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# Atorvastatin increases hepatic fatty acid beta-oxidation in sucrose-fed rats: comparison with an MTP inhibitor

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**Abstract**

We investigated the effects of atorvastatin, a widely used 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, and BMS-201038, a microsomal triglyceride transfer protein (MTP) inhibitor, in sucrose-fed hypertriglyceridemic rats to determine whether the activation of beta-oxidation by these compounds plays a role in their hypotriglyceridemic effect. The decrease in plasma triglyceride concentration and post-Triton very low-density lipoprotein (VLDL) triglyceride concentration, a measure of hepatic triglyceride secretion, by atorvastatin (30 mg/kg p.o.) for 2 weeks was to approximately the same degree as those by BMS-201038 (0.3 mg/kg). Atorvastatin (30 mg/kg) increased hepatic beta-oxidation activity by 54% ($P<0.01$), while BMS-201038 (0.3 mg/kg) had no significant effect. Atorvastatin decreased hepatic triglyceride, fatty acid and cholesteryl ester concentrations by 21% to 39%, whereas BMS-201038 increased these variables by 28% to 307%. In the atorvastatin-treated groups, a significant relationship was seen not only between hepatic beta-oxidation activity and hepatic triglyceride concentration ($R^2=0.535$, $P<0.01$), but also between hepatic and plasma triglyceride concentrations ($R^2=0.586$, $P<0.01$). No effect of atorvastatin on hepatic fatty acid synthesis was observed. These results indicate that the activation of hepatic beta-oxidation by atorvastatin may contribute to the decrease in hepatic triglyceride concentration, leading to its hypotriglyceridemic effect.


*Keywords:* Atorvastatin; BMS-201038; Beta-oxidation; Triglyceride; (Rat)

## 1. Introduction

Recent meta-analyses have demonstrated that the relative risk of coronary heart disease significantly increased with increasing plasma triglyceride concentration (Hokanson and Austin, 1996; Gordon and Rifkind, 1989). Fibric acid derivatives (fibrates) are the drugs of choice for controlling plasma triglycerides, but these may not sufficiently decrease cholesterol in patients with multiple risk factors for coronary heart disease. Combination therapy of a fibrate with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor is effective, owing to the latter's potent effect in decreasing plasma low-density lipoprotein (LDL) cholesterol. However, this combination is associated with an increased risk of myopathy (East et al., 1988).

Atorvastatin, a currently available HMG-CoA reductase inhibitor, has not only a potent LDL cholesterol-lowering effect, but also strong triglyceride-lowering activity (Jones et al., 1998; Stein et al., 2001). This drug also has a longer plasma half life than other inhibitors of this class, and studies in cells (Mohammadi et al., 1998; Funatsu et al., 2001), animals (Burnett et al., 1999) and humans (Bakker-Arkema et al., 1996) indicate that its prolonged inhibition of cholesterol synthesis decreases the hepatic cholesteryl ester pool, leading to a decrease in hepatic very low-density lipoproteins (VLDL) assembly. However, it is not clear why the inhibition of triglyceride secretion in the absence of any effect on hepatic triglyceride metabolism does not result in a compensatory accumulation of triglyceride in the liver.

Although it is generally thought that HMG-CoA reductase inhibitors do not directly inhibit hepatic triglyceride synthesis, our previous results indicated for the first time that repeated, but not single, administration of atorvastatin decreases hepatic triglyceride synthesis in rats, and that this inhibition is caused by the lowering of hepatic fatty acid concentration (Funatsu et al., 2002). Further, the HMG-CoA reductase inhibitors, namely lovastatin (Guzman et al.,

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1993) and NK-104 (Yamamoto et al., 1999), are reported to induce hepatic beta-oxidation in rats. Therefore, in addition to a decrease in hepatic VLDL assembly via cholesteryl ester reduction, HMG-CoA reductase inhibitors also inhibit hepatic triglyceride synthesis by increasing hepatic beta-oxidation activity.

Here, to investigate the relationship between hepatic beta-oxidation activity and plasma triglyceride concentration, we treated sucrose-fed rats, an animal model of endogenous hypertriglyceridemia, with atorvastatin. In addition, we evaluated the effect of BMS-201038, a mitochondrial triglyceride transfer protein (MTP) inhibitor which also decreases plasma triglyceride level, mainly via inhibition of hepatic triglyceride secretion.

