Effects of Phenotype, Sex, and Diet on Plasma Lipids in LA/N-cp Rats (42927)

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Abstract. **The LA/N-corpulent (cp) rat is a recently developed congenic strain which exhibits obesity. The effects of phenotype and sex on serum and lipoprotein lipid content were examined in LA/N-cp rats fed either a control or an atherogenic diet high in saturated fat and protein. Obese rats were pair-fed to equivalent lean animals. Results from this study indicate that sex, phenotype, and diet exert significant effects on plasma and lipoprotein cholesterol content. Plasma cholesterol levels were higher in obese compared with lean rats, females than in males, and rats consuming the atherogenic diet compared with the control diet. Plasma and lipoprotein triglyceride levels were significantly increased only in obese compared with lean animals. The increased plasma cholesterol and triglyceride was observed primarily in the chylomicron and very low density lipoprotein fractions. Increased levels of plasma cholesterol were not a result of increased dietary cholesterol absorption or increased liver cholesterol biosynthesis. These data suggest that LA/N-cp rats can serve as a unique rodent model for the study of the interrelationships between hyperlipidemia, obesity, and coronary heart disease.** [P.S.E.B.M. 1989, Vol 191]

A strong correlation exists between hyperlipidemia and various disease states such as obesity and coronary heart disease (CHD). The basic mechanisms underlying hyperlipidemia in obesity as well as the reasons why hyperlipidemic obese individuals are predisposed to CHD are poorly understood. One reason why these basic questions have remained unanswered is that there are few, laboratory animal models which exhibit hyperlipidemia and evidence of CHD. The rat has generally been considered a poor model for human hyperlipidemia. Rat lipoprotein metabolism is distinctly different than that of humans and as a result rats are resistant to hypercholesterolemia and the development of atherosclerosis (1). While the consumption of diets high in saturated fat and cholesterol tend to elevate serum cholesterol in rabbits and humans, their effects on rats are minimal unless bile acids and/or propylthiouracil are added (2, 3).

In contrast, obese LA/N-cp rats exhibit elevated serum cholesterol and triglycerides when compared with lean littermates (4, 5). Early studies demonstrated that LA/N-cp rats were metabolically responsive to changes in dietary carbohydrate content (5). Preliminary studies also indicated that unlike normal rats, their hyperlipidemic state was responsive to dietary fat manipulation (6, 7). In addition, the Koletsky rat, from which the obese genotype derived, exhibits atherosclerosis with an early death (8). The LA/Jcr-cp rat which differs from the LA/N-cp rat in that it is derived from the fifth backcrossing with the LA/N strain is also prone to the development of early atherosclerotic and myocardial lesions (9, 10).

The goal of this study was to determine whether the plasma and lipoprotein lipid content was different between male and female and lean and obese members of the LA/N-cp strain fed either a control diet or an atherogenic diet high in saturated fat and protein and supplemented with cholesterol. In addition, experiments designed to elucidate the mechanisms responsible for the hyperlipidemic state in LA/N-cp rats were initiated.

Materials and Methods

Experimental Animals and Diets. Male and female lean and obese members of the congenic LA/N-cp strain were utilized in this study. Animals were bred at Drexel University in a colony derived from the breeding stock supplied by Dr. C. T. Hansen at the National Institutes of Health. Obese LA/N-cp rats were homozygous (cp/cp) whereas the phenotypically lean animals, based on normal genetic distribution, were 2:1 mixtures of heterozygotes (cp/+) and homozygotes (+/

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+) (11). Many metabolic responses appear similar in lean (cp/+) and (+/+) LA/N-cp rats (5). Rats were derived from at least 12 backcrosses to the LA/N strain.

Breeding stock was housed in plastic boxes containing wood shavings and was maintained under reverse illumination (light from 1700 to 0500 hr). Experimental animals were housed individually in hanging steel cages. Rats were fed standard rat chow (Purina) from weaning until 14 weeks of age. Animals were then assigned into different groups and administered either the control or the atherogenic diet (Table I). Obese animals were pair-fed to lean animals on the basis of gram of food eaten/kilogram of body weight in order to prevent hyperphagia. Tap water was available at all times. Animals were fed their diets for 8 weeks. Animals were not fasted and were sacrificed in the middle of the dark cycle.

