Redistribution of Glucose From Skeletal Muscle to Adipose Tissue During Catch-Up Fat

A Link Between Catch-Up Growth and Later Metabolic Syndrome

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Catch-up growth, a risk factor for later obesity, type 2 diabetes, and cardiovascular diseases, is characterized by hyperinsulinemia and an accelerated rate for recovering fat mass, i.e., catch-up fat. To identify potential mechanisms in the link between hyperinsulinemia and catch-up fat during catch-up growth, we studied the in vivo action of insulin on glucose utilization in skeletal muscle and adipose tissue in a previously described rat model of weight recovery exhibiting catch-up fat caused by suppressed thermogenesis per se. To do this, we used euglycemic-hyperinsulinemic clamps associated with the labeled 2-deoxy-glucose technique. After 1 week of isocaloric refeeding, when body fat, circulating free fatty acids, or intramyocellular lipids in refed animals had not yet exceeded those of controls, insulin-stimulated glucose utilization in refed animals was lower in skeletal muscles (by 20–43%) but higher in white adipose tissues (by two- to threefold). Furthermore, fatty acid synthase activity was higher in adipose tissues from refed animals than from fed controls. These results suggest that suppressed thermogenesis for the purpose of sparing glucose for catch-up fat, via the coordinated induction of skeletal muscle insulin resistance and adipose tissue insulin hyperresponsiveness, might be a central event in the link between catch-up growth, hyperinsulinemia and risks for later metabolic syndrome.
***Diabetes* 54:751–756, 2005**

Catch-up growth, long considered a process that embodies an accelerated recovery from the detrimental effects of poor growth, is increasingly viewed as a long-term health hazard. This shift in perception derives from an impressive body of evidence suggesting that people who had low birth weight or who were stunted during infancy and childhood, but who subsequently showed catch-up growth, have higher susceptibility for central obesity, type 2 diabetes, and cardiovascular diseases later in life (1–6). The nature of this link between catch-up growth and risks for such chronic diseases remains obscure, although several lines of evidence point to the phase of catch-up growth as a state of hyperinsulinemia. A higher plasma insulin response to a glucose load was indeed demonstrated several decades ago during catch-up growth in infants who were small for gestational age (7), and more recently strong associations have been described between thinness during early infancy and elevated plasma insulin during catch-up growth later in childhood (8–13).

Explanations for this hyperinsulinemic state of catch-up growth have in the past focused on a compensatory increase in food intake and the requirements for higher plasma insulin for accelerating the synthesis of lean and fat tissues. There are, however, several reports, both in humans and in animals, suggesting that catch-up growth is also characterized by a disproportionately faster rate to regain body fat rather than lean tissue (14), a phenomenon of accelerated fat recovery, or "catch-up fat," that still occurs in the absence of hyperphagia (14–18). The possibility therefore arises that sustained reduction in energy expenditure per se (because of decreased thermogenesis in certain organs/tissues) for the purpose of sparing energy for catch-up fat may also be involved in the hyperinsulinemic state of catch-up growth (14). Recent studies from our laboratory support this contention (19). Indeed, we showed that after growth arrest induced by semistarvation, rats exhibiting catch-up fat when refed isocalorically compared to controls over a 2-week period showed sustained suppression of thermogenesis, normal or mildly elevated blood glucose levels, but higher plasma insulin levels after a glucose load even at a time point when their

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Received for publication 30 September 2004 and accepted in revised form 6 December 2004.

FAS, fatty acid synthase; FFA, free fatty acid.

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body fat had not yet exceeded those of controls (19). These studies thus underscore a primary role for suppressed thermogenesis per se, rather than its consequential effect on fat mass, in the hyperinsulinemic state of catch-up growth.

The following key questions remain to be addressed: In which organs and tissues might this suppression of thermogenesis occur? and How might such downregulation of cellular metabolism lead to hyperinsulinemia? Because skeletal muscle is an important contributor to whole-body energy expenditure and a major site for insulin-stimulated glucose disposal, the possibility arises that a reduction in this tissue's metabolic rate might result in a reduction in glucose utilization, thereby leading to hyperinsulinemia. This in turn would serve to redirect the spared glucose toward de novo lipogenesis in adipose tissue, a function that coordinates glucose spared for catch-up fat with blood glucose homeostasis. On the basis of this hypothesis, we have conducted euglycemic-hyperinsulinemic clamps in our rat model of suppressed thermogenesis favoring catch-up fat, with the objective of assessing whether insulin-stimulated glucose utilization of skeletal muscle and adipose tissue would be altered during catch-up growth.

