Control of Synthesis and Secretion of Intestinal Apolipoprotein A-IV by Lipid

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ABSTRACT  Apolipoprotein (apo) A-IV, a component of intestinally secreted, triacylglycerol-rich lipoproteins, has recently been proposed as a physiological controller of gastric function and food intake. Thus, it is important to understand the mechanisms involved in the control of expression, synthesis and secretion of apo A-IV. Apo A-IV is a member of a closely linked, multigene cluster which includes apolipoproteins A-I and C-III. Expression and synthesis of apo A-IV display marked variability with regard to species, tissue, stage of development and response to hormones, but intestinal apo A-IV is consistently stimulated by dietary lipid. The precise molecular mechanisms underlying the response of apo A-IV to lipid have not been clearly defined. Most evidence supports the hypothesis that some aspect of lipid transport is necessary for the apo A-IV response, but only part of this response may be due to a direct effect of intestinal lipid: recent findings suggest a connection between intestinal production of apo A-IV and hormonal and/or neural factors associated with operation of the “ileal brake.” Thus, apo A-IV may play an integrative role in the modulation of both upper gastrointestinal function and ingestive behavior. J. Nutr. 127: 537S–538S, 1997.

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Although apolipoprotein (apo) A-IV was first described almost 20 years ago, its physiological role has not been firmly established. Elegant in vitro experiments have suggested roles for A-IV in certain aspects of lipoprotein metabolism (Bisgaier et al. 1987, Dvorin et al. 1988, Fielding et al. 1972, Goldberg et al. 1990, Stein et al. 1995); however, there has been no direct evidence to date that apo A-IV plays such roles in vivo. Perhaps for this reason, concerted efforts to elucidate the mechanisms involved in the control of the expression and secretion apo A-IV have only recently been undertaken. Recently, in vivo studies (Fujimoto et al. 1992, 1993a and 1993b, Fukagawa et al. 1995, Okumura et al. 1994 and 1995) have provided evidence that apo A-IV may play a broader physiological role than previously suspected. With these recent findings as an impetus, and because of the already documented responsiveness of apo A-IV to dietary fat (Apfelbaum et al. 1987, Hayashi et al. 1990, Weinberg et al. 1990), we have begun to address more systematically the issues relating to the control of apo A-IV by dietary lipid. The focus of the present review will be on the control of apo A-IV expression and secretion by dietary fat.

Apolipoprotein A-IV: a major component of intestinal triacylglycerole-rich lipoproteins. Apolipoprotein A-IV was first described in 1977 (Swaney et al. 1977). In humans, apo A-IV is a 46,000-Da glycoprotein synthesized only by the small intestine and not by the liver (Green et al. 1980). In the rat, apo A-IV is 43,000 Da and is synthesized in both liver and intestine, although the intestine accounts for the major proportion of circulating apo A-IV (Wu and Windmueller 1979). Apo A-IV is a major component of intestinal triacylglycerol-rich lipoproteins (i.e., chylomicrons, VLDL) (Green et al. 1980, Imazumi et al. 1978, Ohta et al. 1985, Swaney et al. 1977). In response to a lipid-containing meal, apo A-IV is secreted into intestinal lymph on chylomicrons (Green et al. 1980, Imazumi et al. 1978, Ohta et al. 1985, Swaney et al. 1977). During subsequent plasma passage and metabolism of chylomicrons, apo A-IV dissociates from this lipoprotein. About 25% is then found circulating in the density range of high density lipoproteins; the rest is found in the lipoprotein-free fraction of plasma (Ghiselli et al. 1986, Lefevre and Roheim, 1984).

