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Short communication

The cholesterolaemic effects of dietary fats in cholesteryl ester transfer protein transgenic mice

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In order to investigate the role of cholesteryl ester transfer protein (CETP) in the cholesterolaemic response to dietary fats, we analysed plasma lipid profiles of CETP-transgenic and control C57BL/6 mice fed standard chow (AIN-93G; AIN), a low-fat diet, and diets high in butter (saturated fatty acids; SFA), high-oleic acid safflower oil (monounsaturated fatty acids; MUFA), and safflower oil (polyunsaturated fatty acids; PUFA) for 5 weeks. Each group contained four or five mice. There were significant diet and diet×genotype effects on plasma total cholesterol (TC; $P = 0{\cdot}035$ and $P = 0{\cdot}008$ respectively), liver TC ($P < 0{\cdot}001$ and $P = 0{\cdot}002$ respectively), and esterified cholesterol (EC; $P = 0{\cdot}002$ and $P = 0{\cdot}001$ respectively); diet effects on plasma triacylglycerol ($P = 0{\cdot}007$), liver free cholesterol ($P < 0{\cdot}001$), and body weight ($P = 0{\cdot}027$); a genotype effect on body-weight gain ($P = 0{\cdot}014$); and a diet×genotype effect on energy intake ($P = 0{\cdot}006$). In transgenic mice the SFA diet caused significantly higher plasma TC than the PUFA diet ($P < 0{\cdot}05$). In control mice MUFA and PUFA diets, but not the SFA diet, caused significantly higher plasma TC than the low-fat and AIN diets ($P < 0{\cdot}05$). Transgenic mice fed PUFA had lower plasma TC ($P = 0{\cdot}040$), while transgenic mice fed MUFA had lower LDL+VLDL-cholesterol ($P = 0{\cdot}013$) than controls in the same dietary groups. Transgenic mice fed MUFA and PUFA diets also had significantly higher liver TC ($P = 0{\cdot}020$ and $P = 0{\cdot}002$ respectively) and EC ($P = 0{\cdot}040$ and $P = 0{\cdot}036$ respectively) than controls fed the same diets. In the present study we showed that: (1) CETP transgenic mice had a cholesterolaemic response to dietary fats similar to that in human subjects; (2) CETP transgenic mice fed PUFA showed significantly lower plasma TC, while those fed MUFA had lower LDL+VLDL-cholesterol than controls; (3) hepatic accumulation of cholesterol, possibly resulting from the combination of the enhanced cholesteryl ester transfer to apolipoprotein B-containing lipoproteins and increased hepatic uptake of cholesterol, may contribute to the cholesterol-lowering effect of MUFA and PUFA in CETP-transgenic mice; (4) CETP may play a role in appetite and/or energy regulation.

Cholesteryl ester transfer protein: Cholesterol: Transgenic mice

Many investigators have examined the effects of different dietary fats on plasma lipid profiles in human subjects (Katan *et al.* 1994). In general, when replacing carbohydrate in the diet, saturated fatty acids (SFA), except stearic acid, raise plasma total cholesterol (TC) and LDL-cholesterol. On the other hand, monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) decrease TC and LDL-cholesterol. The mechanisms

Abbreviations: AIN, AIN-93G; CETP, cholesteryl ester transfer protein; LF, low fat; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TC, total cholesterol.

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Table 1. Composition of experimental diets

