niacin during 6 to 16 hours had a minimal effect on HDL particle uptake by Hep G2 cells. At 24 hours of incubation, there were some marginal effects, and the effect was maximal at 48 hours of incubation with niacin. Similar experiments were performed for incubation periods with gemfibrozil. The incubation of Hep G2 cells with niacin (1 to 3 mmol/L) for 48 hours significantly inhibited the uptake of 125I-LP-AI particles by 15% to 17% (Figure, panel A), whereas the preincubation of Hep G2 cells with gemfibrozil (50 to 400 μmol/L) for 48 hours had no significant effect on the uptake of 125I-LP-AI particles (Figure, panel A). Neither niacin nor gemfibrozil affected the uptake of 125I-LP-AI+All particles by Hep G2 cells (Figure, panel B). Further experiments were performed to examine the effect of niacin and gemfibrozil on the uptake of [3H]CE from LP-AI and LP-AI+All particles by Hep G2 cells. Incubation of Hep G2 cells with either niacin (0 to 3 mmol/L) or gemfibrozil (50 to 400 μmol/L) for 48 hours did not significantly affect the uptake of [3H]CE from LP-AI and LP-AI+All particles by Hep G2 cells (Table 3). However, the CE uptake from LP-AI particles was ~75% greater than that from LP-AI+All particles, indicating that LP-AI particles were more efficient donors of CE per unit of protein.

Discussion

Although the measurement of HDL-C and apoA-I are important lipid profile parameters for cardiovascular risk assessment, recent studies have emphasized that the levels of the LP-AI HDL subfraction may offer greater utility, as indicated in the introduction to the present study. The mechanisms of action of niacin and gemfibrozil to raise HDL are incompletely understood. Using human Hep G2 cells, we have shown that niacin, through inhibiting the uptake/removal of HDL-apoA-I, increases the accumulation of apoA-I in the culture media without affecting apoA-I synthesis.25 The
TABLE 3. Effect of Niacin and Gemfibrozil on the Uptake of [3H]CE-Labeled Lp-AI and Lp-AI+All Particles by Hep G2 Cells

<table>
<thead>
<tr>
<th>[3H]CE Uptake, cpm/mg Protein</th>
<th>[3H]CE-Labeled Lp-AI</th>
<th>[3H]CE-Labeled Lp-AI + All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3067.7±52.3*</td>
<td>1752.2±48.7</td>
</tr>
<tr>
<td>0.5</td>
<td>3112.5±36.1*</td>
<td>1697.9±46.4</td>
</tr>
<tr>
<td>1</td>
<td>3113.3±55.7*</td>
<td>1709.4±40.3</td>
</tr>
<tr>
<td>2</td>
<td>3015.7±52.0*</td>
<td>1716.6±38.1</td>
</tr>
<tr>
<td>3</td>
<td>3125.5±38.8*</td>
<td>1788.4±30.7</td>
</tr>
<tr>
<td>Gemfibrozil, μmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2865.9±50.1*</td>
<td>1693.3±56.6</td>
</tr>
<tr>
<td>50</td>
<td>2845.2±28.6*</td>
<td>1400.9±38.3</td>
</tr>
<tr>
<td>100</td>
<td>2859.5±31.6*</td>
<td>1664.1±34.4</td>
</tr>
<tr>
<td>200</td>
<td>2798.2±34.0*</td>
<td>1658.1±58.8</td>
</tr>
<tr>
<td>400</td>
<td>2862.9±45.0*</td>
<td>1705.1±23.2</td>
</tr>
</tbody>
</table>

Values are mean±SD. *P<0.05 for Lp-AI vs Lp-AI+All.

The major focus of the present study was to assess the effect of niacin-ER and gemfibrozil on LP-AI and LP-AI+All HDL subfractions in patients with low HDL-C. The data indicated that niacin-ER (2 g daily) raised HDL-C by 25%, an effect twice as much as the HDL-C increase afforded by gemfibrozil (1200 mg daily). The HDL-C–raising effect of niacin-ER is consistent with previous report showing a comparable HDL-C increase provided by niacin-ER and immediate-release niacin. These observations clearly indicated that the specific extended-release characteristic of niacin-ER formulation and its once-nightly schedule of administration can retain an HDL-C–raising effect that is comparable to that of immediate-release niacin, with significantly reduced episodes of adverse events, such as flushing. The data on the effect of gemfibrozil to raise HDL-C presented in the present study is in accord with previous studies.

The data on HDL subfraction measurements showed that niacin-ER (2 g daily) during the 19-week treatment period significantly increased LP-AI levels by 24.0% above baseline. Treatment of patients with niacin-ER also significantly increased LP-AI+All particles by 9.5% above baseline; however, the effect was less when LP-AI+All levels were compared with LP-AI levels. Contrary to niacin-ER, gemfibrozil had no consistent effect on LP-AI levels. However, gemfibrozil increased LP-AI+All levels by 4.2%, to 8.0% of their baseline values, an effect comparable to that of niacin-ER. These data suggest that niacin-ER, but not gemfibrozil, significantly increased LP-AI particles, a cardioprotective subfraction of HDL in patients with a low HDL state.

