Differential effects of dietary fat on the tissue-specific expression of the apolipoprotein A-I gene: relationship to plasma concentration of high density lipoproteins[1]

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Abstract Isocaloric substitution of polyunsaturated fat for saturated fat reduces concentrations of total plasma cholesterol and high density lipoproteins (HDL) in nonhuman primates. The biochemical mechanisms through which polyunsaturated fat lowers plasma HDL concentrations are not well understood but must involve changes in HDL production or HDL clearance from plasma, or both. To determine whether dietary polyunsaturated fat (P/S = 2.2) alters apolipoprotein (apo) A-I production, African green monkeys (*Cercopithecus aethiops*) were fed diets containing polyunsaturated fat or saturated fat (P/S = 0.3) each in combination with high (0.8 mg/kcal) and low (0.03 mg/kcal) amounts of dietary cholesterol. Animals fed polyunsaturated fat at either cholesterol level had lower plasma concentrations of total cholesterol and HDL cholesterol. Plasma apoA-I concentration was reduced by 16% by polyunsaturated fat in the high cholesterol group. The rate of hepatic apoA-I secretion, as estimated by the accumulation of perfusate apoA-I during recirculating liver perfusion, was reduced by 19% in animals comsuming the high cholesterol, polyunsaturated fat diet. Hepatic apoA-I mRNA concentrations, as measured by DNA-excess solution hybridization, also were reduced by 22% in the high cholesterol, polyunsaturated fat-fed animals. In contrast, intestinal apoA-I mRNA concentrations were not altered by the type of dietary fat. Plasma apoA-II and hepatic apoA-II mRNA concentrations also were not altered by the type of dietary fat. These data indicate that dietary polyunsaturated fat can selectively alter the expression of the apoA-I gene in a tissue-specific manner. Correlation analysis showed a strong relationship ($r = +0.70$, $P < 0.001$) between plasma apoA-I and hepatic apoA-I mRNA concentrations suggesting that the plasma apoA-I concentration is determined to a significant degree by factors that regulate hepatic apoA-I mRNA concentrations. —**Sorci-Thomas, M., M. M. Prack, N. Dashti, F. Johnson, L. L. Rudel, and D. L. Williams.** Differential effects of dietary fat on the tissue-specific expression of the apolipoprotein A-I gene: relationship to plasma concentration of high density lipoproteins. *J. Lipid Res.* 1989. **30:** 1397–1403.

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Plasma lipoprotein concentrations are important factors in the development of atherosclerotic coronary heart disease. Epidemiological evidence associates increased plasma LDL concentrations with increased coronary heart disease risk and increased HDL concentrations with decreased coronary heart disease risk (1–3). Dietary fat and cholesterol may influence the development of atherosclerosis through effects on the concentrations and properties of lipoprotein particles. Understanding the biochemical mechanisms through which dietary fat and cholesterol alter plasma lipoprotein concentrations is clearly of importance for human health.

It is well recognized that isocaloric substitution of polyunsaturated fat for saturated fat results in reduced concentrations of total plasma cholesterol and LDL in human beings (4, 5), effects anticipated to reduce the risk of cardiovascular disease. Similar effects of polyunsaturated fat on total plasma cholesterol and LDL are seen in the African green monkey, an animal model in which hypercholesterolemia and atherosclerosis can be induced by modest levels of dietary cholesterol (6–9). In this species, reduction of the plasma cholesterol concentration due to a polyunsaturated fat-enriched diet is accompanied by a reduced level of aortic atherosclerosis (9). Paradoxically, polyunsaturated fat also reduces plasma HDL and apoA-I

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; apo, apolipoprotein.

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concentrations in humans (9, 10) and nonhuman primates (6–8), a response that may moderate the beneficial effects on LDL. As in humans, plasma HDL is negatively correlated with atherosclerosis in African green monkeys (11).