Analytical Procedures. Animals were sacrificed by decapitation and plasma was obtained from blood collected into EDTA. Lipoproteins were isolated from plasma via sequential density gradient ultracentrifugation according to a modification (12) of the procedure of Havel *et al.* (13) at the following densities: density < 1.006 (chylomicron), density = 1.006 (VLDL), density = 1.006–1.02 (IDL), density = 1.02–1.05 (LDL), and density = 1.05–1.21 (HDL). Cholesterol absorption was monitored via a 7-day fecal collection following a gavaged dose of 5.17 μmol of [1-^{14}C]cholesterol (New England Nuclear) according to Zilversmit *et al.* (14). One-week pooled fecal samples were homogenized in chloroform:methanol (1:1) and radioactive sterols were extracted with hexane (14). Cholesterol and triglycerides were determined using diagnostic kits (Sigma). Livers were obtained at sacrifice and microsomal fractions prepared (15). The activity of 3-hydroxy-3-methylglutaryl (HMGCoA) coenzyme A reductase, the rate-limiting enzyme of the cholesterol biosynthetic pathway, reflects the rate of cholesterol biosynthesis under most conditions (16). Thus, liver microsomal HMGCoA reductase activity was utilized as an index of cholesterol biosynthetic capacity and was measured as previously described (17). Protein was measured by the Bradford assay (18). Data were analyzed by analysis of variance and Student's *t* test.

Table I. Diet Composition

Component	Control diet (% weight)	Atherogenic diet (% weight)
Casein	10	20
Lactalbumin	10	10
Cellulose	3	4
Sucrose	50	31
Rice starch	18	10
Corn oil	5	—
Coconut oil	—	15
Beef tallow	—	3
Cholesterol	—	1
AIN Mineral mix[a]	3	3
AIN Vitamin mix	1	1
kcal/g	3.97	4.64

[a] Mineral mix and vitamin mix were purchased from Teklad Co, Madison, WI.

Results

Effect of Sex, Phenotype, and Diet on Plasma Total and Lipoprotein Cholesterol Levels. Significant effects of sex, phenotype, and diet were observed among male and female, lean and obese LA/N-cp rats (Table II). The analysis of variance indicated a significant effect of sex on plasma cholesterol levels. Generally, LA/N-cp females of the same phenotype and dietary group tended to have elevated plasma cholesterol levels compared with males (Table II). An exception occurred with female obese LA/N-cp rats consuming the control diet who exhibited plasma cholesterol levels lower than the corresponding males. The increase in plasma cholesterol observed in females was accompanied by consistent increases in chylomicron cholesterol in control-fed rats and in chylomicron and VLDL cholesterol in rats fed the atherogenic diet (Table III). Although the analysis of variance indicated significant effects of sex

Table II. Effect of Phenotype, Sex, and Diet on Plasma Cholesterol Levels in LA/N-cp Rats

Group	*n*	Control diet (mg/dl)	*n*	Atherogenic diet (mg/dl)
Lean males	8	67.6 ± 11.5a*	8	129.7 ± 10.6a
Obese males	6	202.0 ± 32.5b	7	218.8 ± 14.8b
Lean females	5	103.8 ± 27.3c*	9	290.9 ± 38.5c
Obese females	6	151.3 ± 7.0d*	9	302.4 ± 26.0c
		ANOVA		
	Phenotype		$P = 0.0003$	
	Sex		$P = 0.0026$	
	Diet		$P = 0.0001$	

Note. Values within columns with different letters are significantly different by Student's *t* test, $P < 0.05$. * Values within rows are significantly different by Student's *t* test, $P < 0.05$. Data are expressed as mean ± SE.

Table III. Effect of Phenotype, Sex, and Diet On Cholesterol Content of Plasma Lipoproteins in LA/N-cp Rats

Group	Chylomicron (mg/dl)	VLDL (mg/dl)	IDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	*n*
Control diet						
Lean male	37.9 ± 7.0a	14.2 ± 4.5a	2.0 ± 0.7a	4.2 ± 2.2a	42.9 ± 18.1a	9
Obese male	91.3 ± 13.2b	35.9 ± 8.4b	4.7 ± 2.6b,c	3.3 ± 1.5a,b	65.1 ± 21.0b	9
Lean female	59.0 ± 2.8c	2.0 ± 1.4c	2.1 ± 1.8a	0.5 ± 0.5b	10.4 ± 6.3c	9
Obese female	155.7 ± 13.7d	29.4 ± 8.9b	0.1 ± 0.1d	5.8 ± 1.5a	24.2 ± 11.0d	9
Atherogenic diet						
Lean male	58.9 ± 7.6c	27.7 ± 6.0b	3.2 ± 1.6a,b	0.4 ± 0.3b	24.8 ± 7.1d	8
Obese male	86.6 ± 12.4b	45.0 ± 7.7d	3.9 ± 2.7a,b	0.2 ± 0.2b	96.1 ± 17.7e	7
Lean female	166.3 ± 28.8d	158.7 ± 35.1e	19.7 ± 5.8e	0.1 ± 0.1c	57.8 ± 4.9a,b	8
Obese female	221.0 ± 26.2e	133.0 ± 34.8	6.0 ± 2.5c	37.7 ± 9.4d	59.8 ± 10.7a,b	9

Note. Values within columns with different letters are significantly different by Student's *t* test, $P < 0.05$. Data are expressed as mean ± SE.

