Ileal Lipid Infusion Stimulates Jejunal Synthesis of Apolipoprotein A-IV Without Affecting mRNA Levels (44480)

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Abstract. **We examined the effect of ileal infusions of lipid emulsion on mRNA levels and biosynthesis of apolipoprotein A-IV (apo A-IV) in jejunal Thiry-Vella fistulas in rats. The rats were surgically prepared with jejunal Thiry-Vella fistulas; after recovery they were deprived of food, equipped with ileal infusion cannulas, then given 8 hr ileal infusions of fatty acid/monoglyceride emulsions. Mucosal synthesis and transcript levels of apo A-IV in the Thiry-Vella loop were then measured. Lipid infusion produced a two-fold stimulation in incorporation of ^{3}H-leucine into apo A-IV-specific protein, but had no significant effect on apo A-IV mRNA levels. These results support the hypothesis that a lipid-elicited, distal gut-derived, systemic signal stimulates the production of apo A-IV by a post-transcriptional mechanism.** [P.S.E.B.M. 2000, Vol 223]

Apolipoprotein A-IV (apo A-IV) is a major glycoprotein component of intestinally synthesized and secreted triglyceride-rich lipoproteins. Apo A-IV has several proposed roles: modulation of plasma cholesterol and lipoprotein metabolism (1–3), control of food intake (4), and upper gastrointestinal function (5, 6). Most recently, it was shown that apo A-IV may be protective against oxidative alteration of lipoproteins (7) and atherogenesis (8, 9). Thus, it is important to understand the mechanisms responsible for control of synthesis and secretion of apo A-IV. These mechanisms are incompletely understood.

Apo A-IV is synthesized and secreted by the small intestine in response to dietary lipid (10–15), but the mechanisms involved in fat-elicited increases in production of apo A-IV by intestinal mucosa remain obscure. We (13) recently obtained evidence that in response to ileal lipid infusion, a distal gut-derived signal acts to stimulate synthesis of apo A-IV in the proximal jejunum; moreover, in separate studies (15), we found evidence that such a signal may play a physiologic role in the overall response of apo A-IV to a lipid meal. The mechanism for the increase in synthesis of jejunal apo A-IV from this ileal-derived signal is unknown. Whereas duodenal infusion of lipid over a period of hours produces increases in apo A-IV mRNA levels that are sufficient to account for the increase in apo A-IV synthesis in the proximal jejunum (13), it is currently unknown whether the distal gut signal also results in increased apo A-IV mRNA expression in the proximal jejunum. This is an important question in view of recent evidence indicating that i) there is a rapid response of jejunal apo A-IV synthesis within the first few minutes after a lipid meal (15), likely too early to be explained by an increase in apo A-IV gene expression (16), and that ii) this rapid, mRNA-independent response may involve the aforementioned ileal signal (15, 17).

In this study we examined the effects of ileal lipid infusions on synthesis and mRNA levels of apo A-IV in a proximal jejunal Thiry-Vella fistula in rats. In this model (13, 14), a segment of jejunum is physically isolated from intestinally infused lipid, but it retains its neural innervation and blood supply, allowing for unambiguous testing of the role of a systemic signal, arising from the distal gut, in mediating the effect of distal intestinal lipid on proximal intestinal production of apo A-IV.

