Both Intestinal and Hepatic Lipoprotein Production Are Stimulated by an Acute Elevation of Plasma Free Fatty Acids in Humans

Hélène Duez, PhD; Benoît Lamarche, PhD; René Valéro, MD, PhD; Mirjana Pavlic, MD; Spencer Proctor, PhD; Changting Xiao, PhD; Linda Szeto, MSc; Bruce W. Patterson, PhD; Gary F. Lewis, MD

Background — Hepatic lipoprotein production has been shown previously to be regulated by free fatty acid (FFA) flux to the liver, whereas intestinal lipoprotein production is stimulated mainly by ingested fat absorbed from the intestinal lumen. Emerging evidence indicates that intestinal lipoprotein production is increased in insulin resistance and type 2 diabetes mellitus, conditions that are associated with increased levels of circulating FFAs. Here we investigated whether short-term elevation of plasma FFAs stimulates intestinal apolipoprotein (apo) B-48– and hepatic apoB-100–containing triglyceride-rich lipoprotein (TRL) production in humans in the fed state.

Methods and Results — TRL apoB-48 and apoB-100 metabolism were examined in 12 healthy men during a constant fed state. The studies were as follows, respectively: (1) Intralipid/heparin was infused intravenously immediately before and during the kinetics study to induce an ~3-fold difference in plasma FFA compared with the saline study; (2) saline was infused intravenously as a control. apoB-48– and apoB-100–containing TRL production and clearance were determined with a 12-hour primed constant infusion of [D3]l-leucine and multicompartmental kinetic modeling. TRL apoB-48 production rate was 69% higher in the Intralipid/heparin study than in the saline control (5.95 ± 1.13 versus 3.53 ± 0.58 mg/kg per day; P = 0.027), and there was no significant difference in TRL apoB-48 clearance. TRL apoB-100 concentrations were also increased (P < 0.001) and TRL apoB-100 production rate was 35% higher in the Intralipid/heparin study compared with saline (28 ± 4 versus 21 ± 3 mg/kg per day; P = 0.020).

Conclusions — This is the first study to demonstrate that intestinal TRL apoB-48 production is increased after short-term elevation of plasma FFAs in humans in the fed state, similar to the well-described stimulation of hepatic TRL apoB100–containing particles by FFAs. (Circulation. 2008;117:2369-2376.)

Key Words: fatty acids • lipoproteins • lipids

Dyslipidemia is a prominent feature of both insulin resistance and type 2 diabetes mellitus and contributes to the increased risk of cardiovascular events. Characteristic features of the typical dyslipidemia of insulin-resistant states and type 2 diabetes mellitus include elevated plasma triglycerides, increased plasma free fatty acid (FFA) levels, low plasma high-density lipoprotein cholesterol concentration, and an increased number of small, dense low-density lipoprotein particles. The elevation of triglyceride-rich lipoprotein (TRL) particles in insulin-resistant states is contributed to by both hepatic (apolipoprotein [apo] B-100–containing) and intestinal (apoB-48–containing) lipoproteins in fasted and postprandial states. We have shown recently that diet-induced insulin resistance in Syrian Golden hamsters is associated with a marked increase in intestinal lipoprotein production rate in both the fasting and the fed states, because apoB-48–containing intestinally derived lipoproteins have been identified as proatherogenic and their secretion is increased in insulin-resistant states and type 2 diabetes mellitus. It is critical to understand the factors regulating their production and/or clearance.

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Plasma FFAs are generally increased in insulin-resistant states and type 2 diabetes mellitus. This elevation is attributed to saturation of the adipose tissue storage capacity.
and diminished insulin suppression of adipose tissue lipolysis. This in turn leads to increased plasma FFA levels and their diversion toward nonadipose tissues, a phenomenon that can cause lipotoxicity. Defining the role of FFAs in stimulating apoB-containing lipoprotein secretion is crucial in view of the intricate relationship between insulin resistance and the accumulation of TRLs, particularly in the postprandial state. FFA flux to the liver has been shown to act as a driving force for very-low-density lipoprotein (VLDL) triglyceride secretion: Fatty acids enhance apoB-containing lipoprotein secretion in HepG2 cells or cultured hepatocytes, although some controversies exist. Elevation of FFA has been shown to stimulate VLDL assembly and secretion in mice. Furthermore, oleic acid perfusion of primary hamster enterocytes has been recently demonstrated that acute elevation of plasma FFA by Intralipid/heparin (IH) infusion in chow-fed hamster intestinal lipoprotein in insulin-resistant states, this phenomenon has not been examined previously in humans. In the present study, we investigated the effect of acute elevation of FFAs on steady state fed TRL apoB-48 and TRL apoB-100 production and clearance rates in healthy men.

