ApoA-IV: current and emerging roles in intestinal lipid metabolism, glucose homeostasis, and satiety

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Abstract

Apolipoprotein A-IV (apoA-IV) was discovered more than 30 years ago as a major protein component of lymph chylomicrons in the postprandial state (31, 90, 99). Human apoA-IV is found in the apoA-I/C-III/A-IV gene cluster on chromosome 11 (43). This gene cluster is essential for lipoprotein metabolism and the maintenance of plasma lipid levels and, as such, is a modulator of cardiovascular disease risk. In humans, apoA-IV is synthesized only by the small intestine; in rodents a small amount is also synthesized by the liver (31, 51, 84). The jejunum is the major site of apoA-IV synthesis, but it is also produced in the duodenum and ileum (42).

ApoA-IV is secreted into the lymph on chylomicrons in response to lipid feeding. During subsequent metabolism of chylomicrons in the periphery, ∼25% of the apoA-IV is transferred to HDL in the plasma and the rest is found in the lipoprotein-free fraction (24, 69). Therefore, the presence of apoA-IV in the periphery (on chylomicrons, circulating on HDL, and free in the plasma) is linked to intestinal lipid absorption and chylomicron packaging.

Many physiological functions have been ascribed to apoA-IV, including a role in chylomicron assembly and lipid metabolism, a mediator of reverse-cholesterol transport, an acute satiety factor, regulator of gastric function, and, finally, a modulator of blood glucose homeostasis. This review will highlight the evidence for these physiological roles of apoA-IV, as well as emerging evidence of a role for intestinal apoA-IV in mediating chronic disease.

Role of apoA-IV in Chylomicron Assembly and Lipid Absorption

Nearly 40 years after the first description of apoA-IV, a considerable body of evidence links apoA-IV to intestinal triglyceride absorption and secretion. ApoA-IV is responsive to nutritional status, and dietary fat absorption results in increased apoA-IV synthesis and secretion in a dose-dependent manner (39–42). Dietary fat absorption also results in increased plasma apoA-IV levels (32), and in patients with malabsorptive disorders (such as chronic pancreatitis) apoA-IV levels in plasma do not rise in response to a fatty meal (45). ApoA-IV production requires chylomicron synthesis and is upregulated in response to dietary long-chain fatty acids (the absorption of which requires chylomicron synthesis), but not when short-chain fatty acids are absorbed through the portal blood (44). Blocking chylomicron secretion inhibits the rise in apoA-IV synthesis induced by fat absorption (88). Finally, apoA-IV colocalizes with apolipoprotein A-I (apoA-I) and apolipoprotein C-III (apoC-III) in intestinal lymph (10). The presence of apoA-IV in lymph is substantial, as it is the major protein component of lymph chylomicrons (46, 47). This dichotomy between the presence of apoA-IV in lymph and its apparent role of apoA-IV in intestinal triglyceride absorption or secretion is due to the presence of apoA-IV, including a role in chylomicron assembly and lipid metabolism, a mediator of reverse-cholesterol transport, an acute satiety factor, regulator of gastric function, and, finally, a modulator of blood glucose homeostasis. This review will highlight the evidence for these physiological roles of apoA-IV, as well as emerging evidence of a role for intestinal apoA-IV in mediating chronic disease.

Address for reprint requests and other correspondence: A. B. Kohan, Dept. of Nutritional Sciences, University of Connecticut, Advanced Technology Laboratory, 211-D, 1392 Storrs Rd., Unit 4010, Storrs, CT 06269-4010 (e-mail: alison.kohan@uconn.edu).

