Comparison of Fat Storage between Fischer 344 and Obesity-Resistant Lou/C Rats Fed Different Diets

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Abstract

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Objective: We aimed to characterize further the Lou/C (LOU) and Fischer 344 (F344) rat strains for nutritional traits to validate their use as contrasting strains for molecular genetic studies.

Research Methods and Procedures: Five batches of LOU and F344 rats were used to measure caloric intake, weight gain, and body composition when fed a chow diet, a self-selection diet (together with the study of preferences for macronutrients), hypercaloric diets, and a chow diet in a cold environment.

Results: Despite a higher caloric intake when fed a chow diet, LOU rats showed a lower weight gain, final body weight, and percentage of fat tissue, together with a higher percentage of carcass weight, than F344 rats. When fed a self-selection diet, LOU males ingested less protein and more fat than F344 males, and the reverse was observed for females. In this condition, feed efficiency was reduced in LOU but increased in F344 rats compared with the chow diet. Diet-induced obesity was observed in F344 rats but not in LOU rats fed hypercaloric diets. In a cold environment, both LOU and F344 rats displayed an increased percentage of brown adipose tissue compared with control groups, together with a higher caloric intake.

Discussion: The study shows robust nutritional differences between the LOU rat, a lean strain with a low feed efficiency and resistant to diet-induced obesity, and the contrasting F344 rat strain. It also shows the interest in these strains for studying the genetic components of resistance to obesity.

Key words: diet-induced obesity, self-selection diet, body composition

Introduction

Environmental factors such as lack of exercise and excessive food intake correlate with the increased prevalence of obesity in humans (1,2). However, it is also clear that, in a favorable environment, some individuals have a genetic predisposition to store excessive caloric intake mainly as fat or, conversely, to maintain a low percentage of adipose tissue (3). In laboratory rats, when fed a hypercaloric diet, individual rats from an outbred strain differ widely in diet-induced obesity (4). Such a variability in fat storage regulation can be also found among inbred strains, which are useful models to study the genetic components of complex traits such as obesity or, conversely, resistance to obesity (5).

The inbred Lou/C rat (LOU),[1] originating from a Wistar strain (6), has been described as a good model to study healthy aging (7) and resistance to obesity with age (8). Compared with Wistar rats, they exhibit a low caloric intake and a low body weight (9), associated with a stable percentage of adipose tissues throughout life (13% for males and 11% for females) (10), despite the fact that LOU rats also display a preference for fat at the expense of carbohydrates

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[1] Nonstandard abbreviations: LOU, Lou/C; F344, Fischer 344; ME, metabolizable energy; LARD, fat diet; OCC, occidental diet; CTL, control diet.

Table 1. Initial body weight of rats used in the four experiments

		LOU				F344			
		Male		Female		Male		Female	
Experiment	Treatment	*n*	BW ± SE	*n*	BW ± SE	*n*	BW ± SE	*n*	BW ± SE
1		8	285 ± 12	8	169 ± 7	8	347 ± 13	8	196 ± 12
2		6	275 ± 20	9	170 ± 7	8	312 ± 12	9	186 ± 8
3	LARD diet	4	258 ± 16			4	300 ± 13		
	OCC diet	4	252 ± 9			4	287 ± 12		
	CTL diet	2	245 ± 7			4	291 ± 10		
4a	COLD	4	252 ± 6			4	303 ± 12		
	CTL	4	266 ± 5			4	322 ± 8		
4b	COLD	4	245 ± 7			4	308 ± 5		
	CTL	4	239 ± 1			4	276 ± 6		

Values are number of animals (*n*) per sex and treatment, and mean body weight ± SE in grams (BW ± SE).
BW, body weight.

during aging. For those reasons, the LOU strain is considered an interesting model of resistance to the development of obesity. However, thus far, the effect of an excessive caloric intake on their body composition has not been studied in young adult rats.

