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A comparison of extrahepatic lipogenesis from a small glucose meal in obob and gold thioglucose obese mice fed low- or high-fat diets with or without the addition of Δ^{22}-5β-taurocholenic acid

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Extrahepatic fatty acid synthesis from a 250 mg meal of [U-^{14}C]-glucose was measured in epidymal fat pads and the remaining carcass of hyperglycemic obese (obob), gold thioglucose obese, and nonobese controls under conditions of maximum and minimum lipogenesis. Also assessed was the effect of Δ^{22}-5β-taurocholenic acid, previously shown to inhibit hepatic fatty acid synthesis. Both types of obese and nonobese mice were fed for 6 weeks glucose-based diets containing either 1% corn oil or 40% lard with or without the addition of 0.05% taurocholenic acid. In mice fed 1% corn oil, incorporation of labeled glucose into carcass fatty acids was 25% greater in nonobese than obese mice of either type of obesity. On this diet incorporation of labeled glucose into epididymal fatty acids was reduced 83% in hyperglycemic obese mice compared with nonobese littermates. The corresponding reduction in lipogenesis in gold thioglucose obese mice was only 23% compared with nonobese controls. Feeding 40% lard reduced incorporation of labeled glucose into epididymal and carcass fatty acid 67 to 95% compared with mice fed 1% corn oil in both types of obese and nonobese mice whether or not taurocholenic acid had been fed. Both types of obesity or feeding 40% lard reduced lipogenesis in fat pads to a greater extent than glucose uptake by the pads with the reductions additive. Feeding taurocholenic acid reduced pad weight 30% across strain and obesity status, increased uptake of labeled glucose into epididymal fat pads and increased the percentage of the labeled glucose in the pad recovered as fatty acid in both types of obese and nonobese mice when the diet was 1% corn oil. Similarities and differences between the two obesity models are discussed. (J. Nutr. Biochem. 11:87–93, 2000) © *Elsevier Science Inc. 2000. All rights reserved.*

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Introduction

The genetic obesity of hyperglycemic mice (obob) is now known to be caused by the absence of leptin, the product of the ob gene.[1] Leptin is produced in adipose tissue and acts on ob receptors in the brain and elsewhere.[1] Gold thioglucose obesity is a result of a necrotic lesion in the ventromedial hypothalamus resulting from the deposition of gold.[2] In both models insulin resistance and hyperinsulinemia result along with increased hepatic lipogenesis,[3–5] conditions consistent with noninsulin-dependent diabetes mellitus (NIDDM). Reaven[6] has characterized this metabolic state of insulin resistance and hyperinsulinemia as "syndrome X," and argues that it is associated with a number of conditions known to be risk factors for heart disease.

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Table 1 Composition of experimental diets

	Composition (g/100 g diet)				
	Diet 1	Diet 2	Diet 3	Diet 4	Diet 5
Casein (Labco)	20.0	20.0	31.0	31.0	26.0
Salts no. 2 USP XIII	4.0	4.0	4.0	4.0	4.0
Glucose	70.0	70.0	20.0	20.0	45.0
Celluflour	5.0	5.0	5.0	5.0	5.0
Corn oil	1.0	1.0	—	—	20.0
Lard	—	—	40.0	40.0	—
Potassium Δ^{22}-5β-taurocholenate	—	0.05	—	0.05	

Casein and Celluflour were obtained from the Borden Company (New York, NY, USA) and the Chicago Dietetic Supply House (Chicago, IL, USA), respectively. Glucose (Cerelose) and potassium Δ^{22} taurocholenate were obtained from Merck and Company, Inc., (Rahway, NJ, USA). The corn oil and lard were obtained locally. In addition, vitamins were added to all diets to supply the following nutrients per 100 g diet: Thiamin, 1.0 mg; riboflavin, 2.0 mg; pyridoxin, 1.0 mg; calcium pantothenate, 10.0 mg; niacinarnide, 10.0 mg; inositol, 5.0 mg; choline, 100.0 mg; p-aminobenzoic acid, 30.0 mg; biotin, 0.05 mg; folic acid, 0.2 mg; α-tocopherol, 14.2 mg; menadione, 14.1 mg; B_{12} triturate (0.1% trituration with mannitol), 10.0 mg; ergocalciferol, 300 IU; vitamin A palmitate, 1,600 IU.