Multiple roles for apolipoprotein A-IV: cholesterol and lipoprotein metabolism, a possible satiety signal, and a modu-
The physiologic function of apo A-IV is under active investigation. Several actions of apo A-IV in cholesterol and lipoprotein metabolism have been described, including modulation of activity of lipoprotein lipase (Goldberg et al. 1990) and lecithin:cholesterol acyltransferase (Bisgaier et al. 1987, Fielding et al. 1972), binding of HDL to cell membranes (Dvorin et al. 1986), and promotion of cellular cholesterol efflux (Stein et al. 1995), but the physiological significance of these actions remains unclear because no direct in vivo evidence for them has been reported. Moreover, several of these actions are not specific to A-IV; some are shared by apo A-I, which is present in higher concentration in plasma (Dory and Roheim 1981, Kondo et al. 1989, Lagrost et al. 1989, Steinmetz et al. 1988).

A separate line of investigation in rats has provided strong in vivo evidence that apo A-IV may be involved in the control of food intake (Fujimoto et al. 1992, 1993a and 1993b). Intravenous infusion of purified apo A-IV at doses which reproduce plasma levels seen after a lipid meal (Fujimoto et al. 1992) depresses feeding in both meal-fed and freely feeding animals (Fujimoto et al. 1992 and 1993a, Rodriguez et al. 1997). Third cerebroventricular administration of apo A-IV decreases feeding with a potency some 50-fold higher than intravenous infusion (Fujimoto et al. 1993b). Finally, third ventricular administration of anti-rat apo A-IV antiserum stimulates feeding (Fujimoto et al. 1993b). Because available evidence suggests that de novo synthesis of apo A-IV in the brain is unlikely (Elszobregagy et al. 1985), it has been proposed (Fujimoto et al. 1992 and 1993b) that apo A-IV released by the intestine (or perhaps a fragment thereof) may traverse the blood-brain barrier and act in the central nervous system (CNS) to influence feeding behavior. This hypothesis is supported indirectly by the following: 1) demonstration of apo A-IV, as well as other apolipoproteins in cerebrospinal fluid (CSF) (Fujimoto et al. 1993b, D. Puppione, personal communication), 2) increases in CSF levels of apo A-IV after feeding (Fujimoto et al. 1993b) and 3) recent immunohistochemical studies demonstrating specific staining for apo A-IV in astrocytes and glia in rat brain (Fukagawa et al. 1995). Although further work is necessary to clarify the precise role of apo A-IV in the control of food intake, the available evidence suggests that it may act via the CNS.

The most recently discovered action for apo A-IV is as a modulator of upper gastrointestinal function. Intracisternal injections of purified apo A-IV inhibited gastric acid secretion (Okumura et al. 1994) and gastric emptying (Okumura et al. 1995) in rats in a dose-dependent manner. The doses of A-IV used in those studies are thought to reproduce the levels of apo A-IV measured in cerebrospinal fluid after a lipid meal (Fujimoto et al. 1993b). Thus, apo A-IV may be an enterogastrone (Okumura et al. 1994), that is, a humoral mediator of inhibition of gastric acid secretion by intestinal fat. At present it is unknown whether there is a direct link between the effects of apo A-IV on food intake and its effects on gastric function. Apo A-IV could directly influence central feeding mechanisms; alternatively, it could affect feeding through its effects on gastric function, especially via inhibition of gastric emptying (McHugh and Moran 1985). Further work will be necessary to clarify this issue.

The above studies suggest a role for apo A-IV in the integrated control of digestive function and ingestive behavior. In view of these developments and because the intestine contributes the major proportion of apo A-IV to the plasma pool after a meal (Wu and Windmueller 1979), it is important to understand the factors controlling intestinal synthesis and secretion of apo A-IV. These factors are incompletely understood.

