

YM-53601, a novel squalene synthase inhibitor, suppresses lipogenic biosynthesis and lipid secretion in rodents

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1 To better understand how it decreases plasma cholesterol and triglyceride levels, we evaluated the effect of (E)-2-[2-fluoro-2-(quinuclidin-3-ylidene)ethoxy]-9H-carbazole monohydrochloride (YM-53601) on lipogenic biosynthesis in the liver and lipid secretion from the liver in rats and hamsters.

2 Single administration of YM-53601 in cholestyramine-treated rats inhibited triglyceride and free fatty acid (FFA) biosynthesis at a similar dose range to that at which it inhibited cholesterol biosynthesis. YM-53601 inhibited both triglyceride and FFA biosynthesis in hamsters treated with cholestyramine.

3 YM-53601 by single oral administration decreased the enhanced plasma triglyceride levels in hamsters induced by an injection of protamine sulfate, which inhibits lipoprotein lipase (LPL) and consequently increases plasma very low-density lipoprotein (VLDL) triglyceride levels. YM-53601 also decreased the enhanced plasma triglyceride and cholesterol levels in hamsters treated with Triton WR1339, which also inhibits the degradation of VLDL. Plasma cholesterol was significantly decreased as soon as 1 h after single administration of YM-53601 in hamsters fed a normal diet.

4 This is the first report that a squalene synthase inhibitor suppresses lipogenic biosynthesis in the liver and cholesterol and triglyceride secretion from the liver *in vivo*. We therefore suggest that the mechanism by which YM-53601 decreases plasma triglyceride might include these effects. The finding that YM-53601 rapidly decreased plasma cholesterol suggests that this compound may be effective in decreasing plasma cholesterol levels early in the course of treatment of hypercholesterolemia in humans.

British Journal of Pharmacology (2003) **139**, 140–146. doi:10.1038/sj.bjp.0705229

Keywords: YM-53601; squalene synthase; cholesterol; triglyceride; Triton WR1339; protamine sulfate; biosynthesis; secretion; lipogenesis

Abbreviations: FFA, free fatty acid; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LPL, lipoprotein lipase; MTP, microsomal triglyceride transfer protein; PPAR, peroxisome proliferator-activated receptor; VLDL, very low-density lipoprotein

Introduction

In addition to plasma LDL cholesterol, hypertriglyceridaemia is increasingly recognized as an independent risk factor for coronary heart disease (Cullen, 2000). Plasma cholesterol and triglyceride levels are maintained by a balance between lipid biosynthesis in the liver, uptake into the liver, secretion and excretion from the liver, absorption from the small intestine and catabolism in the blood. Some inhibitors of squalene synthase (farnesyl-diphosphate: farnesyl-diphosphate farnesyl transferase, EC 2.5.1.21), an enzyme vital to cholesterol biosynthesis, decrease not only plasma cholesterol but also triglyceride levels in several animal species (Amin *et al.*, 1997; Ugawa *et al.*, 2000; Hiyoshi *et al.*, 2001), a characteristic they share with fibrates, which reduce plasma triglyceride in hyperlipidemia by stimulating peroxisome proliferator-activated receptor (PPAR) α (Monk & Todd, 1987). One of the mechanisms by which stimulation of PPAR α reduces plasma triglyceride is the inhibition of fatty acid and

triglyceride biosynthesis in the liver (Kloer, 1987; Kritchevsky *et al.*, 1979).

(E)-2-[2-fluoro-2-(quinuclidin-3-ylidene)ethoxy]-9H-carbazole monohydrochloride (YM-53601) may belong to a novel class of lipid-lowering agents that inhibit squalene synthase, and thereby lead to reduced cholesterol biosynthesis in animals. In preclinical studies in rodents and rhesus monkeys, YM-53601 significantly decreased the plasma concentration of cholesterol and had a more potent triglyceride-lowering effect than a fibrate (Ugawa *et al.*, 2000), and enhanced the clearance of very low-density lipoprotein (VLDL) (Ugawa *et al.*, 2002). Meanwhile, ER-27856, a squalene synthase inhibitor, suppressed triglyceride biosynthesis in hepatocytes isolated from homozygous Watanabe heritable hyperlipidemic (WHHL) rabbits *in vitro* (Hiyoshi *et al.*, 2001). In the present study, we investigated the effect of YM-53601 on lipogenic biosynthesis *in vivo* on free fatty acid (FFA) and triglyceride biosynthesis.