We reported previously that obob mice fed a glucose-based diet containing 1% corn oil accumulated 10 to 20 times as much fat and cholesterol in the liver, considering both increased concentration and liver hypertrophy, than did nonobese littermates fed this diet.[7,8] We also have demonstrated that under these dietary conditions this accumulation of fat and cholesterol does not occur in gold thioglucose obese mice or their nonobese controls,[9] nor does it occur when obob mice are fed a diet containing 20% corn oil or 40% lard.[7,8] Furthermore, we have shown that feeding the bile acid analog Δ^{22}-5β taurocholenic acid (TC) completely prevented this accumulation of hepatic lipid in obob mice fed the 1% corn oil diet.[8]

It is the purpose of this study to compare directly extrahepatic lipogenesis from a small glucose meal in both types of obese mice and nonobese controls fed low- or high-fat diets with or without the addition of 0.05% taurocholenic acid. The liver data for these experiments have been published.[8,9] We use a model in which a 250 mg meal of [U-^{14}C]-glucose is given to mice by stomach tube and incorporation of label into fatty acids in liver and extrahepatic tissues is measured 2 hours later.[10,11] These conditions are designed to maximize insulin secretion and minimize glucagon secretion, lipolysis, gluconeogenesis, and the recycling of three-carbon units.[12] Plasma glucose rises to a maximum in 10 minutes, and its specific activity remains essentially constant for 1 hour.[10] Baker et al.,[13,14] using this model, demonstrated that over 80% of the newly synthesized fatty acids was derived from the ingested carbon and essentially none of the newly synthesized fatty acids found in adipose tissue were transported from the liver.

Although a number of studies of lipogenesis in genetic or hypothalamic obese mice have been published, as will be cited below, few if any have made a direct comparison of the two, and none was carried out under conditions of maximum and minimum lipogenesis, namely the feeding of low- and high-fat diets. It is the purpose of this study to carry out and report on such a direct comparison.

Methods and materials

Genetic obesity

Adult male hyperglycemic obese mice and their male nonobese littermates (C57BL/6J) were purchased from the Jackson Memorial Laboratory (Bar Harbor, ME USA). Obese and nonobese littermates were maintained on Purina Laboratory Chow for approximately 4 weeks and then fed the experimental diets to be described. The hyperglycemic obese mice (*obob*) and their nonobese littermates (+/?) were weighed, then eight obese and eight nonobese mice were assigned to diets 1 to 4 described in *Table 1*. The diets were glucose based and contained either 1% corn oil or 40% lard with or without the addition of 0.05% TC. Dietary protein was held constant as a percentage of calories.

Hypothalamic obesity

Goldthioglucose obesity was induced in male mice of the ICR strain weighing 25 to 30 grams by intraperitoneal injection of gold thioglucose (Schering-Plough, Madison, NJ USA) at a dose of 800 mg/kg body weight. The survivors were maintained on diet 5 containing 20% corn oil (*Table 1*) for 8 weeks, at which time they were placed on the experimental diets described below. An equal number of control male ICR mice of the same weight were injected with saline and maintained an equal length of time on diet 5 (*Table 1*). The gold thioglucose obese mice and nonobese controls were weighed, then eight obese and eight nonobese mice were assigned to diets 1 to 4 as described above (*Table 1*).

