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PAPER

Long-chain fatty acid uptake is upregulated in omental adipocytes from patients undergoing bariatric surgery for obesity

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OBJECTIVE: To determine the impact of obesity on adipocyte cell size and long-chain fatty acid (LCFA) uptake kinetics in human subjects undergoing laparoscopic abdominal surgery.
SUBJECTS: A total of 10 obese patients (BMI 49.8 ± 11.9 (s.d.) kg/m^2) undergoing laparoscopic bariatric surgery, and 10 nonobese subjects (BMI 24.2 ± 2.3 kg/m^2) undergoing other clinically indicated laparoscopic abdominal surgical procedures.
MEASUREMENTS: Cell size distribution and [^{3}H]oleic acid uptake kinetics were studied in adipocytes isolated from omental fat biopsies obtained during surgery. Adipocyte surface area (SA) was calculated from the measured cell diameters. Plasma leptin and insulin concentrations were measured by RIA in fasting blood samples obtained on the morning of surgery.
RESULTS: The mean SA of obese adipocytes ($41\,508 \pm 5381\ \mu^2$/cell) was increased 2.4-fold compared to that of nonobese adipocytes ($16\,928 \pm 6529\ \mu^2$/cell; $P<0.01$). LCFA uptake in each group was the sum of saturable and nonsaturable components. Both the V_{max} of the saturable component (21.3 ± 6.3 *vs* 5.1 ± 1.9 pmol/s/50 000 cells) and the rate constant k of the nonsaturable component (0.015 ± 0.002 *vs* 0.0066 ± 0.0023 ml/s/50 000 cells) were increased ($P<0.001$) in obese adipocytes compared with nonobese controls. When expressed relative to cell size, V_{max}/μ^2 SA was greater in obese than nonobese adipocytes ($P<0.05$), whereas k/μ^2 SA did not differ between the groups.
CONCLUSION: The data support the concepts that (1) adipocyte LCFA uptake consists of distinct facilitated (saturable) and diffusive processes; (2) increased saturable LCFA uptake in obese adipocytes is not simply a consequence of increased cell size, but rather reflects upregulation of a facilitated transport process; and (3) the permeability of adipocyte plasma membranes to LCFA is not appreciably altered by obesity, and increased nonsaturable uptake in obese adipocytes principally reflects an increase in cell SA. Regulation of saturable LCFA uptake by adipocytes may be an important control point for body adiposity.
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Introduction

Obesity is, virtually by definition, the excessive retention and storage of long-chain fatty acids (LCFA), principally as triglycerides, in adipose and other tissues. Nevertheless, although certain aspects of LCFA disposition, and intermediary metabolism in general, have been widely studied in obese patients and in related animal models of obesity, there have been few studies of the trans-plasma membrane transport and consequent cellular uptake of LCFA in these settings, and none, to our knowledge, in human subjects.

Although cellular LCFA uptake was long considered to be an entirely passive, unregulated process, we and others have established that LCFA enter cells such as adipocytes by two distinct pathways: saturable, and presumably protein-

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mediated transport of LCFA anions and passive 'flip-flop' of protonated LCFA.[1,2] We have also shown that obesity resulting from a variety of causes (eg genetic, dietary) in several rodent species is associated with the tissue-specific upregulation of saturable LCFA uptake by adipocytes, but not by hepatocytes or cardiac myocytes.[3,4] These findings suggest (1) that the selective upregulation of adipocyte LCFA uptake in obesity alters LCFA partitioning, diverting LCFA *away* from tissues where they would be consumed as fuel *to* adipose tissue, where they are stored as triglycerides; and (2) that the increase in saturable LCFA uptake reflects upregulation of specific membrane transport process(es). In animal models such as the *ob/ob* mouse, insulin appears to be an important upregulator and leptin a key downregulator of adipocyte LCFA uptake.[5] The observation that, in particular experimental settings, upregulation of adipocyte LCFA uptake precedes weight gain,[3] whereas downregulation of adipocyte LCFA uptake precedes weight loss[5] further suggests that regulation of saturable LCFA uptake may be an important control point for body adiposity.[6]