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Materials and Methods

Animals, Surgical Preparation, and Experimental Procedure. All experiments used male, Sprague-Dawley rats (300–325 g; Harlan Sprague-Dawley, Indianapolis, IN), housed at 26°C on a 12 hr:12 hr light-dark cycle, with lights on at 06:00; they were allowed free access to standard diet (Teklad Rodent Chow, Harlan, Indianapolis, IN) and water. Initial surgery was conducted 1–2 weeks after rats were delivered. They were deprived of food for 24 hr, then anesthetized with halothane, laparotomized, and equipped with jejunal Thiry-Vella fistulas with modification from the previously described procedure (13). A 20-cm section of proximal jejunum (proximal end about 10 cm distal to the ligament of Treitz) was exposed and transected at its proximal and distal ends, with care taken to preserve all connecting mesentery, including blood supply and extrinsic neural innervation. The proximal end of the segment was ligated closed and had a vinyl cannula (1.27 mm outside diameter (o.d.), Dural Plastics and Engineering, Dural, New South Wales, Australia) inserted. This tube was tunneled under the skin and exteriorized at the nape of the animal's neck. The distal end of the Thiry-Vella segment was left open and exteriorized to the right of the animal's midline and secured to the skin with interrupted 6-0 silk suture. Continuity of the intestine was reestablished by jejuno-jejunostomy (end-to-end) using interrupted 6-0 silk suture. Rapid healing of the intestinal anastomosis necessitated witholding drinking water and solid food for 24 hr and 48 hr, respectively, after surgery. After closure of the abdominal incision, animals were given dorsal subcutaneous injections of sterile 0.15 *M* NaCl to ensure hydration until restoration of fluid access. Animals were allowed to recover from anesthesia for several hours in a warm chamber (30°C) to prevent hypothermia. When fully conscious, they were returned to their home cages. Beginning 24 hr after surgery and continuing on through the recovery period, the Thiry-Vella cannula was used to instill 1 ml of 0.15 *M* NaCl containing 0.28 *M* glucose and 1 m*M* L-glutamine into the Thiry-Vella loop twice daily, to prevent mucosal atrophy. Rats were allowed to recover for 10–14 days, by which time they had recovered their preoperative body weight. At the end of the recovery period, rats were deprived of food overnight, then surgically equipped with ileal infusion cannulas, placed in restraint cages, and given overnight continuous infusions of a glucose-saline solution (145 m*M* NaCl, 0.4 m*M* KCl, 0.28 *M* glucose) at 0.85 ml/ hr. The next morning, rats were given continuous, 8-hr ileal infusions of either glucose-saline solution (control), or lipid emulsion (23.5 μmol/ml 1-monoolein, 47.1 μmol/ml oleic acid, 19 μmol/ml sodium taurocholate, sonicated in phosphate buffered saline [PBS], pH 6.4), at 0.85 ml/ hr. Rationale for this dose of lipid and infusion rate were described previously (13). Previous studies (13) also demonstrated that use of glucose-saline solution as a control infusate yielded similar results albeit at lower expense, as sodium taurocholate in PBS.

Measurement of Mucosal Apo A-IV Synthesis. Methods used were those of Davidson and Glickman (18) as adapted by Hayashi *et al.* (11). At the conclusion of the infusion period, rats were anesthetized with halothane, and a 1-cm segment of the Thiry-Vella loop was taken for isolation of total RNA (see below). Another 10-cm segment of the jejunal Thiry-Vella loop was isolated with ligatures. The loop was then incubated *in situ* for 10 min with luminally instilled ^{3}H-leucine (0.3 mCi, Amersham/Pharmacia Biotech, Piscataway, NJ), then removed and washed with ice-cold PBS containing 20 m*M* L-leucine. The washed segment was placed over ice and cut open longitudinally, then the mucosa was harvested with a glass slide. The mucosa was homogenized in 1.5 ml PBS containing 1% Triton X-100, 2 m*M* leucine, 1 m*M* phenylmethylsulfonyl fluoride, 40 μg chymostatin, 160 μg leupeptin, and 6 μg pepstatin A. The homogenate was centrifuged for 60 min at 100,000*g* for 60 min in a Beckman 50.3 Ti rotor. An aliquot of the cytosolic supernatant was then subjected to precipitation using 10% trichloroacetic acid (TCA) and assayed for protein concentration using a modified Lowry procedure (D_c Assay, Bio Rad, Hercules, CA). Total mucosal protein synthesis was expressed as the ratio of TCA-precipitable radioactivity to protein content. A separate aliquot of cytosolic supernatant was also subjected to specific immunoprecipitation of apo A-IV, using a polyclonal goat anti-rat apo A-IV antiserum described previously (11). Preliminary experiments using reincubation of immunoprecipitated samples with additional antiserum established the amount of antiserum necessary to achieve quantitative immunoprecipitation. All subsequent immunoprecipitations were carried out using an excess of antiserum. Immunoprecipitated apo A-IV was resolved using SDS-PAGE followed by autoradiography. The radioactive band corresponding to apo A-IV was removed from the gel, solubilized using Solvable Tissue and Gel Solubilizer (Dupont/NEN Research Products, Boston, MA), and the radioactivity was measured. Synthesis of apo A-IV was expressed as the amount of immunoprecipitable radioactivity as a percentage of total protein synthesis. This was a valid measure of apo A-IV synthesis, because total protein synthesis (ratio of TCA-precipitable radioactivity to cytosolic protein) was similar between treatments. To determine the specificity of the effect of ileal lipid infusion on synthesis of apo A-IV in the Thiry-Vella fistula, synthesis of apo A-I and apo B_{48} was also measured, using separate aliquots of the same Thiry-Vella mucosa, using polyclonal antibodies against these two apolipoproteins (goat anti-rat apo A-I and rabbit anti-rat apo B_{48}) (11, 19).