Diet…	AIN		LF		SFA, MUFA, PUFA	
Ingredient	g/100 g	g/MJ	g/100 g	g/MJ	g/100 g	g/MJ
Casein	20	11·96	18·82	11·96	23·87	11·96
L-cystine	0·3	0·179	0·28	0·179	0·36	0·179
Maize starch	39·71	23·76	47·98	30·50	12·53	6·28
Dextrinized starch	13·2	7·89	12·42	7·89	15·75	7·89
Sucrose	10	5·98	9·41	5·98	11·93	5·98
Cellulose	5	2·99	4·7	2·99	5·96	2·99
Soyabean oil	7	4·19	0	0	0	0
Safflower oil	0	0	1·88	1·20	2·39	1·20
Experimental oil*	0	0	0	0	21·48	10·77
AIN-93G mineral mix	3·5	2·09	3·29	2·09	4·18	2·09
AIN-93G vitamin mix	1	0·60	0·94	0·60	1·19	0·60
Choline bitartrate	0·25	0·150	0·235	0·150	0·298	0·150
t-Butylhydroquinone	0·0014	0·00084	0·00038	0·00024	0·0048	0·0024
Cholesterol†	0·0385	0·023	0·0362	0·023	0·0459	0·023
Energy (MJ/kg diet)	16·72		15·884		20·064	

AIN, basal (based on AIN-93G; Reeves *et al.* 1993*a*, *b*); LF, low-fat; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
* Butter in the SFA diet, high-oleic acid safflower oil in the MUFA diet, safflower oil in the PUFA diet.
† Cholesterol was not added to the SFA diet.

regulating the cholesterolaemic effects of dietary fats are complicated and still under investigation.

Cholesteryl ester transfer protein (CETP), a key enzyme in the reverse cholesterol transport process and remodelling of lipoproteins, mediates the exchange between cholesteryl ester in HDL and triacylglycerol in apolipoprotein B-containing lipoproteins (Tall, 1995). The objective of the present study was to evaluate the role of CETP in cholesterolaemic effects of dietary fats by comparing the responses of plasma lipoproteins to diets varying in fat quantity and fatty acid composition in C57BL/6 mice expressing and not expressing the human CETP gene.

Experimental methods

Materials

Sucrose, soyabean oil, butter and safflower oil were purchased from local grocery stores. High-oleic acid safflower oil was provided by Loriva Supreme Food Inc. (Ronkonkoma, NY, USA). All other dietary components were purchased from ICN Biochemicals Inc. (Costa Mesa, CA, USA).

Diets

The composition of the five diets used in the present study, all of which were formulated based on the AIN-93G diet (AIN; Reeves *et al.* 1993*a*, *b*), are shown in Table 1. All diets had the same amount of cholesterol (0·023 g/MJ) on an energy basis. Each high-fat diet contained 4·5 % energy from safflower oil, in addition to the respective experimental oil, for supplementation of essential fatty acids and control purposes. The major nutrient composition of the experimental diets, as a percentage of energy content, is presented in Table 2.

Animals

An animal protocol for the experiment was approved by The Ohio State University Institutional Laboratory Animal Care and Use Committee. Male C57BL/6 control and CETP-transgenic mice, 3–8 weeks old, were obtained from Taconic (Germantown, NY, USA). Five control and five transgenic mice were used initially in each diet group. The initial average body weight of each group was approximately 22 g, with no significant difference among groups (data not shown). One control mouse in the AIN dietary group and one transgenic mouse in each of the low-fat (LF) and MUFA dietary groups were removed from the study because of illness. A sample size of four or five animals per group was adequate to determine a 25–28 % difference in two means with a power of 0·8 at $P < 0·05$, assuming SD 20 % (Snedecor & Cochran, 1980). All animals were allowed to adapt to the environment for 1 week while being fed the AIN diet before the 5-week dietary treatment. Animals were housed individually with free access to food and water; the food was changed daily. The food containers were weighed before and after the food was consumed each day in order to monitor the food intake. At the end of the study mice were killed after an overnight fast. Livers were

Table 2. Nutrient composition of experimental diets (% food energy*)

Diet…	AIN	LF	SFA	MUFA	PUFA
Total fat	16·9	5·7	48·6	48·6	48·6
SFA	2·3	0·3	38·1	3·0	3·0
MUFA	3·8	0·7	3·2	33·0	6·9
PUFA	9·4	3·7	4·4	9·8	35·9
Total carbohydrate	64·2	73·4	32·8	32·5	32·5
Sugar	10·1	10·9	10·5	10·4	10·4
Starch	54·1	62·5	22·3	22·1	22·1
Protein	20·2	22·0	20·9	20·7	20·7