The quantitative trait loci analysis is recognized as a valuable approach to find the chromosome regions influencing complex traits such as fat storage (11). The success of this technique lies mainly in the choice of two inbred contrasting strains. The Fischer 344 (F344) strain expresses a number of metabolic and nutritional traits that differ from LOU rats. F344 rats are predisposed to obesity and accumulate lipid excessively in liver and muscle (12). Moreover, there is evidence that, although F344 rats have normal glucose tolerance, they show insulin resistance, leptin resistance, and dyslipidemia (12). F344 rats exhibit traits that are also common in human obesity such as insulin resistance, dyslipidemia, and fat accumulation, generally described as syndrome X.

The aim of this study was to characterize further the LOU and F344 rat strains for nutritional traits and their sensitivity to diet-induced obesity and to validate F344 rats as a contrasting strain to the LOU strain for further molecular genetic studies. Caloric intake, weight gain, and body composition in LOU and F344 rats were measured 1) in a control condition using chow diet and then a self-selection diet of macronutrients, 2) using high caloric diets, and 3) in an environment of 4 °C, inducing an increased energy expenditure.

Research Methods and Procedures

Animals and Housing

LOU and F344 rats were housed in standard cages in a temperature-controlled room (23 ± 1 °C) with a 12:12-hour light:dark cycle (lights on at 7:00 AM). All animals were born and raised in the laboratory from LOU and F344 breeders supplied, respectively, by Harlan (Gannat, France) and Iffa Credo (L'Arbresle, France). They were fed with SAFE-A03 chow [3.2 kcal/g metabolizable energy (ME)] until weaning at 28 days of age and subsequently with SAFE-A04 (2.9 kcal/g ME) chow until the beginning of the experiments. Diets were supplied by SAFE (Scientific Animal Food and Engineering, Villemoisson-sur-orge, France). Water was available ad libitum. Initial mean body weight and number of rats per strain used in each experiment are shown in Table 1.

Experiment 1: Caloric Intake on a Balanced Chow Diet

Eighteen-week-old rats were housed individually and given ad libitum access to the SAFE-A04 chow diet for 2 weeks. Animals, food, and water were weighed once a week for 2 weeks. Mean energy intake (mean of kilocalories ingested per week for 2 weeks per 100 grams of body weight) and feed efficiency (milligrams gained per total ingested kilocalories for 2 weeks) were calculated from food intake and weight gain.

Experiment 2: Food Intake, Percentages of Macronutrients Ingested, and Body Composition on a Self-Selection Diet

Diet. The three macronutrients (protein, carbohydrate, and fat) were presented separately. The protein diet (3.9 kcal/g) was composed of 90.5% total milk proteins (Nutrinov, Rennes, France). Total milk protein is a mixture of casein (85%) and other milk proteins (albumins and globulins). These other milk proteins constitute a direct source

of limiting sulfur amino acids. The carbohydrate diet (3.7 kcal/g) consisted of 80.5% pregelatinized cornstarch and 10% sucrose. The fat diet (7.6 kcal/g) contained 36.2% lard and 54.3% soybean oil. Each diet contained 3.5% minerals (AIN 93-Mx; ICN Pharmaceuticals, Orsay, France), 1% vitamins (AIN 93-Vx; ICN Pharmaceuticals), and 5% α-cellulose (Alphacel; ICN Pharmaceuticals). The protein and carbohydrate diets were in powdered form, whereas the fat diet was semisolid (13).

Protocol. Sixteen-week-old rats were housed individually. Rats were given the self-selection diet for 3 weeks. The three food cups containing macronutrients in each cage were weighed and refilled daily. Rats were also weighed daily. Mean caloric intake was calculated as kilocalories ingested per week per 100 grams of body weight by adding the intake from the three sources. Feed efficiency (milligrams gained per total ingested kilocalories for 2 weeks) was calculated from food intake and weight gain. Percentages of macronutrients were calculated as the relative amount of calories provided by each source against the total calories ingested. Before death at 20 weeks, rats were fed the SAFE-A04 chow for 1 week. Then rats were fasted for one night, weighed, and killed by decapitation (starting at 9:00 AM). Four depots of adipose tissue were carefully removed and weighed: epididymal (around testis and ductus deferens) or periovarian (around ovaries), retroperitoneal (along the posterior wall, from the kidney to the hip region), mesenteric (along the mesentery, starting from the lesser curvature of the stomach and ending at the sigmoid colon), and inguinal (subcutaneous fat between the lower part of the rib cage and the thighs). The addition of the adipose tissues was considered total fat mass. Liver, kidneys, heart, spleen, adrenals, and thymus were weighed. Other internal organs (e.g., lungs, genitals, and intestines) were also removed but not weighed. After dissection, the carcass (i.e., muscle mass and skeleton, excluding the tail) was weighed (14).

