Hypotriglyceridemic Effect of Anka (a Fermented Rice Product of *Monascus* sp.) in Rats

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Experimental rats with hypertriglyceridemia were prepared by feeding a high-fructose diet. Dried Anka powder (2%), a rice product fermented with *Monascus* sp., was mixed with basic high-fructose (30%) or basal-diet feed. Serum and liver lipids were measured after 6 months. The concentrations of serum triglycerides, total cholesterol, VLDL-C, and LDL-C had significantly decreased, whereas that of HDL-C had slightly increased in 30% fructose−Anka-fed rats as compared with the 30% fructose-fed rats, but hepatic lipase activity had increased in the Anka-fed groups. The ratio of lipoprotein lipase/hepatic lipase was not significantly different between 30% fructose−Anka-fed rats and 30% fructose-fed rats. The dietary intake and weight of these two groups were approximately the same. Similar results were obtained in noninduced hypertriglyceridemic rats. The concentrations of triglycerides and cholesterol did not significantly differ in the liver. Interestingly, Anka can suppress serum triglycerides in rats with induced hypertriglyceridemia. The antioxidant enzyme SOD activity was also measured in serum, and no significant change was observed. On the basis of these findings, we suggest that Anka may be used to suppress hypertriglyceridemia and hyperlipidemia in rats and possibly in man.

Keywords: *Anka; Monascus sp.; hypertriglyceridemia; triglyceride; cholesterol; VLDL-C; LDL-C; HDL-C; lipoprotein lipase; hepatic lipase; SOD*

INTRODUCTION

Hyperlipidemia, usually found in elderly people, is caused by lipid metabolic changes. It is a major cause of cardiovascular diseases (Chobanian, 1991) such as atherosclerosis and coronary heart disease. A high level of serum cholesterol has been clearly identified as a risk factor of atherosclerosis and coronary heart disease (Chobanian, 1991), whereas a high level of triglycerides has only recently been proposed to constitute an independent risk factor of coronary heart disease (Cambien et al., 1986; Austin, 1989). The association of serum lipids with coronary heart disease has been studied extensively in middle-aged men and, to a lesser extent, in middle-aged women (Gordon et al., 1977a,b; Kannel et al., 1979; Neaton et al., 1992). Hyperlipidemia is an increasing threat to human health and life.

Anka (or Red Mold Rice; Red Rice) tastes sweet and has mild properties. It is manufactured based on a traditional Chinese remedy and has been used as a Chinese medicine for more than 1000 years. It is also taken as a daily dietary supplement. Red Rice has been used in traditional Chinese medicine to promote digestion and blood circulation. These functions help alleviate the symptoms of hyperlipidemia. Anka is produced by fermenting rice with *Monascus* sp. The monacolin group (monacolin K [mevinolin; lovastatin], J, L, M, X, and dihydromonacolin L) includes secondary metabolites of *Monascus ruber*; they are specific inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol synthesis (Endo, 1979, 1980, 1985; Endo et al., 1985a,b, 1986). Lovastatin (monacolin K; mevinolin), an HMG-CoA reductase inhibitor, is also found in Anka. These compounds are effective in lowering plasma cholesterol levels in various mammalian species, including humans, and are thereby effective for hypercholesterolemia therapy (Endo, 1985).

In the present study, we demonstrate that the effect of Anka can lower lipid levels in male Sprague−Dawley Rats by oral feeding. The data suggest that oral feeding of Anka to rats can result in reduction of serum triglycerides, total cholesterol, VLDL-C, and LDL-C, as well as increased hepatic lipase activity in the liver and lipoprotein lipase activity in adipose tissue.

MATERIALS AND METHODS

Chemicals. Anka (Red Mold Rice; Red Rice) and lovastatin were a gift from Mr. Chin-Chai Fang, President, Standard Pharmaceufical Co., Tainan, Taiwan. Fructose was purchased from Merck (Darmstadt, Germany).

Animals and Treatments. Male Sprague−Dawley (SD) rats (5 weeks old) were purchased from the National Laboratory Animal Breeding and Research Center (Taipei, Taiwan). The rats were housed in stainless steel wire-bottomed cages and acclimated under laboratory conditions (19−23 °C, humidity 60%, 12-h light/dark cycle) for at least 1 week before each study. The weights of rats at the beginning of the study ranged from 200 to 250 g. Ground Purina rat chow (Ralston Purina, St. Louis, MO) and water was provided ad libitum. After 1 week of acclimation, the rats were divided into five groups, six rats per group, and fed different diets: group 1, basal diet (ground Purina rat chow); group 2, 2.0% Anka (Red Rice); group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. The experiments were terminated after 6 months, when the rats were ether-anesthetized. Blood was collected from the tail vein,

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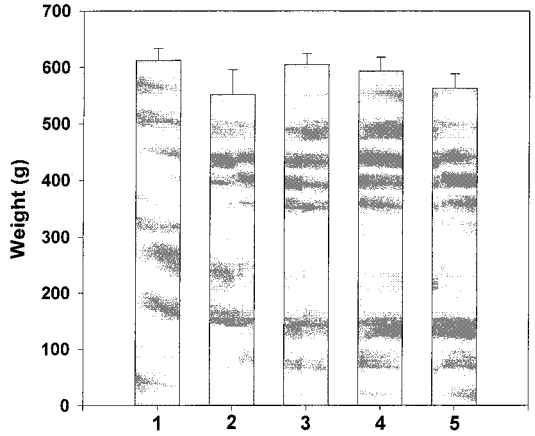

Figure 1. Effect of Anka on the growth of SD rats. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. The experimental period was 6 months.

serum was separated by centrifugation for estimation of triglycerides, total cholesterol, VLDL-cholesterol, LDL-cholesterol, and HDL-cholesterol, and tissues were quickly excised and frozen at −70 °C until use.