AIN, basal (based on AIN-93G; Reeves *et al.* 1993*a*, *b*); LF, low-fat; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
* Values for each component represent percentage of food energy. Food Processor Nutrition Analysis Software; ESHA Research 2000, Salem, OR, USA, was used to compute the amount of each component listed in each diet. When the food ingredient was not listed in the database, we added it using information from the manufacturer of the food ingredient. Values in the ESHA database are analyses published by the US Department of Agriculture.

removed and stored at −70°C; blood was collected into tubes containing a final concentration of 1 mM-EDTA. Plasma was obtained after centrifugation for 10 min at 4°C.

Plasma lipids, lipoproteins and CETP analyses

Plasma TC, HDL-cholesterol, and triacylglycerol were measured enzymically using commercial kits (Sigma Co., St Louis, MO, USA). HDL-cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins. LDL+VLDL-cholesterol was calculated by subtracting HDL-cholesterol from TC. Plasma CETP concentration was measured by a sandwich ELISA as described previously (Chang *et al.* 1999).

Liver cholesterol

Liver TC and free cholesterol contents were measured according to Carlson & Goldfarb (1977). Esterified cholesterol was calculated as the difference between TC and free cholesterol.

Statistical analyses

All statistical analyses were performed using the SAS program (version 6.12; Statistical Analysis System Inc., Cary, NC, USA). Initially, two-way ANOVA was used to analyse the main effects of (diet and genotype) and the interaction of diet×genotype on the lipid and lipoprotein variables investigated. When the diet effect was found to be significant, the least significant difference multiple comparison test was used to determine which two means were different from each other within the same genotype. When the interaction of diet×genotype was found to be significant, the data from transgenic and control mice of the same dietary group were analysed by the *t* test. A two-sided $P < 0{\cdot}05$ was considered statistically significant.

Results

Table 3 shows the plasma lipoprotein profiles, CETP concentration, body weight and liver cholesterol concentrations of control and transgenic mice at the end of the study, and *P* values for the main effects (diet and genotype) and interaction (diet×genotype) of these variables determined by two-way ANOVA. In control groups MUFA and PUFA caused significantly higher plasma TC than LF and AIN diets ($P < 0{\cdot}05$). Compared with the LF diet, on average, 86, 64 and 42 % of the increase in TC occurred in the HDL-cholesterol fraction in the SFA, MUFA and PUFA dietary groups respectively. Plasma triacylglycerol was higher in mice fed PUFA and AIN diets than in those fed the SFA and MUFA diets. Liver TC was significantly higher in mice fed AIN and LF diets than in those fed the SFA and MUFA diets ($P < 0{\cdot}05$). In addition, AIN and LF diets also caused higher liver esterified cholesterol than the three high-fat diets. However, the LF diet caused lower liver free cholesterol than the three high-fat diets.

In transgenic mice the SFA diet caused significantly higher plasma TC than the PUFA diet ($P < 0{\cdot}05$; Table 3). Liver TC was higher in mice fed the AIN and PUFA diets than in those fed the other three diets. Furthermore, liver free cholesterol was higher in mice fed the PUFA diet than in those fed the LF diet, while liver esterified cholesterol was higher in mice fed the AIN and PUFA diets than in those fed the LF and SFA diets.

Transgenic mice consuming PUFA had lower plasma TC than control mice in the same dietary group ($P = 0{\cdot}040$; Table 3). However, the proportions of lipoprotein subfractions remained similar between transgenic and control mice. In addition, a non-significant 16 % decrease in plasma TC was also found in transgenic mice compared with controls in the MUFA dietary group ($P = 0{\cdot}14$). In contrast to the PUFA dietary group, however, the lower plasma TC of transgenic mice in the MUFA dietary group mainly resulted from the significantly lower LDL+VLDL-cholesterol, compared with the controls ($P = 0{\cdot}013$). As a result, transgenic mice fed the MUFA diet when compared with controls consuming the same diet showed a significantly lower LDL+VLDL-cholesterol:TC ($P = 0{\cdot}035$). The transgenic mice fed MUFA and PUFA diets also had significantly higher liver TC ($P = 0{\cdot}020$ and $P = 0{\cdot}002$ respectively) and esterified cholesterol ($P = 0{\cdot}040$ and $P = 0{\cdot}036$ respectively) than controls consuming the same diets. Moreover, transgenic mice in the SFA ($P = 0{\cdot}020$) and MUFA ($P = 0{\cdot}004$) dietary groups consumed less energy than the controls consuming the same diets.