Experiment 3: Effect of Hypercaloric Diets on Caloric Intake and Body Composition

Male rats of each strain were housed in groups of two per cage and received SAFE-A04 chow for 1 week of habituation (Table 1). Then, three different diets were given ad libitum for 5 weeks (from 16 to 21 weeks of age): 1) a fat diet (LARD) diet with access to pork subcutaneous fat (8.5 kcal/g ME) and SAFE-A04 chow (2.9 kcal/g ME); 2) occidental (OCC) diet from SAFE (3.82 kcal/g ME), composed of 16% protein, 16% lipid, 46% carbohydrate, and 1% vitamins; and 3) control (CTL) diet composed of SAFE-A04 chow. Animals, food, and water were weighed every 2 days. Mean energy intake (mean of kilocalories ingested per week for 5 weeks per 100 grams of body weight) and feed efficiency (milligrams gained per total ingested kilocalories for 5 weeks) were calculated from food intake and weight gain. After 5 weeks, the rats were killed as described previously. Animals were weighed, and mesenteric and inguinal fat were removed and weighed.

Experiment 4: Effect of Cold on Caloric Intake and Body Composition

Two subexperiments were carried out separately.

Experiment 4a. Food intake was recorded in 12-week-old male rats of each strain housed in groups of two per cage at room temperature (CTL) or at 4 °C (COLD) (Table 1). Animals, food, and water were weighed before and after 1 week of the experiment. Mean energy intake per week (mean of kilocalories ingested for 1 week per 100 grams of body weight) and feed efficiency (milligrams gained per total ingested kilocalories for 1 week) were calculated from the food intake and weight gain.

Experiment 4b. Twelve-week-old male rats of each strain were housed two per cage at room temperature and at 4 °C for 1 week and killed as described previously for body composition analysis.

During these experiments, rats were fed SAFE-A04 chow ad libitum.

All experiments were conducted in strict compliance with European conventional and institutional regulations.

Statistical Analysis

Data are presented as means ± SE. Organ and tissue weights are expressed as the percentage of total body weight. Food intake, food efficiency, weight gain, and body composition were analyzed by two-way ANOVA, with strain and sex or strain and treatment as main factors. When significant differences were detected, post hoc comparisons of means were performed with the Newman-Keuls test. Statistical significance was set at $p < 0.05$.

Results

Experiment 1: Caloric Intake on a Balanced Chow Diet

Caloric Intake. Strain ($p < 0.001$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.01$) were significant for caloric intake (Table 2). In both sexes, LOU rats ingested more calories than F344 rats. LOU males ingested fewer calories than LOU females, whereas there was no sex difference in F344 rats.

Weight Gain. Strain ($p < 0.001$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.01$) were significant for weight gain. LOU rats gained less weight than F344 rats, and females gained less weight than males. The sex difference was larger in F344 rats.

Feed Efficiency. Strain ($p < 0.001$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.01$) were significant for feed efficiency. LOU rats displayed a lower feed efficiency than F344 in both males and females. In both strains, males showed a higher feed efficiency than females, but the difference was larger in F344 rats.