## 2. Materials and methods

### 2.1. Materials

Enzymatic lipid assay kits (cholesterol C-test, free cholesterol C-test, NEFA C-test and triglyceride G-test Wako) were purchased from Wako (Osaka, Japan). Bovine serum albumin (BSA) and Triton WR-1339 were obtained from Sigma-Aldrich Japan (Tokyo, Japan). [1-$^{14}$C]Acetate (2.2 GBq/mmol) and [1-$^{14}$C]palmitic acid (2.1 GBq/mmol) were obtained from Amersham Pharmacia Biotech (Tokyo, Japan). [1-$^{14}$C]Palmitic acid was conjugated with 12% (w/v) BSA in saline at pH 7.4 in accordance with a previous report (Goldstein et al., 1983). A Bio-Rad DC Protein Assay Reagent Kit was purchased from Bio-Rad Laboratories Japan (Tokyo, Japan). Atorvastatin was provided by Pfizer Pharmaceuticals (Ann Arbor, MI). BMS-201038 was synthesized by Yamanouchi Pharmaceutical. All other chemicals were of reagent grade.

### 2.2. Animals

Five-week-old male Sprague–Dawley rats (Jcl: SD) were purchased from Clea Japan (Hamamatsu, Japan). The animals were housed in metal cages in a temperature- ($23 \pm 2$ °C) and light cycle-controlled colony room (lights on 0730–2030 h) and had free access to water and standard rat chow (CE-2, Clea Japan). Experiments were performed in accordance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical.

After matching for body weight, two or three groups of rats were maintained on standard rat chow (Normal group) or a synthesized high-sucrose diet during the experimental period (Sucrose-induced hypertriglyceridemic groups). The sucrose-enriched diet (Oriental Yeast, Tokyo, Japan) contained 18% casein, 68% sucrose, 8% cottonseed oil, 2% beer yeast, 4% salt, as well as a mix of vitamins, as described previously (Strobl et al., 1989). The control group received 0.5% carboxymethyl cellulose alone, while the hypotriglyceridemic compound (either atorvastatin or BMS-201038)-treated group was given the respective compound suspended in 0.5% carboxymethyl cellulose by daily oral gavage for 2 weeks.

### 2.3. Determination of triglyceride and apoB secretion rate

One hour after the last administration of drug, rats were anesthetized with ether and blood samples for lipid analysis were withdrawn from the fundus oculi using capillary tubes (Funakosi, Tokyo Japan). In vivo rates of hepatic triglyceride secretion were examined by the Triton WR-1339 method according to previously published methods (Baggade et al., 1976). VLDL [density ($d$) < 1.006 g/ml] from post-Triton plasma was isolated at a density of 1.006 g/ml at $145{,}000 \times g$ at 16 °C for 16 h after chylomicron isolation by centrifugation at $36{,}000 \times g$ at 16 °C for 30 min. Post-Triton VLDL triglyceride concentration was determined as an index of hepatic triglyceride secretion rate (Sato et al., 1991). Post-Triton VLDL apoB concentration was also determined by isopropanol method using Post-Triton plasma described previously (Yamada and Havel, 1986).