### Gene expression and developmental control of apo A-IV

The apo A-IV gene is part of a closely linked, tandemly organized and evolutionarily conserved multigene cluster which also includes apolipoproteins A-I and C-III (Elszobregagy et al. 1986, Haddad et al. 1986, Karathanasis 1985). In humans, this cluster has been mapped to the long arm of chromosome 11 (Karathanasis 1985). The sequence for apo C-III lies between those for A-I and A-IV, downstream from the A-I gene and upstream from A-IV; it is transcribed in the reverse direction from the other two (Boguski et al. 1986, Haddad et al. 1986). The close proximity of these genes has prompted speculation that these three proteins may be coordinately regulated (Elszobregagy et al. 1986, Haddad et al. 1986). Detailed examination of this important issue has recently begun. Analysis of the methylation patterns of the A-I/C-III/A-IV gene cluster suggests that the the three genes, despite their close physical association, are independently regulated (Shemer et al. 1991). This conclusion is certainly supported by several studies in rats showing little effect of intestinal lipid on expression, synthesis and secretion of apo A-I (Davidson and Glickman 1985, Davideion et al. 1987, Hayashi et al. 1990b, Steinmetz et al. 1988), whereas apo A-IV is clearly induced by this treatment (see below). However, recent work by Black et al. (1996) in neonatal swine demonstrated parallel increases in mRNA expression and synthesis of both A-IV and C-III in the jejunum in response to duodenal lipid infusion. It is not yet clear whether this finding is unique to the pig, or whether it is unique to this particular stage of development: indeed, Black et al. (1990) found that although jejunal A-I was strongly stimulated by intestinal lipid in newborn pigs, this response is completely lost in the older suckling pig (Black and Davidson 1989). Taken together, the above studies suggest that regulation of the apo A-I/C-III/A-IV gene cluster may be quite complex, with individual members being differentially responsive to developmental, hormonal (see below) and nutritional factors.

Studies of the regulation of the apo A-IV gene reveal species (and possibly age-related) differences with respect to both tissue-specific and hormone-dependent expression of apo A-IV. In both humans and rats, apo A-IV is abundantly expressed in the intestine; however, A-IV is expressed in liver at very low levels in humans, whereas it is expressed at a higher level (but lower than in intestine) in rats (Elszobregagy et al. 1986). In rats, thyroid hormone (Davidson et al. 1988, Lin-Lee et al. 1993, Staels et al. 1990), insulin (Elszobregagy et al. 1985, Uchida et al. 1991), and glucocorticoids (Elszobregagy et al. 1985, Inui et al. 1992, Staels et al. 1990, Uchida et al. 1991) consistently induce A-IV in liver. Intestinal A-IV in rats appears to be unaffected by thyroid hormone (Davidson et al. 1988, Staels et al. 1990) and insulin (Elszobregagy et al. 1985), whereas its response to glucocorticoids is controversial, with some studies showing no effect (Elszobregagy et al. 1985, Inui et al. 1992) and others showing an increase (Staels et al. 1990).

In jejunal explants from 2-d-old piglets, both insulin and hydrocortisone stimulated apo A-IV synthesis (Black and Ellinas 1992).

Several studies have examined alterations in apo A-IV expression during development (Elszobregagy et al. 1985, Steinmetz et al. 1988). In rats, intestinal A-IV undergoes a marked increase in mRNA levels at birth, followed by a decline during the early suckling period (Elszobregagy et al. 1985). Work in newborn piglets demonstrates that the developmental increase in intestinal A-IV expression appears to be related to the onset of triglyceride ingestion (Black and Davidson 1989).

