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A novel experimental model of acute hypertriglyceridemia induced by schisandrin B

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Abstract

Mice were intragastrically treated with single doses (0.05–0.8 g/kg) of schisandrin B (a dibenzocyclooctadiene derivative isolated from the fruit of *Schisandra chinensis*). Twenty-four hours after schisandrin B administration, the serum triglyceride level was increased by 10–235% in a dose-dependent manner. However, the serum low density lipoprotein cholesterol level was significantly decreased by 28% at a dose of 0.8 g/kg. When given once daily (0.01–0.2 g/kg) for 4 days, schisandrin B also dose-dependently elevated the serum triglyceride level (17–134%). Kinetics parameters estimated by Scott's plot analysis of schisandrin B-induced changes in serum and hepatic triglyceride levels were determined: serum—E_{max} (maximal effect)=6 mmol/L (384% increase, $P<0.001$); K_D (affinity)=0.59 mmol/kg; pD_2 (an index of affinity)=6.62; liver—E_{max}=21 μmol/g (68% increase, $P<0.001$); K_D=0.37 mmol/kg; pD_2=6.83. The efficacy of schisandrin B in increasing the triglyceride level was 5.6-fold higher in serum than in liver tissue. Fenofibrate (0.2 g/kg) treatment, when in combination with schisandrin B (0.2 g/kg), for 4 days significantly reduced the schisandrin B-induced increase in serum triglyceride level (by 81%, $P<0.001$). Hepatic triglyceride level was also decreased (by 100%, $P<0.001$) by co-treatment with fenofibrate. Our results suggest that schisandrin B treatment can be used to establish a mouse model of acute hypertrigylceridemia.

Keywords: Schisandrin B; Fenofibrate; Triglyceride; Total cholesterol; Hypertriglyceridemia

1. Introduction

Coronary heart disease, which causes more than twice as many deaths as all forms of malignancy in USA, is the leading cause of death in many countries (Khoo et al., 2003). Both epidemiological and intervention studies have shown that plasma triglycerides are a risk factor for cardiovascular diseases (Csaszar, 2005; Hokanson and Austin, 1996). Disorders of lipoprotein metabolism can lead to hypercholesterolemia, hypertriglyceridemia, or both. Hyperlipidemia may be classified into several subtypes according to the pattern of lipoproteins. Patients suffering from type I and IV hyperlipidemia have a high plasma triglyceride level, but little or no elevation in the plasma total cholesterol level. In recent years, much attention has been focused on the development of drugs used for the prevention and treatment of hyperlipidemia. So far, there are several animal models of hyperlipidemia, including diet-induced and transgenic animal ones, for screening candidate blood lipid-lowering drugs (Hamet, 2004; Hofker et al., 1998; Masucci-Magoulas et al., 1997; Weinstock et al., 1995).

Schisandrin B is isolated from the fruit of *Schisandra chinensis*, a traditional Chinese herb clinically prescribed for the treatment of hepatitis. Studies have shown that schisandrin B can protect against myocardial ischemia–reperfusion injury and chemically induced liver injury in rodents (Chiu and Ko, 2004; Tang et al., 2003; Chiu et al., 2003). The cardio- and hepatoprotective action of schisandrin B is believed to be related to its in vivo antioxidative potential. When mice were orally administered with high doses of schisandrin B for 3 days, there was an apparent increase in plasma lipid levels, which returned to the normal level 3 days after the last dosing (unpublished observation from a previous study by Pan et al., 2002). This observation has led to an attempt to establish an

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animal model of acute hyperlipoproteinemia using schisandrin B. In the present study, we investigated the effect of schisandrin B treatment on serum and hepatic lipid levels in mice.