The biochemical mechanisms through which polyunsaturated fat lowers plasma HDL concentrations are not well understood. Diet-induced alterations in HDL concentrations must arise through changes in production, changes in catabolism, or both. In vivo turnover studies in humans (12) and nonhuman primates (7, 13) suggest that accelerated apoA-I clearance from the plasma may contribute to the reduction of HDL concentrations resulting from polyunsaturated fat-enriched diets. In another study in which saturated or polyunsaturated fat was fed with a high level of cholesterol, no change in the fractional catabolic rate of apoA-I was detected, suggesting indirectly that dietary fat altered the apoA-I production rate (10). More recently, liver perfusion studies have shown a 20% reduction in the production rate of HDL mass in African green monkeys fed polyunsaturated fat as compared to animals fed saturated fat (14). These results suggest that some of the effects of polyunsaturated fat occur at the level of HDL precursor production in the liver, perhaps reflecting alterations in the production of apoA-I. In the present study we have examined this point directly by determining the accumulation rates of apoA-I in liver perfusions and by determining the absolute quantities of apoA-I mRNA in the liver and small intestine of African green monkeys fed diets containing polyunsaturated fat or saturated fat. The results show that hepatic apoA-I production and mRNA concentrations are reduced to the same degree as plasma HDL and apoA-I concentrations in animals fed polyunsaturated fat-enriched diets containing an atherogenic level of cholesterol. The type of fat did not influence the concentrations of hepatic apoA-II mRNA or intestinal apoA-I mRNA. These data indicate that dietary fat can selectively alter the expression of the apoA-I gene in a tissue-specific manner. These data also provide evidence that plasma apoA-I concentrations are determined to a significant degree by factors that regulate the hepatic concentration of apoA-I mRNA.

EXPERIMENTAL PROCEDURES

Animals, diets, and liver perfusion

During a 5 year study, 25 adult male African green monkeys (*Cercopithecus aethiops*) were fed diets containing cholesterol and 40% of calories as fat, either saturated fat (polyunsaturated/saturated fatty acid ratio = 0.3) or polyunsaturated fat (polyunsaturated/saturated fatty acid ratio = 2.2) (8). Within the group of animals fed saturated fat (n = 12), animals consumed diets containing 0.03 mg of cholesterol/kcal (n = 4) or containing 0.8 mg cholesterol/kcal (n = 8). In the polyunsaturated fat group (n = 13), animals consumed diets containing 0.03 mg cholesterol/kcal (n = 5) or containing 0.8 mg cholesterol/kcal (n = 8). Complete descriptions of the diets can be found in reference 15. Animals were prepared for necropsy, and tissues were removed and frozen for storage as described (16). Liver perfusion studies were performed as described (17) with a separate group of 18 monkeys that were fed the higher amount of cholesterol and either saturated fat (n = 9) or polyunsaturated fat (n = 9). Four of the animals used for liver perfusion studies were fed crystalline cholesterol instead of egg yolk cholesterol at 0.74 mg/kcal.

Isolation and characterization of cellular RNA

Total cellular RNA was prepared as described (16). RNA was prepared from large sections of liver (1–2 g) to minimize sampling error. The upper half of the small intestine (duodenum and jejunum) was sectioned into two pieces of equal weight designated intestine 1 and intestine 2. RNA was prepared from a random sample of tissue fragments (1–2 g) from each section of the intestine as described (16). The integrity of all RNA samples was assessed by electrophoresis in a 1.2% agarose gel containing 2.2 M formaldehyde (16).

Probes and solution hybridization

ApoA-I mRNA was measured by DNA-excess solution hybridization with a single-stranded apoA-I cDNA probe exactly as described (16). A similar assay was constructed for apoA-II mRNA. A 370 nucleotide single-stranded probe (of which 333 nucleotides correspond to apoA-II mRNA) was prepared with an M13mp11-apoA-II subclone containing a Pst I-Sst I fragment of human apoA-II cDNA (18) (corresponding to nucleotide +36 to +368 of apoA-II mRNA). Probe synthesis, probe purification, and the hybridization assay were carried out exactly as described (16, 19). S1 nuclease protection analysis (16) showed that the apoA-II cDNA probe was completely protected by RNA from monkey liver or human HepG2 cells (data not shown).