### 2.4. Determination of hepatic fatty acid beta-oxidation activity

One hour after the last administration of drug, rats were anesthetized with diethylether, and blood samples for lipid analysis were withdrawn from the abdominal vena cava, and the livers were then isolated. Fresh liver homogenate (100 μl; 40-mg liver) was incubated in a 24-well tissue culture plate under gentle shaking for 30 min at 37 °C with 900 μl of a substrate mixture consisting of oxygenated Krebs–Ringer phosphate buffer, pH 7.4, which contained 37 KBq [$^{14}$C]palmitic acid conjugated with 12% (w/v) BSA solution. To assay oxidation products, semi-dry filter paper (Advantec®, Toyo Roshi, Tokyo, Japan) saturated with 2 N NaOH was placed over the plate and tightly covered with a foam pad and the plate cover (Muoio et al., 1999). $^{14}CO_2$ produced by liver homogenate was driven from the media to the filter-paper trap by adding 100 μl of 70% (v/v) perchloric acid to each well. After 60 min in a shaking bath at 37 °C, the filter paper discs corresponding to each well were excised, and the radioactivity was counted in a liquid scintillation counter (2200CA, Packard, CT). Each incubation buffer in the wells was collected and centrifuged at 12,000 rpm for 10 min at 4 °C. Acid-soluble metabolites (ASM), a measure of ketone bodies in the liver, were assayed in supernatants of the acid precipitate. Beta-oxidation activity was expressed as the sum of the amount of $^{14}CO_2$ and ASM. Liver protein was solubilized using 1 N NaOH, diluted and quantified with a Protein Assay DC kit (Bio-Rad) using BSA as standard. The reaction was linear in the range of 10–80 mg tissue (around 2–16 mg protein) liver homogenate.

### 2.5. Determination of hepatic lipid concentrations

Liver homogenates were extracted by the method of Folch et al. (1957) using chloroform–methanol (2:1, v/v) as an extraction solvent. Lipids were solubilized with Triton X-100 solution, and hepatic triglyceride, total cholesterol, free cholesterol and nonesterified fatty acid concentrations were determined enzymatically as described previously (Carr et al., 1993). Cholesteryl ester mass was estimated by subtracting the free cholesterol mass from the total cholesterol mass. Plasma lipid concentrations were also determined by standard enzymatic procedures using commercially available kits.

### 2.6. Determination of hepatic fatty acid and cholesterol synthesis

One hour after the last administration of drug, rats received an intraperitoneal injection of [$^{14}$C]acetate (7.4 MBq/kg). One hour later, the animals were anesthetized with diethylether, the livers excised and 250-mg portions weighed and saponified in 15% KOH:95% ethanol for 1.5 h at 75 °C. Nonsaponified lipids were extracted twice with *n*-hexane. Cholesterol was separated by the digitonin precipitate method described previously from the organic phase (Carrella et al., 1999). For fatty acid separation, the aqueous phase was acidified with 12 N HCl and extracted with *n*-hexane (Fujioka et al., 1997), and the organic phase was then evaporated. Hepatic fatty acid and cholesterol synthesis activities were measured as the radioactivity in each fraction per amount of protein in the tissue.

### 2.7. Statistics

All results were analyzed using Statistical Analysis System ver. 6.11 (SAS Institute, NC). The two-tailed Student's *t*-test was used for comparing two means, while the Dunnett multiple range test was used when three or more groups were compared. Results are presented as the mean ± standard error of the mean (S.E.M.). Linear regression analysis was used to study the relationship between variables.

## 3. Results

### 3.1. Plasma triglyceride concentration and its secretion rate

Plasma triglyceride concentration in the sucrose control group increased to 2.4-fold ($P<0.01$) compared to that in the normal chow group (Fig. 1). Plasma triglyceride concentration was decreased in a dose-dependent manner by treatment with both atorvastatin (3 to 30 mg/kg) and BMS-201038 (0.03 to 0.3 mg/kg). VLDL triglyceride concentration after Triton WR-1339 injection (post-Triton VLDL triglyceride) as an index of hepatic triglyceride secretion rate