Serum Lipids. Total cholesterol, HDL-cholesterol, and triglycerides were determined using an Ektachem commercial kit (Johnson and Johnson Clinical Diagnostics, NY), and LDL-cholesterol was measured by using a bioMerieux commercial kit (bioMerieux Vitek, MO). VLDL-cholesterol = total cholesterol − HDL-cholesterol − LDL-cholesterol. Data were checked with a Helena lipid electrophoresis kit (Helena Laboratories, TX).

Liver Lipids. Liver lipids were measured in the same way as those of serum after extracting all lipids according to the method of Folch et al. (1957), and then the lipids were suspended in 1-propanol-2% Triton X-100 (3:20) were emulsified at 70 °C for 20 min (Terada et al., 1998).

Assay of Hepatic Lipase Activity in Liver and Lipoprotein Lipase Activity in Adipose Tissue. Liver or adipose tissue samples were homogenized and centrifuged (Bengtsson-Olivecrona and Olivecrona, 1992). The supernatant was immediately assayed for hepatic lipase activity or lipoprotein lipase activity by a commercial kit from Randox (Randox Laboratories, Antrim, UK).

Assay of Superoxide Dismutase Activity in Serum. Four hundred microliters of ice-cold absolute ethanol/chloroform 62.5:37.5 (v/v) was added to 250 μL of serum in a glass test tube and then thoroughly mixed for at least 30 s and centrifuged at 3000*g* for 5 min at 4 °C. The resulting supernatant was stored between 2 and 8 °C until used for the assay. Serum SOD activity was determined by a commercial kit from Randox (Randox Laboratories).

Statistical Analysis. The results obtained were expressed as the mean ± SE, and the significance of the differences (*p* values) was assessed by Student's *t*-test.

RESULTS

Effects of Anka on Body Weight and Dietary Intake of Rats. Body weights of rats were examined when 5-week-old male SD rats were fed the basal diet (group 1), basal diet containing 2.0% Anka (group 2), and basal diet containing 30% fructose (group 3; hypertriglyceridemic rats) (Hara et al., 1998). In addition, 2.0% Anka (group 4) or 250 mg/kg lovastatin (group 5) was also added to the basal diet containing 30% fructose. The weights of rats in each group after 6 months are given in Figure 1. At the sixth month, average body weight showed no significant difference among the five groups. The dietary intakes of SD rats

Table 1. Food Intake of Experimental Rats

Group	Month after initiation of treatment			
	2	4	6	Mean±SE[b]
	g/day/rat			
1	24.1 ± 1.2	27.4 ± 2.0	30.8 ± 1.7	27.4 ± 3.4
2	24.7 ± 2.3	28.3 ± 2.3	30.5 ± 2.1	27.8 ± 2.9
3	25.7 ± 1.7	32.1 ± 1.2	34.2 ± 2.8	30.7 ± 4.4
4	26.8 ± 1.3	34.6 ± 1.7	37.8 ± 1.7	33.1 ± 5.7
5	25.0 ± 2.1	31.7 ± 1.5	34.9 ± 1.8	30.5 ± 5.1

[a]1. Basal diet; 2. Basal diet + 2.0% Anka; 3. 30% Fructose; 4. 30% Fructose + 2.0% Anka; and 5. 30% Fructose + 250 mg/kg Lovastatin

a. The number of rats in each group is six.

b. $p > 0.1$, no significant difference.

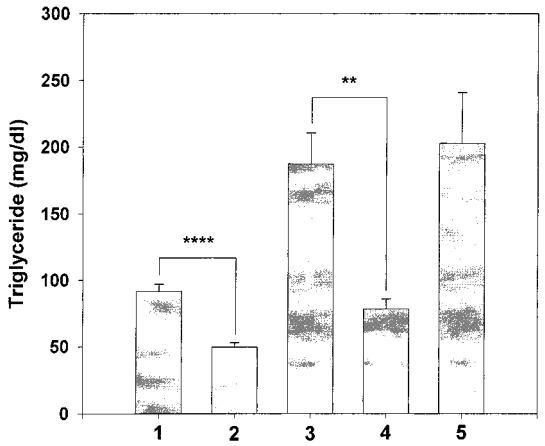

Figure 2. Effect of Anka on serum triglyceride levels in SD rats. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. **Significant differences between groups ($p < 0.005$); ***significant differences between groups ($p < 0.00005$).

in each group are shown in Table 1 and show no significant differences throughout the feeding period. The 30% fructose groups (groups 3, 4, and 5) showed slight but insignificant increases in dietary intakes. The survival rates of all groups were 100% (6/6) during the course of the experiments.