Plasma cholesterol, HDL cholesterol, and apolipoprotein mass determination

Total cholesterol and HDL cholesterol determinations were measured by standardized methods (20). HDL was chromatographically separated from other lipoproteins, and cholesterol was quantified as described previously (21). ApoA-I was quantified by an enzyme-linked immunosorbent assay as previously described (22), and apoA-II was measured by radial immunodiffusion assay (7).

Statistical analysis

Statistical analyses were performed by two-way analysis of variance or Student's *t*-test. In the case of significant interactions of dietary fat and cholesterol, all pairwise comparisons were made with Student's *t*-test, and the significance level was corrected using the Bonferoni technique (23).

RESULTS

Adult male African green monkeys were maintained on low or high cholesterol-containing diets including 40% of calories as either saturated or polyunsaturated fat. Concentrations of total plasma cholesterol, HDL-cholesterol, apoA-I, and apoA-II were determined for each animal several times during the 5 year study, and mean (± SEM) values for each group are shown in **Table 1.** Total plasma cholesterol and HDL cholesterol concentrations were responsive to the type of dietary fat and the level of dietary cholesterol. In the high cholesterol diet group, total plasma cholesterol and HDL-cholesterol concentrations were lower by 13% and 28%, respectively, in the polyunsaturated fat-fed animals. A dietary fat effect on plasma apoA-I was evident only in the high cholesterol diet groups in which apoA-I concentrations were 16% lower in the polyunsaturated fat-fed animals as compared to the saturated fat-fed animals. Although this decrease in plasma apoA-I concentration did not reach statistical significance due to the small number of animals per group, the magnitude of the decrement is nearly identical to that reported in previous studies (7, 14, 15). The present animals are, in fact, a subset of those from one such study in which plasma HDL-cholesterol and apoA-I concentrations were significantly reduced in animals fed the high cholesterol, polyunsaturated fat-containing diet (15). The mean decrement in plasma apoA-I concentration seen in this subset (Table 1) is thus representative of the change in the larger group (15) or as reported in other studies (7, 14). Also as reported previously (15), the plasma apoA-II concentration was similar in all diet groups.

In order to determine the importance of hepatic apoA-I production rates in the reduction of plasma apoA-I concentrations in polyunsaturated fat-fed animals, recirculating liver perfusions were carried out with a separate group of animals that received the higher level of dietary cholesterol in combination with either polyunsaturated or saturated fat. The rate of apoA-I accumulation in perfusate medium was determined by enzyme-linked immunoabsorbent assay. As shown in **Table 2**, the perfusate apoA-I accumulation rate was 19% lower in the polyunsaturated fat-fed animals. This difference is similar to that seen for the plasma apoA-I concentration suggesting that reduced hepatic apoA-I production contributes to the reduced plasma apoA-I concentration in polyunsaturated fat-fed animals.

ApoA-I mRNA concentrations were measured to determine whether the reduced rate of hepatic apoA-I production was due to changes in mRNA abundance. ApoA-I mRNA was measured by DNA-excess solution hybridization with a single-stranded apoA-I cDNA as described previously (16). As shown in **Table 3**, the apoA-I mRNA concentration was 22% lower in livers of animals fed the higher level of cholesterol with polyunsaturated fat as compared to saturated fat. Since the interaction in the analysis of variance was significant ($P < 0.02$), all pairwise comparisons were made by the Student's *t*-test corrected with the Bonferoni technique (23). This analysis indicated that the 22% decrement in apoA-I mRNA concentration in livers of polyunsaturated fat-fed animals (at the higher level of dietary cholesterol) was significant at the $P = 0.01$ level. This result suggests that the reduced hepatic apoA-I production rate in the polyunsaturated