We here describe studies of the uptake kinetics of 9,10-[^{3}H]oleic acid (OA) by omental adipocytes isolated from obese patients undergoing laparoscopic bariatric surgical procedures, and compare the results with those obtained with omental adipocytes isolated from nonobese individuals undergoing a variety of other, clinically indicated laparoscopic procedures. Although it was not possible to obtain samples of liver and cardiac muscle for studies of LCFA uptake in these patients, the upregulation of adipocyte LCFA uptake observed in the obese subjects suggests that in human as well as rodent obesity, alterations in LCFA partitioning that favor storage over metabolism contribute to the obese phenotype.

Methods

Patients

The study population consisted of 20 patients undergoing clinically indicated abdominal laparoscopic surgical procedures, who consented to removal of an omental fat sample during surgery for studies of LCFA transport and a venous blood sample for the measurement of plasma levels of insulin and leptin. A total of 10 of the patients (five males, five females) were obese, and were undergoing bariatric surgical procedures related to their obesity. Four of them (two males, two females) had elevated fasting blood glucose concentrations. These ranged from 141 to 170 mg/dl at operation, but none was on medications likely to influence glucose or fatty acid metabolism for at least 2 weeks prior to surgery. The other 10 patients (five males, five females) were nonobese, and were undergoing a variety of clinically indicated laparoscopic procedures, including donor nephrectomy (4), cholecystectomy (2), inguinal hernia repair (1), removal of a mucinous cystadenoma (1), relief of celiac compression (1), and repair of a hiatal hernia for relief of symptoms of gastroesophageal reflux disease (GERD) (1). None was diabetic, had a significant chronic inflammatory disease or malignancy, or was on medications likely to influence glucose or fatty acid metabolism at the time of surgery. The protocol and consent documents and procedures for these studies were approved by the Institutional Review Board (IRB) of the Mount Sinai School of Medicine.

Materials

OA was purchased from NEN Life Science Products (Boston, MA, USA), type I collagenase for adipocyte isolation from Sigma (St Louis, MO, USA), fatty acid-free bovine serum albumin (BSA) from Boehringer Mannheim (Indianapolis, IN), and human insulin-specific- and leptin-specific RIA kits from Linco Research, Inc. (St Charles, MO, USA).

Preparation of isolated adipocytes

Single cell suspensions of human adipocytes were prepared from the omental fat samples by collagenase digestion, as previously described.[7–9] All preparations used in subsequent studies met established viability criteria.[9] Optimal viability was achieved by maintaining the cells at room temperature in Dulbecco's modified Eagle's medium (DMEM) after isolation, and rewarming them to 37°C just prior to use. The distribution of cell diameters in each preparation was determined by direct microscopy at $\times 100$, using a graduated eyepiece reticle with which measurements of cell diameter were recorded in arbitrary units (U). After conversion to micrometers (μ) ($1\,U = 9.6\,\mu m$), the corresponding mean cell surface area (SA), in μ^2, was calculated.[10]

LCFA uptake studies

Cell aliquots from each preparation were incubated at 37°C in DMEM containing 500 μM BSA[11,12] and one of five different concentrations of OA, such that the OA:BSA molar ratio (v) was 0.25, 0.5, 1.0, 1.5, or 2.0 : 1. The initial velocity (V_0) of cellular oleate uptake from each test solution was determined by a standard, rapid filtration technique[7–9,13] from four samples obtained in triplicate over the initial 30 s of incubation, during which uptake was a linear function of time.