Table 1. Demographic Characteristics and Fasting Biochemical Parameters of Subjects

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<th>Insulin, pmol/L</th>
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<th>Plasma Triglycerides, mmol/L</th>
<th>Plasma TC, mmol/L</th>
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Mean ± SEM 47.92 ± 2.39 82.3 ± 2.07 27.23 ± 0.89 50.0 ± 0.1 52.7 ± 5.5 0.48 ± 0.06 1.33 ± 0.16 4.58 ± 0.14 11.18 ± 2.0 55.5 ± 6.4

BMI indicates body mass index; TC, total cholesterol.

Methods

Subjects
The demographic characteristics and fasting biochemical profiles of the 12 healthy, male participants in the present study are outlined in Table 1. See the online-only Data Supplement for more details.

Experimental Protocol for Lipoprotein Kinetics Studies
All 12 subjects underwent 2 separate lipoprotein kinetics studies (IH and saline), in random order, 4 to 6 weeks apart. Because the infusion of Intralipid (a synthetic triglyceride emulsion that provides a source of mainly polyunsaturated fatty acids) and heparin (to activate lipoprotein lipase) raises both FFAs and glycerol, 2 control studies were performed, 1 with saline and 1 with glycerol infusion (the latter only in a subset of 5 subjects).

After an overnight fast, kinetics studies were performed in a constant fed state because apoB-48 levels are extremely low in the fasted state, and in pilot studies we found that the mass of TRL-apoB48 was too low in fasted humans to accurately assess isotopic enrichment for calculation of kinetic parameters. To achieve this constant fed state, the subject was instructed to ingest 3 identical hourly volumes of a liquid food supplement for the first 3 hours starting at 4 AM (Hormel Great Shake Plus, Hormel Health Labs; 49% calories from fat, 38% from carbohydrates, 13% from proteins), each hourly aliquot equivalent to 1/17th of their total daily caloric needs. After the first 3 hours (after 7 AM), the subjects ingested the same formula every half hour for the remainder of the 17-hour duration of the study. Five hours later, all subjects received a bolus, 10 mol/kg bolus, 10 mol/kg per hour for 12 hours of deuterated leucine (1-[5.5,5,5-H]-leucine; 98%, Cambridge Isotope Laboratories, Andover, Mass), and apoB-containing lipoprotein particle production and clearance rates were calculated as described previously. See the online-only Data Supplement for details.

Laboratory Methods
See the online-only Data Supplement for triglyceride, FFA, plasma insulin, and glucose measurements. Blood samples for FFA and triglyceride analyses were collected on ice into tubes containing the lipase inhibitor Orlisat. TRls were isolated, and proteins in the TRL fraction were determined by Lowry’s method, delipidated,
and subsequently separated by SDS-PAGE, with clear separation of the apoB-100 and apoB-48 bands, as shown in Figure 1. Gel bands containing apoB-48 and apoB-100 were excised, hydrolyzed, and derivatized to allow for the determination of plasma leucine isotopic enrichment by gas chromatography/mass spectrometry as described.36 Tracer-to-tracee ratios were calculated from isotopic ratios for each sample according to the formula derived by Cobelli et al.37 See the online-only Data Supplement for details.

ApoB-48 was separated by SDS-PAGE with the use of 3% to 8% Tris-acetate polyacrylamide gels, and it was detected with Western immunoblot techniques as described previously.38 ApoB-100 mass in the TRL fraction was quantified by analytical SDS-PAGE as described previously.39 See the online-only Data Supplement for details.

Calculation of Lipoprotein Production and Clearance Rates by Multicompartmental Modeling

Stable isotope enrichment curves for apoB-48 and apoB-100 were fitted to a 3-compartment model (Figure 1B).33 Each subject was in steady state with respect to apoB-48 and apoB-100 concentrations so that fractional catabolic rate was equivalent to fractional synthetic rate. Production rates were calculated with the use of the fractional catabolic rate of TRL apoB-48 or TRL apoB-100 multiplied by pool size (ie, TRL apoB-48/100 concentration). C, D, Representative study performed during constant enteral feeding in 1 individual. Gel bands containing apoB-48 and apoB-100 were excised and processed for gas chromatography/mass spectrometry analysis of tracer/tracee ratios (TTR) for kinetic modeling. TRL apoB-48 (C) and TRL apoB-100 (D) tracer-to-tracee ratios vs time are depicted.