To define the potential mechanisms of action of niacin and gemfibrozil to modulate HDL subfractions, we performed additional experiments with the use of Hep G2 cells as an in vitro model system. Previously, we have shown that niacin had no effect on apoA-I synthesis but selectively inhibited the uptake/removal of HDL–apoA-I, resulting in increased accumulation of apoA-I in Hep G2 cell culture media. As an extension of our previous study, in the present study, we proposed that the increase in LP-AI particles in niacin-ER–treated patients may be due to decreased hepatic removal/uptake of LP-AI particles. In support of this possibility, our data indicated that niacin significantly inhibited the uptake of radiolabeled LP-AI particles by Hep G2 cells. However, niacin had no significant effect on the uptake of LP-AI+All particles by Hep G2 cells. These data suggest that niacin, by selectively inhibiting the hepatic removal/uptake of LP-AI particles, may lead to the increased retention of LP-AI particles in the circulation. Our observation of greater CE uptake from LP-AI particles compared with LP-AI+All particles observed in niacin-ER–treated patients and may reflect limitations of in vitro studies to in vivo observations. Because LP-AI±All particles, used in uptake studies in Hep G2 cells, were isolated from normal human plasma (but not from individual patients treated with niacin-ER or gemfibrozil), the in vitro data reported do not provide information on the potential in vivo modification of LP-AI±All particles with respect to their uptake properties by hepatocytes in patients treated with niacin-ER or gemfibrozil. Because of inadequate availability of plasma samples from patients treated with niacin-ER and gemfibrozil to isolate large amounts of LP-AI and LP-AI+All particles required for uptake studies, we were unable to measure uptake of these HDL subfractions isolated from patients treated with either drug. This was beyond the scope of the present study protocol. Also, the in vivo catabolism of HDL is complex, and extrahepatic tissues (especially kidney) are significantly involved. However, their role in the catabolism of HDL subfractions is unknown and may also account for lack of a more complete correlation between in vitro and clinical measurements. Although these in vitro studies reported in the present study provide a novel approach for the mechanism of action of niacin to raise LP-AI particles, caution should be taken in direct extrapolation of these data to the in vivo observations in humans. Additional direct plasma kinetic studies with LP-AI and LP-AI+All particles in humans would be very much needed to address the synthetic or catabolic aspects of these particles in control and niacin-treated patients.

Although various regulatory processes involved in the catabolism of HDL–apoA-I or HDL-C are not clearly established, recent studies have indicated that the components of HDL (apoA-I and cholesterol) are taken up or transported by mainly 2 cellular proteins, including (1) cubilin and (2) scavenger receptor type B class I (SR-B1). Using yolk-sac endoderm-like cells, Hammad et al and Kozyraki et al identified cubilin (the recently described endocytic receptor
for intrinsic factor–vitamin B₁₂) as the receptor that mediates HDL holoparticle endocytosis. However, cubulin has not been reported to be present on liver cells. The SR-BI receptor was shown to bind HDL and to mediate the selective uptake or removal of HDL-CEs without the uptake/degradation of HDL–apoA-I. It has been proposed that the SR-BI receptor acts as a “docking” site so that CEAs can be removed after which the HDL particle (depleted of CEAs) “undocks” and recirculates to pick up more CEAs from peripheral tissues. However, there is no evidence that cubulin or SR-B1 is involved in plasma apoA-I metabolism. Hepatic lipase has been shown to play a major role in HDL catabolism by hydrolyzing TGs and phospholipids within HDL particles (see reviews40,41). Recently, Dugi et al42 examined the in vivo role of hepatic lipase in HDL metabolism by injecting recombinant adenovirus expressing hepatic lipase in hepatic lipase–deficient mice. These authors showed that the mice expressing hepatic lipase exhibited significant reductions in cholesterol, HDL-C, apoA-I, and apoA-II and showed enhanced plasma clearance of HDL–apoA-I, HDL–apoA-II, and HDL-CEs. It is conceivable that modulation of these HDL catabolic pathways may play an important role in regulating plasma levels of HDL particles.

Because hepatic lipase is associated with enhanced plasma clearance of HDL–apoA-I/A-II and reduction in HDL, it may be possible that the ability of niacin to decrease hepatic lipase43 may, at least in part, play a role in reduced hepatic removal/uptake of LP-AI particles. Because niacin had no effect on HDL-CE uptake25 and on LP-AI uptake26, we suggest that niacin may not modulate SR-B1-mediated uptake/removal of HDL-CEs. Unlike niacin, gemfibrozil did not inhibit LP-AI uptake by Hep G2 cells. Extrapolation of these in vitro data may, at least in part, explain the inability of gemfibrozil to affect LP-AI particle concentration in patients.

In summary, we have shown that niacin but not gemfibrozil selectively increased LP-AI particles in patients with low HDL. In vitro studies have indicated that niacin but not gemfibrozil significantly decreases the uptake of LP-AI particles by Hep G2 cells. These data suggest that unlike gemfibrozil, niacin by selective inhibition of hepatic LP-AI removal significantly elevates the HDL subtraction LP-AI concentration in patients with the isolated low HDL state. Elevated levels of LP-AI, in turn, may facilitate more efficient reverse CE transport via cholesterol efflux and its efficient removal via the SR-B1 receptor pathway. These data suggest an additional mechanism by which niacin exerts its beneficial effect on atherosclerotic cardiovascular disease.

Acknowledgments

The present study was supported, in part, by Kos Pharmaceuticals and the Long Beach Research Foundation. We thank Phillip D. Simmons for statistical analyses and Shobha H. Ganji for assistance in manuscript preparation.

References


Niacin, but Not Gemfibrozil, Selectively Increases LP-AI, a Cardioprotective Subfraction of HDL, in Patients With Low HDL Cholesterol

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doi: 10.1161/hq1001.096624
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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