The experimental diets were fed for 6 weeks, and daily food consumption, accounting for spillage, was measured 1 day each week. Between 8 and 10 AM on the day of sacrifice the mice were weighed and then given 250 mg of D-glucose including 2.5 μCi [U-^{14}C]-glucose by stomach tube (0.5 mL) and sacrificed 2 hours later by cervical dislocation. At this time the liver and epididymal fat pads were quickly excised, immediately frozen, and stored along with the remaining carcass in a deep-freeze at −20°C. The numbers of mice completing the experiment are listed in *Tables 2* and *3*. Completed group sizes were seven to eight for nonobese groups. Completed group sizes for the obese mice were five to seven due to several unexplained deaths, especially in the obob mice fed the 1% corn oil diet during the 6-week feeding period. The techniques used in preparing and analyzing tissues for radioactivity have been described previously.[10,11] D-[U-^{14}C]-

Table 2 Incorporation of [U^{14}C]-glucose into carcass fat and epididymal fat in obese and nonobese mice fed a low-fat diet*

	Obese		Nonobese	
Taurocholenic acid	−	+	−	+
Hyperglycemic obese mice				
n	5	5	8	8
Carcass (cpm × 10^{-3})	258 ± 18	374 ± 45	378 ± 22	432 ± 61
Pad weight (mg)	1,211 ± 67	1,108 ± 109	341 ± 33	147 ± 10
Total cpm/pad	4,553 ± 304	5,521 ± 355	6,090 ± 693	8,188 ± 1,245
Fatty acid cpm/pad	752 ± 170	1,633 ± 426	4,364 ± 46	7,101 ± 964
% cpm as fatty acid	15.8 ± 2.9	30.3 ± 9.2	72.7 ± 9.2	97.9 ± 9.4
Gold thioglucose obese mice				
n	7	7	7	8
Carcass (cpm × 10^{-3})	337 ± 25	308 ± 41	430 ± 16	363 ± 17
Pad weight (mg)	1,323 ± 218	881 ± 73	536 ± 80	218 ± 19
Total cpm/pad	5,592 ± 593	6,120 ± 1,171	5,398 ± 663	8,910 ± 1,413
Fatty acid cpm/pad	2,616 ± 349	3,561 ± 1,171	3,398 ± 268	7,304 ± 1,014
% cpm as fatty acid	46.9 ± 4.6	50.5 ± 9.0	65.5 ± 3.6	83.4 ± 4.5

	Significant differences between treatments					
	Main effects			Interactions		
	Strains (S)	Obesity (O)	(TC)^3	S × O	S × TC	O × TC
Carcass (cpm × 10^{-3})	0.746	0.015	0.296	0.725	0.075	0.432
Pad weight	0.559	**<0.0005**	**<0.0005**	0.150	0.089	0.920
Total cpm/pad	0.563	0.022	0.017	0.577	0.735	0.158
Fatty acid cpm/pad	0.170	**<0.0005**	**<0.0005**	0.042	0.573	0.032
% cpm as fatty acid	0.158	**<0.0005**	**0.004**	**0.001**	0.377	0.229

*Data expressed as means ± SE. Significance levels at $P = 0.01$ or less are in bold. TC–Δ^{22} 5-β-taurocholenic acid.

TABLE 3 Incorporatio of [U^{14}C]— glucose into carcass fat and epididymal fat pads in obese and nonobese mice fed a high-fat diet*

	Obese		Nonobese	
Taurocholenic acid	−	+	−	+
Hyperglycemic obese mice				
n	6	7	8	8
Carcass (cpm × 10^{-3})	64.1 ± 6.4	65.0 ± 3.4	79.8 ± 4.3	57.0 ± 9.1
Pad weight (mg)	1,142 ± 66	1,309 ± 76	560 ± 73	291 ± 20
Total cpm/pad	5,798 ± 366	7,737 ± 492	5,017 ± 293	3,156 ± 305
Fatty acid cpm/pad	201 ± 17	266 ± 38	1,382 ± 134	957 ± 151
% cpm as fatty acid	3.46 ± 0.24	3.57 ± 0.59	27.2 ± 1.43	29.3 ± 2.80
Gold Thioglucose Obese Mice				
n	7	8	8	8
Carcass (cpm × 10^{-3})	68.5 ± 8.0	100.8 ± 23.6	88.4 ± 14.3	65.6 ± 3.3
Pad weight (mg)	1,212 ± 219	1,299 ± 158	1,213 ± 205	446 ± 55
Total cpm/pad	4,278 ± 533	4,402 ± 499	5,619 ± 537	3,282 ± 396
Fatty acid cpm/pad	133 ± 24	314 ± 98	783 ± 177	701 ± 55
% cpm as fatty acid	3.01 ± 0.27	6.50 ± .39	13.8 ± 2.7	32. ± 9.0