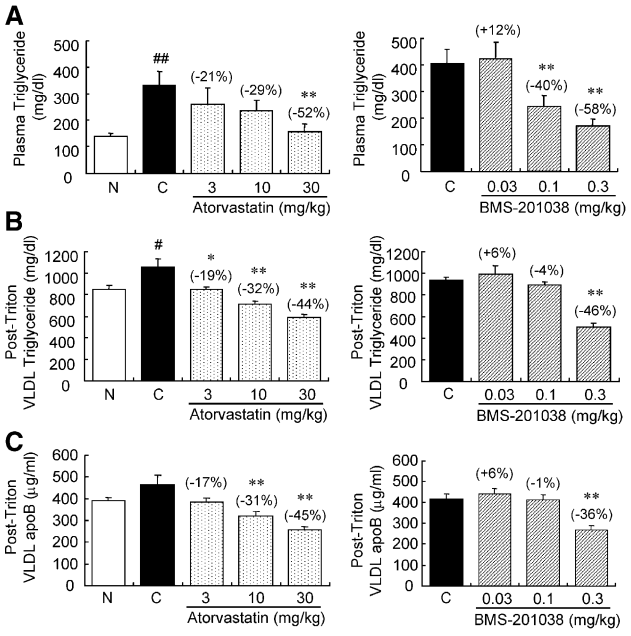


Fig. 1. Effect of atorvastatin and BMS-201038 on (A) plasma triglyceride, (B) post-Triton VLDL triglyceride and (C) post-Triton apoB concentrations in sucrose-fed rats. Rats were maintained for 2 weeks on a normal rat chow diet (N), sucrose-enriched diet alone (C) or with respective compounds. Post-Triton VLDL triglyceride and apoB concentrations were determined by the Triton WR-1339 method as described in Section 2. Results are expressed as the mean ± S.E.M. for six to eight animals. Figures in parentheses represent the percent change against respective control values. $^{\#}P<0.05$ and $^{\#\#}P<0.01$ vs. normal by Student's *t*-test. $*P<0.05$ and $**P<0.01$ vs. control by Dunnett's test.

was also increased by the sucrose diet (Fig. 1). Atorvastatin and BMS-201038 reduced the secretion rate. Further, atorvastatin and BMS-201038 lowered Post-Triton VLDL apoB concentration, indicating that the number of VLDL molecules secreted was reduced by both inhibitors. Although BMS-201038 had more potent hypotriglyceridemic effects than atorvastatin, the decreases in both plasma triglyceride and post-Triton VLDL triglyceride concentrations by atorvastatin (30 mg/kg) were approximately to the same degree as those by BMS-201038 (0.3 mg/kg).

### 3.2. Hepatic beta-oxidation activity

Ketone bodies and $CO_2$ were produced as beta-oxidation products from palmitic acid in the presence of rat liver homogenate. Ketone bodies in the ASM fraction routinely accounted for more than 95% of total oxidation products (<5% of the counts recovered as $CO_2$) (Table 1). Both the mass of $CO_2$ production and the formation of ketone bodies were significantly reduced in the sucrose-diet group compared to those in the normal group ($P<0.01$, Table 1). Atorvastatin (30 mg/kg) increased the production of oxidized metabolites by 42% to 55% ($P<0.01$), indicating the increment of hepatic beta-oxidation activity. However, BMS-201038 (0.3 mg/kg) administration did not affect this value compared with the control group.

Table 1
Effect of atorvastatin and BMS-201038 on hepatic beta-oxidation in sucrose-fed rats

| Treatment | Palmitic acid oxidation (pmol/mg protein) | | |
|---|---|---|---|
| | $CO_2$ production | ASM production | Total activity |
| Normal | 2.4 ± 0.2 | 87.0 ± 4.9 | 89.3 ± 5.1 |
| Control | 1.0 ± 0.1## | 46.4 ± 2.4## | 47.4 ± 2.4## |
| Atorvastatin | 1.4 ± 0.1** | 71.7 ± 5.3** | 73.1 ± 5.4** |
| 30 mg/kg | (+42%) | (+55%) | (+54%) |
| Control | 1.2 ± 0.1 | 58.1 ± 5.1 | 59.3 ± 5.2 |
| BMS-201038 | 1.1 ± 0.1 | 61.0 ± 4.8 | 62.1 ± 4.8 |
| 0.3 mg/kg | (−11%) | (+5%) | (+5%) |

Rats were maintained for 2 weeks on a normal rat chow diet (Normal), sucrose-enriched diet alone (Control) or with respective compounds. Hepatic beta-oxidation activity was determined as the amount of labeled $CO_2$ and acid soluble labeled metabolites (ASM) products from [$^{14}$C]palmitic acid. Results are expressed as the mean ± S.E.M. for five to six animals. Figures in parentheses represent the percent change against respective control values.