Discussion

To our knowledge, the present study is the first to investigate the cholesterolaemic effects of dietary fats in CETP-transgenic mice. Mice have a lipid metabolism distinct from that of human subjects, including the homogenous HDL which is the major plasma lipoprotein (LeBoeuf *et al.* 1983), increased hepatic lipase activity (Peterson *et al.* 1986), the lack of correlation between lipoprotein lipase activity and HDL-cholesterol concentrations (Clee *et al.* 1997), and the absence of CETP. However, we have shown in the present study that in CETP-transgenic mice the plasma cholesterol response to dietary fats resembles that of human subjects. In transgenic mice the diet high in SFA produced higher plasma TC than the PUFA diet. The SFA dietary group also had the highest LDL+VLDL-cholesterol of the five dietary groups. In addition, the lower HDL-cholesterol observed in the PUFA dietary group compared with the MUFA dietary group has also been reported in human subjects (Mata *et al.* 1992*a*, *b*). Thus, CETP may play a role in the cholesterolaemic responses to dietary fats in human subjects as indicated by the significant diet×genotype effect on plasma TC ($P = 0{\cdot}008$). This observation is also in agreement with the finding that transgenic mice expressing both human CETP and apolipoprotein B genes had plasma lipid profiles comparable with those of human subjects (Grass *et al.* 1995).

In the present study transgenic mice fed the PUFA diet had lower plasma TC, while transgenic mice consuming the MUFA diet had lower LDL+VLDL-cholesterol, compared with the respective controls consuming the same diets. In addition, transgenic mice fed MUFA and PUFA diets had higher liver TC and EC concentrations than controls

Table 3. Plasma lipid profiles, body weight (BW) and body-weight gain (BWG) of control and transgenic mice fed different diets varying in level and type of fat for 5 weeks†
(Mean values and standard deviations for no. of mice shown)