Effect of Anka on Serum Triglycerides. Figure 2 illustrates serum triglycerides levels of SD rats fed Anka. Interestingly, the results demonstrate that the concentrations of serum triglycerides of Anka-fed rats (group 2) were significantly lower than those of basal diet-fed rats (group 1) ($p < 0.00005$). A high level of serum triglycerides was induced in 30% fructose-fed rats (group 3). The serum triglyceride level of the 30% fructose−Anka-fed group (group 4) had decreased compared to that of the 30% fructose-fed group (group 3) ($p < 0.005$). In 30% fructose plus lovastatin-fed rats (group 5), the concentration of serum triglycerides did not decrease compared to that of the 30% fructose-fed group (group 3). These data suggest that Anka can significantly decrease the level of serum triglycerides in rats.

Effects of Anka on Total Cholesterol, HDL-C, VLDL-C, and LDL-C. We also examined the levels of total cholesterol, HDL-C, VLDL-C, and LDL-C in the serum of SD rats fed 2.0% Anka powder for 6 months. The results showed that the concentrations of total

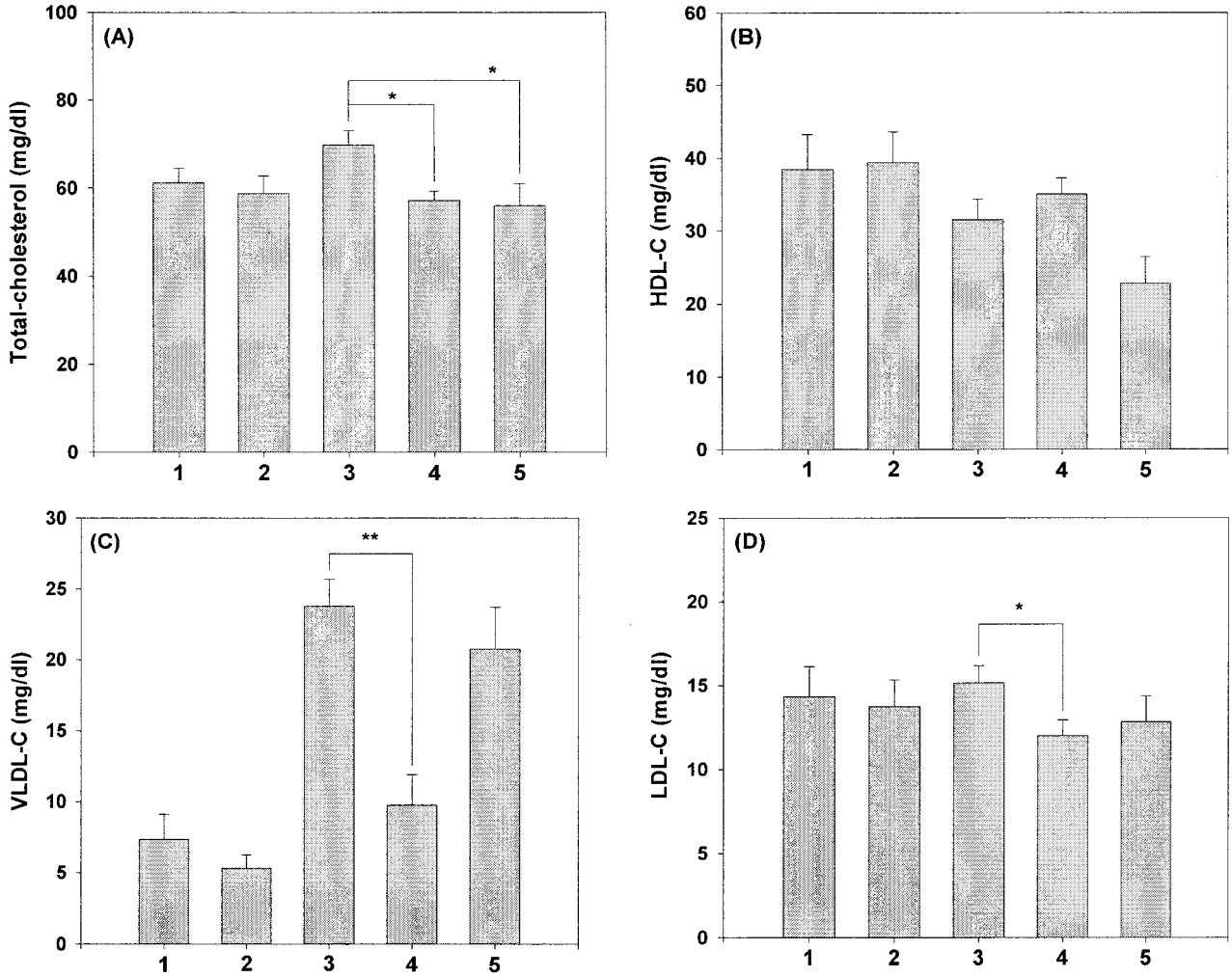

Figure 3. Levels of total cholesterol (A), HDL-C (B), VLDL-C (C), and LDL-C (D) in serum of SD rats fed 2.0% Anka for 6 months. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. *Significant differences between groups ($p < 0.05$); **significant differences between groups ($p < 0.005$).