TABLE 1. Plasma cholesterol, HDL cholesterol, apoA-I and apoA-II concentration

Diet	n	Fat Source	Total Plasma Cholesterol	HDL Cholesterol	Plasma ApoA-I	Plasma ApoA-II
				mg/dl		
Low cholesterol						
	4	S	168 ± 6	79 ± 3	272 ± 26	41 ± 2
	5	PS	143 ± 9	71 ± 5	274 ± 19	44 ± 3
High cholesterol						
	8	S	300 ± 16	115 ± 7	268 ± 10	49 ± 5
	8	PS	260 ± 19	83 ± 7	225 ± 19	43 ± 4
Significance as determined by two-way analysis of variance:						
Dietary fat			$P = 0.038$	$P < 0.004$	NS	NS
Dietary cholesterol			$P < 0.001$	$P < 0.001$	NS	NS
Interaction			NS	NS	NS	NS

Values are mean ± SEM. The mean for each animal represents multiple determinations (n > 4) per animal over at least a 1-year period of study. S, saturated fat; P, polyunsaturated fat; NS, not significant, $P > 0.05$.

TABLE 2. Liver perfusate apolipoprotein A-I accumulation

n	Fat Source	ApoA-I Accumulation
		μg/hr/g liver protein
9	S	102 ± 8
9	PS	83 ± 8

Values are mean ± SEM. Significance as determined by Student's *t*-test is $P = 0.057$. S, saturated fat; P, polyunsaturated fat.

fat-fed animals was due to lower concentrations of apoA-I mRNA. No statistically significant dietary fat effect on hepatic apoA-I mRNA concentration was seen in the animals receiving the lower level of dietary cholesterol. Plasma apoA-I concentrations also were not different between the groups fed the low cholesterol diet (Table 1 and ref. 15).

Hepatic apoA-II mRNA abundance was also measured to determine potential effects of dietary fat on the expression of the apoA-II gene in the liver. In contrast to the result with apoA-I mRNA, liver apoA-II mRNA concentrations were not significantly altered by any of the dietary manipulations (Table 3). Therefore, the effects of dietary cholesterol and fat saturation on hepatic apolipoprotein mRNA levels appears to be specific for apoA-I mRNA.

The concentration of apoA-I mRNA in the small intestine was measured to examine dietary cholesterol and fat effects on a tissue which contains approximately one-half of the total body apoA-I mRNA (16). RNA was prepared from the upper half of the small intestine which was divided into two equal-sized segments designated intestine 1 and 2. These regions of the small intestine contain the highest concentrations of apoA-I mRNA of all regions of intestine and account for about 70% of the total intestinal apoA-I mRNA in the African green monkey (16). As shown in **Table 4**, intestinal apoA-I mRNA concentrations were not different in any of the diet groups. These measurements were made with animals that were fasted for at least 12 h prior to being killed and would not reflect any acute changes in apoA-I mRNA concentration that might occur in response to feeding.

Liver apoA-I mRNA concentrations were directly compared to the plasma apoA-I concentrations for each of the monkeys in the study. **Fig. 1** shows that a positive correlation exists between the hepatic apoA-I mRNA abundance and plasma apoA-I concentration. Values for polyunsaturated fat-fed animals and saturated fat-fed animals fall on the same regression line which shows a correlation coefficient $r = 0.70$ ($P < 0.001$). Correlation of plasma apoA-I versus HDL-cholesterol showed a correlation coefficient $r = 0.4$ while no correlation was seen between hepatic apoA-I mRNA and HDL-cholesterol (data not shown). No significant relationship was seen when intestinal apoA-I mRNA concentrations were plotted versus plasma apoA-I concentrations (data not shown).

TABLE 3. Liver apolipoprotein A-I and A-II mRNA abundance

Diet	n	Fat Source	Apolipoprotein mRNA ApoA-I	Apolipoprotein mRNA ApoA-II
			pg/μg RNA	
Low cholesterol				
	4	S	66 ± 13	50 ± 7
	5	PS	75 ± 8	42 ± 12
High cholesterol				
	8	S	78 ± 4[a]	46 ± 6
	8	PS	61 ± 4[a]	49 ± 3
Significance as determined by two-way analysis of variance:				
Dietary fat			NS	NS
Dietary cholesterol			NS	NS
Interaction			$P < 0.02$	NS

Values are mean ± SEM. S, saturated fat; P, polyunsaturated fat; NS, not significant. The apoA-II mRNA values in the high cholesterol groups represent means from seven animals (S) and five animals (PS).
[a]Significance level is $P = 0.01$ as determined by Student's *t* test.