Table IV. ANOVA for Table III

	Chylomicron	VLDL	IDL	LDL	HDL
Phenotype	0.0001	NS[a]	NS	0.0006	0.0070
Sex	0.0001	0.0007	NS	0.0027	NS
Diet	0.0002	0.0001	0.0023	0.0388	0.0173

[a] Not significant, $P > 0.05$.

Table V. Effect of Phenotype, Sex, and Diet on Plasma Triglyceride Levels in LA/N-cp Rats

Group	*n*	Control diet (mg/dl)	*n*	Atherogenic diet (mg/dl)
Lean males	8	174.1 ± 20.9a	8	176.7 ± 33.9a
Obese males	5	378.2 ± 63.7b	7	315.0 ± 61.6b
Lean females	5	103.5 ± 6.9c*	9	207.5 ± 23.7a
Obese females	5	426.2 ± 94.1b*	8	1113.0 ± 388.4c
ANOVA				
Phenotype		$P = 0.0015$		
Sex		$P =$ NS		
Diet		$P =$ NS		

Note. Values within columns with different letters are significantly different by Student's *t* test, $P < 0.05$. * Values within rows are significantly different by student's *t* test, $P < 0.05$. NS, not significant, $P > 0.05$. Data are expressed as mean ± SE.

on chylomicron, VLDL, and LDL cholesterol, no consistent trends were observed with respect to phenotype and diet (Tables III and IV).

Obese animals consuming the control diet exhibited elevated plasma cholesterol levels compared with lean rats (Table II). Significant effects of phenotype were observed primarily on chylomicron, LDL, and HDL cholesterol levels (Table IV). However, increases in cholesterol content were consistently observed in the chylomicron, VLDL, and HDL fractions of control-fed obese rats relative to lean rats (Table III). Obese males fed the atherogenic diet also exhibited elevated chylomicron, VLDL, and HDL cholesterol levels relative to lean rats.

With respect to the effects of diet, lean LA/N-cp rats demonstrated significantly higher plasma cholesterol levels upon consumption of the atherogenic diet compared with the control diet (Table II). In obese LA/N-cp rats consuming the atherogenic diet, only females exhibited higher plasma cholesterol values. The analysis of variance indicated significant effects of diet on the cholesterol levels of all lipoprotein fractions (Table IV). Yet, only chylomicron and VLDL were consistently elevated by consumption of the atherogenic compared with the control diet (Tables III). Furthermore, the increase in chylomicron and VLDL cholesterol was greater in female compared with male LA/N-cp rats.

Effect of Sex, Phenotype, and Diet on Plasma Total and Lipoprotein Triglyceride Levels. The analysis of variance indicated no significant effect on sex on plasma triglycerides in LA/N-cp rats (Table V). In contrast to plasma triglyceride, chylomicron, VLDL, and LDL triglyceride levels were significantly affected by sex (Tables VI and VII). In lean LA/N-cp rats fed either diet, males exhibited greater chylomicron and lower LDL triglyceride levels than females, whereas in obese rats fed either diet, females exhibited increased chylomicron and VLDL triglyceride levels compared with males.

Although the analysis of variance indicated no significant effects of diet on plasma triglyceride levels, female LA/N-cp rats fed the atherogenic diet exhibited greater triglyceride levels compared with those fed the control diet (Table V). Significant effects of diet were observed on IDL and HDL triglyceride in LA/N-cp rats (Tables VI and VII). Both lean and obese LA/N-cp males fed the atherogenic diet had decreased levels of chylomicron and VLDL triglyceride and increased levels of IDL triglyceride compared with rats consum-

Table VI. Effect of Phenotype, Sex, and Diet on Triglyceride Content of Plasma Lipoproteins in LA/N-cp Rats[a]