RESEARCH DESIGN AND METHODS

Male Sprague Dawley rats (Elevage Janvier, Le Genest Saint Isle, France), aged 6 weeks and caged singly in a temperature-controlled room (22 ± 1°C) with a 12-h light/dark cycle, were maintained on a commercial pelleted chow diet (Kliba, Cossonay, Switzerland) consisting, by energy, of 24% protein, 66% carbohydrates, and 10% fat, and they had free access to tap water. The experiments were conducted after a 1-week period of adaptation in rats selected on the basis of body weight being within ±5 g of the mean body weight (225 g). We used an experimental design similar to that previously described in establishing a rat model for studying the changes in energy expenditure that occur for accelerating fat deposition during refeeding (15–18). This approach allows suppressed thermogenesis specific for fat recovery to be studied in the absence of confounding variables (such as body size, food intake, and differential rates of protein gain) on energy expenditure. In brief, as depicted in Fig. 1, groups of rats are food restricted at 50% of their spontaneous food intake for 2 weeks. After this period of growth arrest, they are refed the same chow diet at a level equal in metabolizable energy content to the spontaneous food intake of control rats that are matched for weight (and hence 2 weeks younger) at the onset of refeeding. The cardinal feature of this experimental design is that comparisons are therefore made between refed animals regaining weight versus spontaneously growing weight-matched controls, with both groups consuming the same amount of food energy. Under these conditions, the refed animals showed an increased rate of body fat gain because of lower energy expenditure than controls. A number of factors that could theoretically contribute to this difference in energetics between refed and control rats (namely age, level of physical activity, and size of organs) have been previously evaluated and were shown to have little or no impact on the difference in energy expenditure between the two groups (15–18). Consequently, under conditions of our refeeding studies, the lower energy expenditure in the refed compared with control rats is explained essentially by the energy spared as a result of a sustained suppression of thermogenesis for the purpose of catch-up fat. Using this rat model of controlled refeeding after growth arrest, three experiments were conducted. In a first experiment, glucose utilization was assessed in skeletal muscle and adipose tissue during refeeding, using euglycemic-hyperinsulinemic clamps in conjunction with the labeled 2-deoxy-glucose technique. To eliminate the impact of an elevated fat mass per se on organ/tissue glucose utilization rates, the clamp studies were conducted on day 7 of controlled refeeding, i.e., at a time point at which body fat of the refed animals had not yet exceeded that of weight-matched controls (17,18). This time point was also shown in our recently reported study (19) to be accompanied by an elevation in plasma insulin levels (with peak values corresponding to ~10 ng/ml) in response to a glucose load; the steady-state plasma insulin was therefore maintained at 10 ng/ml in the clamp studies. In a second experiment of similar design, groups of refed and control animals were killed at time points corresponding to day 0, 7, or 14 of refeeding for