The molecular mechanism for the aforementioned alterations in apo A-IV expression is not well defined. However, it has been shown that human, rat and mouse A-IV genes...
contain sequences in the 5' upstream region that are homologous to consensus sequences for glucocorticoid response elements (Elsourhbagy et al. 1987, Ktistaki et al. 1994, Ochoa et al. 1993). In other studies, it was shown that hepatocyte nuclear factor 4 (HNF-4), a member of the steroid hormone receptor superfamily with no known ligand (Sladek 1993, Sladeket et al. 1990), one of the so-called orphan nuclear receptors, may be involved in the control of apo A-IV expression (Ktistaki et al. 1994, Ochoa et al. 1993). Similar to apo A-IV, HNF-4 is expressed in kidney, liver and intestine (Sladek et al. 1990, Zhong et al. 1993). A region in the proximal promoter region in the 5' flanking sequence of the A-IV gene that binds HNF-4, as well as two other orphan nuclear receptors, v-erba-related receptor 3 (ER-3), and apo A-I regulatory protein (ARP-1) has been identified (Ktistaki et al. 1994). Interestingly, the region in which the cis-acting sequence resides displays remarkable similarity (about 90%) between rat and humans (Elsourhbagy et al. 1987). HNF-4 has been shown to be required for transcriptional activation of apo A-IV, whereas ER-3 and ARP-1 act as repressors (Ktistaki et al. 1994, Ochoa et al. 1993). Consistent with the close physical association between the apo A-I, A-IV and C-III genes, HNF-4, ER-3 and ARP-1 all appear to influence transcription of apo A-I and C-III in a similar fashion as they do A-IV (Ladies and Karathanasis 1991, Ladies et al. 1992, Mietus-Snyder et al. 1992). Finally, it has been demonstrated that a region in the 5' flanking region of the apo C-III gene acts as a positive enhancer element, necessary for the full effect of HNF-4 on A-IV expression (Ktistaki et al. 1994). Although these trans-acting factors appear to be sufficient to explain tissue-specific expression of apo A-IV, there is as yet no direct evidence linking them to either hormone-dependent or developmental regulation of apo A-IV expression. Regulation of these factors themselves is poorly understood at present. Finally, whether these factors are involved in the intestinal A-IV response to dietary lipid remains to be investigated.

**Intestinal synthesis and secretion of apo A-IV.** To date, the only consistent, documented stimulus for intestinal apo A-IV is intestinal absorption and transport of lipid. Studies by our laboratory (Hayashi et al. 1990b, Kalogeris et al. 1994) and others (Apfelbaum et al. 1987, Black et al. 1990, Gordon et al. 1982, Krause et al. 1981) have clearly demonstrated that expression, synthesis and secretion of apo A-IV are stimulated by ingestion or direct gastrointestinal delivery of lipid. Among the major intestinal apolipoproteins (A-I, A-IV and B-48), apo A-IV is the only one so influenced (Apfelbaum et al. 1987, Davidson and Glickman 1985, Davidson et al. 1986 and 1987, Hayashi et al. 1990a and 1990b). Secretion of apo A-IV into intestinal lymph in rats (Hayashi et al. 1990b, Kalogeris et al. 1994) and into serum in rats (Delamatre and Roheim 1983) and humans (Weinberg et al. 1990) markedly increases during acute absorption of lipid. We (Kalogeris et al. 1994) showed that intestinal lymphatic transport of apo A-IV increases in a graded fashion with increasing steady-state levels of intestinal triglyceride transport; this increased secretion of apo A-IV could be explained by graded increases in intestinal mucosal synthesis of A-IV along a proximal-distal gradient (Kalogeris et al. 1994). Available evidence suggests that increased synthesis of A-IV by fat is by a pretranslational mechanism (Apfelbaum et al. 1987). Although it has been shown that increases in intestinal apo A-IV transcription rate and mRNA stability both occur in response to a high fat meal in 14-d-old rats pups (Sato et al. 1992), it is not known whether either or both of these two possible pretranslational mechanisms predominate in adult animals.

Luminal lipid does not come only from dietary sources; indeed, biliary input accounts for a significant amount of lipid delivered to the intestine. This is especially true for phospholipid for which about 90% of the daily load comes from bile (Tso 1994). It has been shown that basal levels (i.e., in the absence of exogenous lipid) of synthesis and secretion of apo A-IV are profoundly reduced by bile diversion (Davidson et al. 1991, Fukagawa et al. 1994). Recently, it was demonstrated in fasting rats that intestinal lymphatic output of apo A-IV displays a circadian rhythm, with peak output occurring just before the midpoint of the dark cycle (Fukagawa et al. 1994). This pattern of A-IV output was closely correlated with those of lymph triacylglycerol, phospholipid and cholesterol. Bile diversion reduced lymphatic output of apo A-IV by 67%, of cholesterol by 81%, and of both triacylglycerol and phospholipid by 90%. Moreover, bile diversion completely abolished the circadian rhythms in outputs of apo A-IV, as well as all of the above lipids (Fukagawa et al. 1994). Thus, an intact enterohepatic circulation is necessary for both normal basal lymphatic output of apo A-IV and its circadian rhythm, although it is not yet clear what component of bile is responsible.