Computations and data fitting

The unbound oleate concentration ($[OA_u]$) in each test solution was calculated from v,[14] using the LCFA:BSA binding constants of Spector *et al*[15] Our rationale for the use of these particular binding constants rather than several alternative, more recently determined values[16–18] has been reported in detail previously.[5]

Based on prior analyses,[2] measurements of initial oleate uptake velocity at values of v from 0.25 to 2.0 were fitted to the sum of a saturable and a nonsaturable function of the

corresponding $[OA_u]$, according to the equation:

$$UT([OA_u]) = (V_{max}[OA_u])/(K_m+[OA_u]) + k[OA_u], \quad (1)$$

in which $UT([OA_u])$ is the experimental measurement of uptake, in pmol/s/50 000 cells, at the stipulated concentration of unbound oleic acid; V_{max} and K_m are, respectively, the maximal uptake velocity of the saturable oleic acid uptake component and the value of $[OA_u]$ at one-half the maximal uptake velocity; and k is the rate constant for nonsaturable uptake.[1–5,9] Data fitting was accomplished using the SAAM II version of the Simulation, Analysis and Modeling (SAAM) program of Berman and Weiss[19] as modified for execution on a lap-top PC computer.[20] SAAM uses an iterative, nonlinear algorithm to compute for each data set values of the V_{max} (pmol/s/50 000 cells) and K_m (nM) of the saturable uptake function, and the rate constant k (ml/s/50 000 cells) for the nonsaturable uptake process, as well as their variances and covariances. Prior studies in isolated hepatocytes and adipocytes have documented that, when measured under the specific conditions employed in the current studies, V_0 and derived parameters such as V_{max} are measures of transmembrane transport. Their values are largely unmodified by such premembrane phenomena as rate-limiting dissociation from albumin and the effects of the pericellular unstirred water layer on substrate availability at the cell surface, or of subsequent intracellular binding or metabolism.[11–13] Further studies, in which an increase in V_{max} was shown to precede an increase in adipocyte size early in the development of obesity,[3] and a decrease in V_{max} preceded a reduction in adipocyte size during leptin-induced weight loss[5] clearly established that changes in V_{max} did not reflect changes in cell volume.

Statistical considerations

Values for physiologic variables are reported as mean ± s.d., calculated according to standard methods of descriptive statistics.[21] The significance of obesity and gender were tested in two-way factorial ANOVAs, using a log transformation to accommodate disparate variances where needed.

Results

Patients

Overall, the obese and nonobese patient groups were similar in age (Table 1). By definition, the obese patients weighed more and had significantly higher BMIs ($P<0.001$). Plasma insulin ($P=0.016$), leptin ($P<0.001$), and glucose ($P<0.001$) concentrations were also significantly higher in the obese patient group, but small increases in cholesterol and triglycerides did not achieve statistical significance.

Adipocytes

Within each isolated adipocyte preparation, the distribution of cell diameters was not Gaussian, but rather skewed to the right, due to the presence of a small subpopulation of very large cells. For this reason, the mean SA per cell within each preparation was calculated from the formula of Di Giralomo *et al*,[10] rather than that of Zinder and Shapiro,[22] since the former more accurately reflects the disproportionate contribution to the total SA of the population derived from these very large cells. At 41 508 ± 5381 μ^2/cell, the mean SA of adipocytes from obese patients was 2.4-fold greater than that of adipocytes from nonobese subjects (16 928 ± 6529 μ^2/cell) (Table 2; $P<0.01$).

LCFA uptake studies

Representative OA uptake studies in adipocyte suspensions from one obese and one nonobese subject are illustrated in Figure 1. Data points are depicted as the mean ± s.d. of triplicate determinations. Each curve clearly consists of distinct saturable and nonsaturable components, and represents a computer fit of the data to Eq (1). Total uptake, as well as each of its components, is appreciably faster in the obese than in the nonobese cells. Computer-fitted curves in all studied individuals are shown in Figure 2. Uptake in all of the obese individuals exceeds that in any of the nonobese subjects.