Table 2. Caloric intake (CI, kilocalories per week per 100 grams of body weight), weight gain (WG, grams per week), and feed efficiency (FE, milligrams per kilocalories) of LOU and F344 rats fed chow diet during 2 weeks (experiment 1)

	LOU		F344		*p*		
	Male ($n = 8$)	Female ($n = 8$)	Male ($n = 8$)	Female ($n = 8$)	Strain	Sex	Strain × sex
CI	126.7 ± 1.7‡**	145.3 ± 2.0‡	111.9 ± 2.3	118.7 ± 3.7	0.001	0.001	0.013
WG	3.1 ± 0.4†¶	1.0 ± 0.1*	7.3 ± 0.7**	1.8 ± 0.2	0.001	0.001	0.006
FE	8.52 ± 1.12†§	5.43 ± 0.33†	18.35 ± 1.53¶	8.08 ± 0.61	0.001	0.001	0.009

Values are means ± SE; *p* values are from two-way ANOVA.
Significantly different from the other group of the same sex: * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$.
Significantly different from the other group of the same strain: § $p < 0.05$, ¶ $p < 0.01$, ** $p < 0.001$.

Experiment 2: Food Intake, Percentages of Macronutrients Ingested, and Body Composition on a Self-Selection Diet

Caloric Intake. Strain ($p < 0.05$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.05$) were significant for caloric intake (Table 3). In males, LOU rats ingested more calories than F344, but there was no significant strain difference in females. In the F344 strain, males ingested fewer calories than females, but there was no significant sex difference in LOU rats.

Weight Gain. Strain ($p < 0.001$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.001$) were significant for weight gain. LOU rats gained less weight than F344 rats. No sex differences were found in the LOU strain, whereas in the F344 strain, males gained more weight than females.

Feed Efficiency. Strain ($p < 0.001$) and sex ($p < 0.01$) main effects and the strain × sex interaction ($p < 0.01$) were significant for feed efficiency. The LOU strain displayed a lower feed efficiency than the F344 strain in both sexes. In LOU rats, no sex difference was found between sexes, whereas in F344 rats, males displayed a higher feed efficiency than females.

Macronutrient Intake. Sex ($p < 0.01$) main effect and the strain × sex interaction ($p < 0.01$) were significant for protein amount (Figure 1). In males, LOU rats displayed a lower protein intake than F344 rats, but the reverse was found in females. The strain × sex interaction ($p < 0.05$) was significant for fat intake. No significant effect for carbohydrate intake was found.

Body Composition. In both sexes, LOU rats displayed a lower body weight, a higher relative carcass weight, and a lower relative skin weight than F344 rats (Table 4). Body composition also revealed significant differences in relative organ weights between strains. In both sexes, LOU rats showed a lower relative total white adipose tissue weight, a higher relative heart weight, and a lower relative spleen weight than F344 rats. Significant differences between

Table 3. Caloric intake (CI, kilocalories per week per 100 grams of body weight), weight gain (WG, grams per week), and feed efficiency (FE, milligrams per kilocalorie) of LOU and F344 rats fed a self-selection diet (experiment 2)

	LOU		F344		*p*		
	Male ($n = 6$)	Female ($n = 9$)	Male ($n = 8$)	Female ($n = 9$)	Strain	Sex	Strain × sex
CI	171.3 ± 3.8†	184.2 ± 4.2	154.3 ± 2.1‡	184.9 ± 2.4	0.020	0.001	0.012
WG	1.6 ± 1.1†	0.8 ± 0.4*	12.8 ± 0.7‡	3.6 ± 1.0	0.001	0.001	0.001
FE	2.95 ± 2.13†	2.46 ± 1.40*	22.26 ± 1.38‡	9.42 ± 2.60	0.001	0.002	0.003

Values are means ± SE; *p* values are from two-way ANOVA.
Significantly different from the other group of the same sex: * $p < 0.05$, † $p < 0.001$.
Significantly different from the other group of the same strain: ‡ $p < 0.05$.