Diet‡	Genotype	*n*		TC (mmol/l)	HDL-C (mmol/l)	LDL+VLDL-C (mmol/l)	HDL-C:TC	LDL+VLDL-C:TC	TG (mmol/l)	CETP (ng/μl)	Liver TC (mg/g)	Liver FC (mg/g)	Liver EC (mg/g)	BW (g)	BWG (g)	Energy intake (KJ/d)
AIN	Control	4	Mean	2·73^{a}	1·63	1·26	0·56	0·44	1·85^{b}	ND	4·70^{c}	2·34^{a,b}	2·36^{b}	24^{a}	4	74·92
			SD	0·36	0·68	0·55	0·2	0·2	0·27		0·76	0·31	0·53	3	2	10·24
	Transgenic	5	Mean	2·90^{A,B}	2·27	0·86	0·73	0·27	1·81^{B}	1·06	4·46^{B}	2·52^{A,B}	1·93^{C}	22^{A}	1	78·97
			SD	0·34	0·19	0·32	0·09	0·09	0·49	0·46	0·26	0·25	0·46	3	1	3·87
LF	Control	5	Mean	2·89^{a}	1·85	1·05	0·63	0·37	1·56^{a,b}	ND	3·90^{b,c}	2·12^{a}	1·79^{b}	24^{a}	3	78·22
			SD	0·23	0·41	0·28	0·12	0·12	0·1		0·94	0·27	0·92	2	1	5·48
	Transgenic	4	Mean	2·85^{A,B}	1·92	0·93	0·67	0·33	1·42^{A,B}	2·46	2·95^{A}	2·31^{A}	0·64^{A}	25^{A,B}	2	82·64
			SD	0·12	0·37	0·3	0·11	0·11	0·25	2·61	0·36	0·2	0·52	1	3	4·37
SFA	Control	5	Mean	3·10^{a,b}	2·04	1·07	0·66	0·34	1·32^{a}	ND	2·89^{a}	2·61^{b,c}	0·28^{a}	26^{a,b}	5	84·36*
			SD	0·31	0·47	0·51	0·16	0·16	0·33		0·26	0·23	0·16	1	1	8·22
	Transgenic	5	Mean	3·43^{B}	2·22	1·21	0·65	0·35	1·18^{A}	1·45	3·32^{A}	2·73^{A,B}	0·57^{A}	25^{A,B}	2	71·93*
			SD	0·36	0·56	0·68	0·19	0·19	0·25	0·59	0·71	0·46	0·27	1	1	4·86
MUFA	Control	5	Mean	3·585^{b}	2·29	1·29*	0·64*	0·36*	1·25^{a}	ND	2·97^{a,*}	2·67^{c}	0·30^{a,*}	26^{a,b}	3	78·37*
			SD	0·45	0·35	0·36	0·09	0·09	0·27		0·22	0·05	0·24	5	4	4·25
	Transgenic	4	Mean	3·00^{A,B}	2·4	0·59*	0·79*	0·21*	1·41^{A,B}	2·57	3·34^{A,*}	2·56^{A,B}	0·78^{A,B,*}	26^{B}	3	67·87*
			SD	0·61	0·69	0·23	0·09	0·09	0·48	1·55	0·11	0·3	0·34	4	2	2·62
PUFA	Control	5	Mean	3·49^{b,*}	2·1	1·38	0·6	0·4	1·73^{b}	ND	3·13^{a,b,*}	2·56^{b,c}	0·56^{a,*}	30^{b}	6	80·52
			SD	0·53	0·92	0·76	0·24	0·24	0·29		0·15	0·13	0·27	5	4	5·94
	Transgenic	5	Mean	2·50^{A,*}	1·64	0·86	0·65	0·35	1·36^{B}	2·42	4·15^{B,*}	2·90^{B}	1·26^{B,*}	26^{B}	2	81·59
			SD	0·53	0·48	0·25	0·09	0·09	0·3	1·27	0·39	0·27	0·47	4	3	6·98
Main effects of ($P =$):																
Diet				0·035§	0·331	0·874	0·740	0·740	0·007§	0·464	<0·001§	<0·001§	0·002§	0·027§	0·346	0·053
Genotype				0·074	0·522	0·037§	0·089	0·089	0·280	<0·001§	0·402	0·078	0·871	0·146	0·014§	0·233
Diet×genotype				0·008§	0·455	0·333	0·700	0·700	0·555	0·464	0·002§	0·001§	0·001§	0·524	0·389	0·006§

a,b,c For control mice mean values within columns with unlike superscript letters were significantly different ($P < 0·05$).
A,B,C For transgenic mice mean values within columns with unlike superscript letters were significantly different ($P < 0·05$).
AIN, AIN-93G (Reeves *et al.* 1993*a*, *b*); LF, low-fat; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; TC, total cholesterol, HDL-C, HDL-cholesterol; VLDL-C, VLDL-cholesterol; TG, triacylglycerols; CETP, cholesteryl ester transfer protein; FC, free cholesterol; EC, esterified cholesterol; ND, not detectable.
Mean values were significantly different from those for the other strain of mice consuming the same diet: *$P < 0·05$.
† For details of procedures, see p. 644.
‡ For details of composition, see Tables 1 and 2.
§ *P* values reached significance.