The V_{max} for saturable oleic acid uptake and the rate constant (k) for nonsaturable uptake were both highly

Table 1 Patient characteristics[a]

Group	*(n)*	*Age (y)*	*Weight (kg)*	*BMI (kg/m²)*	*Insulin (ng/ml)*	*Leptin (ng/ml)*	*Glucose (mg/dl)*	*Cholesterol (mg/dl)*	*Triglycerides (mg/dl)*
Obese									
Male	(5)	49.0 ± 10.7	164 ± 34	56.4 ± 14.4	13.1 ± 5.2	18.6 ± 8.6	122 ± 33	174 ± 40	130 ± 96
Female	(5)	44.4 ± 3.6	115 ± 9	43.2 ± 1.8	10.5 ± 3.9	24.5 ± 5.2	120 ± 33	265 ± 23	163 ± 16
Total	(10)	46.7 ± 7.9	139 ± 35	49.8 ± 11.9	11.8 ± 4.5	21.6 ± 7.4	121 ± 31	224 ± 56	146 ± 67
Nonobese									
Male	(5)	48.2 ± 12.6	78 ± 7	24.9 ± 1.8	8.2 ± 4.6	3.2 ± 2.7	66 ± 10	190 ± 56	142 ± 19
Female	(5)	48.2 ± 11.0	69 ± 12	23.5 ± 2.6	4.9 ± 2.4	7.0 ± 6.3	77 ± 14	177 ± 32	129 ± 44
Total	(10)	48.2 ± 11.2	74 ± 10	24.2 ± 2.3	6.7 ± 4.0	4.9 ± 4.8	72 ± 13	184 ± 43	136 ± 33

[a]All values mean ± s.d.

Table 2 Kinetic parameters of adipocyte LCFA uptake[a]

Group	V_{max} *(pmol/s/50 000 cells)*	K_m *(nM)*	k *(ml/s/50 000 cells)*	*Adipocyte surface area (μ^2/cell)*	$V_{max}' = V_{max}$/*surface area (pmol/s/50 000 cells)*	$k' = k$/*surface area (ml $\times 10^{-8}$/s/μ^2)*
Obese						
Male	24.2±5.9	155±29	0.016±0.0023	44 986±5597	1.07±0.21	0.71±0.05
Female	18.4±5.8	163±116	0.014±0.0004	38 030±1892	0.97±0.31	0.74±0.05
Total	21.3±6.3	159±80	0.015±0.0019	41 508±5381	1.02±0.26	0.73±0.05
Nonobese						
Male	4.0±1.4	98±45	0.0063±0.0023	16 976±8496	0.56±0.34	0.85±0.35
Female	6.1±1.8	125±46	0.0069±0.0026	16 879±4871	0.80±0.40	0.88±0.499
Total	5.1±1.9	111±45	0.0066±0.0023	16 928±6529	0.68±0.37	0.87±0.41

[a]All values mean±s.d.

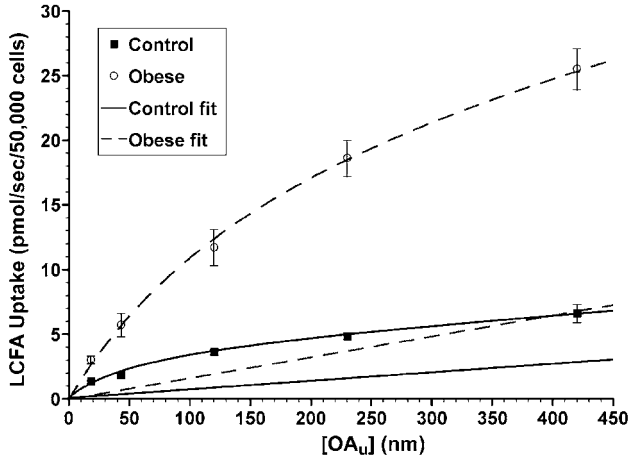

Figure 1 Representative studies of OA uptake by omental adipocytes isolated during bariatric surgery from an obese patient (BMI 80 kg/m^2), and from a nonobese patient (BMI 25 kg/m^2) during a laparoscopic cholecystectomy. Values are means±s.d. of triplicate determinations at five different [OA_u] concentrations. Where no error bars are shown, their range was smaller than the data point symbol. Plotted curves were fitted by computer to the sum of a saturable and a non-saturable function of [OA_u]. Curves representing both total OA uptake and the computer-generated nonsaturable uptake component are shown for each study.