cholesterol in 30% fructose−lovastatin-fed rats (group 5) and in 30% fructose−Anka-fed rats (group 4) were significantly lower than those of 30% fructose-fed rats (group 3) ($p < 0.05$). Those of basal diet-fed rats (group 1) and Anka-fed rats (group 2) showed no significant difference (Figure 3A). Figure 3B shows that HDL-C level did not differ between basal diet-fed rats (group 1) and Anka-fed rats (group 2). The HDL-C levels of 30% fructose−Anka-fed rats (group 4) showed a slight increase as compared to those of 30% fructose-fed rats (group 3), but the difference was not statistically significant. The concentration of HDL-C of 30% fructose−lovastatin-fed rats (group 5) was lower than that of 30% fructose-fed rats (group 3), but the difference was also not statistically significant. Figure 3C illustrates that the level of VLDL-C was significantly lower in 30% fructose−Anka-fed rats (group 4) than that in 30% fructose-fed rats (group 3) ($p < 0.005$), but the levels in 30% fructose−lovastatin-fed rats (group 5) and 30% fructose-fed rats (group 3) showed no difference. The level of VLDL-C in Anka-fed rats (group 2) was a little lower than that in basal diet-fed rats (group 1). At the sixth month, we also found that the level of LDL-C in 30% fructose−Anka-fed rats (group 4) had markedly decreased compared to that of 30% fructose-fed rats (group 3) ($p < 0.05$) (Figure 3D). The levels of LDL-C between basal diet-fed rats (group 1) and Anka-fed rats (group 2) did not differ, and the levels of LDL-C between 30% fructose-fed rats (group 3) and 30% fructose−lovastatin-fed rats (group 5) also did not markedly differ (Figure 3D). These results suggest that Anka can also decrease the levels of total cholesterol, VLDL-C, and LDL-C, and slightly increase the level of HDL-C in serum.

Effect of Anka on Levels of Liver Triglycerides and Cholesterol. The level of stored triglycerides in the liver of 30% fructose-fed rats (group 3) was remarkably elevated as compared with that of basal diet-fed rats (group 1) (Figure 4A). Stored triglycerides in 30% fructose−Anka-fed rats (group 4) were slightly lower, while those in the 30% fructose-fed group (group 3) were significantly elevated as compared to the basal diet (group 1). Levels in 30% fructose−lovastatin-fed rats (group 5) did not significantly differ from those of the 30% fructose-fed group (group 3). Similar results were obtained in basal diet-fed rats (group 1) and Anka-fed rats (group 2). These data suggest that Anka exhibits a weak inhibitory effect on the level of triglycerides in the liver. As illustrated in Figure 4B, the cholesterol level was no different between basal diet-fed rats (group 1) and Anka-fed rats (group 2). The level of stored cholesterol in 30% fructose−Anka-fed rats (group 4) had

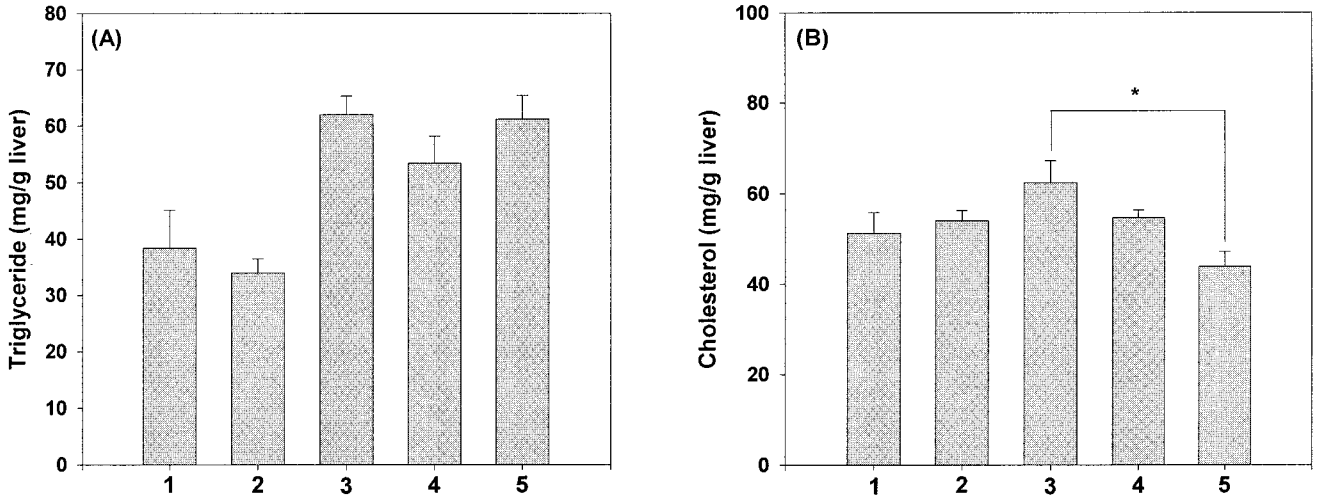

Figure 4. Liver levels of triglycerides (A) and total cholesterol (B) in SD rats fed 2.0% Anka for 6 months. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. *Significant differences between groups ($p < 0.05$).