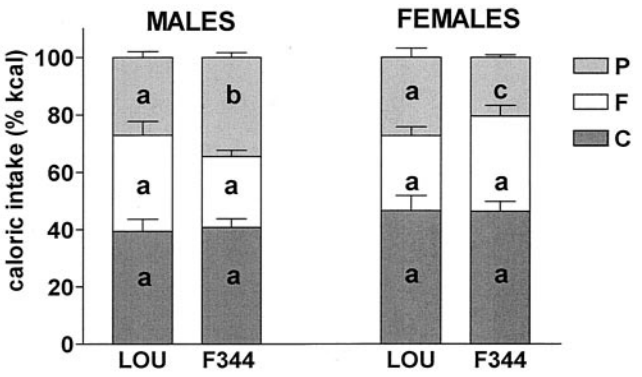

Figure 1: Percentage of macronutrient intake in LOU and F344 rats fed a self-selection diet. The figure shows relative amount of calories provided by proteins (P), fat (F), and carbohydrates (C). [a,b,c] Means within a macronutrient lacking a common superscript differ significantly ($p < 0.05$).

strains within sexes were also found. In males, relative liver weight was lower in LOU rats than in F344 rats. In females, LOU rats displayed lower relative kidneys and adrenals weights than F344 rats. No weight differences were found for interscapular brown adipose tissue or thymus between F344 and LOU rats.

Experiment 3: Effect of Hypercaloric Diets on Caloric Intake and Body Composition

Caloric Intake. A diet ($p < 0.001$) main effect and a strain × diet interaction ($p < 0.05$) were significant for caloric intake (Figure 2). In both strains, rats increased their caloric intake from CTL to OCC diets and from OCC to LARD diets. Within diets, a strain difference was found for the OCC diet only, with LOU rats ingesting more calories than F344 rats. However, for CTL and LARD diets, both strains ingested the same amount of calories.

Weight Gain. Strain ($p < 0.001$) and diet ($p < 0.001$) main effects were significant for weight gain, but no interaction was found. With all diets, LOU rats gained less weight than F344 rats. In the LOU strain, rats fed the OCC and LARD diets gained more weight than rats fed the CTL diet, but no difference was found between OCC and LARD diets. In the F344 strain, rats fed the LARD diet gained more weight than rats fed the OCC or CTL diets, but no difference was shown between CTL and OCC diets.

Feed Efficiency. Strain ($p < 0.01$) and sex ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.05$) were significant for feed efficiency. LOU rats showed a lower feed efficiency than F344 for OCC and LARD diets. In the LOU strain, no differences in feed efficiency were found between diets. In the F344 strain, rats fed with OCC or LARD diets had the same feed efficiency but lower than those fed with CTL diet.

Final Body Weight. Strain ($p < 0.001$) and diet ($p < 0.001$) main effects were significant for final body weight. The significant differences were the same as described for weight gain.

Mesenteric Fat. Strain ($p < 0.001$) and diet ($p < 0.001$) main effects and the strain × sex interaction ($p < 0.001$)

Table 4. Body composition of 20-week-old LOU and F344 rats fed chow diet (experiment 2)

	LOU		F344		*p*		
	Male ($n = 6$)	Female ($n = 9$)	Male ($n = 8$)	Female ($n = 9$)	Strain	Sex	Strain × sex
Body weight (g)	288 ± 8*†	180 ± 3*	369 ± 5†	204 ± 4	0.001	0.001	0.001
Carcass (% BW)	50.3 ± 0.7*†	48.0 ± 0.4*	43.9 ± 1.0	44.2 ± 0.4	0.001	0.100	0.046
Skin (% BW)	18.8 ± 0.4*†	17.9 ± 0.1*	20.1 ± 0.3†	19.2 ± 0.2	0.001	0.001	0.965
WAT (% BW)	4.27 ± 0.20*	4.72 ± 0.17*	8.33 ± 0.35	8.56 ± 0.38	0.001	0.259	0.707
iBAT (% BW)	0.24 ± 0.02	0.30 ± 0.01	0.26 ± 0.01	0.28 ± 0.01	0.963	0.005	0.060
Liver (% BW)	2.93 ± 0.04*	2.99 ± 0.07	3.38 ± 0.10†	2.86 ± 0.04	0.022	0.001	0.001
Heart (% BW)	0.35 ± 0.01*†	0.38 ± 0.00*	0.28 ± 0.01†	0.33 ± 0.00	0.001	0.001	0.250
Spleen (% BW)	0.185 ± 0.004*†	0.219 ± 0.003*	0.215 ± 0.005†	0.259 ± 0.009	0.001	0.001	0.389
Kidneys (% BW)	0.625 ± 0.009	0.610 ± 0.007*	0.638 ± 0.013†	0.693 ± 0.008	0.001	0.030	0.001
Thymus (% BW)	0.113 ± 0.014	0.138 ± 0.030	0.105 ± 0.016†	0.140 ± 0.022	0.700	0.001	0.508
Adrenals (% BW)	0.022 ± 0.002	0.028 ± 0.001*	0.019 ± 0.001†	0.036 ± 0.001	0.137	0.001	0.002