Microsomal triglyceride transfer protein (MTP), which is critical to the assembly and secretion of VLDL in the liver and

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chylomicrons in the intestine (Gregg & Wetterau, 1994), plays an important role in regulating plasma triglyceride. MTP inhibitors are known well to inhibit the secretion of cholesterol and triglyceride, leading to a decrease in plasma cholesterol and triglyceride in preclinical study (Wetterau *et al.*, 1998; Shiomi & Ito, 2001). In the present report, we evaluated the effect of YM-53601 on the secretion of cholesterol and triglyceride from the liver to clarify the mechanism by which it reduces plasma cholesterol and triglyceride. Moreover, as an MTP inhibitor showed a rapid decrease in plasma cholesterol in humans (Wilder *et al.*, 2001), we also evaluated plasma cholesterol changes after a single administration of YM-53601 in hamsters fed a normal diet.

Methods

Materials

YM-53601 was synthesized at the Chemistry Laboratories, Yamanouchi Pharmaceutical Co., Ltd (Tokyo, Japan). Cholestyramine resin and protamine sulfate were obtained from Sigma (St Louis, MO, U.S.A.). Triton WR1339 was purchased from Nacalai Tesque (Kyoto, Japan). [^{14}C] acetate (55 mCi mmol^{-1}) was obtained from American Radiolabelled Chemicals Inc (MO, U.S.A.). Aquasol-2 scintillation fluid was purchased from Packard (Groningen, The Netherlands).

Cholesterol, triglyceride and FFA biosynthesis in rats and hamsters

Male Sprague–Dawley (SD) rats, 4 weeks old, (from SLC, Shizuoka, Japan) and 5-week-old male Syrian golden hamsters (from Hamri, Ibaraki, Japan) were fed a standard rodent diet (CE-2; CLEA Japan Inc., Tokyo, Japan) (Ugawa *et al.*, 2000) including 2.5 and 5% cholestyramine resin for 5 days, respectively, to increase hepatic cholesterol biosynthesis (Amin *et al.*, 1997). YM-53601 was suspended in 0.5% methylcellulose. Rats and hamsters were given a single oral administration of YM-53601 at the concentration of 50 mg kg^{-1} , followed 1 h later by intraperitoneal injection of [^{14}C] acetate ($40.5\text{ }\mu\text{Ci}$ per animal). The rats and the hamsters were anaesthetized with diethyl ether and killed 1 h after the [^{14}C] acetate injection. Cholesterol biosynthesis was assayed as previously described (Tsujita *et al.*, 1986). A volume of 1 ml of plasma and 0.5 g portions of livers were saponified in 15% (w v^{-1}) KOH in ethanol at 75°C for 2 h. Nonsaponified lipids were extracted three times with petroleum ether. Cholesterol was separated by the digitonin precipitate method as described by Carrella *et al.* (1999). Determination of FFA biosynthesis was assayed using the technique of Hasumi *et al.* (1985). Briefly, residue after the above petroleum ether extraction was acidified by adding 1 N HCl and then extracted three times with petroleum ether. The resultant extract was dried and counted. Triglyceride biosynthesis was assayed as previously described (Funatsu *et al.*, 2002a). A measure of 0.2 ml of the plasma and 0.1 g portions of the livers were extracted in chloroform–methanol (2:1), and the solvent evaporated using a centrifugal evaporator (ECD92D-2, Sakuma Seisakusho, Tokyo, Japan). Triglyceride was separated on thin layer chromatography in petroleum ether:diethylether:acetate (80:20:1). Cholesterol, FFA and triglyceride synthesized from [^{14}C] acetate were counted in

Aquasol-2 using a Beckman liquid scintillation counter. The experiment in the plasma of hamsters was performed by the same method as that in the plasma of rats.