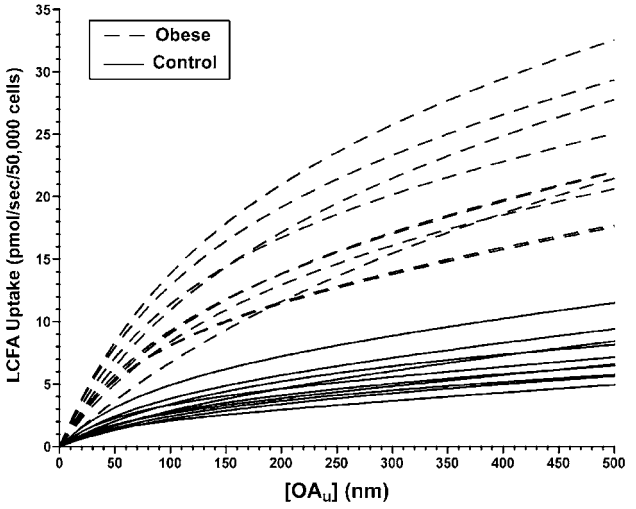

Figure 2 Computer fits to the OA uptake data in 10 obese (dashed lines) and 10 nonobese (solid lines) subjects. There is no overlap between the groups. Kinetic parameters calculated from these curves are presented in Table 2.

significantly increased in obese subjects compared with the values in nonobese subjects (Table 2; $P<0.001$). As reported in multiple animal models of obesity,[3,4] the 4.2-fold increase in V_{max} was appreciably greater than the increase in adipocyte SA. While K_m is increased by a mean of 43% in obese patients, this was not significantly greater than that in the nonobese population in the present study ($P=0.09$), due at least in part to the large variances in this parameter in both populations.

Relationship of LCFA uptake to adipocyte size

Both V_{max} and k were highly correlated with adipocyte SA ($r=0.87$, $P<0.001$ and $r=0.93$, $P<0.001$, respectively), raising the question of whether the increased LCFA uptake in these cells is simply a reflection of increased cell size. To address this issue, it is useful to express V_{max} and k explicitly as functions of cell SA:

$$V_{max}(\text{pmol/s/50 000 cells}) = V_{max}'(\text{pmol/s/SA})\text{SA and} \quad (2)$$

$$k(\text{ml/s/50 000 cells}) = k'(\text{ml/s/SA})\text{SA} \quad (3)$$

where the SA denoted here is that of 50 000 cells. Based on the units in which V_{max} and SA are measured experimentally, the corresponding units for V_{max}' are (pmol $\times 10^{-8}$/s/μ^2), and for k' are (ml $\times 10^{-8}$/s/μ^2) (Table 2). Equations (2) and (3) indicate that correlations between V_{max} and k, on the one hand, and SA, on the other, are to be expected and do not, in and of themselves, provide an answer to the question. However, V_{max}' was significantly increased in adipocytes from obese individuals compared with those from nonobese patients (Table 2, $P<0.05$). For reasons presented in detail earlier,[5] this increase in V_{max}'

indicates that the overall increase in V_{max} and saturable LCFA uptake observed in obese adipocytes is *not* merely reflective of an increased cell size, but rather, indicates upregulation of a membrane transport system mediating LCFA uptake. By contrast, the value of k', while slightly greater in nonobese adipocytes, was not significantly different between adipocytes from obese and nonobese subjects (Table 2, $P>0.1$). Over the range of cell sizes encompassed by obese and nonobese adipocytes, both the magnitude and direction of the small difference observed are consistent with the small increases in the permeability of lipid bilayer membranes to amphipathic molecules that occur with decreases in the radius of curvature.[1,2] Thus, k' reflects the permeability of adipocyte plasma membranes to LCFA per unit SA, and is largely independent of cell size. Accordingly, nonsaturable LCFA uptake at any given $[OA_u]$ can be approximated by

$$UT_{NS}([OA_u]) \cong k'SA[OA_u]. \quad (4)$$

That nonsaturable uptake reflects the product of a permeability term (k') and an area term is consistent with our hypothesis that k is a measure of the rate of passive diffusion ('flip-flop') of LCFA into cells.[1,2,23]