Kohan AB, Wang F, Lo CM, Liu M, Tso P. ApoA-IV: current and emerging roles in intestinal lipid metabolism, glucose homeostasis, and satiety. Am J Physiol Gastrointest Liver Physiol 308: G472–G481, 2015. First published January 15, 2015; doi:10.1152/ajpgi.00098.2014.—Apolipoprotein A-IV (apoA-IV) is secreted by the small intestine on chylomicrons into intestinal lymph in response to fat absorption. Many physiological functions have been ascribed to apoA-IV, including a role in chylomicron assembly and lipid metabolism, a mediator of reverse-cholesterol transport, an acute satiety factor, a regulator of gastric function, and, finally, a modulator of blood glucose homeostasis. The purpose of this review is to update our current view of intestinal apoA-IV synthesis and secretion and the physiological roles of apoA-IV in lipid metabolism and energy homeostasis, and to underscore the potential for intestinal apoA-IV to serve as a therapeutic target for the treatment of diabetes and obesity-related disease.
Evidence supporting the role of apoA-IV in intestinal triglyceride absorption and packaging is significant. In newborn swine enterocytes (IPEC-1 cells) the overexpression of apoA-IV greatly enhances the secretion of triglyceride, cholesterol ester, and phospholipid in chylomicron/VLDL particles (28, 62, 95, 100). This role of apoA-IV in IPEC-1 cells appears to rely on a region of apoA-IV (residues 344–354), the presence of which stimulates the secretion of larger, more triglyceride-rich lipoproteins in a dose-dependent manner (62). This role of apoA-IV may be due to its ability to stabilize the expanding lipid/aqueous interface during lipoprotein synthesis, resulting in the formation of larger triglyceride-rich chylomicrons. For apoA-IV to facilitate the expansion of triglyceride-rich lipoproteins, it is likely that it would interact with apoB in the endoplasmic reticulum (as part of the triglyceride secretory pathway). Studies in both COS and McA-RH7777 hepatoma cells have shown that the endoplasmic reticulum (ER)-retained apoA-IV (tagged with the ER retention signal KDEL) inhibited the early stages of triglyceride-rich lipoprotein assembly (23) and that overexpression of wild-type (WT) apoA-IV is able to modulate the secretory trafficking of apoB leading to an enhancement of particle expansion and triglyceride secretion (95). In addition to this work in cell culture, work by Simon, Weinberg, and colleagues (83) suggests that apoA-IV expression mediates the expression of other triglyceride packaging and nutrient sensing genes in the intestine, which may act to regulate regional lipid absorption.

Despite this evidence, most in vivo studies show that the total loss of apoA-IV or the transgenic overexpression of apoA-IV do not result in a loss or gain of triglyceride secretion, nor in the secretion of triglyceride-deficient chylomicron particles. In the conscious in vivo lymph fistula model to directly assess intestinal lipoprotein secretion (Figs. 1 and 2), apoA-IV KO mice have been shown to have no change in dietary lipid absorption, or in the cumulative secretion of radiolabeled triglyceride into lymph (under both an acute bolus acute dose or continuous intraduodenal lipid infusion paradigms) (47). In mice expressing high levels of human apoA-IV, lipid absorption was measured by using a variety of labeled metabolic tracers and there was no difference found (1). These data suggest apoA-IV is not required for normal dietary lipid absorption.

Although these in vivo studies show that apoA-IV may not be required for triglyceride absorption (since the amount of triglyceride absorbed and secreted was the same between models), not only does the loss of apoA-IV in apoA-IV KO mice result in the secretion of larger chylomicrons from the intestine but these chylomicrons were less rapidly cleared from plasma than WT chylomicrons (Figs. 3 and 4) (46). This suggests that apoA-IV has a previously unknown role in chylomicron metabolism and is therefore important in regulating plasma lipid metabolism. It should also be noted that the chylomicrons derived from the apoA-IV-null animals also metabolized more slowly than those derived from WT animals, suggesting that apoA-IV may not be freely interchangeable between the free and the HDL-bound compartment with the circulating chylomicrons.

This dichotomy in findings between cell culture and in vivo models not only is a conundrum but also remains an important unresolved issue, especially in light of the importance of apoA-IV in mediating cardiovascular disease risk. Overexpression of apoA-IV protects transgenic mice from atherosclerosis caused by either apoE deficiency, LDL receptor deficiency, or cholesterol feeding (8, 16, 72). Interestingly, apoA-IV KO may also confer protection against diet-induced atherosclerosis by decreasing the rise in plasma lipid levels following the feeding of high fat, most notably by decreasing total triglyceride and cholesterol levels (70, 97). Since both the overproduction of chylomicrons during chronic disease (such as diabetes) (12, 15) and their subsequent clearance from plasma are both involved in the development of cardiovascular disease, apoA-IV may indeed be playing multiple important roles. ApoA-IV may be modulating the retention of triglyceride-rich lipoproteins in plasma through its regulation of chylomicron clearance and may also regulate the production of particles (either by stimulating bulk loading or triglyceride onto apoB-containing chylomicrons or by modulating regional gene expression to regulate regional lipid absorption) (46, 62, 83, 95).