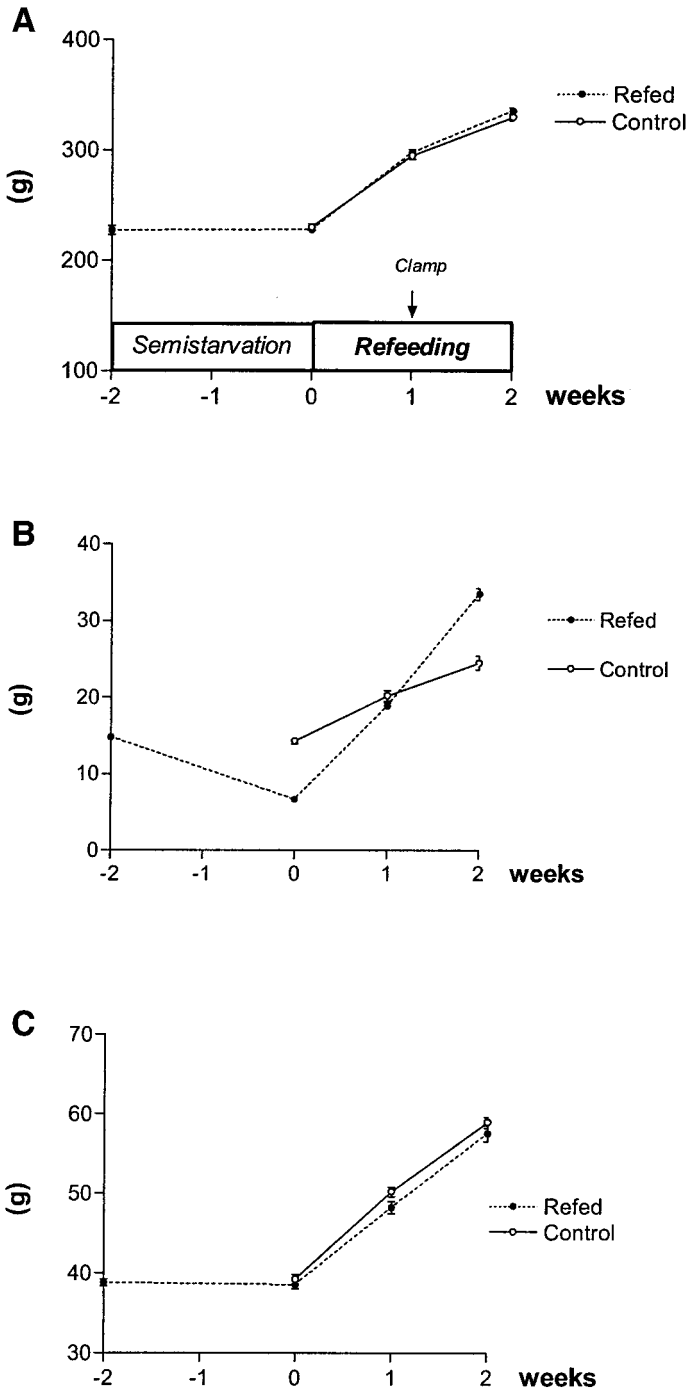

FIG. 1. Body weight (*A*), total fat mass (*B*), and protein mass (*C*) at the onset and after 1 and 2 weeks of isocaloric refeeding after a 2-week period of growth arrest by semistarvation. The groups are refed and weight-matched control. All values are means ± SE (n = 6). The arrow indicates the specific time point (end of week 1) on which the clamp studies were performed.

determination of body composition (fat mass and protein mass) and energy balance. In a third experiment, the refed and control animals were killed after 7 days of refeeding (i.e., at the same time point as that of the clamp study) for determination of skeletal muscle intramyocellular lipids, adipose tissue fatty acid synthase (FAS) activity, and postabsorptive blood glucose, insulin, and nonesterified free fatty acids (FFAs). Animals used in the current studies were maintained in accordance with our institute's regulations and guide for the care and use of laboratory animals.

Determination of body composition. After killing by decapitation, the skull, thorax, and abdominal cavity were incised and the gut cleaned of undigested food. The whole carcasses were dried to a constant weight in an oven

TABLE 1
Energy balance and changes in body weight and body energy stores during 2 weeks of refeeding after semistarvation in refed and control rats

	Control	Refed	*t* test
Weight gain (g)	100 ± 4	108 ± 4	NS
Fat gain (g)	10.2 ± 0.9	26.8 ± 0.8	$P < 0.001$
Protein gain (g)	19.7 ± 0.7	19.0 ± 1.0	NS
Energy gain (kJ)	842 ± 19	1,467 ± 31	$P < 0.001$
ME intake (kJ)	5,203 ± 27	5,150 ± 34	NS
Energy expenditure (kJ)	4,361 ± 47	3,683 ± 42	$P < 0.001$
Efficiency (%)	16.2 ± 0.4	28.5 ± 0.6	$P < 0.001$

All values are means ± SE ($n = 6$). ME, metabolizable energy intake determined from differences between gross energy intake and the energy lost through feces and urine; NS, no statistically significant difference.

maintained at 70°C and subsequently homogenized. Triplicate samples of the homogenized carcass were analyzed for energy content by bomb calorimetry (20) and for fat content by the Soxhlet extraction method (21). Body protein was determined from a general formula relating energy derived from fat, total energy value of the carcass, and energy derived from protein (15).

