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Resveratrol attenuates the expression of HMG-CoA reductase mRNA in hamsters

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Abstract

We investigated the hypolipidemic effect of resveratrol focused on the mRNA expression and hepatic HMG-CoA reductase (HMGR) activity in hamsters fed a high-fat diet. Male Syrian Golden hamsters were fed a high-fat diet containing 0.025% fenofibrate or 0.025% resveratrol for 8 weeks. The concentrations of serum total cholesterol and triglyceride were significantly lower in the resveratrol-fed group than in the control group. The resveratrol contained diet significantly decreased Apo B, Lp(a), and cholesterol–ester–transport protein (CETP) concentrations, but increased Apo A-I levels and the Apo A-I/Apo B ratio. The contents of cholesterol and triglyceride in hepatic tissue were significantly lower in the resveratrol group than in the control group. Real-time PCR analysis revealed that HMGR mRNA expression was significantly lower in the resveratrol group than in the control group. These results indicate that dietary resveratrol reduces serum cholesterol by down-regulating hepatic HMGR mRNA expression in hamsters fed a high-fat diet.

Keywords: Resveratrol; Cholesterol; HMG-Co A reductase; Hamster

Increases in serum cholesterol and triglycerides, accompanied by a reduced high-density lipoprotein (HDL) concentration, are associated with an elevated risk of coronary artery diseases [1]. Many drugs are used to reduce the serum lipid level [2], but although they exert beneficial effects, these drugs have also been shown to cause serious side effects in various clinical settings [3].

Many classes of dietary components and natural compounds have been used to regulate serum lipid concentrations with the aim of reducing the incidence of hyperlipidemia and atherosclerosis [4]. There has been a recent focus on certain polyphenolic compounds as possible hypolipidemic agents. In particular, it has been hypothesized that the antioxidant properties of resveratrol are responsible for the protective effect against cardiovascular diseases observed with moderate intake of red wine. This theory provides the basis for the so-called French paradox [5]—the observation that the incidence of cardiovascular diseases in France is lower than that expected for the French diet, which is rich in saturated fat. Resveratrol (*trans*-3,4′,5-trihydroxystilbene) is a naturally occurring polyphenol present in red wine and berries [6]. Animal studies have revealed that red wine polyphenols are able to inhibit atherosclerotic progression [7]. Various mechanisms have been proposed to explain the anti-atherosclerotic properties of wine and its polyphenol compounds (including resveratrol), including inhibition of low-density lipoprotein (LDL) oxidation [8], modulation of platelet aggregation [9], inhibition of smooth muscle cell proliferation [10], reduction of inflammation in macrophages [11], and modulation of plasma cholesterol levels [12]. Despite the numerous studies indicating that red wine (and possibly the polyphenols therein) affects lipid metabolism and the progression of atherosclerosis, little is known about the

Abbreviations: HF, high-fat diet; FEN, fenofibrate; RES, resveratrol.

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direct effects that individual polyphenols, such as resveratrol, have on cholesterol metabolism-related enzyme activities and gene expression regulating serum and hepatic lipid balance. Accordingly, the present study aimed to elucidate the mechanism underlying the hypolipidemic action of resveratrol intake by investigating the effect of resveratrol on lipid metabolism and hepatic expression of HMG-CoA mRNA in hamsters with diet-induced hyperlipidemia.

Materials and methods

Materials. Resveratrol and fenofibrate were purchased from Sigma–Aldrich (St. Louis, MO, USA). Casein, cholesterol, cellulose, and vitamin and mineral mixtures were purchased from Dyets (Bethlehem, PA, USA). DL-methionine and choline chloride were purchased from Sigma–Aldrich (St. Louis, USA). All other chemicals were of analytical grade or purer.

Animals and diets. Four-week-old male Syrian Golden hamsters purchased from SLC (Shizuoka, Japan) were initially fed a chow diet for 7 days. After acclimation, the hamsters (weighing 80–90 g) were randomly divided into three groups and fed a high-fat diet (HF, $n = 9$), a 0.025%-fenofibrate-supplemented high-fat diet (FEN, $n = 9$), or a 0.025%-resveratrol-supplemented high-fat diet (RES, $n = 9$) for 8 weeks. The experimental diets were based on the AIN-76 diet (American Institute of Nutrition, 1980), and the high-fat diet was prepared by supplementing the basal AIN-76 diet with 15% fat and 1% cholesterol (w/w). The compositions of the experimental diets are listed in Table 1. The animals were maintained at a temperature and humidity of 21–25 °C and 50–60%, respectively, and a 12 h:12 h light:dark cycle (lights on from 06:30 to 18:30 h). All animal procedures were conducted in accordance with the Guidelines for Animal Experimentation of the Korea Food Research Institute.