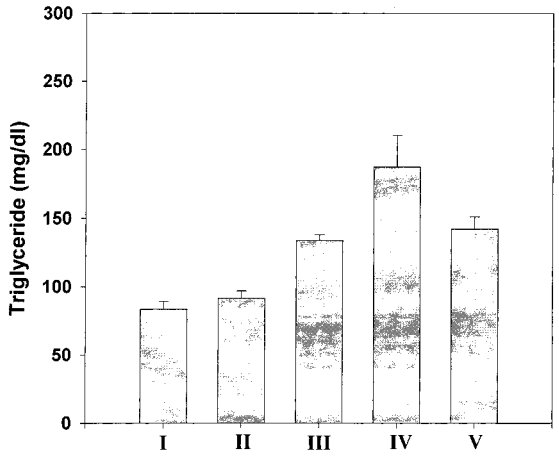

Figure 5. Effect of Anka on serum triglyceride levels in hypertriglyceridemic SD rats. Data are presented as the mean ± SE from six rats per group. Column I, fed basal diet for 3 months; column II, fed basal diet for 6 months; column III, fed 30% fructose for 3 months; column IV, fed 30% fructose for 6 months; column V, fed 30% fructose for 3 months followed by 30% fructose−2.0% Anka for 3 months.

slightly decreased, but was significantly elevated in the 30% fructose-fed group (group 3). The level of liver cholesterol in 30% fructose−lovastatin-fed rats (group 5) was significantly lower than that of 30% fructose-fed rats (group 3) ($p < 0.05$). These results indicate that lovastatin reduces the amount of cholesterol in the liver, and that Anka also shows a similar effect.

Effect of Anka on Serum Triglycerides in Hypertriglyceridemic Rats. We determined whether Anka is able to suppress serum triglycerides after 30% fructose-induced hypertriglyceridemia. The rats were assigned different diets: a basal diet group (6 rats) and a 30% fructose group (12 rats). After 3 months, the levels of serum triglycerides in these two groups were determined (Figure 5; columns I and III). Hypertriglyceridemia was induced in 30% fructose-fed rats (column III) as compared to the basal diet-fed rats (column I) ($p < 0.0005$). The 30% fructose-fed rats (column III) were randomly assigned to one of two groups (six rats per group). One group was constantly fed 30% fructose, and the other was fed 30% fructose−Anka for an additional 3 months (columns IV and V, respectively). The basal diet group (column I) also continued an additional 3 months on the basal diet (column II). The levels of serum triglycerides significantly increased in the 30% fructose-fed group (column IV) compared to those of the basal diet-fed group (column II) ($p < 0.005$) (Figure 5). The level of serum triglycerides of the 30% fructose−Anka-fed group (column V) was suppressed and was lower than that of the 30% fructose-fed group (column IV). These results indicate that Anka can decrease and suppress serum triglycerides in rats with induced hypertriglyceridemia.

Effect of Anka on the Activity of Hepatic Lipase and Lipoprotein Lipase in Liver and Adipose Tissue. We examined the activity of hepatic lipase and lipoprotein lipase in SD rats fed 2.0% Anka for 6 months. Figure 6A shows that the activity of hepatic lipase was enhanced in Anka-fed rats (groups 2 and 4) as compared to that of basal diet-fed rats (group 1) and 30% fructose-fed rats (group 3), respectively. The increment was statistically significant ($p < 0.05$). The 30% fructose−lovastatin-fed rats (group 5) showed no altered hepatic lipase activity. Figure 6B shows that the activity of lipoprotein lipase also increased in Anka-fed rats (groups 2 and 4) as compared to those of basal diet-fed rats (group 1) and 30% fructose-fed rats (group 3), respectively. This increment was not significant ($p > 0.1$). The 30% fructose−lovastatin-fed rats (group 5) showed no altered lipoprotein lipase activity.

Effect of Anka on Adipose Tissue Weight. The weight of epididymal adipose tissue was determined. Relative adipose tissue weight was lower in Anka-fed rats (group 2) than in basal diet-fed rats (group 1); it was lower in 30% fructose−Anka-fed rats (group 4) than in 30% fructose-fed rats (group 3), respectively (Figure 7). These differences were not statistically significant ($p > 0.1$).

Effect of Anka on the Activity of Superoxide Dismutase in Serum. Figure 8 shows that Anka could not affect the activity of SOD in serum between basal diet-fed rats (group 1) and Anka-fed rats (group 2). The activity of SOD had slightly increased in 30% fructose−Anka-fed rats (group 4) compared to that of 30% fructose-fed rats (group 3).