Determination of energy balance and energetic efficiency. Energy balance measurements were conducted during refeeding, as previously described (15–17), by the comparative carcass technique over 2 weeks, during which time the metabolizable energy intake was monitored. Energy expenditure was determined as the difference between energy gain and metabolizable energy intake, and the energetic efficiency was calculated as the percentage of total energy gain per metabolizable energy intake.

Measurement of in vivo glucose utilization during euglycemic-hyperinsulinemic clamps. After 7 days of controlled refeeding, the rats in both the refed and control groups were fasted for 5 h and then anesthetized with sodium pentobarbital (55 mg/kg i.p.). Total glucose utilization (rate of glucose disappearance, or R_d) and hepatic glucose production (rate of glucose appearance, or R_a) were measured during euglycemic-hyperinsulinemic clamps under basal and insulin-stimulated conditions by infusing D-[U-^{14}C]glucose (50 μCi/rat; Amersham, Aylesbury, U.K.), according to a method previously described (22,23). At the end of the euglycemic-hyperinsulinemic clamps, the in vivo insulin-stimulated glucose utilization index of individual tissues, namely several skeletal muscles (tibialis, quadriceps, gastrocnemius, and soleus), three white adipose tissue fat pads (inguinal, epididymal, and retroperitoneal), as well as interscapular brown adipose tissue and heart were determined with the labeled 2-deoxy-D-glucose technique, as previously described (22,23).

Analytical procedures relative to clamp studies. The 2-deoxy-D-[1-^{3}H]glucose and D-[U-^{14}C]glucose specific activities were determined in deproteinized blood samples, as previously reported (22,23). Measurement of tissue concentrations of 2-deoxy-D-[1-^{3}H]glucose-6-phosphate allowed calculation of the in vivo glucose utilization index of individual tissues and was expressed in nanograms per minute per milligram of tissue.

Plasma measurements. Plasma glucose levels were determined by the glucose oxidase method (glucose analyzer; Beckman Coulter, Fullerton, CA), and plasma insulin levels were measured with radioimmunoassay (24). Plasma FFAs were determined using a NEFA C kit (Wako, Neuss, Germany).

FAS activity. FAS activity was measured according to a method described by Pénicaud et al. (25). The freeze-clamped white adipose tissue pads were homogenized on ice in four volumes of freshly prepared proethylene glycol buffer, pH 7.3 (100 mmol/l KH_2PO_4, 5 mmol/l EDTA, and 1.5 mg/ml glutathione in reduced form). After centrifugation, these extracts were assayed using 15 μl of extract in 1.7 ml of FAS buffer (50 mmol/l K-phosphate stock solution, pH 6.8, and 0.1 mg/ml NADPH) and using a spectrophotometer set at 340 nm and 30°C. The readings were performed by sequentially adding 15 μl of extract in 1.7 ml of FAS buffer to the cuvettes, followed by 10 μl of 7.5 mmol/l acetyl-CoA, and followed by 10 μl of 8 mg/ml malonyl-CoA.

Intramyocellular lipid determination. Lipid accumulation was determined using an Oil Red O stain, as described by Russell et al. (26). In brief, muscle sections were incubated in formalin for 10 min and then washed 3 × 30 s in deionized water before being stained for 7 min with the Oil Red O solution. After washing again for 3 × 30 s, the sections were counter-stained with Harris's hematoxylin for 4 min and then rinsed under running tap water for 3 min. The sections were covered with a coverslip and viewed using a Zeiss Axiophot I microscope mounted with an Axiocam color charged coupling device camera. The intramyocellular triglycerides were quantified using the Zeiss KS400 V3.0 program, and ~420 ± 160 fibers were scanned per muscle.