2. Materials and methods

2.1. Chemicals and reagents

Schisandrin B was purified from the petroleum ether extract of dried fruits of *S. chinesis* (Schisandraceae), with the chemical structure being confirmed by comparing thin-layer chromatography (TLC) and spectral characteristic with an authentic standard, as described previously (Ip et al., 1995). The purity of schisandrin B, as determined by high performance liquid chromatography (HPLC) analysis, was higher than 95%. Cholesterol (certificate No. 030814) and bile salt (certificate No. 000710) were from Beijing Chemical Reagent Co. (Beijing, China). Fenofibrate (certificate No. 0405030) was bought from Beijing Yongkang Medical Ltd. (Beijing, China). Carboxymethylcellulose (CMC, certificate No. 971230) was obtained from Beijing Xudong Chemical Plant (Beijing, China). The assay kits for measurement of triglyceride, total cholesterol, low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) levels were bought from Zhongsheng Beikong Bio-technology and Science Inc. (Beijing, China).

2.2. Animal treatment

Adult male ICR mice weighing 26–30 g (Grade II, certificate No. SCXK(jing)2002-0003) were purchased from Vital River Lab Animal Co. Ltd. (Beijing, China). All animals were maintained on a 12-h light/dark cycle at a temperature 20–21 °C, with a humidity of 50–55%. Animals had access to food and water ad libitum and eight mice were housed per cage. Before the experiment, mice were allowed a 4-day habituation period in the laboratory in which the tests were carried out. Mice were orally administered schisandrin B, which was suspended in either olive oil or 0.5% CMC. Control animals received the vehicle at 10 ml/kg. Positive control animals were intragastrically administered a mixture of cholesterol (2 g/kg) and bile salt (0.5 g/kg) suspended in the vehicle (either olive oil or 0.5% CMC). Blood and liver tissue samples were obtained from animals after a 12-h fast and then subjected to biochemical analyses. All experimental protocols were approved by the University Committee on Research Practice in Beijing University of Chinese Medicine.

2.3. Determination of lipid concentrations

Whole blood samples were obtained from the orbital vein of mice, and serum samples were prepared by centrifuging the whole blood for 8 min at 2000×*g*. Samples were frozen at −20 °C until biochemical analysis within 5 days. Liver tissue sample was homogenized in 9 volumes of 0.9% (w/v) NaCl homogenizing solution by two 10-s bursts of a tissue disintegrator at 13,500 rpm and then centrifuged at 2000×*g* for 15 min. Levels of triglyceride, total cholesterol, LDL-C, and HDL-C in serum samples and supernatants of liver homogenates were measured using commercially available assay kits.

2.4. Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) and expressed as means ± S.E.M. Inter-group difference was detected by Dunnett's test using SPSS12.0 software. Comparison between two groups was done by using Student's *t*-test. The difference was considered significant when $P<0.05$. The kinetics of schisandrin B-induced increases in serum and hepatic triglyceride levels were analyzed with Scott's plots, with values of E_{max} (maximal effect), K_D (affinity) and pD_2 (an index of affinity) being estimated.

3. Results

3.1. Effect of schisandrin B treatment on serum lipid levels in mice

As shown in Table 1, treatment with single oral doses of schisandrin B (0.05–0.8 g/kg in olive oil) increased serum triglyceride levels by 10–235% 24 h post dosing in mice. In contrast, the LDL-C level was significantly decreased by 28% at a dose of 0.8 g/kg. Schisandrin B treatment produced no detectable changes in serum total cholesterol and HDL-C levels in mice. While cholesterol/bile salt treatment (2/0.5 g/kg) did

Table 1
Effect of schisandrin B treatment on serum lipid levels in mice

Groups	Doses (g/kg)	Triglyceride (mmol/L)	Total cholesterol (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Single dose					
Control	–	1.24±0.15	3.88±0.23	3.48±0.20	0.36±0.05
Schisandrin B	0.05	1.37±0.13	3.70±0.12	3.40±0.12	0.36±0.02
	0.2	2.46±0.16[a]	3.40±0.10	3.03±0.11	0.30±0.02
	0.8	4.15±0.26[a]	3.64±0.14	3.09±0.13	0.26±0.02[b]
Cholesterol Bile salt	2 0.5	1.02±0.07	4.46±0.19	3.77±0.20	1.03±0.08[a]
Four doses					
Control	–	1.19±0.06	3.99±0.11	3.61±0.11	0.45±0.04
Schisandrin B	0.01	1.08±0.06	3.91±0.18	3.63±0.13	0.52±0.02
	0.05	1.39±0.12	4.25±0.15	3.99±0.14	0.51±0.02
	0.2	2.78±0.41[a]	4.29±0.18	3.91±0.16	0.41±0.02
Cholesterol Bile salt	2 0.5	0.73±0.05[a]	6.76±0.87[b]	4.10±0.35	1.90±0.06[a]