Values are means ± SE; *p* values are from two-way ANOVA.
Significantly different from the other group of the same sex (* $p < 0.01$).
Significantly different from the other group of the same strain († $p < 0.01$).
% BW, percentage of body weight; WAT, total white adipose tissue; iBAT, interscapular brown adipose tissue.

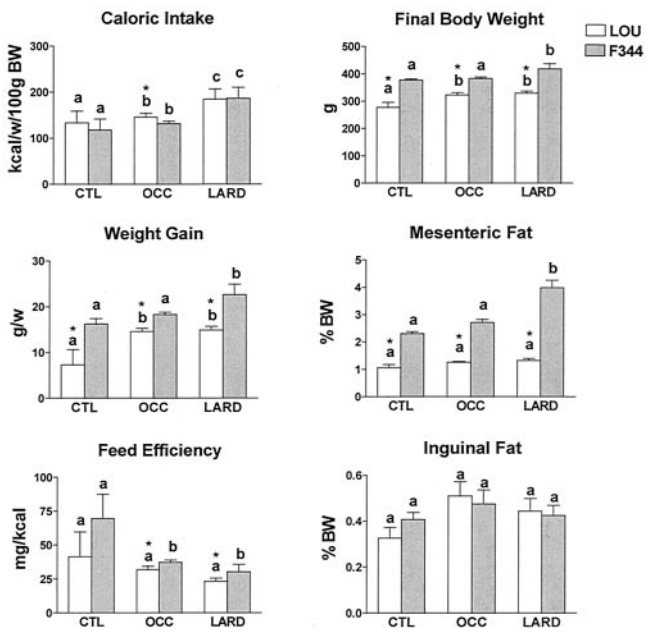

Figure 2: Effect of hypercaloric diets on food intake and body composition of 16-week-old LOU and F344 rats (experiment 3). Rats were fed for 5 weeks either on CTL, OCC, or LARD. BW, body weight; w, week. [a,b,c] Columns within a strain lacking a common superscript differ significantly ($p < 0.05$).* Significantly different from the other group of the same diet ($p < 0.05$).

were significant for the percentage of mesenteric fat. With all diets, LOU rats displayed a lower percentage of mesenteric fat. In the LOU strain, no differences were found among diets. In the F344 strain, the percentage of mesenteric fat was higher in rats fed the LARD diet.

Inguinal Fat. The effect of diet was significant ($p < 0.05$), but the post hoc test did not reveal group differences.

Experiment 4a: Effect of Cold on Caloric Intake

Caloric Intake. Strain ($p < 0.05$) and treatment ($p < 0.001$) main effects were significant for caloric intake, without interaction (Table 5). LOU rats ingested more calories than F344 rats, and caloric intake was higher in animals exposed to cold.

Weight Gain. Strain ($p < 0.001$) and treatment ($p < 0.001$) main effects were significant for weight gain, without interaction. LOU rats gained less weight than F344 rats in both CTL and COLD treatments. In both strains, weight gain was higher in the CTL group than in the COLD group.