consuming the same diets. It has been shown that PUFA and MUFA, in contrast to SFA, prevented diet-induced hepatic LDL receptor suppression in hamsters (Kurushima *et al.* 1995) and enhanced LDL receptor activity in BHK-21 cells (Bucci *et al.* 1998). Possibly, in the presence of CETP more cholesteryl ester was transferred from HDL to apolipoprotein B-containing lipoproteins that were subsequently cleared by hepatic LDL receptors. Thus, the combination of accelerated cholesterol transfer to apolipoprotein B-containing lipoproteins and increased hepatic uptake of these lipoproteins resulted in significantly lower LDL+VLDL-cholesterol in transgenic mice fed the MUFA diet ($P = 0{\cdot}013$) and a 38 % but non-significant ($P = 0{\cdot}24$), decrease in plasma LDL+VLDL-cholesterol in transgenic mice consuming PUFA. This viewpoint is further supported by the significantly higher liver TC ($P = 0{\cdot}020$ and $P = 0{\cdot}002$ respectively) and EC ($P = 0{\cdot}040$ and $P = 0{\cdot}036$ respectively) observed in transgenic mice fed MUFA and PUFA diets compared with controls consuming the same diets. The absence of this cholesterol-lowering effect in transgenic mice fed the SFA diet was possibly a result of the inability of SFA to maintain hepatic LDL receptor activity (Bucci *et al.* 1998).

Our data suggested that the expression of CETP in this strain of transgenic mice, in which the human CETP gene was attached to apolipoprotein A-I promoter instead of its natural flanking region, was not regulated by dietary fats or cholesterol. This finding was contradictory to that in CETP mice with the natural flanking region that contained cholesterol response element (Gauthier *et al.* 1999), in which the expression of CETP was up regulated by dietary cholesterol (Jiang *et al.* 1992). In view of the lack of the DNA sequences required for its regulation, it is reasonable that the expression of the transgene would be different in the strain of mice used in the present study. The expression of apolipoprotein A-I, whose promoter controlled the expression of the CETP transgene in this animal model, is regulated by neither dietary fats nor cholesterol in intestine, and is also not affected by dietary fats in the liver when cholesterol consumption is low (Sorci-Thomas *et al.* 1989). Thus, considering the low dietary cholesterol level we used in the present study, the apolipoprotein A-I promoter that controlled the expression of CETP in this strain of mice did not respond to either dietary fat or cholesterol. Thus, plasma CETP levels did not differ significantly among the five diet groups.

Surprisingly, we also showed a significant genotype effect on body-weight gain ($P = 0{\cdot}014$), diet effect on body weight ($P = 0{\cdot}027$), and diet×genotype effect on energy intake ($P = 0{\cdot}006$). These results may indicate that CETP plays a role in appetite regulation and/or energy metabolism. This hypothesis warrants further research.

We fully recognize the relatively low statistical power of the present study, resulting from the limited number of animals in each group. The expected HDL-cholesterol lowering effect of CETP was not statistically significant. It may become significant with larger sample sizes. However, the present study did show some interesting and statistically significant effects on lipid metabolism in this potentially-useful animal model and suggest future research directions. In summary, in the present study, we showed that: (1) CETP-transgenic mice had a cholesterolaemic response to dietary fats similar to that in human subjects; (2) CETP-transgenic mice fed PUFA showed significantly lower plasma TC levels, while those fed MUFA had lower LDL+VLDL-cholesterol than controls; (3) the hepatic accumulation of cholesterol, possibly resulting from the combination of the enhanced cholesteryl ester transfer to apolipoprotein B-containing lipoproteins and increased hepatic uptake of cholesterol, may contribute to the cholesterol-lowering effect of MUFA and PUFA in CETP-transgenic mice; (4) CETP may play a role in appetite and/or energy regulation.

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References

Bucci C, Seru R, Annella T, Vitelli R, Lattero D, Bifulco M, Mondola P & Santillo M (1998) Free fatty acids modulate LDL receptor activity in BHK-21 cells. *Atherosclerosis* **137**, 329–340.

Carlson SE & Goldfarb S (1977) A sensitive enzymatic method for determination of free and esterified tissue cholesterol. *Clinica Chimica Acta* **79**, 575–582.

Chang CK, Tso TK, Snook JT, Zipf WB & Lozano RA (1999) Sandwich enzyme-linked immunosorbent assay for plasma cholesteryl ester transfer protein. *Clinical Biochemistry* **32**, 257–262.