	Significant differences between treatments					
	Main effects			Interactions		
	Strain (S)	Obesity (O)	(TC)^3	S × O	S × TC	O × TC
Carcass (cpm × 10^{-})	0.081	0.809	0.699	0.468	0.330	0.019
Pad weight	0.027	**<0.0005**	0.045	0.055	0.126l	**0.001**
Total cpm/pad	**0.001**	**<0.0005**	0.119	**<0.0005**	0.061	**<0.0005**
Fatty acid cpm/pad	**0.006**	**<0.0005**	0.490	**0.008**	0.196	0.030
% cpm as fatty acid	0.463	**<0.0005**	0.036	0.240	0.082	0.139

*Data expressed as means ± SE. Significance levels $P = 0.01$ or less are in bold. TC–Δ^{22}-5β-taurocholenic acid.

Table 4 Percentage reductions in lipogenesis as a result of feeding high-fat diet*

	Obese mice		Nonobese mice	
Taurocholenic acid	−	+	−	+
C57BL/6J Strain				
Carcass	75	83	79	87
Epididymal fat pad	73	84	68	86
ICR Strain				
Carcass	80	67	80	82
Epididymal fat pad	95	91	77	90

*Data from *Tables 2 and 3* for mice fed 40% lard divided by data for mice fed 1% corn oil × 100.

glucose was obtained from New England Nuclear Corporation (Boston, MA USA) and had a specific activity of 10 to 15 mCi/mmole. Carcass and epididymal fat was measured as total fatty acid extractable after saponification. Counting was carried out using a Packard Tri-Carb liquid scintillation counting system model 314EX (Packard Instrument Co. Inc., Meriden, CT USA) and toluene-Liquiflor phosphor. All counts were corrected for quenching using a trace amount of ^{14}C-palmitic acid in phosphor.[10] Results are presented as means ± SE. The data were analyzed as two separate three-way analyses of variance using SPSS for Windows, one for mice fed 1% corn oil and the other for mice fed 40% lard. In each the main effects were strain (C57BL/6J vs. ICR), obesity status (obese vs. nonobese), and the presence or absence of taurocholenic acid in the diet. None of the three-way interactions were significant and are therefore not shown.

Results

1% Corn oil diet

Data showing the incorporation of [U-^{14}C]-glucose into fatty acid in the carcass in mice fed the 1% corn oil diet are shown in *Table 2*. Incorporation across strain or TC was 25% higher in nonobese compared with obese mice ($P = 0.015$), with no significant interactions. The marginal significance ($P = 0.075$) of the strain × obesity interaction reflects that TC increased incorporation in the C57BL/6J strain and decreased incorporation in the ICR strain.

Also shown in *Table 2* are data showing incorporation into fatty acids in the epididymal fat pad. The weight of the pad was significantly affected by obesity status ($P < 0.0005$) or by feeding TC ($P < 0.005$) with no significant interactions. Pads from obese mice of either type were 3.5 times larger than nonobese mice of either strain whether or not TC had been fed. Feeding TC reduced pad weight 30% across strain and obesity status. Uptake of [U-^{14}C]-glucose into the epididymal fat pad revealed main effects only for obesity status and TC. Uptake was 30% greater in nonobese than obese mice across strain and TC ($P = 0.022$). Uptake also was 30% greater in mice fed TC across strain and obesity status ($P = 0.017$). In spite of the fact that the epididymal fat pad was more than three times larger in hyperglycemic obese (hgo) than in nonobese hyperglycemic (nhgo) mice, incorporation of labeled glucose into pad fatty acid was 83% less in hgo than in nhgo mice ($P < 0.0005$). This reduction in lipogenesis occurred to a much smaller extent in gold thioglucose obese (gtgo) than in nonobese control (ngtgo) mice (23%), as shown by the significance of the two-way interaction ($P = 0.001$). The two mouse strains did not differ significantly in the incorporation of labeled glucose into fatty acids in epididymal fat pads across obesity status and whether or not TC was fed.