Measurement of Apo A-IV mRNA Levels. At the conclusion of the infusion period and immediately prior to harvesting of the 10-cm segment incubated with ^{3}H-leucine, a 1-cm section of the jejunal Thiry-Vella mucosa was obtained as described above, and total RNA was isolated using the RNeasy RNA isolation kit (Qiagen, Inc., Valencia, CA) with the manufacturer's suggested protocol. Isolated RNA was stored at –80°C until analysis.

A full-length rat intestinal apo A-IV cDNA clone (pSP64AIV) was kindly provided by Dr. Jeffrey Gordon, Washington University, St. Louis, MO. A 438-bp fragment was obtained by digesting pSP64AIV with *Sac I*. The fragment was subcloned into pGEM-3Z (Promega, Madison, WI) to obtain pGEM3Z-AIV; this *Sac I* fragment was labeled with [γ-^{32}P]dCTP to a specific activity of 1×10^9 cpm/ng using the Ready-to-Go random primer oligo kit (Pharmacia, Piscataway, NJ). Northern blotting was performed as previously described (20). After autoradiography, blots were stripped and reprobed for 18s ribosomal RNA (Ambion, Austin, TX). Relative levels of apo A-IV mRNA in control (glucose-saline) versus lipid-infused rats were determined by densitometric analysis, normalized to the 18s signal.

Statistical Analysis. Data were analyzed by Student's *t* test. Differences were considered significant if $P < 0.05$.

Results

Animals tolerated the ileal infusions well; there was no evidence of malabsorption of the infused loads (i.e., no diarrhea).

Total protein synthesis, assessed by specific activity of Thiry-Vella mucosal cytosolic supernatants, was unaffected by ileal infusate. Specific activity of glucose-saline (control) and lipid-infused mucosal cytosolic supernatants were 0.87 ± 0.13 and 0.94 ± 0.11 dpm/ng protein, respectively. Apo A-IV immunoprecipitated as a single band migrating at 43 kDa (Fig. 1A). Compared with control infusion, ileal lipid infusion produced about a 2-fold increase in apo A-IV synthesis in jejunal Thiry-Vella mucosa (Fig. 1B). This increase is comparable to those reported previously using this preparation (13, 14). There was no significant effect of ileal lipid infusion on synthesis of either apo A-I or apo B_{48} (Table I).

We obtained good quality total RNA in our preparations (Fig. 2A); densitometry of the 28s and 18s bands revealed a ratio of 28s/18s RNA of 2.3–2.5. Northern blot analysis of apo A-IV mRNA revealed a single, 1.7-kb species in Thiry-Vella mucosa from control and lipid-infused rats (Fig. 2A). There was no significant effect of lipid infusion on apo A-IV mRNA levels over the course of the infusion period (Fig. 2B).