Results

Demographic and Biochemical Characteristics, Fasted Plasma Lipids, and TRL Composition of Subjects

The clinical characteristics of subjects at baseline are provided in Table 1. All subjects were healthy men with no previous history of cardiovascular, gastrointestinal, or systemic illness or surgical intervention within 6 months before the studies. No subject was taking medications, and they were all normoglycemic. To exclude those with gross dyslipidemia from the study, individuals whose total cholesterol was >5.3 mmol/L, triglycerides >2 mmol/L, high-density lipoprotein cholesterol <0.9 mmol/L, or low-density lipoprotein cholesterol >3.2 mmol/L were excluded.

Glycerol Control Study

Glycerol infusion had no effect on either plasma FFA (saline 0.22±0.01 versus glycerol 0.19±0.03 mmol/L, P=0.454), plasma triglycerides (saline 2.00±0.36 versus glycerol 2.17±0.10 mmol/L, P=0.732), or TRL apoB-48 or TRL apoB-100 levels compared with saline (saline 23.6±12.9 versus glycerol 17.5±7.1 mg/L, P=0.597 and saline 80.3±17.1 versus glycerol 87.7±12.8 mg/L, P=0.259, respectively). In addition, apoB-48 and apoB-100 production and clearance rates did not differ between glycerol and saline infusion studies. For clarity and because power calculation estimated that n=64 subjects would be needed to detect a significance difference...
between saline and glycerol at $P=0.05$ with 80% power, all additional descriptions and illustrations of results will compare only the IH and saline control studies.

**Effect of Acute Elevation of FFAs on Plasma and TRL Lipid and Apolipoprotein Concentrations in the Constant Fed State**

IH infusion caused a significantly sustained rise in plasma FFA levels, whereas plasma FFA concentration progressively declined in the saline infusion study, resulting in a $>3$-fold difference in concentration during the kinetics study between IH and saline infusions ($P<0.0001$ by 2-factor ANOVA for repeated measures) (area under the curve [AUC] [mean±SEM]: IH $12.31±5.66$ mmol/L per hour versus saline $4.61±1.29$ mmol/L per hour; $P=0.0006$) (Table 2 and Figure 2A). IH infusion also caused a significant increase in plasma triglyceride levels (Table 2 and Figure 2B), much of it likely contributed to by the infusion of Intralipid itself. As expected, plasma and TRL/triglyceride levels increased in response to feeding and then remained stable during the 12-hour kinetics study. In the fed state, IH infusion significantly increased plasma triglycerides compared with the saline infusion ($P<0.0001$) (AUC [mean±SD]: IH $12.31±5.66$ mmol/L per hour versus saline $3.35±2.58$ mmol/L per hour; $P=0.004$) (Table 2 and Figure 2B). We also found a significant increase in TRL/triglyceride concentration in subjects when they were infused with IH compared with the saline control (AUC [mean±SD]: IH $58.61±31.23$ mmol/L per hour versus saline $24.95±10.26$ mmol/L per hour; $P=0.005$) (Table 2). TRL apoB-48 concentration increased with feeding and then remained stable during the 12-hour kinetics study with saline infusion. During feeding, there was a significant increase in TRL apoB-48 concentration after IH infusion compared with saline ($P<0.005$) (AUC [mean±SD]: IH $12.31±5.66$ mmol/L per hour versus saline $4.61±1.29$ mmol/L per hour; $P=0.006$) (Table 2 and Figure 2C). Similarly, TRL apoB-100 concentrations increased to a greater extent during the 12-hour kinetics study with IH infusion compared with saline ($P<0.003$) (AUC [mean±SD]: IH $1.82±0.46$ g/L per hour versus saline $1.40±0.51$ g/L per hour; $P=0.001$) (Table 2 and Figure 2D).