Data analysis and statistics. The data were analyzed by two sample tests, either an unpaired *t* test or by the Mann-Whitney (nonparametric) test for comparisons between two groups. The statistical treatment of data were performed using the computer software Statistik, version 4.0 (Analytical Software, St. Paul, MN).

RESULTS

Body composition and energy balance during catch-up fat. In our rat model of catch-up fat after growth arrest, the end of semistarvation (or onset of refeeding) is characterized by the observation that the semistarved and control animals display no differences in either body weight or protein mass. However, compared with control rats, the semistarved animals have 50% less fat mass (Fig. 1) and ~8 g more body water, which compensates for the loss in fat mass (data not shown). During the course of refeeding on an isocaloric basis relative to the controls, the refed rats gained fat at a rate that is 2–3 times greater than that of controls. As a result of this catch-up fat, body fat (but not protein mass) of the refed animals was greater than that of controls 2 weeks later (Fig. 1). This elevated rate in total fat deposition during refeeding, in the absence of differences in energy intake or in protein mass, is explained by a 15% lower energy expenditure and a near doubling of energetic efficiency in the refed group compared with controls (Table 1).

In vivo glucose utilization during euglycemic-hyperinsulinemic clamps. In the studies reported here, all comparisons between refed and control rats were made at a time point when body fat in the refed animals had not yet exceeded that of controls, i.e., at 1 week of refeeding (Fig. 1). At this time point, basal (postabsorptive) plasma insulin concentrations were significantly higher in the refed animals than in controls (Table 2), consistent with our previous observations (19). During the clamps, plasma insulin concentrations were raised to steady-state values of ~10 ng/ml, and plasma glucose was clamped at ~145 mg/100 ml in both the refed and control groups. As shown in Table 2, no significant differences between refed and control groups were found in the glucose infusion rate, i.e., in the amount of glucose infused to maintain euglycemia, and in the whole-body glucose utilization rate (both in the

TABLE 2
Metabolic parameters during basal and euglycemic hyperinsulinemic clamps in control and refed rats at week 1 of refeeding

	Control	Refed	Two-sample tests
Plasma glucose (mg/100 ml)			
Basal	159 ± 4	174 ± 5	$P < 0.05$
Insulin-stimulated	144 ± 5	143 ± 3	NS
Plasma insulin (ng/ml)			
Basal	2.25 ± 0.26	3.10 ± 0.27	$P < 0.05$
Insulin-stimulated	10.3 ± 1.6	10.3 ± 0.9	NS
Glucose infusion rate ($mg \cdot min^{-1} \cdot kg^{-1}$)	21.8 ± 1.2	19.6 ± 0.7	NS
Whole-body glucose utilization rate ($mg \cdot min^{-1} \cdot kg^{-1}$)			
Basal	8.4 ± 1.0	10.3 ± 0.8	NS
Insulin-stimulated	20.0 ± 1.1	17.8 ± 1.1	NS

All values are means ± SE ($n = 8$–9). NS, no statistically significant difference.