Discussion

Because the Thiry-Vella fistula rat incorporates a viable segment of jejunum that is removed from continuity with the rest of the small bowel (and thus its lumen is unexposed to ileally infused lipid), yet retains its blood supply and neural innervation, this model allows unambiguous testing of the role of a distal gut signal in mediating the effect of ileal lipid infusion on jejunal synthesis of apo A-IV, independent of the possible direct effects of luminal lipid (13). The present results not only confirmed previous findings that ileal lipid infusion produces a systemic signal that

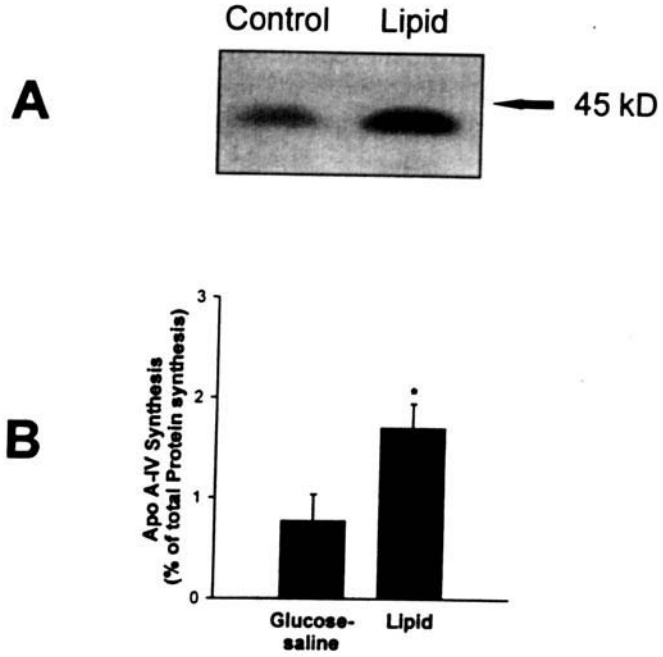

Figure 1. Apo A-IV synthesis, measured by *in situ* incorporation of ^{3}H-leucine into apo A-IV-specific protein in the mucosa of jejunal Thiry-Vella fistulas after 8 hr control (glucose-saline solution) or lipid (monoolein/oleic acid emulsion) infusions into the terminal ileum. (A) Representative fluorogram of immunoprecipitated apo A-IV from cytosolic supernatants of a control and a lipid-infused rat. Molecular weight marker shows migration of ovalbumin standard (45 kDa). (B) Apo A-IV synthesis, as a percentage of total protein synthesis. Total protein synthesis was determined as the ratio of TCA-precipitable radioactivity to total cytosolic protein; apo A-IV-specific synthesis was expressed as the percentage of total protein synthesis accounted for by apo A-IV-specific, immunoprecipitated radioactivity. Values are means ± SEM for five rats (control) and six rats (lipid). Asterisk denotes significant difference between control and lipid-infused groups ($P < 0.05$).

Table I. The Effect of Ileal Lipid Infusion on Mucosal Synthesis of Apo A-I and Apo B_{48} as a Percentage of Total Protein Synthesis in a Jejunal Thiry-Vella Fistula

Apolipoprotein	Control	Lipid
A-I	0.68 ± 0.17	0.65 ± 0.31
B_{48}	0.85 ± 0.20	0.90 ± 0.08

Note. Rats with jejunal Thiry-Vella fistulas were given ileal infusions of either glucose-saline solution (control) or monoolein/oleic acid emulsions (lipid). Then incorporation of ^{3}H-leucine into total and apolipoprotein-specific protein in Thiry-Vella mucosa was measured. Total protein synthesis was determined as the ratio of TCA-precipitable radioactivity to total cytosolic protein; apolipoprotein-specific synthesis was expressed as the percentage of total protein synthesis accounted for by apolipoprotein-specific immunoprecipitated radioactivity. Values are means ± SEM for five rats (control) and six rats (lipid) (same animals as depicted in Figs. 1 and 2).

stimulates synthesis of apo A-IV in a jejunal Thiry-Vella loop, but also showed that this occurs in the absence of an accompanying change in jejunal mucosal apo A-IV mRNA levels.