With regard to the stimulation of intestinal apo A-IV by dietary lipid, several lines of evidence support the hypothesis that assembly and transport of chylomicrons is necessary for the A-IV response to dietary lipid, although, once again, this may depend upon either or both of species and/or stage of development tested. The first group of studies used Pluronic L-81 (L-81), a hydrophobic surfactant that specifically and reversibly blocks chylomicron transport. When rats are infused with lipid + L-81, intestinal lipid digestion and absorption are unaffected, but the absorbed lipid accumulates in the intestinal mucosa and is not transported into lymph (Tso et al. 1980 and 1981). It has been shown that L-81 preferentially blocks chylomicron transport from the intestine; VLDL secretion is unaffected (Tso and Gollamudi 1984, Tso et al. 1981). A key observation is that when L-81 is infused, the increase in apo A-IV synthesis and lymphatic secretion normally observed in response to dietary lipid is also blocked (Hayashi et al. 1990b). When L-81 is removed, lymphatic lipid transport immediately increases, as the accumulated mucosal lipid is transported out of the enterocytes on chylomicrons. Removal of L-81 similarly reverses the blockade of apo A-IV transport. There is a lag period between the output of lipid and that of A-IV (lipid occurring first) with reversal of L-81 blockade, suggesting that lipid transport stimulates A-IV (Hayashi et al. 1990b). Because L-81 has little effect on lipid digestion and uptake, nor does it inhibit triglyceride resynthesis, it is thought that control of A-IV synthesis and secretion by lipid transport may be related to events in the subsequent phases of the chylomicron assembly and secretory pathway. A second piece of evidence that lymphatic apo A-IV output depends upon chylomicron transport comes from studies in which we examined intestinal synthesis and lymphatic secretion of apo A-IV in response to intestinal infusion of fatty acids differing in chain length (and therefore, route of transport from the intestine). Infusion of long-chain fatty acids (myristic, C-14; oleic, C-18 and arachidonic, C-20), which are transported via the lymph on chylomicrons, stimulates synthesis and output of apo A-IV, whereas medium- and short-chain fatty acids (caprylic, C-8 and butyric, C-4), primarily transported as free fatty acids in the portal vein, elicited a negligible A-IV response (Kalogeris et al., 1996a). This latter finding in rats differs from results in neonatal swine by Black et al. (1996), who observed similar increases in jejunal A-IV mRNA expression and synthesis in response to infusions of both medium-chain (8:0, 10:0) and long-chain triglyceride mixtures. Results of the above rat studies strongly favor the hypothesis of Hayashi et al. (1990b) that some aspect
of the transport of chylomicrons is required to stimulate apo A-IV. However, in light of the recent findings in newborn pigs (Black et al. 1996), it is unclear whether this aspect of the control of apo A-IV is common to all species or developmental stages. Systematic studies addressing this particular issue are needed. Moreover, the mechanism whereby dietary lipid stimulates intestinal A-IV remains obscure. Either intracellular events associated with the lipid transport process, other systemic (i.e., hormonal or neural) signals associated with lipid transport, or all of these mechanisms could influence expression and secretion of apo A-IV.