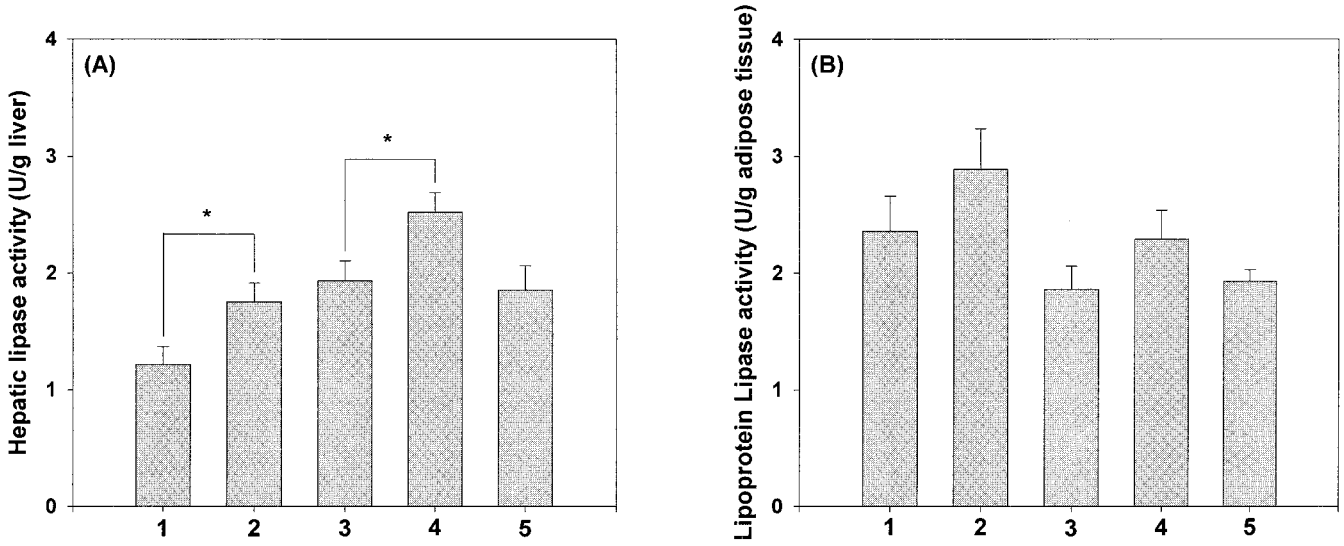

Figure 6. Effect of Anka on the activity of hepatic lipase (A) and lipoprotein lipase (B) in the liver and adipose tissue of SD rats. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin. *Significant differences between groups ($p < 0.05$).

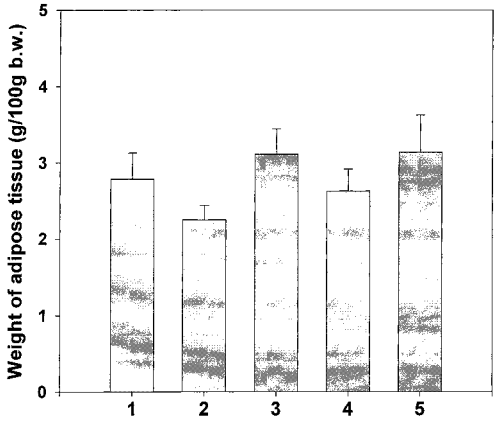

Figure 7. Effect of Anka on the weights of epididymal adipose tissue in SD rats. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin.

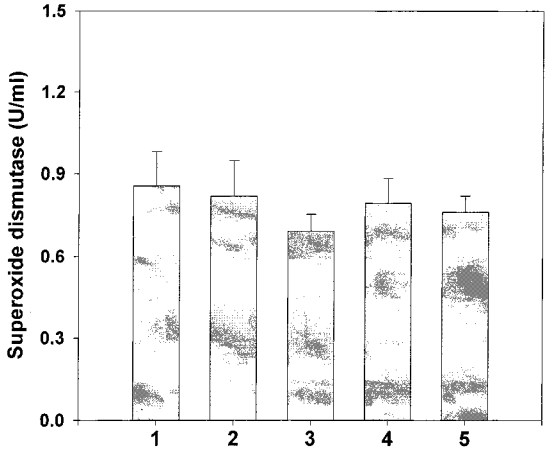

Figure 8. Effect of Anka on the activity of superoxide dismutase in the serum of SD rats. Data are presented as the mean ± SE from six rats per group. Group 1, basal diet; group 2, 2.0% Anka; group 3, 30% fructose; group 4, 30% fructose and 2.0% Anka; group 5, 30% fructose and 250 mg/kg lovastatin.

DISCUSSION

Hypercholesterolemia and hypertriglyceridemia, as predisposing factors for atherosclerosis and coronary heart disease (CHD), are of concern and have been intensively studied (Adlersberg, 1951; Albrink et al., 1961; Brown et al., 1965; Kannel et al., 1971; Epstein and Ostrander, 1971). Several workers have also investigated the associations of plasma cholesterol and lipoprotein concentrations with atherosclerosis. Increased levels of plasma cholesterol, LDL-C, and VLDL-C are risk factors contributing to the development of coronary heart diseases (Hollman et al., 1996) and atherosclerosis (Reaven and Witztum, 1996). The association of serum lipids with coronary heart disease has been studied extensively in middle-aged men and, to a lesser extent, in middle-aged women (Gordon et al., 1977a,b; Kannel et al., 1979; Neaton et al., 1992). In middle-aged populations, coronary heart disease risk is positively associated with total cholesterol and LDL-C and inversely associated with HDL-C. Additional coronary heart disease risk factors include cigarette smoking, above-optimal blood pressure, and diabetes mellitus. In this study, significantly lowered serum triglycerides, total cholesterol, VLDL-C, and LDL-C, and slightly increased serum HDL-C were observed in 30% fructose-2% Anka-fed rats compared with 30% fructose-fed rats. Similar results were also seen in induced-hypertriglyceridemic rat models. Our results strongly suggest that Anka exerts an anti-hyperlipidemic effect and therefore might have a protective effect against the atherosclerotic and coronary heart disease process.