We judged the Thiry-Vella preparation viable, based on our measurements of total protein synthesis and the effect of lipid infusion on apo A-IV synthesis. Although absolute

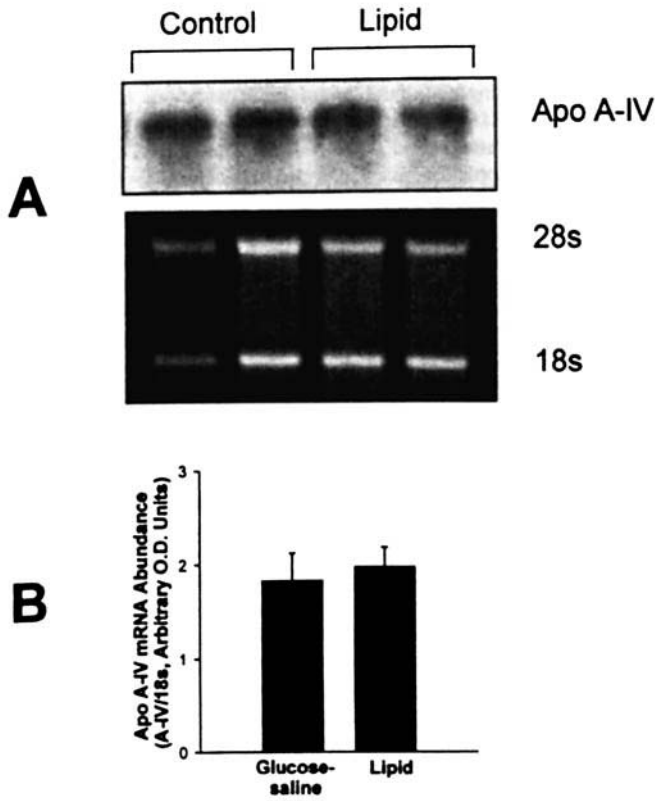

Figure 2. Apo A-IV mRNA levels in jejunal Thiry-Vella fistulas after 8-hr ileal infusions of either control (glucose-saline) solution or lipid emulsions, determined by Northern blot analysis. (A) Representative Northern blot of apo A-IV mRNA and 28s and 18s RNA from two representative control-infused, and two representative lipid-infused rats from the full data set summarized in B. (B) Densitometric analysis of relative levels of jejunal Thiry-Vella mucosal apo A-IV mRNA levels from control versus lipid-infused rats. Values are means ± SEM ratio of apo A-IV/18s (arbitrary absorbance units) from same control (n = 5) and lipid-infused (n = 6) animals as shown in Figure 1.

levels of total protein synthesis were somewhat lower than what we usually find in intact jejunal mucosa (14, 21), we observed stimulatory effects of ileal lipid on apo A-IV synthesis that were of similar magnitude as we previously reported in intact jejunum in response to ileal or duodenal lipid infusion (12, 13), gastric bolus lipid administration (15), and intravenous infusions of the distal gut hormone, peptide tyrosine tyrosine (PYY) (21). Moreover, we previously documented the ability of Thiry-Vella mucosa to respond to direct perfusion with lipid by increasing apo A-IV synthesis (13). These observations supported the validity of the Thiry-Vella fistula model for the purposes of the present study.

We used the approach of slow, continuous ileal infusion of a low dose of lipid to control precisely the amount and rate of lipid delivered to the distal intestine, and to minimize the possibility that direct ileal delivery of lipid might overwhelm the ability of the mucosa to handle the load (13). Although such a model might be considered semi-physiologic, it nevertheless produces levels of ileal and cecal luminal and wall lipid (13), and jejunal apo A-IV responses similar to those observed in intact jejunum in response to gastrically delivered meals (15), and to physiologic doses of PYY (21). Moreover, in view of the characteristics of the apo A-IV response, it is increasingly clear that this model is likely more relevant than our previously used duodenal infusion model (12–14) for studying the potential role of distal gut neural and/or hormonal signals in the response of intestinal apo A-IV to a lipid meal (discussed below).