## $P<0.01$ vs. normal.

** $P<0.01$ vs. control by Student's *t*-test.

### 3.3. Hepatic lipid concentrations

As shown in Table 2, the sucrose diet increased hepatic triglyceride, fatty acid and cholesteryl ester concentrations, while it decreased hepatic free cholesterol concentration compared to values in the normal chow group. Atorvastatin (30 mg/kg) decreased hepatic triglyceride, fatty acid and cholesteryl ester concentrations by 37% ($P<0.05$), 21% ($P<0.01$) and 39% ($P<0.05$), respectively, compared with control group values. In contrast, BMS-20103 (0.3 mg/kg) resulted in marked increases in these hepatic lipid concentrations. In particular, hepatic triglyceride and cholesteryl ester concentrations in the BMS-201038-treated group were increased by 307% ($P<0.01$) and 144% ($P<0.01$), respectively, compared with the control group.

Table 2
Effect of atorvastatin and BMS-201038 on hepatic lipid concentrations in sucrose-fed rats

| Treatment | Hepatic lipid concentration | | | |
|---|---|---|---|---|
| | Triglyceride (mg/g tissue) | Fatty acid (μEq/g tissue) | Free cholesterol (mg/g tissue) | Cholesteryl ester (mg/g tissue) |
| Normal | 6.6 ± 0.7 | 4.8 ± 0.3 | 2.2 ± 0.1 | 0.7 ± 0.1 |
| Control | 16.9 ± 1.4## | 6.0 ± 0.3# | 2.0 ± 0.0## | 1.3 ± 0.1## |
| Atorvastatin | 10.7 ± 1.4* | 4.8 ± 0.3** | 2.0 ± 0.0 | 0.8 ± 0.1* |
| 30 mg/kg | (−37%) | (−21%) | (0%) | (−39%) |
| Control | 15.8 ± 1.2 | 6.5 ± 0.3 | 2.0 ± 0.0 | 1.1 ± 0.1 |
| BMS-201038 | 64.2 ± 4.3** | 8.3 ± 0.3** | 2.1 ± 0.2 | 2.6 ± 0.1** |
| 0.3 mg/kg | (+307%) | (+28%) | (+5%) | (+144%) |

Rats were maintained for 2 weeks on a normal rat chow diet (Normal), sucrose-enriched diet alone (Control) or with respective compounds. Results are expressed as the mean ± S.E.M. for six animals. Figures in parentheses represent the percent change against respective control values.

# $P<0.05$ vs. normal.

## $P<0.01$ vs. normal.

* $P<0.05$ vs. control.

** $P<0.01$ vs. control by Student's *t*-test.

### 3.4. Hepatic fatty acid and cholesterol synthesis

Hepatic fatty acid synthesis activity in the sucrose control group increased 2.5-fold ($P<0.01$) as compared with that in the normal chow group (Fig. 2). No effect of atorvastatin on hepatic fatty acid synthesis was seen. In contrast, atorvastatin strongly lowered hepatic cholesterol synthesis by 70% ($P<0.01$) compared to the control group.

### 3.5. Relationship between hepatic beta-oxidation activity and plasma triglyceride concentration

To assess whether hepatic beta-oxidation activity plays any role in the reduction in plasma triglyceride concentration, the overall relationships between hepatic beta-oxidation activity and hepatic and plasma triglyceride concentrations were tested. As shown in Fig. 3, there was a significant inverse relationship between hepatic beta-oxidation activity and hepatic triglyceride concentration in atorvastatin-treated rats ($R^2$=0.535, $P<0.01$). Hepatic triglyceride and plasma triglyceride concentrations also correlated well with each other ($R^2$ = 0.586, $P<0.01$), indicating that increased hepatic beta-oxidation is associated with a decrease in both plasma and hepatic triglyceride concentration. In contrast, there was no relationship between hepatic beta-oxidation activity and