Anka is produced by fermentation of rice by the microorganism *Monascus* sp. Potent inhibitors of HMG-CoA reductase have been isolated from *Monascus ruber*, which include monacolin J, K (mevinolin; lovastatin), L, M, X, and dihydromonacolin L (Endo, 1979, 1980, 1985; Endo et al., 1985a,b, 1986). Lovastatin, an HMG-CoA reductase inhibitor, is also found in Anka. These compounds are effective in lowering plasma cholesterol levels in various mammalian species, including humans, and are thereby effective in hypercholesterolemia therapy (Endo, 1985). These data suggest that Anka may be able to inhibit cholesterol concentrations in serum and liver

because of its potent inhibition of cholesterol synthesis. Interestingly, in the present study, Anka was found to suppress an increase of serum triglycerides when rats had been induced to be hypertriglyceridemic. Furthermore, lovastatin is devoid of hypotriglyceridemic action under similar animal experimental conditions. In view of the fact that hypertriglyceridemia and hypercholesterolemia may occur simultaneously in some hyperlipidemic patients, Anka may be regarded as a better remedy for some hyperlipidemic patients in the future.

Questions remain as to the mechanism of reducing serum triglycerides in Anka-fed rats. Are triglycerides stored in the liver or adipose tissue? In our data, triglycerides were not stored in the liver or adipose tissue, because the levels of triglycerides of the liver and adipose tissue did not increase in Anka-fed rats, but slightly decreased. Therefore, we propose that the synthesis of triglycerides may be inhibited in the liver or there may be enhanced uptake by extrahepatic tissues. Still, there is another possibility that triglycerides are rapidly metabolized by oxidation.

Hepatic lipase activity increased in Anka-fed rats compared to control rats. Experimental and clinical data indicate that elevated hepatic lipase activity is associated with conditions predisposed to accelerated atherosclerosis (Olivecrona and Olivecrona, 1995). In humans, hepatic lipase activity correlates with the fractional removal rate of HDLs, while an inverse correlation is present between this parameter and the lipoprotein lipase/hepatic lipase ratio (Brinton et al., 1991). Clinical observations confirm these physiopathologic findings. Moreover, reduced lipoprotein lipase and increased hepatic lipase activities have been measured in hypertriglyceridemic patients with coronary heart disease, in comparison with patients with normal triglyceride levels (Karpe et al., 1993). However, it seems that the lipoprotein lipase/hepatic lipase ratio is more important, and this ratio is lower in hypertriglyceridemia. In our data, the lipoprotein lipase/hepatic lipase ratio of group 3 was significantly lower (0.960 ± 0.175) than that in group 1 (1.942 ± 0.241) ($p < 0.005$), but the ratio did not significantly differ between groups 3 and 4 (0.960 ± 0.175 vs 0.907 ± 0.189), or groups 1 and 2 (1.942 ± 0.241 vs 1.64 ± 0.203) (Figure 6). Therefore, the levels of HDL-C were still slightly higher in Anka-fed rats, although the hepatic lipase was higher. It seems that the possible adverse effect of elevated hepatic lipase is counteracted by the elevated lipoprotein lipase.

LDL oxidation plays an important role in the development of atherosclerosis (Steinberg, 1997). Oxidized LDL can promote atherogenesis by its cytotoxicity, its chemotactic effects on monocytes, its inhibitory effects on macrophage motility, and its uptake by the macrophage scavenger receptor, resulting in stimulation of cholesterol accumulation and hence foam cell formation. There are several studies suggesting that naturally occurring antioxidants in the diet may play a role as antiatherosclerotic agents. Lovastatin (mevinolin; monacolin K) has been shown to induce a lesser but significant decrease in lipid peroxides, indicating that lovastatin may have antioxidant activity (Singh et al., 1997). In this study, we found that SOD activity in serum only slightly increased in Anka-fed rats. The activity of SOD may be enhanced in long-term treatment.

In summary, the levels of serum triglycerides, total cholesterol, VLDL-C, and LDL-C significantly decreased, and the level of the HDL-C slightly increased in 30% fructose−Anka-fed rats as compared with those in 30% fructose-fed rats. Noninduced hypertriglyceridemic rat models also exhibit similar results. Interestingly, Anka can also suppress the level of the serum triglycerides in rats with induced hypertriglyceridemia. The significance of these results suggests that Anka can be used as a hypotriglyceridemic agent in the future.

ABBREVIATIONS USED

HDL-C, high-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; SOD, superoxide dismutase.

LITERATURE CITED

Adlersberg, D. Hypercholesteremia with predisposition to atherosclerosis: an inborn error of lipid metabolism. *Am. J. Med.* **1951**, *11*, 600−614.

Albrink, M. J.; Meigs, J. W.; Man, E. B. Serum lipids, hypertension, and coronary artery disease. *Am. J. Med.* **1961**, *31*, 4−23.

Austin, M. A. Plasma triglyceride as a risk factor for coronary heart disease. The epidemiologic evidence and beyond. *Am. J. Epidemiol.* **1989**, *129*, 249−259.

Bengtsson-Olivecrona, G.; Olivecrona, T. Converse, C. A., Skinner, E. R., Eds.; Assay of Lipoprotein Lipase and Hepatic Lipase. In *Lipoprotein Analysis. A Practical Approach*; Oxford University Press: Oxford, 1992; pp 169−185.

Brinton, E. A.; Eisenberg, S.; Breslow, J. L. Increased apo A−I and apo A-II fractional catabolic rate in patients with low high-density lipoprotein-cholesterol levels with or without hypertriglyceridemia. *J. Clin. Invest.* **1991**, *87*, 536−544.

