The lowering of hepatic fatty acid uptake improves liver function and insulin sensitivity without affecting hepatic fat content in humans

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The lowering of hepatic fatty acid uptake improves liver function and insulin sensitivity without affecting hepatic fat content in humans. Am J Physiol Endocrinol Metab 295:E413–E419, 2008. First published May 27, 2008; doi:10.1152/ajpendo.00744.2007.—Lipolysis is not the only source of fatty acids. Lipodystrophy represents an unphysiological state associated with liver steatosis in which endogenous fatty acids may be one major source of triglyceride precursors (25, 27). However, in the normal situation, the meal provides nutrients, suppressing their endogenous release during a time in which higher insulin levels promote lipid storage. Thus, high-fat diets are also associated with liver steatosis (12). Overall, the relative contribution of lipolysis in regulating liver fat content in the normally fed, healthy individual is still unclear.

Although the implication of fatty acid release in the determination of insulin resistance and liver damage is well established (10, 17), whether the mechanistic link relies on the accumulation of fat in the organ with respect to other potential elements, such as oxidative metabolism and stress, has been the focus of investigations. By using the antilipolytic drug acipimox, Carey et al. (8) showed recently that the improvement in glucose homeostasis induced by the drug was related to the content of fat in the liver, as measured before the administration of the agent. The assessment of liver fat content was not repeated after the intervention to test whether changes in this variable might be mediators of the systemic effects of the drug (8). Bajaj and colleagues (2, 3) have demonstrated that a sustained, 1-wk reduction in fatty acid release improves hepatic insulin sensitivity in subjects with a strong family history of diabetes and reduces skeletal muscle lipotoxicity by lowering the levels of long-chain fatty acyl-CoA compounds in patients with type 2 diabetes. Although intramyocellular triglyceride content was not measured in this study, the decrease in long-chain fatty acyl-CoA correlated strongly with the improvement in peripheral (muscle) insulin sensitivity following acipimox treatment. These changes were independent of plasma adiponectin concentrations.

The present study was undertaken to establish whether 1) lipolysis is the major determinant of liver fatty acid uptake in fasting humans in vivo and 2) the beneficial effects of fatty acid lowering on glucose metabolism can be explained by a reduction in liver triglyceride content. To this end, two subgroups of healthy subjects were investigated, one in which positron emission tomography (PET) was used to measure hepatic fatty acid uptake before and after the acute lowering of fatty acids and the other in which magnetic resonance spectroscopy (MRS) was employed in the assessment of liver fat content before and after both acute and sustained inhibition.
fatty acid release. Subjects representative of the normal population, i.e., sedentary, middle-aged, intermediate body mass index (BMI), were selected because the main target of the study was around the physiological role of lipolysis and the mechanisms of fatty acid lowering in reducing the risk of early lipotoxic complications in which the simultaneous occurrence of multiple abnormalities or disease would have increased the number of confounders.

METHODS

Study design. The study design is summarized in Fig. 1. Sixteen healthy subjects were enrolled after a screening visit consisting of a medical history, physical examination, and oral glucose tolerance test. None of them had a history of cardiac symptoms or disease or was regularly taking any medication. Three subjects had one first-degree relative with diabetes but normal glucose tolerance (2-h postglucose load glycemia 4.2, 4.5, 6.2), glycosylated hemoglobin (5.0, 5.4, 5.5%), and no outlying baseline characteristics. Subjects were subdivided in two BMI- and age-matched groups of n = 8 each to be allocated to the PET or the magnetic resonance (MR) study. Both PET and MR evaluations were conducted with an identical interventional protocol before and after the acute administration of acipimox. MR studies were also repeated after 1 wk of drug administration, during which patients were forbidden alcohol intake and were instructed to observe a weight-maintaining diet, i.e., to keep their lifestyle. Subjects received a written time schedule for acipimox administration, they were instructed to return unused medication, and they were interviewed at each visit to ensure continuing compliance. Cardiac PET data from the above eight subjects have been used in a previous report (30). The protocol was approved by the Ethics Committee of Southwest Finland Healthcare District. All subjects gave written informed consent.