It is unknown how many apoA-IV molecules are secreted from the intestine per chylomicron particle or whether these changes during chronic disease states are due to the potential role of apoA-IV in chylomicron clearance and its major role in modulating glucose homeostasis. Another point worth noting is the fact that apoA-IV protects lipoproteins from oxidative processes (72) and so it may be an extremely complicated task to sort out the relative importance of the various roles played by apoA-IV in lipid metabolism and cardiovascular events asso-

Fig. 1. Structure of the intestinal villus. The surface of the small intestine is comprised of fingerlike projections, called villi and crypts. A continuous sheet of epithelial cells, which are the primary absorptive cells of the intestine, covers the villi and crypts. Below the absorptive epithelium is the intestinal lamina propria and a lymphatic capillary (lacteal), which is surrounded by a blood capillary network. Dietary triglyceride and lipophilic compounds are transported from the absorptive enterocyte into the lacteal and eventually into the mesenteric lymph duct (©2010 Marcia Hartsock, MA, CMI).
inhibits food intake (21, 22). Subsequent studies have deter-
mined that central and peripheral administration of recombi-
nant apoA-IV inhibits food intake and is not toxic (21, 56, 61),
whereas administration of apoA-I at comparable doses has no
effect on satiety (21). These observations suggest that both
intestinal apoA-IV (secreted in response to dietary lipids) and
exogenous apoA-IV injected in the periphery can regulate food
intake.

ApoA-IV Regulation of Gastric Emptying and Secretion

Lipid, particularly long-chain triglyceride, inhibits gastric
motor and secretory function (38). Free fatty acids of chain
length 12 or greater are much more effective in the inhibition of
gastric motility than C10 fatty acids (38). Intestinally ab-
sorbed long-chain fatty acids are resynthesized into triglyceride
in the enterocytes and are subsequently secreted in chylomi-
crons (89). Mesenteric lymph enriched with chylomicrons
collected from lymph fistula rats reduces gastric motor function
(27). In contrast, when chylomicrons are removed from the
chylous lymph, gastric motility significantly increases. In sub-
sequent studies, purified recombinant apoA-IV was shown to
significantly inhibit gastric motility (26, 27); in contrast,
apoA-IV KO mice have significantly faster gastric emptying
and greater secretion of gastric acid after an ingested meal (98).
It has been demonstrated that this mechanism involves a
negative feedback of apoA-IV containing chylomicrons on
gastric motility via cholecystokinin-1R (CCK-1R) on capsai-
cin-sensitive vagal afferent nerve terminals (26).

Role of apoA-IV in Glucose Homeostasis and Insulin
Secretion

Recently, studies in apoA-IV KO mice have revealed a
novel role for apoA-IV in glucose metabolism and insulin
secretion (92). ApoA-IV KO mice are glucose intolerant,
accompanied with attenuated insulin secretion upon glucose
challenge, suggesting that apoA-IV is essential for physiolog-
ical blood glucose control. Administration of exogenous
apoA-IV (in an amount equivalent to the amount secreted in
response to a fatty meal) dramatically improved glucose toler-
ance along with the restoration of insulin secretion (92).
Therefore, it is likely that, physiologically, the apoA-IV se-
creted after a fat-rich meal could be rapid and sufficient enough
to stimulate insulin secretion.

As an endogenous regulator of insulin secretion, intestinal
apoA-IV comprises one of the components of the enteroinsul
ar axis, i.e., the collective signaling pathways between the gut
and the pancreatic islets that control nutrient-dependent insulin
secretion. ApoA-IV has a half-life of ~7–8 h, which is much
longer than that of typical incretins such as GLP-1 and GIP
(44), whose half life is a few minutes. For example, the
glucose-lowering effect of a single injection of apoA-IV lasts
~12 h in KKAY diabetic mice (92).