Group	Chylomicron (mg/dl)	VLDL (mg/dl)	IDL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Control diet					
Lean males	194.5 ± 30.7a	79.0 ± 15.2a	13.2 ± 4.5a,d	9.6 ± 1.6a	13.4 ± 1.9a,b
Obese males	314.7 ± 54.2b	140.8 ± 36.3b	6.3 ± 2.1b	43.4 ± 9.0b,c	26.5 ± 5.9c,d
Lean females	147.7 ± 20.3c	53.6 ± 10.1c	9.5 ± 2.2a	31.2 ± 5.1d	16.9 ± 2.2a,b
Obese females	671.4 ± 115.4d	644.2 ± 102.1d	8.8 ± 2.8a,b	37.5 ± 9.0b,d	19.9 ± 2.2c,d,e
Atherogenic diet					
Lean males	147.7 ± 18.7c	38.1 ± 6.8e	37.6 ± 11.0c	28.4 ± 9.8e	30.9 ± 6.9f
Obese males	212.1 ± 25.4a	113.2 ± 20.6b	16.0 ± 2.8d	27.0 ± 3.6e	19.5 ± 5.1e
Lean females	63.5 ± 7.5e	94.6 ± 22.0a	22.8 ± 6.0e	54.2 ± 12.8c	22.0 ± 2.5d,e
Obese females	1370.3 ± 196.8f	849.7 ± 151.1f	20.4 ± 4.4d,e	45.1 ± 9.4b	54.4 ± 13.2g

[a] Number of animals same as in Table III. Footnote is the same as footnote to Table III.

Table VII. ANOVA for Table VI

	Chylomicron	VLDL	IDL	LDL	HDL
Phenotype	0.0001	0.0001	0.0328	NS[a]	NS
Sex	0.0001	0.0001	NS	0.0157	NS
Diet	NS	NS	0.0001	NS	0.0113

[a] Footnote same as footnote to Table IV.

ing the control diet. In contrast, lean and obese females fed the atherogenic diet had elevated levels of VLDL, IDL, and HDL triglyceride.

Phenotype was the only parameter studied which exerted significant effects on plasma triglycerides (Table V). Obese animals exhibited from two to five times more plasma triglyceride than lean rats, irrespective of sex or diet. This increase was reflected in all cases by increases in chylomicron and VLDL triglyceride (Tables VI and VII). In contrast, IDL triglyceride was lower in obese male LA/N-cp rats fed either diet compared with lean rats.

Effect of Sex, Phenotype, and Diet on Cholesterol Absorption and Biosynthesis. Cholesterol absorption was monitored via a determination of the fecal recovery of an orally administered dose of ^{14}C-cholesterol. Under the experimental conditions used, most of the labeled cholesterol should have appeared in the feces during the first 2 days following the oral dose (14, 19). No difference in the excretion of labeled cholesterol was observed between lean and obese animals on either regimen (Table VIII). However, animals consuming the atherogenic diet excreted higher levels of ^{14}C-cholesterol compared with those consuming the control diet.

Cholesterol synthesis was monitored by examining the activity of HMGCoA reductase, a rate-limiting enzyme in the cholesterol biosynthetic pathway. No significant effects of sex or diet on rat liver microsomal HMGCoA reductase activity were observed (Table IX). However, HMGCoA reductase activity in control-fed obese females was higher than that in obese males or in obese females fed the atherogenic diet.

Table VIII. Effect of Phenotype and Diet on Fecal Cholesterol Excretion in Male LA/N-cp Rats

Group	*n*	Control diet (% administered dose excreted)	*n*	Atherogenic diet (% administered dose excreted)
Lean	10	40.0 ± 2.8a	8	75.1 ± 9.0b
Obese	8	43.2 ± 3.3a	8	69.5 ± 9.0b

Note. Values with different letters are significantly different by Student's *t* test, $P < 0.05$. Data are expressed as mean ± SE.

Table IX. Effect of Sex, Phenotype, and Diet on Liver HMG Coenzyme A Reductase Activity in LA/N-cp Rats

Group	*n*	Control diet (pmoles min^{-1} mg^{-1})	*n*	Atherogenic diet (pmoles min^{-1} mg^{-1})
Lean males	8	10.22 ± 2.1a	8	6.84 ± 1.3a, b
Obese males	6	5.26 ± 0.4b	7	8.57 ± 0.3a
Lean females	5	21.67 ± 1.0c*	9	8.13 ± 1.51a, b
Obese females	6	3.60 ± 0.9b, d	9	5.29 ± 1.19b, c
ANOVA				
Phenotype				$P = 0.0010$
Sex				$P =$ NS
Diet				$P =$ NS

Note. Values within columns with different letters are significantly different by Student's *t* test, $P < 0.05$. * Values within rows are significantly different by Student's *t* test, $P < 0.05$. NS, not significant, $P > 0.05$. Results expressed as mean ± SE.