Cholesterol and triglyceride secretion in hamsters

Male Syrian golden hamsters weighing approximately 150 g were fed a standard rodent diet, CE-2. YM-53601 was suspended in 0.5% methylcellulose. The hamsters were given a single oral administration of YM-53601 at the concentration of 30 mg kg^{-1} , followed 5 min later by intravenous injection of Triton WR1339 (400 mg kg^{-1}) into the brachial vein. The hamsters were anaesthetized with diethyl ether and killed 2 h after treatment with Triton WR1339. The evaluation of cholesterol and triglyceride secretion using protamine sulfate was performed as previously described (Tsutsumi *et al.*, 1993). Briefly, protamine sulfate at the concentration of 25 mg kg^{-1} was intravenously administered to hamsters *via* the brachial vein. After 5 min, YM-53601 was administered at the concentration of 50 mg kg^{-1} and, 2 h later, blood was drawn to measure plasma total cholesterol and triglyceride. Plasma total cholesterol and triglyceride were measured enzymatically using a Cholesterol-C Test Wako and Triglyceride-G Test Wako (from Wako Pure Chemical Industries, Ltd, Osaka, Japan), respectively.

Plasma cholesterol lowering effect in hamsters

Male Syrian golden hamsters (Hamri, Ibaraki, Japan) weighing 140–170 g were fed a standard diet, CE-2. YM-53601 was suspended in 0.5% methylcellulose and given to hamsters in a single oral dose of 50 mg kg^{-1} . The control group was administered an equal volume of the 0.5% methylcellulose vehicle solution. Blood specimens were obtained from the femoral vein using a glass capillary at 0, 1, 2, 4 and 6 h after administration. Plasma total cholesterol was measured enzymatically as described above.

Statistical analysis

Results are presented as the mean \pm s.e.m. The effect of YM-53601 was evaluated by two-way repeated analysis of variance (ANOVA) using the Statistical Analysis System (SAS) (Figure 5). When a significant change was noted, the effect of YM-53601 was analyzed using Student's *t*-test in comparison with control animals for each hour. In other experiments, the effect of YM-53601 was analyzed using Student's *t*-test. $P < 0.05$ was considered to be significant.

Ethical considerations

All experiments were performed in accordance with the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical.

Results

YM-53601 inhibited *in vivo* FFA and triglyceride biosynthesis

To increase cholesterol biosynthesis activity, rats were treated with 2.5% cholestyramine in the diet for 5 days. They were

then given a single p.o. administration of YM-53601 at doses of 30 and 100 mg kg⁻¹ followed 1 h later by i.p. injection of [¹⁴C] acetate. Results showed that YM-53601 inhibited cholesterol biosynthesis from acetate in a dose-dependent manner in the plasma of rats (Figure 1a). This result was similar to that in rats fed a standard rodent diet (Ugawa *et al.*, 2000). At the same time, YM-53601 inhibited both FFA and triglyceride biosynthesis in rats treated with cholestyramine over the same dose range at which it inhibited cholesterol biosynthesis (Figure 1b, c). YM-53601 showed similar effects on the biosynthesis of cholesterol, FFA and triglyceride in the livers of rats (Figure 2).

To examine the effect of YM-53601 on the biosynthesis of FFA and triglyceride in hamsters, where it shows a decreasing effect on both plasma cholesterol and triglyceride, hamsters were treated with 5% cholestyramine in the diet for 5 days.