Experiments in isolated islets have examined the direct
effect of apoA-IV on β-cell insulin secretion. ApoA-IV in-
duces a dose-dependent increase in insulin release when the
islets are exposed to 20 mM, but not 3 mM glucose. In
addition, functional KATP and calcium channels are required
for the action of apoA-IV on insulin secretion, but apoA-IV
does not act directly to stimulate calcium influx (92). Mem-
brane depolarization by closure of the KATP channels acti-
vates voltage-gated Ca²⁺ channels and leads to Ca²⁺ influx,
which triggers the exocytosis of insulin. Instead, the action of apoA-IV seems to lie downstream of Ca\(^{2+}\)/H\(_\text{11001}\) influx and amplify insulin exocytosis (92). Although these data suggest apoA-IV acts on the late stages of insulin secretion, the precise molecular mechanism remains to be elucidated. ApoA-IV exhibits high-affinity binding to isolated human hepatocellular plasma membranes, which is saturable, reversible, and specific, supporting the idea that a membrane protein is involved in binding (96). However, a specific receptor for apoA-IV has not been discovered to date. However, apoA-IV is able to enter the hepatocyte and interact with the transcription factor NR1D1 (52). ApoA-IV inhibits gluconeogenesis through NR1D1. Thus, through the insulinotropic and the antigluconeogenic action of apoA-IV, apoA-IV plays an important role in glucose homeostasis following the ingestion of food.

We have proposed that it is the change in circulating apoA-IV levels between fasting and feeding (rather than the absolute level of circulating level of apoA-IV) that stimulates insulin secretion. This may be another reason why the loss of regulation in apoA-IV that occurs in response to a chronic high-fat diet correlates with poor glucose homeostasis (3, 41, 49, 55, 59, 94).

**Actions of ApoA-IV in the Brain**

Compelling evidence suggests that central (rather than circulating) apoA-IV is important for the control of food intake and body weight: 1) when \(^{125}\)I-labeled apoA-IV is injected intravenously in mice, this apoA-IV does not cross the blood brain barrier (81); 2) intracerebroventricular (ICV) injection of apoA-IV significantly and dose dependently reduces food intake without eliciting signs of toxicity (22); 3) apoA-IV mRNA and protein are present in the rat hypothalamus neurons (54); using immunohistochemistry, apoA-IV distribution is found in brain areas involved in energy homeostasis, including the arcuate (ARC) and ventromedial hypothalamic, paraventricular, and dorsomedial nuclei and the nucleus of the solitary tract (NTS) (81); finally, 4) double-staining immunohistochemistry
with a neuronal marker revealed apoA-IV is largely present in neurons.

Circadian Rhythm of Hypothalamic apoA-IV

To determine the roles of central apoA-IV in the regulation of daily food intake, Liu et al. (58) examined the diurnal patterns of hypothalamic apoA-IV gene and protein expression. In freely feeding rats, the hypothalamic apoA-IV mRNA and protein levels were found to peak 3 h after lights on and to reach a nadir 3 h after lights off (the normal feeding period of rodents). To make sure that this was not just a coincidence, we restricted the feeding period to 4 h during the light cycle. In the food-restricted rats, the daily patterns of the apoA-IV fluctuation were altered with a marked decrease in hypothalamic apoA-IV mRNA and protein levels during the 4-h feeding period of the light phase. Although corticosterone (Cort) secretion temporally coincided with the decreasing phase of apoA-IV in the hypothalamus, the diurnal expression of hypothalamic apoA-IV is not regulated by Cort because depletion of Cort by adrenalectomy significantly decreased, rather than increased, hypothalamic apoA-IV mRNA and protein levels (58). The observations that apoA-IV levels in the hypothalamus were inversely related to food intake during the normal diurnal cycle as well as in the period of restricted feeding implies that hypothalamic apoA-IV is involved in the regulation of daily food intake.

Interaction of apoA-IV with Other Neuro- and Endocrine Peptides in the Regulation of Food Intake and Energy Metabolism

Neuropeptide Y. Neuropeptide Y (NPY) is a hypothalamic neuropeptide with regulatory action on food intake. Liu et al. (57) have demonstrated there is an interaction of apoA-IV with NPY. ICV injection of NPY alone significantly increased hypothalamic apoA-IV expression in a dose-dependent manner (57). Although intraduodenal infusion of lipid also increased hypothalamic apoA-IV mRNA levels, there was no further significant increment with the combination of ICV injection of NPY and lipid infusion, indicating that there is a lack of potentiation in the regulation of hypothalamic apoA-IV gene expression by both NPY and lipid. One possibility to explain why administered NPY increases apoA-IV gene expression is to maintain a balance between these two opposing factors, thereby regulating food intake, which could be further investigated in apoA-IV KO mice.