Sample preparation. After consuming the experimental diets for 8 weeks, the hamsters were allowed to fast for 12 h and then sacrificed under diethyl ether anesthesia. Blood from the abdominal aorta was collected in a tube and centrifuged at 1500*g* for 15 min to separate the serum, which was stored at −70 °C until analysis. The liver and the epididymal fat pad were excised, weighed, and stored at −70 °C until use. Samples of the resected liver were later used for analysis of the lipid contents, histology, and real-time PCR analysis.

Lipid analyses. Serum total cholesterol, HDL–cholesterol, free cholesterol, free fatty acid, and triglyceride levels were measured using commercial enzyme kits (Eiken, Japan), as were serum Apo A-I, Apo B, cholesterol–ester–transport protein (CETP), and Lp(a) concentrations. Hepatic lipids were extracted according to the method of Folch et al. [13]. Hepatic total cholesterol and triglyceride levels were measured using commercial enzyme kits (Eiken, Japan).

Hepatic HMG-CoA reductase activity. Hepatic microsomes were prepared according to the method of Hulcher and Oleson [14] with slight modifications. Two grams of liver tissue were homogenized in 8 ml of ice-cold buffer (pH 7.0) containing 0.1 mM triethanolamine, 0.02 mM EDTA, and 2 mM dithiothreitol (DTT; pH 7.0). The homogenates were centrifuged for 10 min at 10,000*g* at 4 °C. The supernatants were then ultracentrifuged at 100,000*g* for 60 min at 4 °C. The resulting microsomal pellets were redissolved in 1 ml of homogenization buffer without DTT, the microsomal protein concentrations were determined using the method of Bradford [15], and were finally analyzed for their HMG-CoA reductase (HMGR) activities. The microsomal HMGR activities were measured with [^{14}C]-HMG-CoA as the substrate, based on a modification of the method of Shapiro et al. [16].

Oil-Red O staining. After the animals were sacrificed, liver tissues were removed and each liver lobe was cut into small pieces. To detect fat deposition in the liver, frozen sections were rinsed with distilled water, stained with 0.18% Oil-Red O (ORO; Sigma–Aldrich) and 60% 2-propanol (Sigma–Aldrich) for 20 min at 37 °C, and then rinsed with distilled water. We observed the liver tissues under a microscope (Olympus IX71, Japan, Tokyo) and photographed the samples with a digital camera (Olympus DP71, Japan, Tokyo).

Real-time PCR analysis. Real-time quantitative PCR was performed in triplicate in 384-well plates using a sequence detection system (Prism 7900, Applied Biosystems). Each 20 μl reaction mixture consisted of SYBR Green Master Mix (Applied Biosystems) combined with the forward primer sequence (5′GCCGGCAGCTCCTCTCCAC3′) and reverse (3′AGCCTTCCGTTGTTGCCATTG5′) primer sequences of HMGR. The cycling conditions were: 50 °C for 2 min and 95 °C for 10 min, followed by 40 cycles of 95 °C for 30 s, 60 °C for 30 s, and 72 °C for 30 s. Each of the 384-well real-time quantitative PCR plates included serial dilutions (1, 1/2, 1/4, 1/8, and 1/16) of cDNA, which were used to generate standard curves for HMGR and GAPDH.

Statistics. All statistical analyses were carried out with ANOVA and Duncan's multiple-range test using SAS (Cary, NC, USA), with a value of $p < 0.05$ selected as the cutoff for statistical significance.

Table 1
Compositions of the experimental diets (unit: g/kg diet)

	HF[c]	FEN[d]	RES[e]
Casein	200	200	200
Corn oil	50	50	50
Cocoa butter	70	70	70
Coconut oil	30	30	30
Cholesterol	10	10	10
Corn starch	340	340	340
Sucrose	200	200	200
Cellulose	50	50	50
Mineral mixture[a]	35	35	35
Vitamin mixture[b]	10	10	10
Methionine	3	3	3
Choline bitartrate	2	2	2
Fenofibrate	—	0.25	—
Resveratrol	—	—	0. 25

[a] AIN-76 mineral mixture.
[b] AIN-76 vitamin mixture.
[c] High-fat diet.
[d] Fenofibrate (0.025%)-supplemented high-fat diet.
[e] Resveratrol (0.025%)-supplemented high-fat diet.