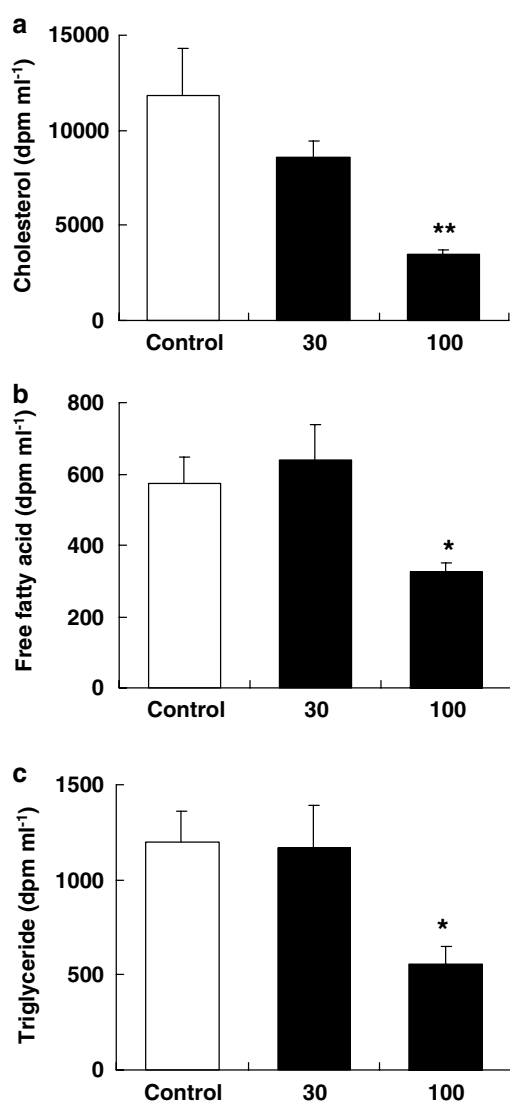


Figure 1 *In vivo* inhibition of *de novo* cholesterol, FFA and triglyceride biosynthesis from acetate by YM-53601 in the plasma of rats. Synthesized [¹⁴C] cholesterol (a), FFA (b) and triglyceride (c) were measured. See Methods section for details. Statistical analysis *versus* control was carried out using Dunnett's multiple comparison test. **P* < 0.05, ***P* < 0.01, *versus* control. Each value represents the mean ± s.e.m. of data obtained in four or five animals.

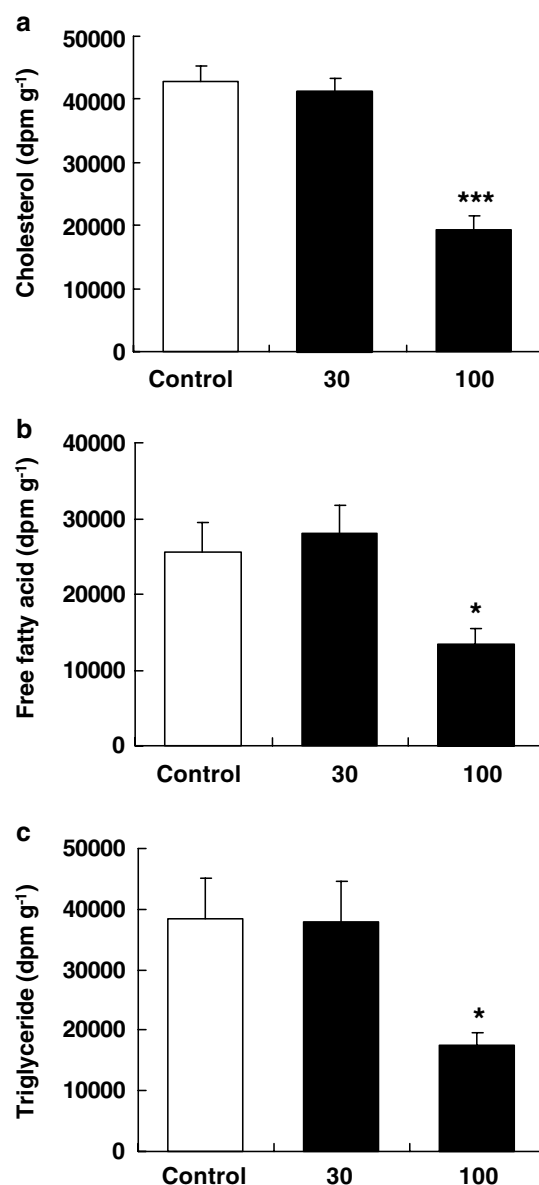


Figure 2 *In vivo* inhibition of *de novo* cholesterol, FFA and triglyceride biosynthesis from acetate by YM-53601 in the liver of rats. Synthesized [¹⁴C]-cholesterol (a), FFA (b) and triglyceride (c) were measured. See Methods section for details. Statistical analysis *versus* control was carried out using Dunnett's multiple comparison test. **P* < 0.05, ****P* < 0.001 *versus* control. Each value represents the mean ± s.e.m. of data obtained in four or five animals.

They were then given a single p.o. administration of YM-53601 at a dose of 50 mg kg⁻¹ followed 1 h later by i.p. injection of [¹⁴C] acetate. Similar to the results in rats, YM-53601 inhibited the biosynthesis of not only cholesterol but also both FFA and triglyceride in the plasma of hamsters treated with cholestyramine by 94 and 64%, respectively (Table 1).