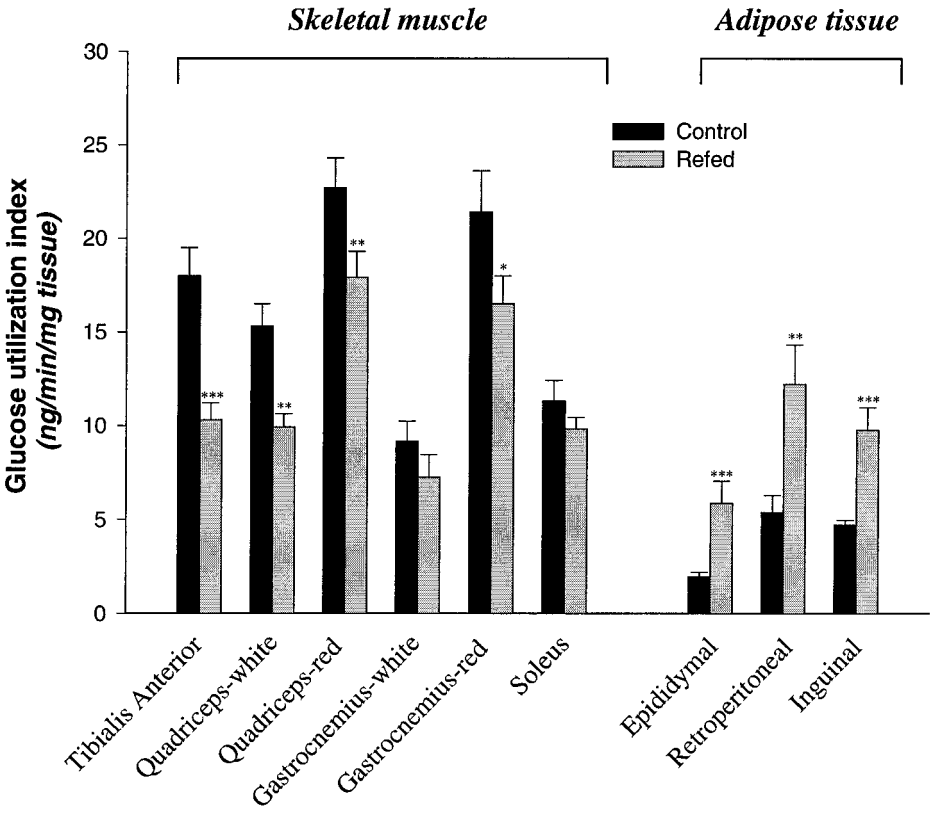

FIG. 2. Glucose utilization rate (ng · min^{-1} · mg^{-1} tissue), as assessed by hyperinsulinemic-euglycemic clamps associated with labeled 2-deoxyglucose, in individual tissues from refed and control rats. All values are means ± SE (n = 7–9). Levels of statistical significance of differences relative to controls are indicated as follows: ***P < 0.001; **P < 0.05; *P = 0.08.

basal state and under insulin stimulation). Furthermore, the hepatic glucose production rate in response to insulin was not different from 0 in both groups (data not shown). By contrast, as shown in Fig. 2, marked differences between the refed and control animals were found in the tissue-specific insulin-stimulated glucose utilization index. This was lower in skeletal muscles from refed animals than in controls, with the differences being statistically significant for tibialis anterior (−43%, $P < 0.001$), white quadriceps (−35%, $P < 0.02$), and red quadriceps (−21%, $P < 0.05$) or close to reaching statistical significance for the red gastrocnemius muscle (−20%, $P = 0.08$). The insulin-stimulated glucose utilization index also tended to be lower in the white gastrocnemius muscle (−20%), soleus muscle (−13%), and heart (−6%, data not shown) in refed animals than in controls, although these differences failed to reach statistical significance ($P > 0.1$). Similarly, the insulin-stimulated glucose utilization index of brown adipose tissue tended to be lower in the refed rats than in controls (−35%, $P = 0.1$) (data not shown). In marked contrast, the insulin-stimulated glucose utilization index in epididymal, retroperitoneal, and inguinal white adipose tissue depots was higher in refed animals than in controls, with the magnitude of the increase being threefold in epididymal fat pads ($P < 0.001$) and twofold in retroperitoneal and inguinal fat pads ($P < 0.02$).

Muscle lipids and adipose FAS activity. Based on the above-mentioned results, another study of similar design was conducted to determine the intramyocellular lipid content of the skeletal muscle, which showed the greatest and least reduction (the tibialis anterior muscle and the soleus muscle, respectively) in the insulin-stimulated glucose utilization index . Furthermore, the activity of FAS, a key enzyme involved in de novo lipogenesis, was assessed in the epididymal white adipose tissue pad, which showed the most marked increase in the insulin-stimulated glucose utilization index. The results, presented in Table 3, indicate that the intramyocellular lipid contents of the tibialis anterior and soleus muscles were not higher, but actually were lower, in the refed rats than in controls. FAS activity in epididymal fat pads from the refed animals was significantly higher than that from controls by ~50–100%, depending whether the data are expressed by tissue or by protein.