Melanocortin system. Hypothalamic melanocortin system plays an important role in the regulation of body weight. α-Melanocyte-stimulating hormone (α-MSH) derived from proopiomelanocortin (POMC) neurons exerts a tonic inhibitory influence over feeding through melanocortin type 3 and 4 receptors (MC3/4-R) in the hypothalamus. Agouti-related protein (AgRP) is a peptide produced in the ARC, which antagonizes MC3/4-R. Therefore, when administered centrally, AgRP elicits hyperphagia (17). Consistent with this, it has been demonstrated that ICV administration into the third ventricle (i3vt) of metallothionein-II (MT-II), a synthetic MC3/4-R agonist, potently reduces feeding (57), whereas i3vt administration of SHU9119, a synthetic MC3/4-R antagonist, blocks the anorectic effect of MT-II (33). These data suggest that the brain apoA-IV system suppressed food intake by stimulating the ARC POMC system (81). Gotoh et al. (29) also found that ICV administration of MT-II potentiated a subthreshold dose of apoA-IV suppression of 30-min feeding in rats, and the anorectic effect of ICV apoA-IV was almost completely attenuated by a subthreshold dose of SHU9119. These data support a synergistic interaction between apoA-IV and melanocortins that reduces food intake by acting downstream of the ARC.

Leptin. Leptin is a peptide synthesized and secreted by adipocytes (9, 20). Like apoA-IV, leptin reduces food intake (35, 80) and it interacts synergistically with apoA-IV in this regard (14, 82). Leptin is an important component of lipid homeostasis and its circulating level is directly correlated with the amount of fat in the body (20). Thus a high-fat diet increases plasma leptin levels in obese humans and rodents (5, 10, 20). Leptin directly acts on leptin receptors in intestinal cells (6, 32, 34, 71) and attenuates the lipid-induced stimulation of apoA-IV synthesis and secretion (14, 66). Consumption of a high-fat diet initially increases plasma apoA-IV levels in rodents; however, chronic consumption of a high-fat diet results in an attenuation of this effect on apoA-IV (41, 59, 94). This suggests that the elevation of circulating leptin induced by high-fat feeding might attenuate intestinal apoA-IV response to the consumption of a lipid meal. Animal studies also support this notion. Intestinal apoA-IV levels are markedly increased in ob/ob mice, which lack the ability to make leptin. Further studies are required to determine the molecular mechanism in the regulation of intestinal apoA-IV by leptin, but it is possible that leptin decreases intestinal apoA-IV gene expression to transport fewer lipids from the small intestine to the circulation.

Central administration of leptin decreases food intake and increases energy expenditure. Shen et al. (82) demonstrated that the hypothalamic apoA-IV mRNA levels is significantly lower in leptin-deficient obese (ob/ob) mice than WT controls. Intragastric infusion of a lipid emulsion significantly stimulated hypothalamic apoA-IV gene expression in lean controls but not in ob/ob mice. When leptin was intraperitoneally administered daily for 5 days, it significantly stimulated apoA-IV mRNA levels in the hypothalamus of ob/ob mice, compared with the pair-fed controls. Additionally, the fasting-induced reduction of apoA-IV mRNA levels was also restored by centrally administered leptin. Shen et al. also demonstrated that apoA-IV is present in leptin-sensitive phosphorylated signal transducer and activator of transcription-3 (pSTAT3)-positive cells of the ARC as determined by immunohistochemistry (82). The stimulatory effect of leptin on apoA-IV protein expression was significantly attenuated by the suppression of STAT3 expression by small interfering RNA (siRNA) in cultured primary hypothalamic neurons. These observations imply that leptin can regulate apoA-IV gene and protein expression in the hypothalamus, and such effects are at least partially via the STAT3 signaling pathway. More importantly, ICV coadministering subthreshold doses of leptin (1 μg) and apoA-IV (0.5 μg) leads to a significant reduction of food intake in rats, indicating the existence of a functional synergistic interaction between leptin and apoA-IV, leading to suppression of food intake. The differential effect of leptin on apoA-IV expression in the hypothalamus and the enterocytes is intriguing and deserve to be further investigated.