Liver PET imaging. Two antecubital venous catheters were inserted, one in the right arm for blood sampling. Free fatty acid (FFA) metabolism was measured using PET with [11C]acetate and [11C]palmitate. Imaging studies were performed after a fasting period of ≥10–12 h and repeated after acute reduction of serum FFA levels by acipimox (259 mg of Olbetam, twice orally, 1 h between doses; Pharmacia). The positron-emitting tracers [11C]acetate and [11C]palmitate were produced as described previously (13, 19). The subjects were positioned supine in the GE Advance whole body PET scanner (General electric). A transmission scan was done for photon attenuation correction of emission data. Next, an intravenous bolus of [11C]acetate was given and a dynamic scan of the hepatic region performed to quantify the time course and inflow of acetate in the liver resulting from the balance of oxidation and de novo lipogenesis. After allowing 1 h for residual tracer decay, subjects received an intravenous bolus of [11C]palmitate with the simultaneous start of a 30-min (5 × 60, 10 × 30, 2 × 60, and 90 × 120 s) dynamic emission scan to assess liver FFA uptake. Plasma glucose and serum insulin levels were determined at baseline, and FFA concentrations were determined at three time points (0, 15, and 30 min) during the [11C]palmitate scan. Arterialized blood was obtained in frequent samples for the measurement of plasma radioactivity.

PET data processing. PET data were corrected for dead time, decay, and measured photon attenuation. Images were processed using a standard reconstruction algorithm. Large circular regions of interest were placed on three to five consecutive image planes in the right lobe of the liver to extract hepatic [11C]acetate and [11C]palmitate time-activity curves. Such measurements were averaged to generate one tissue time-activity curve per patient. Input functions were metabolite corrected by exponential extrapolation of the descending portion of the plasma time-activity curve. Liver [11C]acetate time-activity curves were normalized by the injected dose for visual inspection, and the areas under the normalized concentration curves were estimated by the trapezoid rule for statistical evaluation of the inflow of tracer in the organ. Data were interpreted according to the notion that [11C]acetate may be oxidized or used for de novo lipogenesis in the liver. Plasma and tissue [11C]palmitate time-activity curves were analyzed graphically to derive the fractional uptake constant (Ki), which is given by the slope of the linear fit of the data (20). The Ki represents the rate constant regulating irreversible uptake. The kinetics of [11C]palmitate in the liver shows progressive accumulation, which is indicative of the existence of an irreversible compartment during the current measurement time, as represented by the deposition of complex lipids. Because a compartmental model to describe PET-derived [11C]palmitate kinetics in the liver has not been developed and validated yet, we used a graphical method that is independent of assumptions on the configuration of the biological system and simply describes (by a plot) the progressive change of tissue vs. plasma tracer concentrations. According to the generalization of this model (14), the occurrence of a linear relationship between the plotted variables attests the appropriateness of the approach to quantify irreversible uptake. Reproducibility of this analysis was tested in a separate group of six subjects undergoing repeated measurements before and after 3 mo of placebo in whom Ki was 0.140 ± 0.007 vs. 0.142 ± 0.014 min on the two occasions, respectively (unpublished observations). The rate constant Ki was multiplied by serum FFA levels to estimate the uptake of FFAs by the liver in μmol min −1·ml −1 of tissue.

Circulating FFA levels were determined three times during each PET scan (0, 15, and 30 min) to document the absence of significant changes during either the fasting or the acipimox experiments (not significant). Plasma concentrations of [11C]palmitate over time were used to calculate the whole body substrate clearance, as ratio of the injected dose to the area under the tracer concentration curve (T = 0 → ∞). The latter was calculated through the trapezoid method. The clearance of [11C]palmitate was multiplied by serum FFA levels to obtain the rate of fatty acid appearance (numerically equaling disappearance) in the circulation (μmol/min) and subsequently normalized to subjects’
body weight. The assumption was made that the clearance of palmitate is representative of the overall FFA clearance, as supported by others (18).

**MR imaging and spectroscopy.** Abdominal fat volumes and hepatic triglyceride content were determined with MRI and MRS, respectively. MR evaluations were performed after a fasting period of ≥8 h and repeated after acute reduction of serum FFA levels by acipimox (259 mg of Olbetam, twice orally, 1 h between doses). Then, patients were continued on the medication for 1 wk (259 mg of Olbetam, 4× times daily orally at 6-h intervals, i.e., at 600, 1200, 1800, and 2400), and MR was repeated a third time at the end of the treatment period (17). Fasted FFA levels were still suppressed by 60% of baseline fasting levels. After 1 wk of acipimox intake (n = 7; see below), FFA levels were still suppressed by ~60% of baseline fasting values. One tablet was missed on one occasion by one subject.

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**Statistical analysis.** All data are presented as means ± SE. Differences in paired data were evaluated using Student’s paired t-test. Regression analyses were carried out using standard techniques. A value of P < 0.05 was considered statistically significant.