YM-53601 inhibited the secretion of cholesterol and triglyceride from the liver

To evaluate the effect of YM-53601 on the secretion of cholesterol and triglyceride from the liver, an important

Table 1 Effect of YM-53601 on cholesterol, free fatty acid and triglyceride biosynthesis in hamsters

YM-53601 (mg kg ⁻¹)	Cholesterol (mg kg ⁻¹)	Free fatty acid (dpm ml ⁻¹)	Triglyceride (mg kg ⁻¹)
0	1750 ± 145	4956 ± 1297	11083 ± 2628
50	1249 ± 128*	274 ± 28*	4010 ± 492*

Data are represented as mean ± s.e.m. (*n* = 4 or 5). Synthesized [¹⁴C] cholesterol, free fatty acid and triglyceride were measured. See Methods section for details. Statistical analysis *versus* control was carried out using Student's *t*-test. **P* < 0.05 *versus* control.

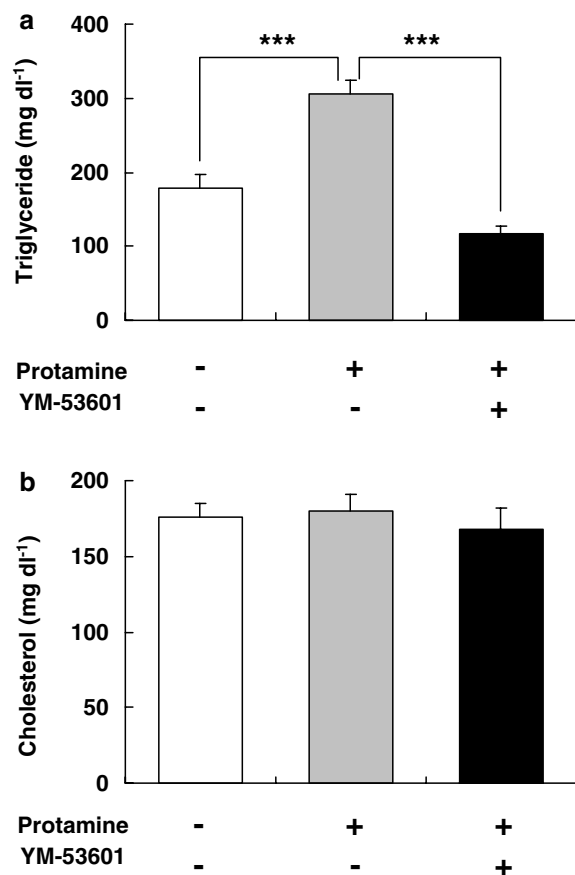


Figure 3 Effect of YM-53601 on plasma triglyceride and cholesterol in hamsters treated with protamine sulfate. Plasma triglyceride (a) and cholesterol (b) were measured in hamsters treated with protamine sulfate (25 mg kg⁻¹), YM-53601 (50 mg kg⁻¹) or both. See Methods section for details. Statistical analysis was carried out using Student's *t*-test. ****P* < 0.001 between each treatment. Each value represents the mean ± s.e.m. of data obtained in six animals.

pathway in the regulation of plasma cholesterol and triglyceride, a hamster model involving treatment with Triton WR1339 or protamine sulfate was used, in which plasma VLDL degradation through the lipoprotein lipase (LPL) pathway is inhibited, resulting in an increase in VLDL level. The validity of this model for this purpose has been established (Tsutsumi *et al.*, 1993; Lefebvre *et al.*, 1997). Figure 3a shows that intravenous protamine sulfate at the concentration of 25 mg kg⁻¹ resulted in a significant 1.7-fold increase in plasma triglyceride level in hamsters. Single oral administration of