Mice were intragastrically treated with schisandrin B (0.05–0.8 g/kg in olive oil). Animals in the cholesterol and bile salt (i.e. positive control) group were treated with cholesterol (2 g/kg) plus bile salt (0.5 g/kg). Control mice received the vehicle (i.e. olive oil) at 10 ml/kg. Twenty-four hours after the last dose, serum levels of triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured as described in Materials and methods. Values given are the means ± S.E.M., with $n=10$.

[a] Significantly different vs. the control (i.e. vehicle) group ($P<0.001$).

[b] Significantly different vs. the control (i.e. vehicle) group ($P<0.01$).

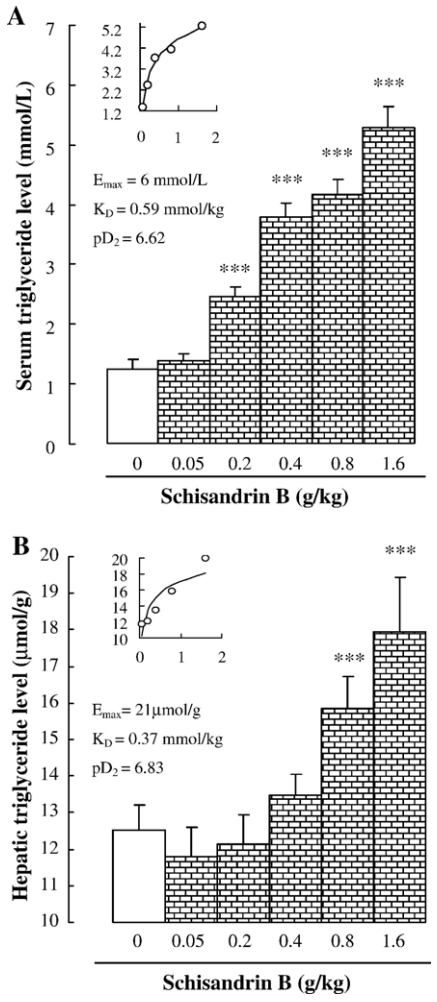

Fig. 1. Kinetics of schisandrin B-induced hypertriglyceridema in mice. Mice were intragastrically treated with schisandrin B at increasing doses (0.05–1.6 g/kg in olive oil). Control mice (i.e. 0 g/kg) received the vehicle at 10 ml/kg. Twenty-four hours after dosing, serum and liver tissue samples were obtained and triglyceride levels were measured. The insets A and B are respective Scott's plots for serum and liver, with values of kinetic parameters (E_{max}, K_D, and pD_2) being shown. Values given are the means ± S.E.M., with $n = 10$. ***$P < 0.001$ vs. the vehicle control group.

not change the serum triglyceride and total cholesterol level, it caused a significant increase in the LDL-C level (186%) but not the HDL-C level. When mice were treated with daily doses of schisandrin B (0.01–0.2 g/kg) for 4 days, the serum triglyceride level was also dose-dependently increased (by 17–134%) 24 h after the last dose. No significant changes were detected in serum total cholesterol, LDL-C and HDL-C levels. Treatment with cholesterol/bile salt at a daily dose of 2/0.5 g/kg for 4 days significantly decreased the serum triglyceride level (39%), but serum total cholesterol and LDL-C levels were elevated (69% and 322%, respectively). The cholesterol/bile salt treatment did not produce any detectable change in the serum HDL-C level. Daily treatment with schisandrin B, either intragastrically in 0.5% CMC or subcutaneously in olive oil, also dose-dependently increased the serum triglyceride level, but to a much smaller extent than that seen after intragastric administration with olive oil as vehicle (data not shown).