Data showing percentage of the label found as fatty acid in the epididymal fat pad are presented in *Table 2*. There was not a significant main effect attributable to strain, but there was for obesity status ($P < 0.0005$), and the interaction of strain with obesity was highly significant ($P = 0.001$). The percentage of fat pad radioactivity recovered as fatty acid was three times greater in gtgo than in hgo mice, but 10% less in ngtgo than in nhgo mice. Feeding TC significantly increased the percentage of label recovered as fatty acid in obese and nonobese mice of either strain ($P = 0.004$) with no significant interactions.

40% Lard diet

Data showing the incorporation of [U-^{14}C]-glucose into carcass fatty acid when the mice were fed a diet containing 40% lard are reported in *Table 3*. As expected, incorporation into extrahepatic fatty acids was greatly reduced. The reductions in incorporation of labeled glucose into extrahepatic fatty acids resulting from feeding a high level of dietary fat are shown in *Table 4*. The reductions ranged from 67 to 95% for both types of obese and nonobese mice whether or not TC had been fed. There was no clear difference in effect of dietary fat in either type of obese mice compared with nonobese controls.

As shown in *Table 3* the weights of the epididymal fat pads were not significantly different in gtgo than in hgo mice, but were twice as large in ngtgo than nhgo mice (strain × obesity interaction $P = 0.055$). Feeding TC reduced pad weights 50 to 65% in nonobese mice of either strain, but not in obese mice (obesity × TC interaction $P = 0.001$). The uptake of labeled glucose into the fat pads showed significant main effects attributable to strain, obesity status, and TC, and in several of the interactions.

As was the case for mice fed the 1% corn oil diet, the percentages of radioactivity recovered as fatty acid in the fat pads showed large differences attributable to both obesity status and feeding TC. Only 3% and 3.5% of the label was recovered as fatty acid in gtgo and hgo mice, respectfully, compared with 13.8% and 27.2% in ngtgo and nhgo mice ($P = 0.0005$). Feeding TC increased the percentage of label found in fatty acid in obese or nonobese mice of either strain ($P = 0.036$). This was the case whether the diet was 40% lard (*Table 3*) or 1% corn oil (*Table 2*).

Discussion

The hypothalamus is of central importance in receiving and integrating satiety and adiposity signals that regulate food intake and energy homeostasis.[15] Satiety signals include a number of peptides secreted from the gut in response to the act of eating and digesting foods. Adiposity signals include the ob gene product leptin, which is secreted from adipose tissue, and insulin, which is secreted from the beta cells in the pancreas. The circulating concentrations of both leptin and insulin are proportional to adipose mass and both act centrally in the same areas of the hypothalamus.[15]

Both types of obesity investigated in the current study crucially involve the hypothalamus. Hgo mice of genotype *obob* are obese because of a failure to secrete the ob gene product leptin from adipose tissue acting on the hypothalamus, and gtgo mice are obese because of the destruction of the "satiety center" in the ventromedial nuclei of the hypothalamus caused by deposition of gold. Both exhibit insulin resistance, are hyperinsulinemic, and among other defects exhibit increased hepatic lipogenesis from various substrates.[5] However, they differ fundamentally in that hgo mice are essentially devoid of circulating leptin whereas gtgo mice are not. Leptin-insulin relationships and direct effects of leptin on glucose and lipid metabolism in various tissue are discussed elsewhere.[9]