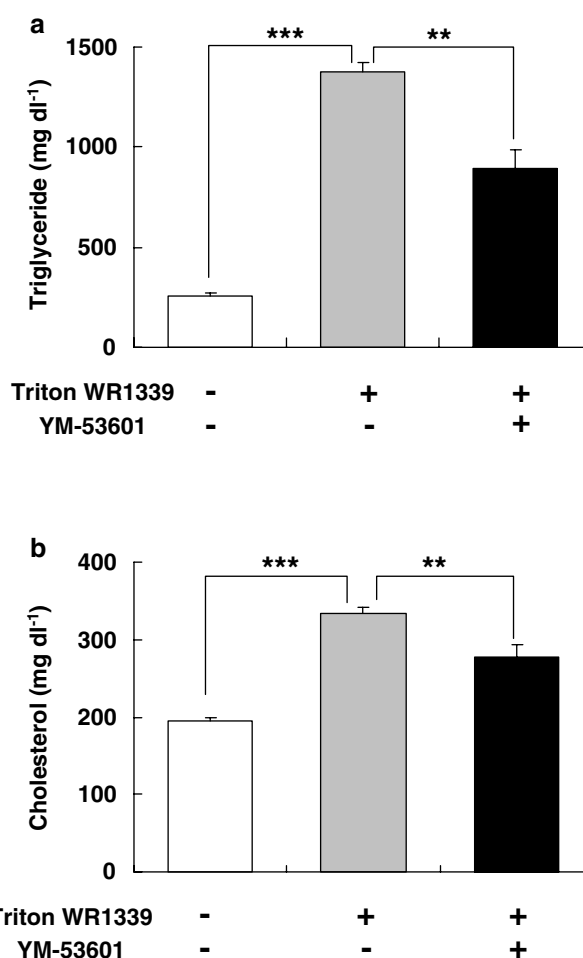


Figure 4 Effect of YM-53601 on plasma triglyceride and cholesterol in hamsters treated with Triton WR1339. Plasma triglyceride (a) and cholesterol (b) were measured in hamsters treated with Triton WR1339 (400 mg kg⁻¹), YM-53601 (30 mg kg⁻¹) or both. See Methods section for details. Statistical analysis was carried out using Student's *t*-test. ***P* < 0.01, ****P* < 0.001 between each treatment. Each value represents the mean ± s.e.m. of data obtained in six animals.

YM-53601 significantly decreased this elevated triglyceride level by 62%. On the other hand, protamine sulfate did not affect the plasma cholesterol level and YM-53601 showed no effect on this variable in hamsters (Figure 3b). In Figure 4a and b, hamsters were given a single p.o. treatment with YM-53601 at a dose of 30 mg kg⁻¹ followed 5 min later by intravenous injection of Triton WR1339 at the concentration of 400 mg kg⁻¹. Plasma triglyceride in hamsters was significantly increased 5.4-fold by 2-h treatment with Triton WR1339 (nontreated with Triton WR1339: 257 ± 17 mg dl⁻¹; treated with Triton WR1339: 1375 ± 49 mg dl⁻¹). Prior administration of YM-53601 at 30 mg kg⁻¹ significantly decreased plasma triglyceride by 35% in hamsters treated with Triton WR1339 (Figure 4a). Meanwhile, plasma cholesterol was also significantly increased 1.7-fold on intravenous injection of Triton WR1339 at 400 mg kg⁻¹ (nontreated with Triton WR1339: 195 ± 5 mg dl⁻¹; treated with Triton WR1339: 334 ± 8 mg dl⁻¹). Prior administration of YM-53601 at 30 mg kg⁻¹ significantly decreased plasma cholesterol by 17% in hamsters treated with Triton WR1339 (Figure 4b).

YM-53601 reduced plasma cholesterol on single administration

As described above, YM-53601 showed an effect on cholesterol biosynthesis in the liver and secretion from the liver on single administration. To confirm the plasma cholesterol-lowering efficacy of YM-53601 on single administration, plasma cholesterol levels were evaluated after single oral administration. Figure 5 shows that single oral administration at a dose of 50 mg kg^{-1} significantly decreased plasma cholesterol by 26% compared to the control group as early as 1 h after administration. This cholesterol-lowering effect gradually but significantly increased until 6 h after single administration by 22, 41 and 49% at 2, 4 and 6 h, respectively, compared to the control group. (Figure 5).

Discussion

This study aimed to evaluate the mechanism by which the squalene synthase inhibitor YM-53601 decreases plasma cholesterol and triglyceride. YM-53601 may belong to a novel class of lipid-lowering agents which inhibit squalene synthase activity, leading to reduced cholesterol biosynthesis in animals. Preclinical studies in rats, guinea pigs, hamsters and rhesus monkeys demonstrated that YM-53601 significantly reduces plasma concentrations of nonHDL cholesterol. These previous results also demonstrated that YM-53601 has a potent triglyceride-lowering effect (Ugawa *et al.*, 2000). It is well known that plasma cholesterol and triglyceride levels are maintained by a balance between lipid biosynthesis in the liver, uptake into the liver, secretion and excretion from the liver, absorption from the small intestine and catabolism in the blood. In the present study, we focused on the effect of YM-53601 on FFA and triglyceride biosynthesis, and on cholesterol and triglyceride secretion in rodents.