**RESULTS**

The characteristics of study subjects are shown in Table 1. The two subgroups were well matched for age, BMI, insulin sensitivity, and metabolic profile. The difference in fasting FFA levels between the groups might depend on an ~3– to 4-h longer fasting period, which is due to tracer preparation of PET scans in the morning. The acute administration of acipimox decreased triglyceride levels by ~10% (P < 0.05) and suppressed FFA levels by 85% on average. The systemic clearance of fatty acids (ml·min⁻¹·kg⁻¹; Fig. 2) was increased to slightly counteract the more pronounced decrease in the whole body turnover of FFAs (product of the clearance and the FFA levels, μmol·min⁻¹·kg⁻¹). The latter takes into account FFA levels and thus reflects the mass flux of substrate, whereas the calculation of clearance is independent of changes in FFA levels. After 1 wk of acipimox intake (n = 7; see below; Table 2), FFA levels were still suppressed by ~60% of baseline fasting values. One tablet was missed on one occasion by one subject. The intervention induced a further decrease in triglyceride levels accompanied by a small reduction in Hb A1c and plasma glucose levels, falling short of statistical significance. Fasting insulin levels were significantly lowered, indicating higher insulin sensitivity, as demonstrated by the calculated indexes. Liver enzymes [alanine aminotransferase (ALT) and γ-glutamyltranspeptidase] were decreased by 10–20%. The change in FFA levels was the stronger correlate of drug-induced variations in plasma glucose (r = 0.81, P = 0.03) and insulin sensitivity (r = 0.88, P < 0.01).

**Liver FFA metabolism and fat content.** PET images from one patient could not be analyzed reliably, and this subject was excluded from paired analyses. The changes in liver [11C]palmitate kinetics are shown in Fig. 3. The acute suppression of FFA levels resulted in an increase in [11C]acetate inflow to the organ; the areas under the tissue concentration curves were significantly larger (P < 0.05). Acipimox increased the fractional uptake of [11C]palmitate, representing the percentage of circulating FFAs that is taken up by the organ in the unit time (Fig. 2). This change correlated with the elevation in the systemic clearance of the tracer. These effects were minimal compared with the pronounced decrease in circulating FFA.

| Table 1. Characteristics of study subjects at baseline and after acute FFA lowering |
|-----------------------------------------|------------------|------------------|
| **Baseline (fasting)**                  | **PET Group**    | **MRS Group**    |
| Age, yr                                 | 55±4             | 57±4             |
| BMI, kg/m²                               | 26±2             | 26±1             |
| Fasting glucose, mmol/l                 | 5.6±0.1          | 5.2±0.1          |
| 2-h OGTT/glucose, mmol/l                | 5.3±0.4          | 5.4±0.6          |
| Glycosylated hemoglobin, %              | 5.5±0.0          | 5.7±0.1          |
| Fasting insulin, mU/l                   | 7.0±1.5          | 6.4±0.8          |
| C-peptide, ng/ml                        | 0.73±0.12        | 0.72±0.06        |
| Triglyceride, mmol/l                    | 1.0±0.1          | 1.0±0.1          |
| Cholesterol, mmol/l                     | 5.3±0.2          | 4.8±0.1          |
| LDL, mmol/l                             | 3.1±0.3          | 2.9±0.2          |
| HDL, mmol/l                             | 1.7±0.2          | 1.4±0.1          |
| HOMA index (22.5/glucose × insulin)     | 1.46±0.284       | 1.51±0.20        |
| Hepatic IS (22.5/glucose × insulin)     | 0.82±0.144       | 0.74±0.29        |
| **Acute acipimox**                      |                  |                  |
| Glucose, mmol/l                         | 5.4±0.1          | 5.3±0.1          |
| FFA, mmol/l                             | 0.08±0.02       | 0.07±0.01†       |
| Triglyceride, mmol/l                    | ND               | 0.9±0.1†         |

Values are means ± SE; n = 8. FFA, free fatty acids; PET, positron emission tomography; MRS, magnetic resonance spectroscopy; BMI, body mass index; OGTT, oral glucose tolerance test; HOMA, homeostasis model assessment; IS, insulin sensitivity; ND, not determined. *P < 0.05 between groups; †P < 0.05 vs. baseline.
baseline measurements; the association was driven mostly by the one subject with abnormal liver fat, in whom a 2% decrease was observed. No significant relationship between changes in liver insulin sensitivity and in liver fat content could be shown (Fig. 4).

**DISCUSSION**

To the best of our knowledge, this study provides first evidence on the combined effects of FFA lowering on directly measured liver fatty acid uptake, systemic metabolism, and hepatic fat content in humans in vivo. The data show that a reduction in adipose tissue FFA release, provoked here by the use of acipimox, greatly decreased liver fatty acid uptake in the fasting state. As a consequence, liver and systemic insulin sensitivity were improved, together with liver function, as assessed by hepatic enzyme levels. These changes occurred in the absence of any variation in the accumulation of triglycerides in the organ.