The results reported here are similar to those observed after intragastric bolus injections of lipid (10, 15), but not in response to slow, continuous duodenal lipid infusions (12–14). In the latter studies, lipid emulsions were duodenally infused using rates on the low end of what might be considered physiological (22). Under those conditions, the capacity of the intestine to absorb and transport the incoming lipid greatly exceeded the rate of input, so that all the lipid was transported within the first half of the small intestine. Virtually no lipid reached the ileum, and ileal apo A-IV synthesis was not stimulated (12). On the other hand, gastric delivery of a lipid bolus does produce rapid initial delivery of fat to more distal reaches of the gut (15), due to initial "dumping" of gastric lipid prior to activation of gastric emptying regulatory mechanisms. Indeed, we showed that as much as 15% of a gastrically delivered lipid load reaches the distal gut within 30 min, in amounts clearly sufficient to produce significant increases in ileal synthesis of apo A-IV (15). More recently, we have found that after a similar gastric lipid bolus, the rapid rise in jejunal apo A-IV synthesis was not accompanied by a rise in jejunal apo A-IV mRNA levels (23). In view of these considerations, an important implication of the present results is that the mechanism responsible for stimulating jejunal apo A-IV synthesis in response to ileal lipid infusion may be similar to that operating in response to the more physiological method of gastric lipid delivery, but the mechanism seems to be different from that operating in response to slow, continuous duodenal lipid infusion.

The identity of the fat-elicited, distal gut signal is currently unknown (13, 14). However, available evidence indicates that capsaicin-sensitive afferent nerve signals are not responsible (14), whereas the ileal/colonic hormone, PYY, may be such a signal (21). In this regard, it is interesting that, similar to the present findings on the effects of ileal lipid infusion on jejunal apo A-IV production, physiologic doses of exogenous PYY stimulate jejunal apo A-IV synthesis and increase lymphatic secretion and plasma levels of apo A-IV without affecting A-IV mRNA levels (21). Further work is needed to determine whether endogenous PYY is responsible for the effects reported here.

We recently showed that a gastric fat bolus that rapidly produces significant increases in intestinal apo A-IV synthesis within 30 min (15), has no effect on mucosal apo A-IV mRNA levels until between 2 and 4 hr. The early, rapid rise in apo A-IV synthesis was not blocked by the transcriptional inhibitor, actinomycin D; moreover, within 30 min there was a shift in the distribution of mucosal apo

A-IV mRNA from the unbound ribonucleoprotein to the actively translating, polyribosome fraction of cytoplasm (23). These results suggest a lipid-induced translational mechanism for control of apo A-IV at the level of initiation during the early minutes following a fat meal, which could account for the equally rapid increases in lymphatic secretion and plasma levels of apo A-IV seen after such a meal (15). This rapid production and secretion of apo A-IV is of potential physiologic significance in view of apo A-IV's documented actions as a putative satiety signal (4) and a postprandial, lipid-stimulated antioxidant (7). The data also suggest a second phase requiring several hours, which may involve transcriptional upregulation of apo A-IV, possibly *via* direct contact of the jejunal mucosa with lipid—a mechanism separate from the rapid-onset translational mechanism. Taken together with the findings obtained from the gastric bolus model, the present data obtained using the Thiry-Vella fistula rat suggest that the ileal-derived signal may solely stimulate translational initiation of jejunal apo A-IV, thus explaining the inability of ileal lipid infusion to produce increases in jejunal apo A-IV mRNA levels. Details of this mechanism await further elucidation; also, further work is necessary to determine if a similar mechanism is involved in the response to PYY.

In summary, we demonstrated that ileal lipid infusion stimulates jejunal synthesis of apo A-IV, without a corresponding increase in apo A-IV mRNA levels. We hypothesize that a fat-elicited, distal gut signal stimulates production of apo A-IV protein in the proximal intestine by a post-transcriptional mechanism. The role of this mechanism in the integrative apo A-IV response to a fat meal remains to be determined.

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