We demonstrated that YM-53601 showed inhibitory effects on lipid biosynthesis in the liver and plasma of rats, and that

these effects were similar in both character and degree. In a previous report, a decrease in sterol synthesis and acceleration of fatty acid synthesis was observed in the serum of rats treated with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (Endo *et al.*, 1977), which reduces VLDL secretion in Japanese White rabbits (Miyazaki & Koga, 2002); further, these effects were similar to those seen using liver samples (Endo *et al.*, 1977). We therefore conclude that YM-53601 inhibited hepatic lipid biosynthesis in hamsters. It has been shown that ER-27856, a squalene synthase inhibitor, suppresses triglyceride biosynthesis in hepatocytes isolated from homozygous WHHL rabbits *in vitro* (Hiyoshi *et al.*, 2001). In the present study, YM-53601 inhibited biosynthesis of FFA and triglyceride *in vivo* in the same concentration range as that at which it inhibited cholesterol biosynthesis. Fibrates, which stimulate PPAR alpha, reduce plasma triglyceride in hyperlipidemia. They are well known to suppress biosynthesis of FFA and triglyceride, leading to a subsequent decrease in plasma triglyceride level (Kritchevsky *et al.*, 1979; Kloer, 1987). Further, a significant correlation between hepatic triglyceride biosynthesis and plasma triglyceride concentration has been shown (Funatsu *et al.*, 2002a). These findings suggest that the decrease in plasma triglyceride by YM-53601 may result from inhibition of FFA and triglyceride biosynthesis. Inhibition of triglyceride biosynthesis has been demonstrated by two different agents, YM-53601 and ER-27856, which have different core structures. This indicates that inhibition of FFA and triglyceride might be an effect common to squalene synthase inhibitors. In fact, another novel squalene synthase inhibitor, RPR 107393, decreased plasma triglyceride in rats and marmosets (Amin *et al.*, 1997). The mechanism by which FFA and triglyceride biosynthesis is inhibited, however, is not precisely known.

Most plasma triglyceride occurs as VLDL and chylomicron particles in circulating blood. The former derives from the liver and the latter from lymph vessels through the intestine. Triton WR1339 acts on VLDL particles such that the degradation of particles is inhibited, leading to an increase in plasma triglyceride and cholesterol levels (Millar *et al.*, 2002). In contrast, protamine sulfate acts on LPL directly to inhibit its activity, which in turn enhances plasma triglyceride levels but has no effect on plasma cholesterol level (Tsutsumi *et al.*, 1993; Kaye & Galton, 1975). Both the Triton WR1339 and protamine sulfate treatment models are known to be suitable for evaluating the effects of drugs on VLDL secretion from the liver. YM-53601 effectively inhibited triglyceride secretion of VLDL from the liver in both. One mechanism by which YM-53601 reduces plasma triglyceride might therefore derive from inhibition of VLDL secretion from the liver. YM-53601 also decreased plasma cholesterol in hamsters treated with Triton WR1339. As VLDL includes not only triglyceride but also cholesterol, the decrease in VLDL particle degradation by Triton WR1339 induced an increase in cholesterol. Inhibition of cholesterol secretion from the liver by YM-53601 may have resulted from the inhibition of triglyceride biosynthesis followed by a decrease in triglyceride secretion. Thus, the decrease in the amount of triglyceride in the liver as a result of inhibition of triglyceride biosynthesis may have reduced the quantity of VLDL particles secreted from the liver. Another possibility is that the triglyceride and cholesterol content in VLDL particles may be reduced as a result of inhibition of their biosynthesis by YM-53601.

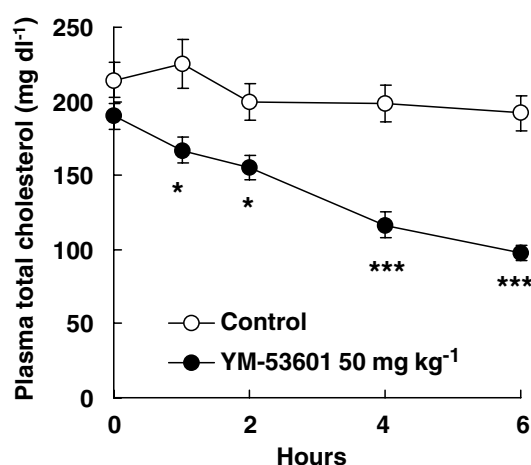


Figure 5 Time course of cholesterol-lowering effect on single administration of YM-53601 in hamsters. Plasma cholesterol level was evaluated in hamsters. See Methods section for details. There was a significant difference ($P < 0.001$) between control and YM-53601 groups using two-way repeated ANOVA testing. Statistical analysis *versus* control at each time point was carried out using Student's *t*-test. * $P < 0.05$, *** $P < 0.001$ *versus* control. Each value represents the mean \pm s.e.m. of data obtained in six animals.