The effect of dietary lipid on intestinal apo A-IV expression and secretion may be mediated indirectly. As described above, strong evidence links intestinal apo A-IV synthesis and secretion to lipid absorption and transport, but the mechanism for this effect is unknown. Recently, we obtained evidence that the linkage between lipid transport and stimulation of apo A-IV may be, in part, indirect. Impetus for this work came from studies in which we gave duodenal infusions of emulsions containing graded doses of triacylglycerol to rats and measured both regional lipid distribution and mucosal synthesis of apo A-IV at various sites along the length of the intestine (Kalogeris et al. 1994). We found that despite significant amounts of lipid present only in the proximal half of the gut, A-IV synthesis was stimulated in the proximal three quarters of the gut, even in segments of intestine where there was negligible lipid. This suggested that there may be other factors associated with lipid transport, but independent of the presence of lipid itself, that are capable of stimulating apo A-IV in the gut. To test this hypothesis, we performed a series of experiments comparing the effects of proximal vs. distal intestinal infusion of lipid on expression and synthesis of apo A-IV in both proximal and distal intestine (Kalogeris et al. 1996c). Initially, we examined A-IV synthesis in proximal jejunum and terminal ileum after either duodenal or ileal infusions of lipid. After duodenal lipid infusion, both A-IV synthesis and mRNA levels were elevated two- to threefold compared with control infusions in the jejunum, but ileal A-IV synthesis and mRNA abundance were unaffected. Earlier work established that under the conditions of our duodenal infusion, the amount of lipid reaching the ileum was negligible, suggesting that the lack of effect of duodenal lipid infusion on ileal A-IV expression was due to an insufficient exposure of the distal gut to lipid. We examined this possibility in a second set of studies in which lipid was delivered to either the duodenum or directly to the ileum. Ileal lipid infusion stimulated ileal A-IV synthesis and in addition, unexpectedly, stimulated proximal jejunal A-IV synthesis. Subsequent experiments in rats equipped with jejunal or ileal Thiry-Vella fistulas demonstrated the following: 1) ileally infused lipid elicits an increase in proximal jejunal A-IV synthesis independent of the presence of jejunal lipid, and 2) both ileum and more distal sites may be involved in the stimulation. These results suggest the existence of a signal, arising from the distal gut, capable of stimulating synthesis of apo A-IV in the proximal gut.