Feed Efficiency. Strain ($p < 0.001$) and treatment ($p < 0.001$) main effects were significant for feed efficiency, without interaction. LOU rats displayed a lower feed efficiency than F344 rats in both CTL and COLD treatments. In both strains, feed efficiency was higher in the CTL group than in the COLD group.

Experiment 4b: Effect of Cold on Body Composition

A strain ($p < 0.001$) main effect and the strain × treatment interaction ($p < 0.05$) were significant for the relative carcass weight (Table 6). Relative carcass weight was higher in LOU rats than in F344 rats, but no differences were significant between treatments. However, in F344 rats, relative carcass weight was lower for COLD.

Strain ($p < 0.001$) and treatment ($p < 0.05$) main effects were significant for relative skin weight, without interaction. LOU rats displayed a lower relative skin weight, without interaction, and COLD induced a decrease of relative skin weight.

A strain ($p < 0.01$) main effect was significant for percentage of liver, without interaction. Percentages of liver were lower for LOU rats.

Strain ($p < 0.001$) and treatment ($p < 0.05$) main effects were significant for relative mesenteric fat weight, without

Table 5. Effect of a 1-week exposure to cold on caloric intake (CI, kilocalories per week per 100 grams of body weight), weight gain (WG, grams per week), and feed efficiency (FE, milligrams per kilocalorie) of 12-week-old LOU and F344 male rats (experiment 4a).

	LOU		F344		*p*		
	CTL ($n = 4$)	COLD ($n = 4$)	CTL ($n = 4$)	COLD ($n = 4$)	Strain	Treatment	Strain × treatment
CI	259 ± 6	301 ± 11†	247 ± 6	277 ± 4†	0.016	0.001	0.369
WG	2.3 ± 1.2*	−6.0 ± 1.0*†	13.2 ± 3.7	0.3 ± 1.3†	0.001	0.001	0.092
FE	3.43 ± 1.84*	−8.02 ± 1.83*†	16.56 ± 2.12	0.43 ± 1.56†	0.001	0.001	0.182

Values are means ± SE; *p* values are from two-way ANOVA.
Significantly different from the other group of the same treatment (* $p < 0.01$).
Significantly different from the CTL group of the same strain († $p < 0.01$).

Table 6. Effect of a 1-week exposure to cold on body composition of 12-week-old LOU and F344 male rats (experiment 4b)

	LOU		F344		*p*		
	CTL ($n = 4$)	COLD ($n = 4$)	CTL ($n = 4$)	COLD ($n = 4$)	Strain	Treatment	Strain × treatment
Carcass (% BW)	58.6 ± 0.4†	58.6 ± 0.5†	52.7 ± 0.4	51.0 ± 0.4‡	0.001	0.074	0.050
Skin (% BW)	17.7 ± 0.3†	16.6 ± 0.6†	21.3 ± 0.24	20.4 ± 0.4	0.001	0.016	0.843
Liver (% BW)	4.32 ± 0.05	3.88 ± 0.10*‡	4.50 ± 0.07	4.50 ± 0.21	0.007	0.109	0.102
Mesenteric fat (% BW)	1.18 ± 0.08	0.82 ± 0.11†‡	2.02 ± 0.10	1.85 ± 0.08	0.001	0.012	0.291
Inguinal fat (% BW)	0.41 ± 0.04	0.59 ± 0.08*	0.62 ± 0.08	1.02 ± 0.11	0.001	0.003	0.197
iBAT (% BW)	0.18 ± 0.01	0.23 ± 0.02‡	0.18 ± 0.02	0.24 ± 0.01‡	1.000	0.004	1.000

Values are means ± SE; *p* values are from two-way ANOVA.
Significantly different from the other group of the same treatment: * $p < 0.01$, † $p < 0.001$.
Significantly different from the other group of the same strain: ‡ $p < 0.05$.
BW, body weight; iBAT, interscapular brown adipose tissue.

interaction. LOU rats displayed lower relative mesenteric fat weight, and COLD reduced relative mesenteric fat weight.