Results

Diet consumption, growth, and tissue weight

Supplementing hamsters fed a high-fat diet for 8 weeks with 0.025% fenofibrate (FEN group) or 0.025% resveratrol (RES group) led to decreases in the final body weight compared to the HF group. These reductions in body weight occurred despite the fact that the diet intakes and feed efficiency ratios did not differ significantly between the groups (Table 2). The liver was significantly lighter in the RES group than in the HF group (Table 2), and did not differ between the FEN and HF groups. The weight of epididymal adipose tissue did not differ between the experimental groups (Table 2).

Serum lipids

Table 3 lists the serum lipid levels of the experimental animals. The total cholesterol level was significantly ($p < 0.05$) lower in the FEN and RES groups than in the HF group, and did not differ between the FEN and RES

Table 2
Changes in body weight, food intake, feed efficiency ratio and weight of liver and epididymal adipose tissue

	HF	FEN	RES
Body weight (g)			
Initial	84.9 ± 3.00	84.7 ± 2.95	84.92 ± 2.52
Final	144.8 ± 1.11[a]	133.1 ± 2.82[b]	129.9 ± 3.59[b]
Food intake			
FI (g/day)	6.88 ± 0.15	6.61 ± 0.32	7.19 ± 0.60
FER	0.143 ± 0.01	0.128 ± 0.01	0.110 ± 0.01
Tissue weight (g/100 g body weight)			
Liver	6.87 ± 0.12[a]	7.20 ± 0.16[a]	6.03 ± 0.29[b]
EPI	3.02 ± 0.14	2.80 ± 0.17	2.88 ± 0.18

Data are mean ± SE values of nine hamsters per group. Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$, as assessed using Duncan's multiple-range test. HF, high-fat diet group; FEN, fenofibrate (0.025%)-supplemented high-fat diet group; RES, resveratrol (0.025%)-supplemented high-fat diet group; FER, feed efficiency ratio; EPI, epididymal adipose tissue.

groups. The serum triglyceride levels were 57% lower in the RES group than in the HF group, and did not differ between the HF and FEN groups. The HDL–cholesterol concentration did not differ significantly between the experimental groups. The serum free-cholesterol concentration was lower in the RES group than in the HF group. The free fatty acid level was not changed in the RES and FEN groups compared with the HF group. The atherogenic index was 24% and 40% lower in the FEN and RES groups, respectively, than in the HF group (Table 3).

Serum apolipoproteins and CETP

Table 3 also presents the serum apolipoprotein levels of the experimental animals. The Apo A1 level was higher in the FEN and RES groups than in the HF group. Serum Apo B and Lp(a) concentrations were both lower in the FEN and RES groups than in the HF group. The CETP level was lower in the RES group than in the HF group, but did not differ between the FEN and HF groups. The Apo A1/Apo B ratio was higher in the FEN and RES groups than in the HF group.

Liver lipids contents and histopathology

Table 4 lists the effects of resveratrol on liver total cholesterol, triglyceride, and total lipid levels in the hamsters. The liver total cholesterol level was lower in the RES group than in the HF group, and the liver triglyceride level was 36% lower ($p < 0.05$) in the RES group than in the HF group. The liver total lipid contents were 16% and 20% lower in the FEN and RES groups, respectively, than in the HF group, but there was no difference between the RES and FEN groups. These results were further confirmed by Oil-Red O staining of the hepatic tissue (Fig. 1). To clarify whether the reduction of lipid accumulation was indeed induced in the liver by resveratrol intake, the liver tissues were stained with Oil-Red O (Fig. 1), which clearly revealed decreases in lipid accumulation in hepatocytes in response to feeding with fenofibrate and resveratrol diets. The reduction in the proportion of lipid droplets in the liver was markedly lower in the RES group than in the HF group.

Table 4
Effects of experimental diets on hepatic lipid contents

	HF	FEN	RES
Total lipid (mg/g liver)	211.5 ± 11.2[a]	177.7 ± 4.4[b]	168.4 ± 3.3[b]
Cholesterol (mg/g liver)	85.4 ± 1.9[a]	80.1 ± 2.5[ab]	72.3 ± 1.7[b]
Triglyceride (mg/g liver)	57.9 ± 1.4[a]	44.5 ± 2.4[b]	37.0 ± 1.4[c]

Data are mean ± SE values of nine hamsters per group. Values in the same column not sharing common superscript letters are significantly different at $p < 0.05$, as assessed using Duncan's multiple-range test. HF, high-fat diet group; FEN, fenofibrate (0.025%)-supplemented high-fat diet group; RES, resveratrol (0.025%)-supplemented high-fat diet group.