As previously reported, using conditions favoring lipogenesis (1% corn oil diet combined with a 250 mg glucose meal), the levels of incorporation of labeled glucose into hepatic fatty acids in obese mice of either strain or nonobese mice of either strain were closely similar and the incorporation of labeled glucose into hepatic fatty acid in obese mice of either strain was two to three times higher than the corresponding values in nonobese mice.[8,9] These increases in hepatic lipogenesis in obese mice, whether hgo or gtgo, compared with nonobese mice, are comparable to increases observed in earlier studies even though experimental conditions varied somewhat.[7,16,17]

In contrast to the liver, incorporation of [U-^{14}C]-glucose into fatty acids in the carcass or epididymal fat pads was lower in either type of obese mice fed either diet when compared with nonobese controls. This reduced rate of lipogenesis was greater in epididymal fat pads of hgo compared with nhgo mice than in gtgo compared with ngtgo mice. The observation that fatty acid synthesis from a 250 mg meal of [U-^{14}C]-glucose is reduced in the total carcass and in epididymal fat in both types of obese mice, especially obob mice, when compared with the corresponding nonobese mice, is consistent with their insulin resistant state and the accumulation of body fat. Hems et al.[18] observed increased whole body lipogenesis in obob as compared with +/? mice when measured with $^{3}H_2O$. However, these researchers fed a stock diet, did not give a meal, and administered only a tracer amount of isotope intraperitoneally. These are not optimal conditions to use for measuring lipogenesis. Cooney et al.[16] measured the incorporation of $^{3}H_2O$ into epididymal fat pad fatty acids in gtgo mice and nonobese controls following a 2-hour access to stock diet. Overnight-fasted gtgo and ngtgo mice were followed for 12 weeks following injection of the gold thioglucose. At 4 weeks incorporation of the tritiated water per gram of pad weight in gtgo mice was 150% that of ngtgo mice. However, by 12 weeks the situation was reversed and at this time the corresponding value was 30%, results that are consistent with ours. This group also reported that the insulin response in the gtgo mice following a small 0.5 g meal of stock diet was robust,[17] but was impaired following intravenously injected glucose, suggesting an impairment in insulin response to circulating glucose.[19]

Cawthorne and Cornish[20] observed that fatty acid synthesis in hgo mice was not inhibited by feeding fat. It also has been reported that, although feeding hgo or nhgo mice a diet high in polyunsaturated fatty acids decreased mRNA levels for acetyl coenzyme A (CoA) carboxylase and fatty acid synthase (FAS), mRNA expression for these enzymes was higher for obese than nonobese mice.[21,22] This suggested to the authors that "obese mice may be resistant to polyunsaturated fatty acid feedback control of gene expression."[21] Our previously published[8,9] and the current results argue against this hypothesis. We reported that incorporation of [U-^{14}C]-glucose into hepatic fatty acids was reduced 68% and 72%, respectively, in hgo or nhgo mice fed 20% corn oil compared with 1% corn oil when the labeled glucose was added to the diet and fed for 24 hours prior to sacrifice.[7] When a 250 mg meal of the labeled glucose was administered to hgo and nhgo mice fed 1% corn oil or 40% lard, as in the current study, the reduction in incorporation into hepatic fatty acids in the mice fed 40% lard was 89% and 91%, respectively, in hgo and nhgo mice.[8] Comparable results were obtained with gtgo and ngtgo mice fed these diets.[9]

As mentioned earlier, in our experimental conditions in nonobese mice, plasma glucose rises to a maximum in 10 minutes and remains nearly constant for 1 hour.[10] Essentially none of the newly-synthesized fatty acids found in adipose tissue were derived from liver, and 80% were derived from carbon ingested in the meal (i.e., glucose).[13,14] Although these parameters have not been measured in obese mice of either type, the observation that hepatic lipogenesis from glucose was increased in hgo and gtgo mice[8,9] suggests that reduced extrahepatic lipogenesis in the obese mice cannot be explained by changes in hepatic lipogenesis. In addition, although it is possible that the specific activity of postprandial plasma glucose may have been somewhat reduced in both types of obese mice with hyperglycemia and insulin resistance, it would not appear likely that this would negate the large treatment effects we have observed.