Correlations among measured variables

V_{max} was highly significantly correlated with both body weight ($r=0.908$) (Figure 3) and BMI ($r=0.869$) ($P<0.01$ in each case). As expected, both plasma insulin and leptin concentrations were also correlated with BMI ($r=0.669$ and 0.635, respectively) and body weight ($r=0.680$ and 0.640, respectively) ($P<0.01$ in each instance). As a result, there were significant correlations between insulin ($r=0.662$) and leptin ($r=0.754$) concentrations and V_{max} ($P<0.01$).

Discussion

Obesity is widespread in the US, and carries with it profound health issues with enormous health care costs.[24,25] It is a major risk factor for noninsulin-dependent diabetes mellitus (NIDDM), and is associated with excess morbidity and mortality from many causes, including cardiovascular disease, liver disease, and cancer. As summarized by Leibel *et al*,[26] only three basic mechanisms or a combination thereof can lead to the development of obesity: (I) a relative increase in energy intake; (ii) a relative decrease in energy expenditure; and (iii) preferential partitioning of ingested calories to storage as fat. As the most energy-dense nutrient, changes in LCFA disposition may play a role in each of these mechanisms.

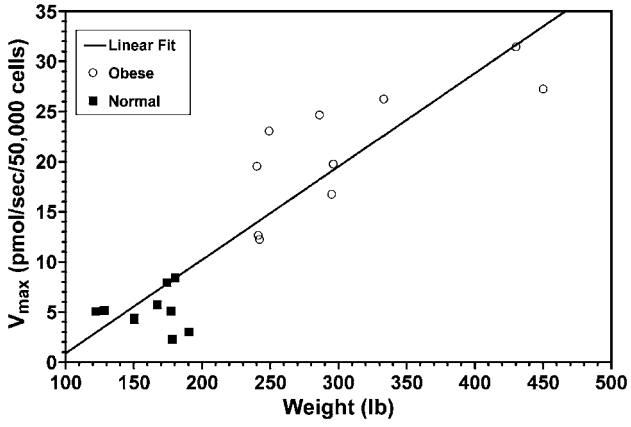

Figure 3 Relationship between body weight and the V_{max} for saturable LCFA uptake. The correlation coefficient ($r=0.908$) is highly significant ($P<0.01$).

LCFA are major energy substrates, key components of cell membranes, precursors of important signaling molecules and other biologic mediators, and critical intracellular regulators of gene expression. Their entry into cells was long believed to occur by passive diffusion through the lipid bilayer of plasma membranes. However, recent work has clearly established that LCFA enter many cell types by both the facilitated, protein-mediated transport of LCFA anions and the passive diffusion ('flip-flop') of the uncharged, protonated fatty acid.[1,2] Based on determination of the $t_{1/2}$s for the movement of a fatty acid molecule across the plasma membranes of isolated rat adipocytes and hepatocytes, the facilitated process is at least 10-fold faster than that of passive flip-flop.[2,23] Under basal physiologic conditions, more than 90% of LCFA uptake by hepatocytes, adipocytes, and cardiac myocytes occurs via the saturable, facilitated process.[9,11,13,27,28]

Altered LCFA disposition is typical of both obesity and NIDDM.[29,30] Indeed, some believe that such changes are the primary disturbances in these conditions.[31–34] Animal models have been very useful in studying this process. The discovery of leptin and the role of leptin deficiency in the *ob/ob* mouse in 1994[35] opened the door to an explosion of information about the existence and roles of numerous hormones, as well as systemic and localized neuropeptides, involved in complex regulatory loops that modulate feeding behavior, energy expenditure, and various aspects of intermediary metabolism (reviewed in Friedman and Halaas[36]).