Cholecystokinin. The secretion of cholecystokinin (CCK) by the intestinal L cells is stimulated by the consumption of lipid
and protein. The fat-induced stimulation is associated with the formation and secretion of chylomicrons (36, 37). CCK stimulates gallbladder contraction and pancreatic enzyme secretion, modulates intestinal motility, and inhibits food intake (13, 25, 104). Exogenous administration of CCK reduces short-term food intake in experimental rats by reducing meal size (25, 67), and this satiating effect is abolished by deactivation of vagal afferents with capsaicin, vagotomy, or CCK-1R antagonist. Thus the satiation signals are relayed via CCK-1R on vagal afferent nerves (64, 74, 75, 77, 79). Secretion of CCK and apoA-IV are both induced by fat absorption and this lipid-induced stimulation is dependent on chylomicron formation (30, 37, 74). In addition, both act peripherally (through either intraperitoneal or intravenous administration) as well as centrally to reduce food intake (22, 25, 63, 93).

We conducted a series of experiments to determine whether there is interaction between CCK and apoA-IV on the control of food intake and whether this is mediated via CCK-1R on vagal afferent fibers. Using subthreshold doses of either apoA-IV or CCK a combination of both produces a short-term satiation for 1 h and this satiation effect is attenuated by the CCK-1R antagonist lorglumide (61). As the doses of CCK and apoA-IV are increased, the satiating effect is prolonged. Furthermore, we reveal that apoA-IV-elicited satiation is greatly attenuated in CCK-KO mice (60). In contrast, CCK-induced satiating response is greater in apoA-IV KO mice owing to increased CCK-1R expression in the nodose ganglia and/or NTS (102). These findings suggest that endogenous apoA-IV and CCK interact with each other to reduce food intake via CCK-1R and systemic apoA-IV requires an intact CCK system in order to it to work physiologically. This working model was first proposed by Raybould and colleagues (26) that the stimulation of apoA-IV release induced by lipid absorption results in the stimulation of CCK secretion, followed by activation of the vagal nerves via a CCK-1R-dependent pathway.

Circulating apoA-IV does not cross the blood-brain barrier (81) but is able to increase CCK-elicited activity in vagal afferent fibers, which discharge via a CCK-1R-dependent pathway in vitro (26). Blockade of CCK-1R using lorglumide significantly reduces apoA-IV-induced satiation, suggesting that CCK-1R on vagal afferent nerves plays an important role in relaying apoA-IV-induced anorectic signals to the brain (60). Subdiaphragmatic vagal deafferentation (SDA) is a surgical procedure that eliminates all neuronal signals mediated via vagal afferent fibers from the upper gut, including the liver, while leaving half of the vagal efferent fibers intact (4, 68). We have demonstrated that Long-Evans rats with SDA have attenuated apoA-IV-elicited satiation effect (60). These findings support the notion that systemic apoA-IV and CCK work codependently to suppress food intake and peripheral apoA-IV requires an intact CCK system and CCK-1R on vagal afferent nerves to exert its satiety effects in the brain.

Regulation of apoA-IV Synthesis and Secretion

ApoA-IV synthesis and secretion are stimulated by active lipid absorption and chylomicron formation in the small intestine (36, 37). Interestingly, neither protein nor carbohydrate absorption by the small intestine effects apoA-IV secretion. The stimulation of apoA-IV secretion occurs rapidly (within half an hour following the beginning of active lipid absorption) (21). ApoA-IV synthesis and secretion rely on chylomicron formation. This effect is abolished when chylomicron formation is inhibited (37), and in studies in which short-chain fatty acids are infused directly into the intestine (which are directly secreted into the portal vein) there is no stimulation of apoA-IV synthesis and secretion (42).

Fasting and refeeding modulates both circulating and central apoA-IV levels (54). Feeding overnight (the normal feeding periods for rodents) significantly decreases apoA-IV gene expression in both the jejunum and hypothalamus. Fasting with low-fat chow in fasting rats for 4 h evokes a pronounced increase of apoA-IV gene expression in jejunum, but not in the hypothalamus. However, refeeding with lipid restores apoA-IV mRNA levels in both jejunum and hypothalamus in fasted animals.

Effects of Obesity and Chronic High-Fat Diet on apoA-IV

Plasma apoA-IV is known to rise after a fatty meal. However, in obese humans, fasting plasma apoA-IV levels are higher than in normal-weight individuals (18, 19, 91). This increase in fasting plasma apoA-IV also correlates with higher plasma triglyceride levels both at fasting and in response to a lipid meal (18, 19, 91). This increase in plasma apoA-IV levels may be due to a loss of regulation of apoA-IV in the intestine during obesity. Hints at a mechanism come from studies in rodents, where apoA-IV is acutely downregulated in response to a high-fat meal (103) but is not downregulated in the face of a chronic high-fat diet (3, 41, 49, 55, 59, 94). This loss of responsiveness may be an important factor in the effectiveness of apoA-IV in regulating food intake and insulin secretion, both of which are disturbed in obese individuals.