Clee SM, Zhang H, Bissada N, Miao L, Ehrenborg E, Benlian P, Shen GX, Angel A, LeBoeuf RC & Hayden MR (1997) Relationship between lipoprotein lipase and high density lipoprotein cholesterol in mice: modulation by cholesteryl ester transfer protein and dietary status. *Journal of Lipid Research* **38**, 2079–2089.

Gauthier B, Robb M, Gaudet F, Ginsburg GS & McPherson R (1999) Characterization of a cholesterol response element (CRE) in the promoter of the cholesteryl ester transfer protein gene: functional role of the transcription factors SREBP-1a, -2, and YY1. *Journal of Lipid Research* **40**, 1284–1293.

Grass DS, Saini U, Felkner RH, Wallace RE, Lago WJ, Young SG & Swanson ME (1995) Transgenic mice expressing both human apolipoprotein B and human CETP have a lipoprotein cholesterol distribution similar to that of normolipidemic humans. *Journal of Lipid Research* **36**, 1082–1091.

Jiang XC, Agellon LB, Walsh A, Breslow JL & Tall A (1992) Dietary cholesterol increases transcription of the human cholesteryl ester transfer protein gene in transgenic mice. Dependence on natural flanking sequences. *Journal of Clinical Investigation* **90**, 1290–1295.

Katan MB, Zock PL & Mensink RP (1994) Effects of fats and fatty acids on blood lipids in humans: an overview. *American Journal of Clinical Nutrition* **60**, 1017S–1022S.

Kurushima H, Hayashi K, Toyota Y, Kambe M & Kajiyama G (1995) Comparison of hypocholesterolemic effects induced by dietary linoleic acid and oleic acid in hamsters. *Atherosclerosis* **114**, 213–221.

LeBoeuf RC, Puppione DL, Schumaker VN & Lusis AJ (1983) Genetic control of lipid transport in mice. I. Structural properties and polymorphisms of plasma lipoproteins. *Journal of Biological Chemistry* **258**, 5063–5070.

Mata P, Alvarez-Sala LA, Rubio MJ, Nuno J & De Oya M

(1992*a*) Effects of long-term monounsaturated- vs polyunsaturated-enriched diets on lipoproteins in healthy men and women. *American Journal of Clinical Nutrition* **55**, 846–850.

Mata P, Garrido JA, Ordovas JM, Blazquez E, Alvarez-Sala LA, Rubio MJ, Alonso R & de Oya M (1992*b*) Effect of dietary monounsaturated fatty acids on plasma lipoproteins and apolipoproteins in women. *American Journal of Clinical Nutrition* **56**, 77–83.

Peterson J, Bengtsson-Olivecrona G & Olivecrona T (1986) Mouse preheparin plasma contains high levels of hepatic lipase with low affinity for heparin. *Biochimica et Biophysica Acta* **878**, 65–70.

Reeves PG, Nielsen FH & Fahey GC Jr (1993*a*) AIN-93 purified diets for laboratory rodents: final report of the American Institute of Nutrition ad hoc writing committee on the reformulation of the AIN-76A rodent diet. *Journal of Nutrition* **123**, 1939–1951.

Reeves PG, Rossow KL & Lindlauf J (1993*b*) Development and testing of the AIN-93 purified diets for rodents: results on growth, kidney calcification and bone mineralization in rats and mice. *Journal of Nutrition* **123**, 1923–1931.

Snedecor GW & Cochran WG (1980) *Statistical methods*, 7th ed. Ames, IA: The Iowa State University Press.

Sorci-Thomas M, Prack MM, Dashti N, Johnson F, Rudel LL & Williams DL (1989) Differential effects of dietary fat on the tissue-specific expression of the apolipoprotein A-I gene: relationship to plasma concentration of high density lipoproteins. *Journal of Lipid Research* **30**, 1397–1403.

Tall A, (1995) Plasma lipid transfer protein. *Annual Review of Biochemistry* **64**, 235–257.