Our studies in the *fa/fa* rat[3] and the *ob/ob*, *db/db*, *fat*, and *tubby* mouse models of genetically determined obesity[4,5] as well as both rat and mouse models of dietary obesity[4] found that the V_{max} for saturable LCFA uptake in adipocytes was appreciably upregulated in every instance. In virtually all of the models studied, saturable uptake per unit of SA (V_{max}') was significantly increased in adipocytes from obese animals compared to appropriate controls (Figure 4), suggesting that the increase in saturable uptake resulted from upregulation of a facilitated membrane transport system.[5] By contrast, the increase in k in the absence of a significant increase in k' indicated that the increased nonsaturable uptake reflected passive diffusion across the increased SA of enlarged obese adipocytes. All of these observations have been confirmed in the present study in human omental adipocytes.

Several further observations in the animal model studies have not yet been confirmed in man. In particular, the

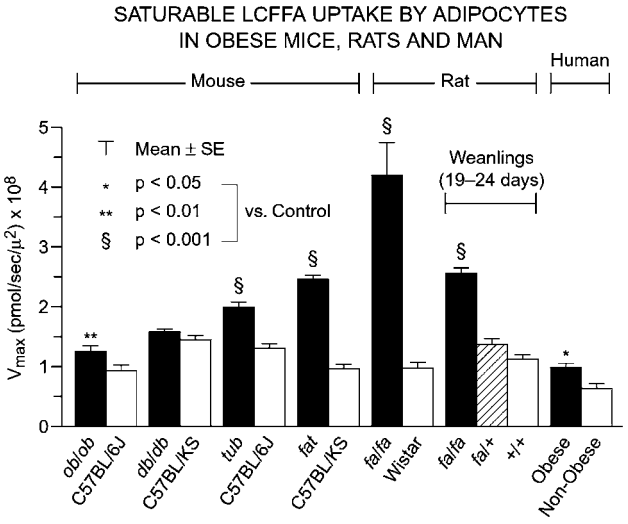

Figure 4 Comparison of V_{max}' (pmol $\times 10^{-8}$/s/μ^2) in adipocytes from obese and nonobese subjects. Human data are from the current study. Data in obese mice and rats and appropriate control strains are replotted from Berk *et al.*[3,4] Saturable LCFA uptake/μ^2 of adipocyte SA was increased in all groups. All differences were significant except in *db/db* mice.

upregulation of saturable LCFA uptake was found to be tissue-specific, in that, in marked contrast to adipocytes, saturable LCFA uptake by hepatocytes and cardiac myocytes from obese animals was virtually unchanged from control values.[2,3] We have not yet had an opportunity to study LCFA uptake kinetics in human liver or cardiac muscle. The increase in adipocyte LCFA uptake in weanling Zucker fatty (*fa/fa*) rat pups was found to precede by several days enlargement of adipocytes and weight gain,[3] whereas the rapid downregulation of saturable LCFA uptake that results from leptin infusion in the *ob/ob* mouse precedes reductions in food intake, increased locomotor activity, and weight loss.[5] Again, it has not yet been possible to make analogous observations in man. Several lines of observation in animals have led us to speculate that insulin normally upregulates, and leptin downregulates, saturable LCFA in adipocytes.[3–5] We consider that the significant correlation observed between plasma insulin levels and V_{max} in the current studies is consistent with the first of these speculations. The correlation between leptin levels and V_{max} may, by contrast, be a manifestation of leptin resistance.