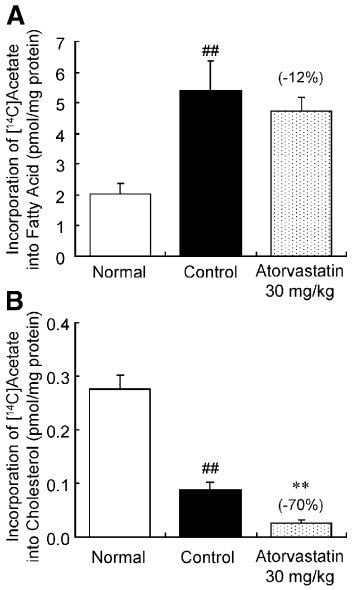


Fig. 2. Effect of atorvastatin on hepatic (A) fatty acid and (B) cholesterol synthesis from exogenous [$^{14}$C]acetate in sucrose-fed rats. Rats were maintained for 2 weeks on a normal rat chow diet (Normal), sucrose-enriched diet alone (Control) or with atorvastatin. Results are expressed as the mean ± S.E.M. for six animals. Figures in parentheses represent the percent change against respective control values. ## $P<0.01$ vs. normal and ** $P<0.01$ vs. control by Student's *t*-test.

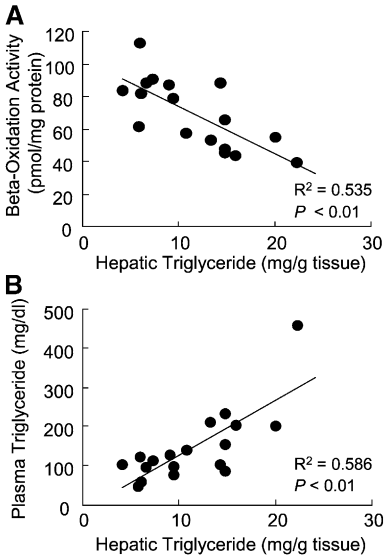


Fig. 3. Correlation between hepatic triglyceride concentration and (A) hepatic beta-oxidation or (B) plasma triglyceride concentration in atorvastatin-treated rats. The data from Tables 1 and 2 were integrated. (A) Palmitic acid oxidation activity versus hepatic triglyceride concentration in sucrose-fed rats ($R^2 = 0.535$, $P < 0.01$). (B) Hepatic triglyceride versus plasma triglyceride concentration in sucrose-fed rats ($R^2 = 0.586$, $P < 0.01$).

hepatic triglyceride concentration in BMS-201038-treated rats ($R^2 = 0.058$, data not shown).

## 4. Discussion

Our findings indicate that atorvastatin increases hepatic beta-oxidation, which in turn reduces hepatic triglyceride concentration, inhibits hepatic triglyceride secretion and lowers plasma triglyceride concentration in sucrose-fed rats. In addition, our data suggest that inhibition of hepatic triglyceride secretion by MTP inhibition by BMS-201038 does not affect hepatic beta-oxidation, and causes a compensatory increase in hepatic triglyceride concentration.

Two indirect mechanisms have been suggested to explain the reduction in plasma triglyceride level with atorvastatin. First, its marked inhibition of cholesterol synthesis suppresses the assembly and secretion of hepatic VLDL secretion (Mohammadi et al., 1998). Second, increased hepatic LDL receptor by atorvastatin leads to increased clearance not only of plasma LDL but also of VLDL remnant particles, resulting in the reduction of both cholesterol and triglyceride levels (Aguilar-Salinas et al., 1998). In addition to these mechanisms, our previous study indicated that reduced levels of hepatic fatty acids caused by long-term treatment with atorvastatin seems to be responsible for reduced hepatic triglyceride synthesis and triglyceride secretion (Funatsu et al., 2002). In the present study, it was shown that beta-oxidation activity of the liver in atorvastatin-treated rats was significantly increased (Table 1), but no effect on hepatic fatty acid synthesis was observed (Fig. 2) in hypertriglyceridemic rats. Furthermore, the increase of hepatic beta-oxidation was inversely associated with the reduction of hepatic triglyceride concentration (Fig. 3). Hepatic triglyceride and plasma triglyceride concentration also correlated to each other. These observations indicate that there is a reciprocal relationship between hepatic beta-oxidation and both hepatic and plasma triglyceride concentrations. Likewise, in the liver perfusion experiments of Ide and Ontko (1981), both the hepatic triglyceride concentration and the triglyceride secretion rate were increased when the hepatic beta-oxidation was blocked with 2-tetradecylglycidate, thereby indicating that the activity of fatty acid oxidation in the liver is a key determinant of the amount of triglyceride-rich VLDL production.