Insulin increases glucose uptake[23,24] and lipogenesis[23] in adipose tissue. Resistance to insulin-stimulated glucose disposal is a characteristic of adiposity and NIDDM.[5,6] Increased consumption of dietary fat, especially saturated fat, leads to adiposity and also leads to insulin resistance independent of adiposity.[25] In our study, the percentages of radioactivity in epididymal fat pads found as fatty acid were 15.8% and 46.9% in hgo and gtgo mice, respectively, when 1% corn oil was fed (*Table 2*). The signaling pathways involved in the effect of insulin on glucose uptake and lipogenesis in epididymal adipose tissue recently have been outlined and discussed by Denton et al.[26] Stimulation of glucose uptake is via GLUT-4, and stimulation of lipogenesis is via increased activity of pyruvate dehydrogenase and acetyl CoA carboxylase. A reasonable interpretation of our

data just discussed is that both adiposity and dietary fat inhibit fatty acid synthesis more than glucose uptake by the epididymal fat pads and the inhibitions are additive.

TC appears to affect lipid metabolism in white adipose tissue but it is not clear if these effects are independent of previously described effects in the liver.[8,9] TC increased uptake of labeled glucose into epididymal fat pads in both types of obese and nonobese mice when the diet was 1% corn oil but not when the mice were fed 40% lard. Perhaps more interesting is the observation that the percentage of the label in the fat pad recovered as fatty acid was increased by TC in obese and nonobese mice of both strains fed either diet. Again whether this is a direct effect on adipose tissue or an indirect effect secondary to an effect on lipoprotein metabolism in the liver remains to be determined.

Conclusions

As a preface to drawing conclusions, it is acknowledged that the gtgo mice were larger but leaner than the hgo mice and also were derived from a different strain. However, for none of the variables for which data are presented for mice fed 1% corn oil was there a significant main effect attributable to strain (*Table 2*). On the 40% lard diet (*Table 2*), the main effects of total and fatty acid counts per minute (cpm)/pad were significant but the main effect attributable to strain of the percentage of epididymal fat pad counts present as fatty acid was not, nor were any of the interactions with strain significant. In addition, all the important differences between the two types of obesity, as discussed below, were observed in mice fed the 1% corn oil diet, where strain was not an important factor.

Hgo and gtgo mice were comparable in exhibiting decreased extrahepatic fatty acid synthesis from a glucose meal compared with nonobese controls. In contrast in both obese models hepatic fatty acid synthesis was elevated.[8,9] The reductions in extrahepatic fatty acid synthesis from glucose as a result of feeding a high-fat diet were comparable in both models of obesity as well as their nonobese controls. Where they differ markedly, as pointed out in the introduction, is in hepatic cholesterol and fatty acid metabolism when fed a 1% corn oil diet. When fed this diet hgo mice accumulate large amounts of cholesterol and fat in the liver, completely preventable by concurrently feeding the bile acid analog TC.[8,9] This does not occur when nhgo, gtgo, or ngtgo mice are fed this diet. On the 1% corn oil diet following the 250 mg meal of labeled glucose, the proportion of label recovered as fatty acid from the epididymal fat pads was only one-third as high in hgo as in gtgo mice (15.8% vs. 46.8%). Concurrent feeding of TC with the 1% corn oil diet to hgo mice doubled the proportion of label recovered as fatty acid in the fat pads (15.8% vs. 30.3%) but had little effect on this parameter in gtgo mice fed this diet (46.9% vs. 50.4%).

It recently has been reported that hgo mice are characterized by increased high density lipoprotein levels, defective hepatic catabolism of apoA-I and apoA-II, and decreased apoA-I mRNA, and that these deficits were reversed by leptin.[27] Based on our results in this and previous papers,[8,9] we suggest that this or a related defect in hepatic lipoprotein metabolism in hgo mice also is characterized by an alteration in hepatic bile acid metabolism interacting with linoleic acid or one of its metabolites. Further investigation is clearly needed.

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