DISCUSSION

The results of this study indicate that when monkeys were fed an atherogenic level of cholesterol, dietary polyunsaturated fat significantly decreased the rate of hepatic apoA-I production. This effect of polyunsaturated fat appears to be mediated at the level of the hepatic apoA-I mRNA concentration which was reduced by 22% in the polyunsaturated fat-fed animals in the high cholesterol group. In contrast to the effect on the apoA-I mRNA concentration, hepatic apoA-II mRNA levels were not changed by dietary polyunsaturated fat. In stud-

TABLE 4. Intestinal apolipoprotein A-I mRNA abundance

Diet	n	Fat Source	Apolipoprotein A-I mRNA Intestine 1	Apolipoprotein A-I mRNA Intestine 2
			pg/μg RNA	
Low cholesterol				
	4	S	162 ± 26	104 ± 17
	5	PS	134 ± 22	118 ± 12
High cholesterol				
	5	S	144 ± 18	118 ± 11
	5	PS	159 ± 11	119 ± 3
Significance as determined by two-way analysis of variance:				
Dietary fat			NS	NS
Dietary cholesterol			NS	NS
Interaction			NS	NS

Values are mean ± SEM. S, saturated fat; P, polyunsaturated fat; NS, not significant.

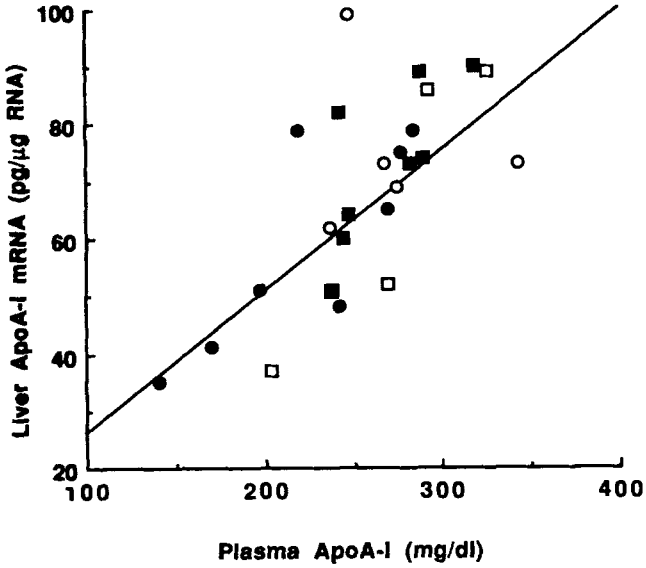

Fig. 1. Correlation between hepatic apoA-I mRNA concentrations and plasma apoA-I concentrations. Data points represent the values from each of the animals in the study. Plasma apoA-I values represent means from determinations on at least four separate samples from each animal. The correlation coefficient for the regression line, $r = 0.70$, is significant at the $P < 0.001$ level. Open circles, low cholesterol, polyunsaturated fat; closed circles, high cholesterol, polyunsaturated fat; open squares, low cholesterol, saturated fat; closed squares, high cholesterol, saturated fat.

ies to be reported elsewhere, apoB-100 mRNA concentrations and apoE mRNA concentrations and the production of apoB-100 and apoE by the liver also were not altered by dietary polyunsaturated fat (Prack, M. M., M. Sorci-Thomas, F. L. Johnson, D. L. Williams, and L. L. Rudel, unpublished results). Thus, the polyunsaturated fat effect on hepatic apolipoprotein production appears specific to apoA-I. Interestingly, dietary polyunsaturated fat did not alter the apoA-I mRNA concentration in the small intestine. These data indicate that dietary polyunsaturated fat can selectively alter the expression of the apoA-I gene in a tissue-specific manner.