Finally, alterations in saturable LCFA uptake in several rodent obesity models[3–5] and in differentiating mouse 3T3-L1 preadipocytes[37,38] have been consistently associated with parallel changes in the expression, at both mRNA and protein levels, of putative LCFA transporters such as plasma membrane fatty acid binding protein ($FABP_{pm}$) and fatty acid translocase (FAT/CD36).[3–5] Indeed, the correlation between V_{max} and expression of mRNA levels for these transporters in some studies has achieved a value of $r = 0.99$.[3] As recently reviewed,[6] the former of these has proven identical to the mitochondrial isoform of aspartate aminotransferase (mAspAT).[39–41] Nevertheless, its presence on adipocyte and hepatocyte plasma membranes has been firmly established by immunofluorescence, immunohistochemical, and immunoelectron microscopic techniques and by immunoprecipitation from highly purified plasma membrane preparations,[6] while its function as a plasma membrane LCFA transporter was demonstrated in antibody inhibition,[28] transfection,[42] and microinjection[43] experiments. Relative mRNA levels in these published studies were assayed principally by Northern hybridization analysis. In assaying the corresponding mRNA levels in the human adipocyte samples obtained in the present studies, we found frequent discrepancies between the results obtained by microarray, RT-PCR, and Northern hybridization assays. While we believe that these inconsistencies reflect a technical artefact, we are reluctant to express an opinion about mAspAT gene expression in human obesity pending full resolution of this unexpected problem, which in no way alters the interpretation of the oleic acid kinetic studies.

Based on observations to date in both rodents and man, it is our hypothesis that regulation of adipocyte LCFA uptake in response to imbalances between energy intake and energy expenditure from any cause is an important control point for body adiposity, both in terms of quantity and distribution (Figure 5). In particular, tissue selective upregulation of LCFA uptake by adipocytes would be expected to alter the partitioning of this energy dense nutrient, diverting it away from tissues where it is oxidized as fuel and into adipose tissue, where it is stored as fat. While the data obtained thus

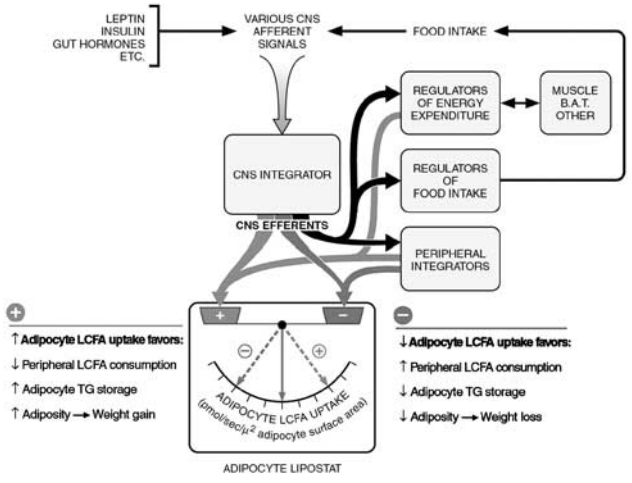

Figure 5 Regulation of adipocyte LCFA uptake controls body adiposity. Although the primary genetic defects in well-studied animal models of obesity are in the CNS (*db* mouse, Zucker fatty rat) or in peripheral tissues (*ob* mouse), all such defects, as well as animal models of dietary obesity, result in selective upregulation of facilitated LCFA by adipocytes. This suggests that regulation of adipocyte LCFA uptake represents a final, common pathway for control of body adiposity resulting from a diversity of primary causes. The upregulation of adipocyte LCFA uptake observed in the present study suggests that a similar regulatory process applies to human adiposity. Reproduced from Clinics in Liver Disease[44] with permission.

far are fully consistent with this hypothesis, a full understanding of the role of fatty acid transport in the pathogenesis of obesity will require parallel studies of rates of lipolysis. These will be included in our future investigations.

Owing to the central role of LCFA in intermediary metabolism, a detailed understanding of cellular LCFA disposition, including their transmembrane transport, will yield important insights into the pathophysiology of obesity and the pathogenesis of obesity-related NIDDM and the entire spectrum of nonalcoholic fatty liver disease.[44] Our efforts to clarify in fine detail the mechanisms involved in membrane transport of LCFA are directed at improving understanding of the underlying pathophysiology of an important group of diseases.

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