In contrast, phenotype did exert significant effects on cholesterol biosynthetic activity. Lean animals consuming the control diet, irrespective of sex, exhibited elevated HMGCoA reductase activities compared with obese animals. Differences in enzyme activity between lean and obese animals were not apparent when rats were fed the atherogenic diet.

Discussion

Rats are generally poor models for the study of lipid-related disorders as they do not exhibit clinically significant hyperlipidemia unless they are rendered hypothyroid (2). In this report, we present evidence that nonfasting obese LA/N-cp rats exhibit clinically significant hyperlipidemia which has been defined in man as serum cholesterol and triglyceride levels in excess of 240 and 250 mg/dl, respectively (20, 21). In the fed state, obese LA/N-cp rats have a more pronounced elevation of triglycerides (2- to 5-fold) than cholesterol (1.5- to 3-fold) compared with fed lean animals. In our study the highest cholesterol and triglyceride concentrations were observed in obese females fed the atherogenic diet. Clinically, significant hyperlipidemia in humans is well correlated with the development of CHD (22, 23). Early evidence of atherosclerosis has been detected in both male and female obese LA/Jcr-cp rats, a closely related strain with similar parentage (9, 10).

Most of the lipoprotein fractions were elevated in both cholesterol and triglyceride content in obese compared with lean animals. The majority of excess lipid in obese animals was observed in the lower density lipoprotein fractions, especially chylomicron and VLDL. This is in agreement with a previous report by Dolphin *et al.* (24) studying fasted rats and is consistent with the finding of large triacylglycerol-rich and apolipoprotein B-poor VLDL in obese LA/N-cp rats. Elevated VLDL cholesterol is also observed in obese humans (25). The increase in chylomicron and VLDL cholesterol in fed, obese rats was accompanied by a decrease in the percentage of total cholesterol transported in the HDL fraction. This profile results in an increased β:α lipoprotein ratio. Increased β:α ratios have been positively correlated with the incidence of CHD in man (26).

Unlike humans, rat serum lipid levels generally do not reflect dietary consumption unless chemical or surgical intervention is undertaken (2). In contrast, lean and obese LA/N-cp rats are responsive to diet and exhibit increased plasma cholesterol concentrations when fed a diet high in saturated fat and protein. The increased cholesterol content in rats fed the atherogenic diet was observed in the lower density lipoprotein fractions. In contrast to plasma cholesterol, plasma triglyceride concentrations were unaffected by diet.

Higher plasma lipid concentrations were generally observed in fed, female LA/N-cp rats compared with males. This is in agreement with the findings of Dolphin *et al.* (24) in fasted rats. Females also exhibited a greater elevation of plasma cholesterol and triglycerides in response to consumption of the atherogenic diet than did males. However, obese male LA/N-cp rats demonstrate more pronounced evidence of atherosclerosis than do females (10).

The mechanisms responsible for the observed hyperlipidemia in obese rats is presently unknown. In simplistic terms, hypercholesterolemia can result from increases in cholesterol synthesis and/or decreases in cholesterol excretion. Decreases in HMGCoA reductase activity in obese compared with lean animals suggest that hypercholesterolemia in obese rats is not a result of increased liver sterol synthesis. In contrast, obese humans on an ideal body weight basis produce up to twice as much cholesterol per day as normal individuals (27). It is also unlikely that hypercholesterolemia in these animals results from decreased cholesterol excretion as no differences in fecal sterol excretion of an oral dose of ^{14}C-cholesterol were observed between lean and obese animals. The increase in cholesterol excretion observed in both lean and obese animals consuming the atherogenic diet most likely reflects a decreased efficiency of cholesterol absorption that occurs as a function of increasing dietary cholesterol (27). Rather, the most likely explanation for the observed hyperlipidemia in obese rats is either a decrease in lipid clearance from and/or an increase in lipid secretion into the plasma compartment. In obese sand rats, obesity is associated with accelerated triglyceride secretion (28). Increased rates of VLDL triglyceride production/secretion have also been reported in obese humans (29). There is also evidence of defects in serum lipid clearance in hyperlipidemic humans (30). Studies are currently in progress in this laboratory to discriminate between these mechanistic possibilities.

The observed clinically significant hyperlipidemia, diet responsiveness, elevated β/α lipoprotein profile, and susceptibility to early atherosclerosis suggest that obese LA/N-cp rats may serve as a unique rodent model for the study of hyperlipidemia and atherogenesis as well as obesity. Thus, future study of LA/N-cp rats may provide a useful system in which to probe the complex metabolic interrelationships among hyperlipidemia, obesity, and CHD.

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