3.2. Kinetics of schisandrin B-induced hypertriglyceridemia in mice

The kinetics of the schisandrin B-induced increases in serum and hepatic triglyceride levels were analyzed by Scott's plot. Mice were intragastrically treated with increasing doses of schisandrin B (0.05–1.6 g/kg in olive oil) and serum/liver tissue samples were obtained 24 h later. As shown in Fig. 1, schisandrin B dose-dependently increased serum triglyceride (10–325%) and hepatic triglyceride (8–43%) levels, with E_{max} values being 6 mmol/L and 21 μmol/g, respectively. In addition, K_D and pD_2 values were estimated to be 0.59 mmol/kg and 6.62, respectively, in serum and 0.37 mmol/kg and 6.83, respectively, in liver tissue.

3.3. Effect of schisandrin B treatment on hepatic triglyceride and total cholesterol levels in mice

Treatment with a single oral dose of schisandrin B (0.8 g/kg in olive oil) significantly increased the hepatic triglyceride level

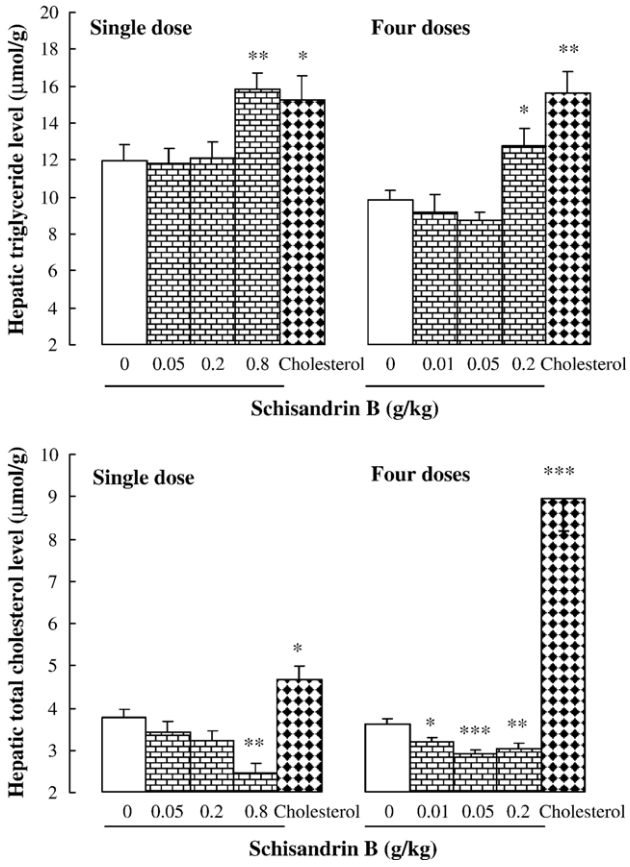

Fig. 2. Effect of schisandrin B treatment on hepatic triglyceride and total cholesterol levels in mice. Mice were intragastrically treated with single doses (0.05–0.8 g/kg in olive oil) or multiple doses (0.01–0.2 g/kg × 4) of schisandrin B. Animals in the cholesterol groups (i.e. positive control) were treated with cholesterol/bile salt as described in Table 1. Control mice (i.e. 0 g/kg) received the vehicle at 10 ml/kg. Liver tissue samples were obtained 24 h after the last dose. Hepatic triglyceride and total cholesterol levels were measured as described in Table 1. Values given are the means ± S.E.M., with $n = 10$. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ vs. the vehicle control group.

(by 33%) 24 h post dosing, but it reduced the hepatic total cholesterol level by 35% (Fig. 2). However, cholesterol/bile salt (2/0.5 g/kg)-treated mice showed significant increases in both hepatic triglyceride (28%) and total cholesterol (24%) levels. Treatment with multiple oral doses of schisandrin B (0.2 g/kg × 4) significantly increased the hepatic triglyceride level (by 30%), but the hepatic total cholesterol level was decreased (by 12–20%) at all doses tested (0.01–0.2 g/kg). Cholesterol/bile salt treatment (2/0.5 g/kg × 4) significantly increased the hepatic triglyceride and total cholesterol levels (by 59% and 147%, respectively).