Our results are consistent with studies in which other HMG-CoA reductase inhibitors, namely lovastatin (Guzman et al., 1993) and NK-104 (Yamamoto et al., 1999), also exhibited an increase in fatty acid oxidation in rat liver, via carnitine palmitoyltransferase I activation. It has also been reported that HMG-CoA reductase inhibitors stimulate peroxisome proliferator-activated receptor alpha (PPARα) activity by inhibiting the mevalonate pathway (Martin et al., 2001), which is considered to activate beta-oxidation (Latruffe et al., 2000). On the basis of these data, the activation of hepatic beta-oxidation by HMG-CoA reductase inhibitors may contribute to the decrease in hepatic triglyceride concentration, leading to a hypotriglyceridemic effect.

We also evaluated the effect of another type of hypotriglyceridemic compound, BMS-201038, a potent MTP inhibitor (Wetterau et al., 1998). MTP activity has been found only in the liver and intestine, where it seems to play an important role in triglyceride-rich lipoprotein secretion from these tissues (Wetterau and Zilversmit, 1986). Consistent with their previous results in normal rats, BMS-201038 potently lowered plasma triglyceride concentration and reduced hepatic triglyceride secretion (Fig. 1). The decreases in these variables by BMS-201038 (0.3 mg/kg) were similar to those observed with atorvastatin (30 mg/kg). Since we wanted to know whether atorvastatin has the same characteristics in its effect on hepatic triglyceride metabolism when the inhibitory activity of atorvastatin on hepatic triglyceride secretion was adjusted to that of BMS-201038, BMS-201038 was evaluated at 0.3 mg/kg in subsequent studies relating to hepatic triglyceride metabolism.

Interestingly, the effects of atorvastatin and BMS-201038 on hepatic lipid concentration were greatly different even when their inhibitory effects on hepatic triglyceride secretion were comparable. BMS-201038 increased hepatic triglyceride and cholesteryl ester concentrations of 307% and 144%, respectively (Table 2). No incremental effect of BMS-201038 on hepatic beta-oxidation was observed (Table 1). These accumulations of hepatic neutral lipids by BMS-201038 seem to result from the same mechanism as that of its hypotriglyceridemic effect, that is, MTP inhib-

ition, as has been reported in patients with abetalipoproteinemia (Gregg and Wetterau, 1994). These results also support our hypothesis that the decrease in hepatic triglyceride synthesis by atorvastatin leads to a decrease in hepatic triglyceride secretion without hepatic triglyceride accumulation, as indicated in our previous study (Funatsu et al., 2002). In contrast, BMS-201038 does not seem to have any effect on hepatic triglyceride metabolism, which may cause the accumulation of triglyceride in the liver.

It is known that there are significant differences between rat and human hepatocyte cultures in response to peroxisome proliferators (Chance et al., 1995). Agius et al. (1991) found that palmitate beta-oxidation was 50% less in human hepatocyte cultures than in those of rat hepatocytes. From these findings, it should be pointed out that the beta-oxidation pathway may be somewhat minor, and that the cholesterol ester pathway (Mohammadi et al., 1998) may contribute more to a decrease in hepatic VLDL secretion in humans. However, further studies are needed to clarify the relative partitioning of these two pathways.

In conclusion, we have demonstrated that atorvastatin (30 mg/kg) significantly enhanced hepatic beta-oxidation activity in sucrose-fed hypertriglyceridemic rats whereas the MTP inhibitor BMS-201038 (0.3 mg/kg), which inhibited hepatic triglyceride secretion to a comparable degree to atorvastatin, had no significant effect. We have also shown that atorvastatin decreased hepatic triglyceride, fatty acid and cholesteryl ester concentrations in these rats, whereas BMS-201038 increased these variables significantly. In the atorvastatin-treated groups, there was a significant inverse relationship between hepatic beta-oxidation activity and hepatic triglyceride concentration ($P < 0.01$). These results suggest that activation of hepatic beta-oxidation by atorvastatin may contribute to a decrease in hepatic triglyceride concentration, and thus be responsible for its hypotriglyceridemic effect.

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