Strain ($p < 0.001$) and treatment ($p < 0.01$) main effects were significant for relative inguinal fat weight, without interaction. LOU rats displayed lower relative inguinal fat weight, and COLD increased relative inguinal fat weight.

A treatment ($p < 0.01$) main effect was significant for relative brown adipose tissue weight. COLD increased relative brown adipose tissue weight.

Discussion

These results showed large differences in nutritional characteristics and fat storage capacity between LOU and F344 rat strains and showed why these two inbred rat strains should be of interest as models for the study of genetic components involved in resistance to obesity.

The main observation was that, when fed the different diets (chow, OCC, LARD, self-selected), LOU rats always showed a lower body weight gain than F344 rats, despite an equivalent or even higher caloric intake. The body weight difference was explained mainly by a percentage of fat two times lower in LOU rats. Feed efficiency was higher in males than in females, the sex difference being larger in the F344 strain. Previous studies with the LOU rat have shown that this strain ingests fewer calories than the Wistar strain (7,15), and these results show the relevance of using LOU and F344 rats as contrasting strains for further genetic studies. A striking result of this study is the larger difference in feed efficiency between the two strains when offered a self-selection diet compared with a chow diet. In both sexes, self-selection of macronutrients resulted in a lower feed efficiency in LOU rats, and the reverse was true for F344 rats, thereby increasing the difference between the two strains. Moreover, when fed hypercaloric diets, both strains increased caloric intake with the energy value of diets, and, in addition, F344 rats also increased the amount of mesenteric fat with increasing caloric intake. This is a further illustration of resistance to obesity in the LOU strain, which has already been described in aging rats (10).

Understanding the origin of these nutritional differences and their consequences on body composition will require further studies. Both male and female LOU rats exhibited a lower body weight and percentage of skin, together with a higher percentage of carcass weight. This might be a source of differential energy expenditure between the two strains because of increased protein synthesis, muscular activity, and/or glycogen storage. The lower feed efficiency measured in LOU rats together with a lower amount of fat tissue also suggests that there is an increased loss of energy by thermogenesis in this strain. No difference between strains was found in the relative weight of brown adipose tissue, which is known to increase energy expenditure by heat dissipation (16), but further functional studies will be necessary to discard this hypothesis. Finally, the bigger liver of F344 rats could be the result of a higher triglyceride storage linked to their insulin resistance (12). We also observed a differential regulation of white adipose tissues in F344 rats between the intraabdominal (mesenteric) and subcutaneous (inguinal) fat compartments. Indeed, inguinal fat seemed

insensitive to the increase of caloric intake compared with mesenteric fat. Regional differences in the binding of hormone to receptors (such as glucocorticoid receptors) (17) or selective innervation (18) might be involved in the tissue-specific variation of fat storage. Finally, when energy expenditure is increased (COLD), LOU and F344 rats seem to use distinct regulatory pathways. In a cold environment, rats increase nonshivering thermogenesis by the brown adipose tissue (19) and also increase their caloric intake (20). Indeed, in a cold environment, both LOU and F344 rats displayed an increased percentage of brown adipose tissue compared with control groups, together with a higher caloric intake. However, LOU rats did not manage to maintain their body weight because of a lower feed efficiency in both CTL and COLD treatments compared with F344 rats.

Conclusion and Perspectives

LOU rats have more carcass and less fat weight than F344 rats, despite a higher amount of food intake. Furthermore, the lower feed efficiency of LOU rats is further decreased by self-selection of macronutrients, contrary to F344 rats, which increase their feed efficiency. This shows that the strain difference is not caused by specific needs of the Lou rat that would not be fulfilled by the chow. LOU rats are also resistant to diet-induced obesity, and feed efficiency cannot be improved in the case of energy mobilization, such as during cold exposure. The results of these experiments show robust nutritional differences between the LOU rat, a lean strain with a low feed efficiency and resistant to diet-induced obesity, and the F344 rat strain. These strains are, therefore, suited for further study of the pathophysiological mechanisms and molecular genetic bases of resistance to obesity.

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