TABLE 3
Basal (postabsorptive) plasma parameters, intramyocellular lipids, and adipose tissue FAS activity in control and refed rats at 1 week of refeeding

	Control	Refed	Two-sample tests
Plasma parameters			
Glucose (mg/100 ml)	125 ± 2	129 ± 3	NS
Insulin (ng/ml)	2.15 ± 0.14	3.25 ± 0.31	$P < 0.02$
FFA (mmol/l)	0.396 ± 0.023	0.386 ± 0.037	NS
Skeletal muscle, intramyocellular lipids (arbitrary units)			
Tibialis anterior	3.02 ± 0.64	1.62 ± 0.32	$P = 0.08$
Soleus	12.0 ± 1.10	7.32 ± 1.15	$P < 0.02$
Adipose tissue, FAS activity			
μU · g tissue^{-1} · min^{-1}	782 ± 120	1,568 ± 83	$P < 0.001$
μU · g protein^{-1} · min^{-1}	55.7 ± 4.9	87.4 ± 3.8	$P < 0.002$

All values are means ± SE (n = 6). NS, no statistically significant difference.

DISCUSSION

Lower energy expenditure (because of diminished thermogenesis) is often associated with hyperinsulinemia in a variety of animal models of obesity (27), although it is not clear whether the state of hyperinsulinemia precedes or is a consequence of the development of excess adiposity. In the rat model of weight recovery used here, we previously showed that the elevated efficiency for catch-up fat is attributed primarily to diminished thermogenesis (18), and that the hyperinsulinemic state of catch-up fat could be linked to suppressed thermogenesis per se rather than to increased fat mass and/or an elevation in circulating FFAs (19). Using the same study design for the assessment of insulin-stimulated glucose utilization index by euglycemic-hyperinsulinemic clamps, evidence is presented here that this phenomenon of suppressed thermogenesis favoring catch-up fat is also characterized by insulin resistance in skeletal muscle and insulin hyperresponsiveness in adipose tissue.

Thus, although in response to insulin, whole-body glucose utilization, as assessed by infusing ^{14}C-labeled glucose during the clamps, was not different between the refed and control groups, the additional use of labeled 2-deoxyglucose at the end of the clamps revealed that insulin-stimulated glucose utilization was lower in skeletal muscle from refed animals than from controls. In general, the magnitude of this reduction tended to be more pronounced in muscles that are predominantly fast glycolytic or fast oxidative-glycolytic (20–43% reduction) compared with muscles that are predominantly slow oxidative, like the soleus muscle (<15% reduction). Furthermore, there was also a tendency for insulin-stimulated glucose utilization to be lower both in brown adipose tissue and, to a much lesser extent, in the heart (a slow-oxidative muscle), but these differences failed to reach statistical significance. By contrast, insulin-stimulated glucose utilization was markedly elevated (by two- to threefold) in all three white adipose tissue fat pads studied, whether the fat depots are located more centrally in the intra-abdominal region (epididymal and retroperitoneal) or more peripherally below the skin (inguinal). It should be emphasized that these data about divergent glucose utilization in skeletal muscle and adipose tissue were obtained with plasma insulin clamped at ~10 ng/ml, which is three to five times greater than that observed in the basal (postabsorptive) state (Table 2), and which corresponds to peak postprandial plasma insulin values that we previously found after a glucose load in refed animals showing catch-up fat on the same chow diet (19). In other words, the lower glucose utilization rate in skeletal muscle, concomitant with the elevated glucose utilization rate in adipose tissue, is shown here under clamp-study conditions that mimic postprandial hyperinsulinemia, which typically occurs under real-life (everyday feeding) conditions.

This redistribution of insulin-stimulated glucose utilization away from skeletal muscle toward adipose tissue is demonstrated here in an experimental setting whereby differences in glucose utilization in muscle and adipose tissue between refed and control rats cannot be explained by differences in substrate supply (because both groups consumed the same amount of chow on a day-to-day basis) or in total body fat or circulating FFAs (because they were not different between refed and control groups at the time point at which the clamp studies were conducted, i.e., after 7 days of refeeding). Similarly, the state of insulin resistance in skeletal muscle cannot be attributed to excess lipid storage in muscle cells because histological staining of muscles, harvested at the same time point as for the clamp studies, revealed that intramyocellular lipid content in muscles from refed animals was not higher than in controls. In fact, the intramyocellular lipid content was lower in muscles from the refed animals, possibly reflecting an increased utilization of muscle lipid stores in the face of decreased glucose utilization. Taken together, these data suggest that muscle insulin resistance and adipose tissue hyperresponsiveness in the refed animals are not related to an excess substrate (FFA) supply or to increased total body fat or ectopic fat storage, but rather they are associated with the state of hyperinsulinemia and suppressed thermogenesis per se.