**Effects of Acute Elevation of FFAs on Hepatic and Intestinal Lipoprotein Production and Clearance Rates in the Fed State**

We next questioned whether the greater increase in TRL apoB-48 and TRL apoB-100 concentration in the IH study versus saline was due to a lower clearance rate of TRL apoB-48 and apoB-100 particles, higher production rate, or both. The fractional catabolic rate of TRL apoB-48 or TRL apoB-100 was not significantly different between saline and IH infusion studies (Figure 3). In contrast, the production rate of TRL apoB-48 was 69% higher in subjects infused with IH compared with saline (IH $5.95±1.13$ mg/kg per day versus saline $3.53±0.58$ mg/kg per day; $P=0.027$), demonstrating that an acute elevation of plasma FFAs stimulates intestinal lipoprotein particle production (Figure 3). Similarly, the production rate of TRL apoB-100 was 35% higher in subjects infused with IH compared with saline (IH $27.9±4.0$ mg/kg per day versus saline $20.7±2.7$ mg/kg per day; $P=0.02$).

**Discussion**

Insulin-resistant states and type 2 diabetes mellitus are accompanied by elevated plasma FFAs and increased plasma
concentrations of TRLs, including intestinally derived apoB-48–containing TRLs in both fasted and fed states. FFA delivery to the liver has been shown previously to stimulate hepatic VLDL production in the fasted state, whereas the effect of plasma FFAs on intestinal lipoprotein production has not been examined previously in humans. In the present study, we examined whether an acute elevation of FFAs also stimulates the production of hepatic and intestinally derived TRL particles in healthy humans in the fed state. An infusion of IH was used to raise plasma FFA concentration in the constant fed state, and intestinal apoB-48– and apoB-100–containing TRL metabolism was examined with the use of stable isotope enrichment techniques. Plasma triglycerides, TRL triglycerides, TRL apoB-100, and TRL apoB-48 concentrations were significantly higher in the IH infusion study compared with the saline control study, and this increase was associated with a higher production rate of intestinal and hepatic TRL particles but no difference in their rate of clearance. Glycerol alone had no effect on triglycerides or apoB concentrations or their metabolism compared with saline, indicating that the effect of IH was due to the FFAs released by heparin-stimulated lipoprotein lipase lipolysis of the synthetic triglyceride emulsion and was not due to the release of glycerol. Thus, we have shown, for the first time in humans, that an acute elevation of plasma FFAs stimulates intestinal lipoprotein production.

We have shown previously that intestinal lipoprotein production is increased after acute elevation of plasma FFA by IH in fasted, insulin-resistant, chow-fed Syrian Golden hamsters. The present study extends these observations to humans. In humans, because plasma TRL apoB-48 mass is relatively low, it was necessary for technical reasons to study the metabolism of apoB-48–containing lipoproteins in the fed rather than in the fasted state. It is important to appreciate, therefore, that our observation of higher TRL apoB-48 production in the IH study occurred on a background of high-fat feeding, in which there is ongoing absorption of luminal fatty acids. We do not know whether we would have observed similar findings in the fasted human, were it technically possible to perform those studies, but extrapolations...
Elevation of FFA in insulin resistance is due to combined resistance to insulin-mediated suppression of lipolysis in adipose tissue and reduced fatty acid trapping by insulin-resistant adipocytes. Ectopic fat deposition appears when the normal buffering capacity of adipose tissue is impaired or exceeded, especially during postprandial periods, and is characterized by diversion of FFAs from adipose depots and lipid deposition in nonadipose tissue (liver, muscle, heart, and pancreatic β-cells). In the insulin-responsive tissues (muscle, liver), FFA accumulation usually leads to altered insulin signaling and sensitivity. Although there was no way for us to measure it directly in the present study, it is highly likely that the FFA overload impaired insulin sensitivity of intestinal enterocytes. Indeed, a recent study has shown, using enterocytes from fructose-fed hamster, that intestinal apoB-48–containing lipoprotein overproduction was associated with impaired insulin signaling, that is, reduced Akt and IRS1 phosphorylation, and increased ERK signaling. Because insulin has been shown to acutely inhibit intestinal TRL secretion, it is plausible that the elevation of FFA may have indirectly stimulated intestinal TRL secretion by impairing the inhibitory effect of insulin.