The current study documents that the liver responds in a counteractive fashion to the acute reduction in FFA supply from the circulation. Opposing the nearly complete suppression in circulating FFA levels determined by acipimox, the fraction of FFAs entering the organ via active extraction was increased from 0.16 to 0.21 l/min. In the balance between these reciprocal forces, the former prevailed by far under the fasting conditions of the present assessments, with a net outcome of a 79% decrease in liver FFA uptake during acipimox administration.

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Notably, the persistence of a higher fractional extraction of fatty acids by the organ may have consequences once the meal is introduced and the provision of substrate is no longer restricted, as discussed in the following paragraph. Our data indicate that, given a typical whole organ volume of 1.5 L and a systemic FFA disappearance of 727/1100681 (baseline) and 118/1100623 (acipimox) mol/min in the current dataset, the liver is responsible for 22/11006159/110062% at fasting and 21/11006269/110062% after acipimox (not significant) of the whole body consumption of fatty acids. It can be extrapolated that any impairment in the ability of the liver to subtract and process circulating FFAs would result in significant substrate overflow to other organs. Confirming previous evidence, peripheral insulin sensitivity was enhanced after acipimox treatment. This observation is in accord with recent findings in humans (8). Importantly, our data show a significant reduction in liver enzymes and triglyceride levels, together with an improved hepatic insulin sensitivity, as computed from fasting measurements. The choice of indirect, albeit validated (5, 16), markers of insulin sensitivity in place of the insulin clamp technique with glucose tracer infusions was dictated by the demanding nature of PET and MR scans, and the number of visits, together with the working age of the subjects. Our findings are in accord with the ones in patients with type 2 diabetes, in whom fasting endogenous glucose production, as measured by gold-standard methods, did not change, but insulin levels were almost halved after a similar 1-wk acipimox regimen, and the basal hepatic insulin resistance index was significantly reduced, by 47%, on average (3). These same authors showed improved insulin-induced suppression of endogenous glucose production during clamp studies in patients with a strong family history of diabetes (2).

The main finding of the study was that a dramatic reduction in fasting FFA uptake by the liver had no effect on the content of triglycerides in the organ. Successful suppression of FFA has been demonstrated with an identical protocol (2, 3). Subjects in the current study were reporting adherence to protocol instructions and were fully compliant. Fasting FFA levels were measured 3 h after medication intake and throughout the end-visit glucose tolerance test, lasting an additional 2 h (data not shown). Since acipimox was administered every 6 h, the documented 5-h suppression of lipolysis is supportive of target achievement. In the 1-wk study, the lack in endogenous FFAs may have been compensated by meal-derived fatty acids delivered in the form of chylomicron remnants to the systemic circulation together with the upregulation of the hepatic fractional extraction rate induced by acipimox. Meal compensation cannot explain the persistency of liver triglyceride stores in the acute acipimox evaluation. One possibility is that the organ adjusts to a lower supply of fatty acids by limiting the export of triglyceride, in line with the progressive reduction in serum triglyceride levels observed here. The acute administration of acipimox has been shown to provoke a shift in release from triglyceride-rich to smaller and denser VLDL, resulting in lower circulating levels of triglycerides, despite no change in the total number of exported lipoprotein particles (15). In addition, the lack of endogenous FFAs may promote a compensatory increase in de novo lipogenesis to replace a slower but continuing mobilization of stored lipids (4). To our knowledge, there are no studies investigating the independent effects of fatty acid lowering on lipogenesis. The accelerated inflow...
and retention of acetate observed here after the acute inhibition of lipolysis may lend support to the above hypothesis. According to this reasoning, during the fasting state, glucose would serve as substrate for energy provision and fatty acid synthesis, thus explaining an improved hepatic insulin sensitivity. De novo lipogenesis could be further promoted during the 1-wk depletion of endogenous FFAs at times when meals were introduced to provide alternative nutrients for energy purposes and facilitate the diversion of glucose in stores (4, 14). The current MRS technique has been shown to be the most accurate noninvasive method for assessing liver fat content; it has a reported detection limit of as low as 0.5% and is therefore recommended especially in the case of low liver fat content (26). The calculations in this study were done according to the work published in 1999 by Szczepaniak et al. (28) in which the authors performed the biochemical vs. 1H-MRS validation for detection of levels and changes in levels of tissue triglyceride content. Finally, we cannot exclude that a longer time may be necessary for a measurable depletion in liver triglyceride; for example, the buildup of liver steatosis due to parenteral nutrition with lipid emulsions requires weeks (6, 22), but our findings showed no trend while prolonging the suppression of fatty acids from 1 day to 1 wk.