This divergent regulation of in vivo glucose utilization by skeletal muscle and adipose tissue, reported here during weight recovery, has been previously observed under various metabolic states characterized by hyperinsulinemia. Indeed, after chronic administration of exogenous insulin using minipumps (28,29) or after chronic intracerebroventricular infusion of neuropeptide Y (30,31) in the rat, elevated circulating insulin levels were shown to coexist with skeletal muscle insulin resistance and adipose tissue hyperresponsiveness. Whether the hyperinsulinemia observed in these metabolic states or during catch-up fat is the cause or consequence of skeletal muscle insulin resistance is unclear, but it is likely to contribute to fat accretion by stimulating de novo lipogenesis in adipose tissue. Thus, in intracerebroventricular neuropeptide Y–infused hyperinsulinemic rats, glucose uptake and the activity of acetyl-CoA carboxylase were found to be increased in white adipose tissue (30). In the current study, basal (postabsorptive) insulin levels are clearly higher (by ~50%) in the refed animals than in controls, and this state of hyperinsulinemia during catch-up fat is associated with markedly elevated FAS activity, a key enzyme for de novo lipogenesis, in white adipose tissue.

Taken together, our data are consistent with the hypothesis that skeletal muscle, which is a major site for glucose disposal in the fed state, might also be a major site for energy conservation (and hence glucose sparing) directed at catch-up fat during catch-up growth. The hyperinsulinemia and concomitant skeletal muscle insulin resistance during weight recovery would serve to achieve both blood glucose homeostasis and the rapid replenishment of fat stores by diverting circulatory glucose away from utilization in skeletal muscle and toward de novo lipogenesis in adipose tissue. Consistent with this hypothesis is the demonstration that selective inactivation of the muscle insulin receptor gene in mice (which leads to selective insulin resistance in skeletal muscle) leads to hyperinsulinemia and promotes redistribution of substrates to adipose tissue, thereby contributing to maintain blood glucose homeostasis while promoting increased adiposity (32). Within the context of weight recovery after growth arrest or weight loss, such coordinated redistribution of glucose from skeletal muscle utilization to lipogenesis in adipose tissue probably had survival value because it

enables the rapid replenishment of fat stores without compromising blood glucose homeostasis under conditions of intermittent periods of food availability, which prevailed during much of mammalian evolution.

Despite its "adaptive" nature within the context of a lifestyle of famine and feast, this state of hyperinsulinemia, relatively mild-to-moderate skeletal muscle insulin resistance, and adipose tissue hyperresponsiveness confers to the phase of weight recovery a greater susceptibility toward the deleterious consequences of a modern lifestyle characterized by low physical activity and high-fat energy-dense diets. As we previously demonstrated (19), a shift in the composition of the diet from complex carbohydrates to animal fat led to a more pronounced state of hyperinsulinemia, hyperglycemia, and excess adiposity in rats studied during weight recovery than in controls rats growing spontaneously. Because the phase of catch-up growth may last for several years in humans (33), the results reported here suggest that the phenomenon of suppressed thermogenesis for the purpose of sparing glucose for catch-up fat, via the coordinated induction of skeletal muscle insulin resistance and adipose tissue insulin hyperresponsiveness, might be a central event in the link between catch-up growth, hyperinsulinemia, and risks for later metabolic syndrome.

ACKNOWLEDGMENTS

This work was supported by the Swiss National Science Foundation (grants 3200B0-10215, 3157129.99, and 31-65416.01) and by the Roche Research Foundation (Switzerland). This study was part of the Geneva Program for Metabolic Disorders (for P.C.-R., C.C.-T., and F.R.-J.).

We thank Claudette Duret and Marcella Klein for excellent technical support.

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