Table 3
Effects of experimental diets on serum lipid and apolipoprotein concentrations

	HF	FEN	RES
Serum lipid concentration			
Total cholesterol (mg/dl)	646.1 ± 26.9[a]	569.9 ± 27.9[b]	529.4 ± 16.5[b]
Triglyceride (mg/dl)	759.8 ± 29.9[a]	655.9 ± 18.6[a]	442.1 ± 43.6[b]
HDL–cholesterol (mg/dl)	123.4 ± 5.18	123.0 ± 2.76	138.7 ± 6.29
Free cholesterol (mg/dl)	199.7 ± 11.8[a]	175.7 ± 3. 8[b]	142.1 ± 5.9[c]
Free fatty acid (μEq/l)	4243.6 ± 123.4	3636.4 ± 90.4	4088.0 ± 245.8
Atherogenic index	4.66 ± 0.48[a]	3.54 ± 0.15[ab]	2.78 ± 0.11[b]
Serum apolipoproteins			
Apo A1 (mg/dl)	32.07 ± 0.28[b]	38.92 ± 0.99[a]	38.02 ± 0.67[a]
Apo B (mg/dl)	41.26 ± 1.27[a]	29.69 ± 1.30[b]	25.62 ± 2.11[b]
Lp(a) (mg/dl)	22.12 ± 1.98[a]	12.75 ± 0.42[b]	8.83 ± 0.48[c]
Apo A1/Apo B	0.78 ± 0.05[c]	1.31 ± 0.04[b]	1.49 ± 0.05[a]
CETP (pmole/μl/h)	22.74 ± 0.54[a]	21.90 ± 0.42[a]	19.57 ± 0.45[b]

Data are mean ± SE values of nine hamsters per group. Values in the same row not sharing common superscript letters are significantly different at $p < 0.05$, as assessed using Duncan's multiple-range test. HF, high-fat diet group; FEN, fenofibrate (0.025%)-supplemented high-fat diet group; RES, resveratrol (0.025%)-supplemented high-fat diet group.

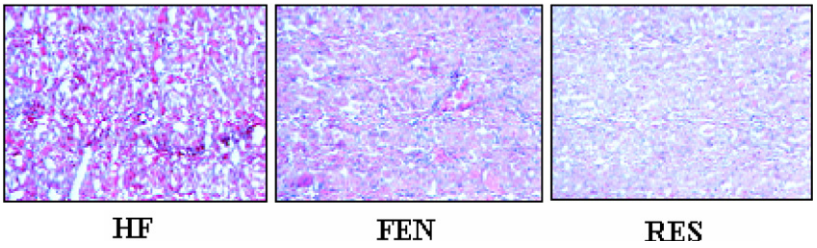

Fig. 1. Representative images of the Oil-Red O staining of liver tissues. HF, high-fat diet; FEN, fenofibrate (0.025%)-supplemented high-fat diet; RES, resveratrol (0.025%)-supplemented high-fat diet.

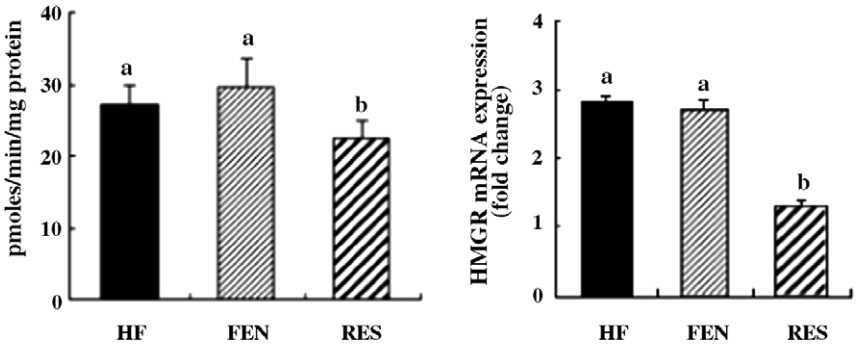

Fig. 2. Effects of experimental diets on HMG-CoA reductase activity and hepatic gene expression of HMGR mRNA. Those bars not sharing common superscript letters are significantly different at $p < 0.05$, as assessed using Duncan's multiple-range test. HF, high-fat diet; FEN, fenofibrate (0.025%)-supplemented high-fat diet; RES, resveratrol (0.025%)-supplemented high-fat diet.