3.4. Effect of fenofibrate treatment on schisandrin B-induced increase in serum and hepatic triglyceride levels in mice

Mice were daily intragastrically administered schisandrin B (0.2 g/kg in olive oil), fenofibrate (0.05 and 0.2 g/kg in olive oil) or a combination of schisandrin B (0.2 g/kg) and fenofibrate (0.05 or 0.2 g/kg) for 4 days. Serum and liver tissue samples were obtained 24 h after the last dose. As shown in Fig. 3, while fenofibrate treatment (0.05 and 0.2 g/kg) did not change the serum triglyceride level in vehicle-treated (i.e. schisandrin B-untreated) mice, it attenuated the schisandrin B-induced increase in serum triglyceride level, with the extent of inhibition being 81% at a dose of 0.2 g/kg. In contrast, fenofibrate treatment decreased hepatic triglyceride levels in both vehicle- and schisandrin B-treated mice, with the extent of inhibition being 32% and 100%, respectively, at a dose of 0.2 g/kg.

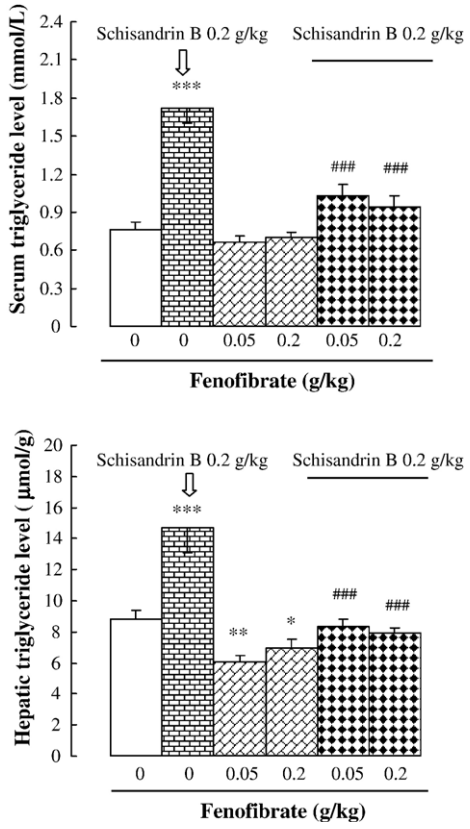

Fig. 3. Effect of fenofibrate treatment on the schisandrin B-induced increase in serum and hepatic triglyceride levels in mice. Mice were intragastrically treated with schisandrin B at a daily dose of 0.2 g/kg, with or without fenofibrate (0.05 or 0.2 g/kg) for 4 days. Control mice received the vehicle at 10 ml/kg. Twenty-four hours after the last dose, serum and liver tissue samples were obtained and triglyceride level is measured. Values givens are the mean ± S.E.M., with $n = 10$. $^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$ vs. the control group. $^{\#\#\#}P<0.001$ vs. the schisandrin B-treated group.

4. Discussion

Hyperlipidemia is characterized by elevated plasma/serum total cholesterol and triglyceride levels which are well over normal values in the population. Patients with type I hyperlipidemia have very high plasma triglyceride and chylomicron levels and usually exhibit reduced levels of the lipoprotein lipase that appears in plasma after heparin administration. In patients with type I hyperlipidemia, a decrease in fat intake will cause a marked reduction in plasma lipid levels. Patients with type IV hyperlipidemia with elevated with plasma levels of triglyceride and very low-density lipoprotein-cholesterol (VLDL-C) exhibit carbohydrate inducibility, that is, the feeding of high-carbohydrate diet results in increased lipid levels. In the present study, schisandrin B was found to increase serum triglyceride but not total cholesterol levels and thus the resultant hypertriglyceridemic state resembled that of type I or IV hyperlipidemia in humans. High-fat and excessive carbohydrate intake cause hypertriglyceridemia associated with an increase in hepatic triglyceride secretion and a decrease in triglyceride clearance in rats (Funatsu et al., 2003; Boivin and Deshaies, 1995). When β-oxidation is greatly inhibited, fatty acids are mainly esterified into triglyceride and caused hypertriglyceridemia (Klein et al., 1998; Eaton et al., 1997). Given the elevation of both serum and hepatic triglyceride levels, it is possible that schisandrin B can stimulate the esterification of fatty acids and/or inhibit β-oxidation.