Brown, D. F.; Kinch, S. H.; Doyle, J. T. Serum triglyceritles in health and in ischaemic heart disease. *N. Engl. J. Med.* **1965**, *273*, 947−952.

Cambien, E.; Jacqueson, A.; Richard, J. L.; Warnet, J. M.; Ducimetiere, P.; Claude, J. R. Is the level of serum triglyceride a significant predictor of coronary death in "normocholesterolemic" subjects? The Paris prospective study. *Am. J. Epidemiol.* **1986**, *124*, 624−632.

Chobanian, A. V. Single risk factor intervention may he inadequate to inhibit atherosclerosis progression when hypertension and hypercholesterolemia coexist. *Hypertension* **1991**, *18*, 130−131.

Endo, A. Compactin (MG236B) and related compounds as potential cholesterol lowering agents that inhibit HMG-CoA reductase. *J. Med. Chem.* **1985**, *28*, 401−405.

Endo, A.; Monacolin, K. A new hypocholesterolemic agent that specifically inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase. *J. Antibiot.* **1980**, *33*, 334−336.

Endo, A.; Monacolin, K. A new hypocholesterolemic agent produced by a Monascus species. *J. Antibiot.* **1979**, *32*, 852−854.

Endo, A.; Hasumi, K.; Nakamura, T.; Kunishima, M.; Masuda, M. Dihydromonacolin L and monacolin Y new metabolites those inhibit cholesterol biosynthesis. *J. Antibiot.* **1985a**, *38*, 321−327.

Endo, A.; Hasumi, K.; Negishi, S. Monacolins J and L, new inhibitors of cholesterol biosynthesis produced by Monascus ruber. *J. Antibiot.* **1985b**, *38*, 420−422.

Endo, A.; Komagata, D.; Shimada, H. Monacolin M. A new inhibitor of cholesterol biospthesis. *J. Antibiot.* **1986**, *39*, 1670−1673.

Epstein, F. H.; Ostrander, L. D., Jr. Detection of individual susceptibility toward coronary disease. *Frog. Cardiovosr. Dis.* **1971**, *13*, 324−342.

Folch, J.; Lees, M.; Sloane, S, G. H. A simple method for the isolation and purification of total lipids from animal tissues. *J. Biol. Chem.* **1957**, *226*, 497−509.

Gordon, T.; Castelli, W. P.; Hjortland, M. C.; Kannel, W. E.; Dawber, T. R. Predicting coronary heart disease in middle-aged and older persons: the Framingham Study. *JAMA* **1977a**, *238*, 497−499.

Gordon, T.; Castelli, W. P.; Hjortland, M. C.; Kannel, W. E.; Dawber, T. R. High-density lipoprotein as a protective factor against coronary heart disease. *Am. J. Med.* **1977b**, *62*, 707−714.

Hara, T.; Cameron-Smith, D.; Cooney, G. J.; Kusunoki, M.; Tsutsumi, K.; Storlien, L. H. The actions of a novel lipoprotein lipase activator, NO-1886, in hypertriglyceridemic fructose-fed rats. *Metabolism* **1998**, *47*, 149−153.

Hollman, P. C.; Hertog, M. G. L.; Katan, M. B. Role of dietary flavonoids in protection against cancer and coronary heart disease. *Biochem. Soc. Trans.* **1996**, *24*, 785−789.

Kannel, W. B.; Castelli, W. P.; Gordon, T.; McNamara, P. M. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. *Ann. Intern. Med.* **1971**, *74*, 1−12.

Kannel, W. E.; Castelli, W. P.; Gordon, T. Cholesterol in the prediction of atherosclerotic disease. *Ann. Intern. Med.* **1979**, *90*, 85−91.

Karpe, F.; Tornvall, P.; Olivecrona, T.; Steiner, G.; Carlson, L. A.; Hamsten, A. Composition of human low-density lipoprotein: effects of postprandial triglyceride-rich lipoproteins, lipoprotein lipase, hepatic lipase and cholesteryl ester transfer protein. *Atherosclerosis* **1993**, *98*, 33−49.

Neaten, J. D.; Blackbum, H.; Jacobs, D.; Kuller, L.; Lee, D.-J.; Sheruin, R.; Shih, J.; Stamler, I.; Wentwonh, D. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. *Arch. Intern. Med.* **1992**, *152*, 1490−1500.

Olivecrona, G.; Olivecrona, T. Triglyceride lipases and atherosclerosis. *Curr. Opin. Lipidol.* **1995**, *6*, 291−305.

Reaven, P. D. Witztum, J. L. Oxidized low-density lipoproteins in atherogenesis: role of dietary modification. *Annu. Rev. Nutr.* **1996**, *16*, 51−71.

Singh, R. B.; Singh, N. K.; Rastogi, S. S.; Wander, G. S.; Aslam, M.; Onouchi, Z.; Kummerow, F. A.; Nangia, S. Antioxidant effects of lovastatin and vitamin E on experimental atherosclerosis in rabbits. *Cardiovasc. Drugs Ther.* **1997**, *11*, 575−580.

Steinberg, D. Low-density lipoprotein oxidation and its pathobiological significance. *J. Biol. Chem.* **1997**, *272*, 20963−20966.

Terada, M.; Mizuhashi, F.; Tomita, T.; Murata, K. Effects of mepanipyrim on lipid metabolism in rats. *J. Toxicol. Sci.* **1998**, *23*, 235−241.

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