Hepatic HMG-CoA reductase activities and expression of HMGR mRNA

The activities of the hepatic cholesterol biosynthesis-regulating enzyme HMGR after eight weeks of experimental diet consumption are shown in Fig. 2. The activity of HMGR was lower in the RES group than in the HF group, whereas the FEN group showed no significant change. The effects of dietary resveratrol supplementation on HMGR mRNA levels in the liver were examined by real-time PCR. The levels of HMGR mRNA were the same in the HF and FEN groups. However, supplementation with 0.025% resveratrol resulted in a significant decrease in liver HMGR mRNA levels (Fig. 2), which correlated with reduced enzyme activities.

Discussion

In this study, we investigated the hypolipidemic effect of resveratrol in hamsters with diet-induced hyperlipidemia. Lipoprotein metabolism in hamsters is comparable to that in humans because of similarities in the metabolic components and mechanisms for metabolism of both lipoproteins and bile acids [17]. The hamster therefore represents an ideal small-animal species for studying lipid and lipoprotein metabolism.

A cholesterol-rich diet appears to induce free-radical production followed by hypercholesterolemia, which is a major risk factor for atherosclerosis and is related to occlusive vascular diseases [18]. In the present study we found that the serum cholesterol concentration was significantly lowered by the consumption of resveratrol. This result is similar to that reported by Auger et al. [7].

Resveratrol has been shown to have hypolipidemic properties in rat feeding studies, where it lowered triglyceride and serum cholesterol levels [19]. In contrast, a study in rabbits showed no difference in cholesterol concentrations between a control group and a group that received oral resveratrol [20].

In the present study using hamsters, the concentrations of serum triglycerides, free cholesterol and total cholesterol, and the atherogenic index were lower in the RES group than in the HF group, and both resveratrol and fenofibrate increased the ratio of Apo A1 to Apo B.

Stein et al. [21] reported that a diet supplemented with 2% cholesterol resulted in a rapid development of hypercholesterolemia and increased CETP activity in hamsters. A reduction in CETP activity was observed after resveratrol supplementation in this study, suggesting that resveratrol indirectly affected the intravascular processing of lipoproteins by reducing the transfer of cholesteryl ester from HDL to VLDL. Although there is controversy as to whether the role of CETP is pro- or anti-atherogenic, studies in humans suggest that if CETP deficiency is associated with lower HDL–cholesterol concentrations, then the role of CETP appears to be proatherogenic [22]. In the present study, resveratrol lowered serum CETP activity without affecting HDL–cholesterol concentrations. Thus, a beneficial effect of resveratrol in reducing proatherogenic lipoproteins can be postulated. However, the hypolipidemic

action of resveratol is complex and warrants further investigation in a clinical setting.

A high-fat and cholesterol-containing diet induces hepatic cholesterol and triglyceride accumulation and an overweight liver [23]. However, in this study resveratrol supplementation decreased the liver weight and lowered hepatic cholesterol and triglyceride contents, though neither the resveratrol nor the fenofibrate supplement affected the serum triglyceride concentration.

HMG-CoA reductase is an enzyme that has received extensive study. It catalyzes the reduction of HMG-CoA to CoA and mevalonate, which is the rate-limiting reaction in the de novo synthesis of cholesterol. HMG-CoA reductase is the target of statins, a class of drugs that are highly effective in controlling hypercholesterolemia; statins inhibit cholesterol biosynthesis by blocking the substrate's access to the active site of the enzyme [24].

The present study found that the activity of hepatic HMGR was lower in the RES group than in the HF group. Endo [25] reported that, similar to atorvastatin, red wine polyphenolics inhibited HMGR. Moreover, we found that supplementation with 0.025% resveratrol decreased HMGR mRNA expression. This indicates that resveratrol inhibits cholesterol synthesis by altering hepatic HMGR.

The present results also suggest that resveratrol is very effective as a lipid-lowering agent in hamsters with diet-induced hyperlipidemia. These effects of resveratrol may be mediated via decreased HMGR activity and down-regulation of HMGR mRNA expression.

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