We also report that TRL apoB-100 concentrations were increased by the infusion of IH because of increased TRL apoB-100 production rate, with no significant change in catabolic rate. We have previously reported that an acute elevation of plasma FFAs stimulates VLDL secretion in humans in the fasted state. In the present report, we demonstrate that this observation pertains to the fed state as well. Indeed, in the constant fed state, as is the case for the present studies, a large proportion of ingested fatty acids (up to 15%) are taken up by the liver and incorporated into hepatic VLDL triglyceride and contribute significantly to VLDL triglyceride secretion from the liver. The time frame of our kinetics study, that is, beginning 5 hours after the start of hourly formula ingestion, is sufficient for this process to occur because it has been shown that dietary fatty acids appear in VLDL triglycerides as early as 2 hours after fat ingestion. We believe that VLDL secretion was already stimulated in both the saline and the IH studies, as evidenced by increased TRL apoB-100 concentrations in the saline group in the fed state compared with the fasted value and by the higher
rates of production of TRL apoB-100 that we observed compared with production rates reported previously by others in fasted humans.49,50 Nevertheless, elevation of plasma FFAs in a constant fed state further increases both hepatic and intestinal TRL production.

Quantitatively, intestinal lipoprotein overproduction probably does not contribute greatly to the typical postabsorptive hypertriglyceridemia of insulin-resistant states and type 2 diabetes mellitus in humans because apoB-48 mass in fasted plasma is approximately one hundredth to one tenth of apoB100 mass.51 In the present study, the absolute production rate of hepatic (apoB-100) lipoproteins was 5- to 6-fold greater than the production rate of intestinal (apoB-48) lipoproteins in both the saline and the IH studies. Despite the fact that apoB-100–containing lipoprotein mass is quantitatively far greater than that of apoB-48, an increase in apoB-48 production in certain conditions may contribute to postprandial lipemia and could contribute significantly to atherogenesis if intestinal lipoproteins are shown to be highly atherogenic, as has been proposed by some.13,14 We speculate that chronic intestinal overproduction of apoB-48 primes the intestine to rapidly and efficiently facilitate the absorption of ingested fat, enhancing the assembly and secretion of intestinal TRL and hence contributing to postprandial lipemia. The prevailing concept is that postprandial lipemia in these conditions results in part from competition between ingested chylomicrons and the expanded pool of VLDL, with consequent delayed clearance of endogenous (B-100–containing) and exogenous (B-48–containing) TRL particles.52,53 Increased efficiency and rapidity of production of chylomicrons in conditions of insulin resistance and type 2 diabetes mellitus may also contribute to the typical postprandial lipemia of these conditions. This area requires extensive further investigation.

In conclusion, the present report provides evidence that intestinal apoB-48–containing TRL production is stimulated by a short-term elevation of plasma FFAs in healthy humans. We speculate that chronic elevation of plasma FFAs, as seen in insulin-resistant and diabetic individuals, is likely to play an important role in the overproduction of intestinal lipoprotein that has recently been observed in these conditions.13,16

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Disclosures

None.

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40. Deleted in proof.

CLINICAL PERSPECTIVE
Dyslipidemia is a prominent feature of both insulin resistance and type 2 diabetes mellitus and contributes to the increased risk of cardiovascular events in these conditions. The typical hypertriglyceridemia of insulin-resistant states has been determined in numerous previous studies to be due predominantly to overproduction of hepatic (apolipoprotein B-100-containing) very-low-density lipoproteins, as well as impairment in the clearance of these particles from the circulation. The mechanism of hepatic very-low-density lipoprotein overproduction in insulin resistance is complex, but elevated free fatty acid flux, predominantly from insulin-resistant adipose tissue to the liver, is an important mechanism accounting for this phenomenon. Recent studies in animal models of insulin resistance and in humans have demonstrated that the production rate of intestinal (apolipoprotein B-48-containing) chylomicrons is also increased in insulin-resistant states. Intestinal chylomicron production is stimulated mainly by fat ingestion, which is efficiently absorbed from the intestinal lumen by the intestinal enterocyte and packaged into chylomicron particles, which enter the circulation via the lymphatic duct. Here we have shown, for the first time in humans, that an acute elevation of plasma free fatty acids stimulates not only hepatic but also intestinal triglyceride-rich lipoprotein production. We speculate that chronic elevation of plasma free fatty acids, as seen in insulin-resistant and type 2 diabetic individuals, is likely to play an important role in the overproduction of intestinal lipoproteins, thereby contributing to the dyslipidemia of insulin-resistant humans.
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