Independent of the mechanisms underlying the above observation, the resulting effect of a preserved content of fat in the liver indicates that adaptive responses come into play to maintain a pool of lipids in the organ. We may speculate on the occurrence of signaling elements operating in the liver to provoke the return of fat stores to a predefined “set point.” The finding of the present study is novel in humans, and confirms previous data in rats (1a), to which acipimox was given in different dosages and study durations, showing a neutral effect on liver triglyceride content. The preservation of the ability to store lipids has recently been suggested as protective mechanism (31).

One most important finding in the current study was that, despite no change in lipid content, liver and systemic insulin sensitivities were improved during the intervention and accompanied by a significant decrement in liver enzymes, reflecting reduced organ damage. Because the endogenous release of FFAs, i.e., the target of the present intervention, is most active in the fasting state, at a time in which FFAs are predominantly used in oxidative metabolism, our data indicate that this metabolic process is primarily responsible for the beneficial systemic and hepatic action of acipimox independent of the organ content of triglyceride in humans. This interpretation finds indirect support in previous evidence in patients with type 2 diabetes, in whom a similar treatment reduced systemic fatty acid oxidation, and skeletal muscle oxidative precursors, i.e., long-chain fatty acyl-CoA compounds (3). Our evidence is not intended to indicate that liver steatosis is of no detriment to the organ and to the entire body. What is strongly suggested by our data is that the removal of triglyceride stores from the liver is not necessary for fatty acid lowering to determine the observed improvement. In turn, a reduced formation of reactive oxygen species caused by the inhibition of fatty acid oxidation under the current treatment may be of more relief in subjects with lower lipid stores in whom lipid peroxidation would become secondarily minimal. This line of events is in complete agreement with the second-hit hypothesis, explaining lipotoxicity as the reverse sequence (23), in which the relative contribution of liver fat may be amplified in patients with overt steatosis. As a matter of fact, subjects with higher liver fat content at baseline were more resistant to the effects of the drug to reduce circulating triglyceride and ALT levels (P = 0.03 and P = 0.17, respectively, data not shown) and showed a worse peak glycemnic response to a glucose load in recently reported acute studies in humans (8).

Some potential limitations merit consideration. First, the number of subjects in each subgroup could not be numerous, given the complexity of the current study and the participation of some subjects in other substudies (30). Because the reported PET results appeared appropriately powered to demonstrate a very tight relationship between lipolysis and liver FFA uptake, and since PET scans involve some radiation exposure, we did not find it justified to extend the number of healthy subjects undergoing the procedure. The current sample size was expected to be sufficient to detect clinically relevant changes on the basis of previous studies that adopted a similar protocol (2, 3). In fact, the current findings appear conclusive within the limits of the population investigated here. Concerning the absence of significant changes in liver fat content, given the attention paid at gathering reproducible results and the known sensitivity of the current technique, a change below the detection limit may be unlikely to fully explain the findings. Second, subjects with high liver fat content were not included in the current study. Numerous abnormalities, including impaired glucose tolerance, are typically associated with high liver fat content, becoming independent causes of metabolic toxicity and independent targets of acipimox. The study was not aimed at exploring the therapeutic potential of acipimox, but it was focused on the physiological mechanisms involving lipolysis in the regulation of liver FFA uptake and in the generation of metabolic risk, and we selected apparently healthy individuals to avoid confounders in this context and, more importantly, to characterize a very initial phase in the lipotoxic cascade. However, this investigation is not intended to rule against the importance of complementary studies seeking more remarkable benefits in disease patients that, if proven, might be partly due to a more powerful effect of acipimox on liver fat content once the latter is elevated. Nevertheless, the findings of this study implicate oxidative stress as an early response of the liver to FFA exposure. As a matter of fact, the current findings lend support to the concept that steatohepatitis may be benefiting the most from FFA lowering, since oxidative stress has been implicated in the pathogenesis of the inflammatory progression.

In summary, these data highlight three concepts for future study of hepatic lipotoxicity and steatosis. First, liver fatty acid uptake is mostly dependent on the delivery of the substrate in humans. Second, the reduction in endogenous fatty acid provision improves insulin sensitivity and liver metabolism and function independently of changes in the liver content of triglycerides. Third, the acute and the sustained inhibition of lipolysis and hepatic fatty acid uptake fails to deplete liver fat in healthy human subjects.

GRANTS

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