The effect of YM-53601 on VLDL secretion seems to be partial as shown in Figure 3, because Triton WR1339 completely inhibits the metabolism of VLDL particles. However, YM-53601 completely inhibited the increase in plasma triglyceride in protamine sulfate-treated hamsters, indicating an increase in the protamine sulfate-insensitive clearance of VLDL. These results are in apparent conflict with our previous findings, in which YM-53601 enhanced the VLDL clearance rate, an effect which was lost on pretreatment with protamine sulfate (Ugawa *et al.*, 2002). We are now examining the cause of this discrepancy.

The inhibition of cholesterol secretion in VLDL particles from the liver may reduce plasma cholesterol levels in hypercholesterolemia. MTP plays a critical role in the assembly and secretion of VLDLs in the liver and chylomicrons in the intestine (Gregg & Wetterau, 1994). An MTP inhibitor showed a decreasing effect on plasma triglyceride and cholesterol in humans (Farnier *et al.*, 2001). Moreover, another MTP inhibitor reduced levels after only a single oral dosage in humans (Wilder *et al.*, 2001). In the present study, YM-53601 inhibited triglyceride and cholesterol secretion and decreased plasma cholesterol in a time-dependent manner after single administration in hamsters fed a normal diet. In addition, YM-53601 decreased plasma triglyceride under the same conditions (Ugawa *et al.*, 2002). Moreover, atorvastatin, HMG-CoA reductase inhibitor, shows a lowering effect on not only cholesterol but also triglyceride in the plasma of humans (Nawrocki *et al.*, 1995; Bakker-Arkema *et al.*, 1996; Jones *et al.*, 1998; Stein *et al.*, 1998). In rats, atorvastatin reduces VLDL secretion from the liver (Funatsu *et al.*, 2002a). As shown in the present paper, YM-53601 also inhibits secretion from the liver. Taken together, these results suggest that YM-53601 may also reduce both plasma cholesterol and triglyceride in humans.

As reduced lipid secretion by YM-53601 might arise from the results of cholesterol and triglyceride biosynthesis, we do

not expect that hepatic steatosis will be observed. This is different from the case of MTP inhibitors, which solely inhibit lipid secretion from the liver and therefore do not act on lipid biosynthesis. BMS-201038 increased hepatic triglyceride by 307% in rats, but atorvastatin which also inhibits cholesterol and triglyceride biosynthesis, as well as VLDL secretion, did not (Funatsu *et al.*, 2002b). Moreover, in *in vivo* experiments with YM-53601, we have not observed plasma alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases in animals including monkeys at the dose range which shows a plasma lipid-lowering effect (data not shown). These results suggest that YM-53601 may show a lipid-lowering effect in humans without interfering with liver function.

In conclusion, YM-53601, which may belong to a novel class of lipid-lowering agents which inhibit squalene synthase activity, inhibited FFA and triglyceride biosynthesis in rats and hamsters. YM-53601 also inhibited the secretion of triglyceride and cholesterol in VLDL from the liver. We therefore suggest that the mechanism by which YM-53601 decreases plasma triglyceride in animals may include both the inhibition of FFA and triglyceride biosynthesis, and the inhibition of VLDL secretion from the liver. These results appeared after single oral administration of YM-53601. Probably as a result of these effects, plasma cholesterol was decreased by single oral administration of YM-53601 in hamsters. We therefore conclude that YM-53601 holds promise as a lipid-lowering agent for the treatment of hypercholesterolemia and hypertriglyceridemia in humans.

We would like to express our gratitude to Drs Isao Yanagisawa, Yuichi Iizumi, Koyo Matsuda and Shin Naganuma for their helpful contributions. We also thank Mr Tsukasa Ishihara for synthesizing YM-53601, and Dr Guy Harris for his assistance in the preparation of the manuscript.

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(Received November 18, 2002

Revised January 27, 2003

Accepted February 4, 2003)