Triglyceride primarily exists in chylomicrons and VLDL-C. While the former is formed by intestinal mucosal cells during the absorption of dietary fat, the latter is manufactured in the liver in response to a high carbohydrate meal. In clinical situations, while hypertriglyceridemia is commonly observed in patients with diabetes mellitus, uremia, and alcoholism, therapeutic agents, such as oral contraceptives, β-adrenergic blocking agents and isotretinoin, can increase serum triglyceride concentrations (Witztum, 1996). Interestingly, abdominal obesity has also been found to be associated with postprandial hyperlipidemia (Blackburn et al., 2003). Schisandrin B, which is relatively non-toxic at high doses (Ko and Mak, 2004), can effectively induce hypertriglyceridemia in animals, with minimal undesirable side effects. Thus, schisandrin B-induced hypertriglyceridemia is not a result of toxicity.

Changes in plasma triglyceride levels reflect a dynamic process involving the removal of triglyceride from the blood and synthesis/secretion of triglyceride from the liver. If a drug such as schisandrin B enhances the hepatic synthesis and/or secretion of triglyceride, the blood triglyceride level will be increased. While the kinetics of the drug–receptor or enzyme interaction can be conveniently investigated in vitro, kinetic parameters of drug action can be also obtained in vivo (Pan and Han, 2004). As

the regulation of serum and hepatic triglyceride levels is mediated by enzymes and/or receptors, the schisandrin B-induced increase in serum/hepatic triglyceride level may result from the inhibition and/or stimulation of enzymes and/or receptors. In the present study, Scott's plot analysis indicated a linear dose–effect relationship of schisandrin B-induced increases in serum and hepatic triglyceride levels. E_{max} values estimated from serum and hepatic changes showed that schisandrin B was 5.6-fold more effective in elevating the triglyceride level in serum than in liver tissue. The observation of no difference in pD_2 values between serum and liver suggests that the triglyceride-elevating action of schisandrin B in both compartments is mediated by the same enzyme or receptor.

In this regard, subcutaneous administration of schisandrin B was found to be less effective than intragastric administration in elevating the serum triglyceride level. Intragastric administration of schisandrin B, using olive oil as vehicle, seemed to facilitate intestinal absorption, thereby accentuating the triglyceride-increasing effect of schisandrin B. When the skin of subcutaneously treated mice was excised, it was found that schisandrin B was not completely absorbed from the injection site in the mice subcutaneously treated with schisandrin B.

Fibric acid derivatives are a class of lipid-modifying drugs mainly used in patients with elevated triglyceride levels. Fenofibrate, which is one of the most widely used fibric acid derivatives, is a useful therapeutic option for patients with primary combined dyslipidemias or secondary dyslipidemias (Tsimihodimos et al., 2005; Curnew, 1994). Fenofibrate, when administered at 0.3 g/day, is especially good at lowering the triglyceride level. The drug increases lipolysis and the elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing the production of apoprotein C-III, an inhibitor of lipoprotein lipase activity. Results obtained from the present study indicate that fenofibrate treatment could attenuate the schisandrin B-induced increases in serum and hepatic triglyceride levels. The schisandrin B-induced elevation in serum triglyceride level may therefore serve as an animal model of hypertriglyceridemia.

In conclusion, our results indicate that schisandrin B treatment can markedly increase the serum triglyceride level, but without affecting the serum total cholesterol level, in mice. The schisandrin B-induced elevation in serum triglyceride level, which resembles type I or IV hyperlipidemia in humans, can be used as a mouse model for screening candidate lipid-lowering drugs.

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