The distal intestine is known to play an important role in the control of gastrointestinal function. Nutrient (especially lipid) delivered to the ileum results in inhibition of gastric emptying (Lin et al. 1990, MacFarlane et al. 1983), decreased intestinal motility and transit (MacFarlane et al. 1983, Spiller et al. 1984) and decreased pancreatic secretion (Harper et al. 1979). Ileal nutrient also inhibits food intake (Meyer et al. 1994, Welch et al. 1985). The mechanism for these effects (collectively termed the “ileal brake”) (Spiller et al. 1984) appears to be related to the release of one or more peptide hormones from the distal gut (Aponte et al. 1985 and 1989, Jin et al. 1993, Pappas et al. 1985, 1986a and 1986b, Savage et al. 1987). These effects have traditionally been considered operative only in the event of abnormal delivery of undigested nutrients to the distal gut, such as in malabsorption syndromes (Spiller et al. 1984). However, growing evidence supports the notion that, because of the rapid gastric emptying during the early phases of a meal, nutrient reaches the distal gut even under more normal conditions (Lin et al. 1990, Meyer et al. 1994). Indeed, in recent studies, we administered a gastric bolus of \(^{3}H\)-triolein—labeled Intralipid (0.1 g of fat, approximately half the amount that a rat would consume in a single meal of standard semipurified diet) to rats and measured luminal and mucosal distribution of radiolabeled lipid at various times after the load. By 15–30 min, radiolabeled lipid was spread evenly throughout the entire gut, with 10–15% of the load recovered in the ileum and cecum combined. Presence of substantial amounts of lipid in these distal sites persisted for at least 4 h after the load. Under identical experimental conditions, we found rapid (i.e., within 15–30 min) stimulation of apo A-IV synthesis throughout the intestine, including the ileum. This was associated with significant stimulation of luminal output and plasma levels of apo A-IV by 30 min after the gastric lipid load (Rodriguez et al. 1997). Thus, it is becoming increasingly clear that even under normal conditions, a far greater length of intestine could be involved in the control of gastric and upper gut function than has been previously recognized. The ileal brake may play a role in the normal control of gut function. Our findings suggest that another possible effect of the ileal brake is to stimulate synthesis and release of apo A-IV. Another implication of the present study is that the release of apo A-IV may itself be a component of the ileal brake. This notion is supported by the studies demonstrating a role for apo A-IV in the control of food intake (Fujimoto et al. 1992, 1993a and 1993b), as well as more recent work by Okumura et al. (1994 and 1995), who demonstrated that intracerebral administration of purified apo A-IV to rats inhibits both gastric acid secretion and gastric emptying. At present, the most likely hormonal mediator of the ileal brake is peptide tyrosine-tyrosine (PYY), which is a member of a peptide family that includes pancreatic polypeptide (PP), neuropeptide Y (NPY) and fish pancreatic peptide Y (PY) (Larhammar et al. 1993). PYY is synthesized in endocrine cells in the ileum and large intestine (Adrian et al. 1987, Aponte et al. 1985, Hill et al. 1991, Tatemoto 1982, Taylor 1985), and is released in response to intestinal nutrients, especially lipid (Adrian et al. 1987, Aponte et al. 1985, Jenkins et al. 1992, Jin et al. 1993, Pappas et al. 1986a and 1986b, Taylor 1985), specifically long-chain fatty acids (Hill et al. 1991). However, PYY may not be the only mediator of the ileal brake; for example, perfusion of the intestine with fat produces a greater suppression of pentagastrin-stimulated acid secretion than does PYY (Pappas et al. 1986b), indicating that the enteroendocrine effect of fat is mediated by more than one factor. The recent data of Okamura et al. (1994 and 1995) suggest that apo A-IV may also act as an enteroendocrine. We now have preliminary data implicating PYY in the control of intestinal apo A-IV: continuous intravenous infusion of physiologic doses of PYY elicits significant increases in both synthesis and lympathic output of apo A-IV in rats (Kalogeris et al. 1996b); we are presently testing the hypothesis that the effect of distal gut lipid on proximal jejunal synthesis of apo A-IV is mediated by PYY. If this hypothesis is confirmed, it would be the first evidence for involvement of a gastrointestinal hormone in the control of expression and secretion of an intestinal apolipoprotein, thus bringing together two heretofore separate areas of research in gastrointestinal physiology. The possibility that
be addressed before a comprehensive understanding of the physiology of apo A-IV can be achieved. Thus, our model is grossly oversimplified, and it is certain that modifications will be necessary as results of ongoing and future experiments accumulate.

In summary, intestinal apo A-IV is an interesting protein stimulated by dietary lipid, with a potentially important physiological role in the integrated control of digestive function and ingestive behavior, as well as a presumed role in aspects of cholesterol and lipoprotein metabolism. Although mechanisms involved in the control of its expression and secretion from the intestine have only recently begun to be systematically examined, the aforementioned progress suggests that our level of understanding in this area is on the verge of a rapid acceleration, a result of the fruitful combination of insights gained from whole-animal experiments with modern molecular biological techniques.

**LITERATURE CITED**


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**FIGURE 1** Proposed pathway for control of apolipoprotein (apo) A-IV by intestinal lipid. Fat in the proximal intestine stimulates expression, synthesis and secretion of apo A-IV in a proximal-distal gradient in the intestine, depending upon the total lipid load. This effect is dependent on presence of lipid in the regions where apo A-IV is expressed. Fat in the distal gut (ileum, cecum) also stimulates apo A-IV, both in the ileum and in the proximal jejunum. This latter effect is independent of the presence of jejunal lipid and is presumably mediated by a signal released in response to the presence of lipid in the distal intestine. This signal may be peptide YY (tyrosine-tyrosine) (PYY), although other gut hormones have not been unequivocally ruled out.
Dietary Fat and Apolipoprotein A-IV