Correlation analysis revealed a significant positive relationship between plasma apoA-I concentrations and liver apoA-I mRNA concentrations (Fig. 1). The results of this animal-by-animal correlation indicate that the hepatic concentration of apoA-I mRNA is an important factor in determining the plasma apoA-I concentration. Further support for this idea is the recent demonstration that the two- to threefold higher plasma concentration of HDL and apoA-I in African green monkeys as compared to cynomolgus monkeys is largely explained by differences in the rate of hepatic apoA-I production and correspondingly higher concentrations of hepatic and intestinal apoA-I mRNA (16).

The liver and the small intestine each contain about 50% of the the total body apoA-I mRNA in the African green monkey, suggesting that each organ contributes equally to the plasma apoA-I concentration (16). If it is assumed that intestinal apoA-I production was not altered by dietary fat, as suggested by intestinal apoA-I mRNA concentrations, a 32% decrease in hepatic apoA-I production is needed to account for the 16% decrease in the plasma apoA-I concentration (Table 1 and ref. 15). The finding that dietary polyunsaturated fat produced only a 22% reduction in hepatic apoA-I mRNA concentration and a 19% reduction in apoA-I accumulation in liver perfusate may indicate that dietary fat also influences the clearance of apoA-I from the plasma. Several previous studies in humans (12), African green monkeys (7), and rhesus monkeys (13) have, in fact, shown increased fractional catabolic rates of apoA-I due to dietary polyunsaturated fat. Thus, it appears that the reduction in plasma apoA-I and HDL concentrations by dietary polyunsaturated fat is the result of effects on both apoA-I production by the liver and apoA-I clearance from the plasma. It is not known whether these two effects are due to independent actions of dietary fat or to a common action that alters both metabolic pathways.

The dietary fat effect on hepatic apoA-I mRNA concentrations could be due to changes in apoA-I mRNA transcription or to changes at posttranscriptional steps such as mRNA processing or mRNA stability. How dietary fat could produce such changes in an mRNA-selective and tissue-specific manner is unknown. Since the dietary fat effect on apoA-I mRNA occurred only in animals fed the higher level of cholesterol, it is possible that the effect arises from dietary fat-mediated changes in cellular cholesterol metabolism and is not a direct result of the fat itself. This appears to be the case in the hamster in which saturated fat is known to facilitate the down-regulation of hepatic LDL receptor-dependent LDL uptake by dietary cholesterol (24, 25). In the hamster, the effects of dietary fat are very small unless cholesterol is also present in the diet (25). A similar effect may occur in the African green monkey in which a high level of dietary cholesterol is needed in order to detect a dietary fat effect on hepatic apoA-I mRNA abundance. The absence of a dietary fat effect at the lower level of dietary cholesterol may reflect a difference in sensitivity as compared to the hamster but not necessarily a difference in the cellular mechanism through which these lipids act. Polyunsaturated fat-fed monkeys accumulate more hepatic cholesteryl ester and secrete lipoprotein particles containing more cholesteryl ester than saturated fat-fed monkeys (17). It is possible that dietary fat alters a regulatory pool of cellular cholesterol or a metabolite in the sterol biosynthetic pathway that secondarily alters expression of the apoA-I gene.

In contrast to the effects on apoA-I, the concentration of plasma apoA-II and the concentration of hepatic apoA-II mRNA were not altered by the type of dietary fat. Previous studies have shown that plasma apoA-I and

apoA-II have different fractional catabolic rates and dissimilar kinetics of equilibration between chylomicrons and HDL (7, 12). The results of the present study further support the idea that the two major HDL apolipoproteins are regulated noncoordinately at the level of production as well as at the level of clearance from the plasma. In addition, our evidence indicates that while the liver and intestine produce apoA-I, the intestine does not produce apoA-II in the monkey (26). Therefore, the factors controlling tissue specific expression are different for these two HDL apolipoproteins.

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