ApoA-IV gene expression in the hypothalamus is affected by the obesity induced by high-fat diet (HFD). In Long-Evans rats fed a HFD (20%), low-fat diet (LFD) (4%), or standard chow (Chow) for 2, 4, 6, 8, or 10 wk, Liu et al. (59) found that the body weights in HFD-fed rats are significantly greater than that in rats fed LFD and Chow diets. LF and Chow rats had comparable hypothalamic apoA-IV mRNA, which is consistent with the observations that intestinal and plasma apoA-IV protein levels were comparable across dietary groups and time. However, a slow and progressive diminution in hypothalamic apoA-IV mRNA over time was observed in HFD-fed rats, and the apoA-IV mRNA levels became significantly lower than that of LFD or Chow rats by 10 wk. Additionally, intragastric infusion of lipid emulsion to overnight-fasted animals significantly increased hypothalamic apoA-IV gene expression only in LFD and Chow rats, but not in HFD-fed rats. These results suggest that chronic consumption of a HFD significantly attenuates hypothalamic apoA-IV gene expression, as well the response of apoA-IV gene expression to dietary lipids (59). These observations raise the possibility that impaired apoA-IV gene expression in the hypothalamus could contribute to HFD-induced obesity.

The mechanism by which intestinal apoA-IV becomes desensitized to dietary fat and whether this process is reversible are important frontiers in the biology of apoA-IV since this insensitivity may be a contributing factor to problems with plasma lipid levels and glucose homeostasis during obesity.
Conclusion and Future Directions

Increasing evidence suggests that apoA-IV plays important roles in the integrated control of metabolic diseases including obesity, cardiovascular disease, and diabetes. The rapid rise of circulating apoA-IV after fat ingestion is also consistent with its involvement in the short-term regulation of satiety and glucose homeostasis. Interestingly, both rodent and human studies suggest that intestinal apoA-IV synthesis and secretion were initially increased under high-fat feeding but become less responsive to fat after chronic consumption (3, 41, 49, 55, 59, 94). This stimulation in the face of a fatty meal may be integral to the ability of apoA-IV to regulate food intake and body weight. Therefore, strategies (such as bariatric surgery) that can restore or increase the normal response of apoA-IV to lipid feeding may have a beneficial effect on weight control.

Roux-en-Y gastric bypass (RYGB) results in significant and lasting weight loss in morbidly obese patients. In addition to this weight loss, greater than 80% of obese patients with RYGB exhibit an accompanying amelioration of Type 2 diabetes (87). The mechanism for this effect is still unknown. Growing evidence suggest that bypass of the foregut alters the hormonal output of the intestine that regulate appetite, satiety, glucose homeostasis, and energy metabolism (7).

An intriguing study in obese patients first demonstrated a potential role for apoA-IV in ameliorating diabetes after gastric bypass. Initially, plasma apoA-IV decreases markedly in obese subjects in a short time after gastric surgery or undergoing weight loss, but plasma apoA-IV levels rise significantly 17 mo after RYGB (11). In agreement with other studies, body weight, diabetes, obesity-related comorbidities, and medication used were decreased in these obese patients following RYGB. It is noted that mortality is decreased by 40% in obese subjects after RYGB, especially cardiovascular-related deaths (2).

As mentioned earlier in this review, apoA-IV also possesses anti-inflammatory and antiatherogenic properties. ApoA-IV has been reported to reduce the host susceptibility to atherogenesis by decreasing the secretion of proinflammatory cytokines and diminishing atherosclerotic lesions in mice (76). It is tempting to speculate that an increase of circulating apoA-IV may contribute to weight loss as well as the improvements in inflammation and cardiovascular disease after RYGB.

This idea is supported by another recent human study, which investigated the effect of RYGB on body weight and cardiovascular risk factors after one year (73). HDL cholesterol and apoA-IV protein were found significantly increased after RYGB. More importantly, there is a strict linear relationship between weight loss and apoA-IV levels. Although this is not a cause-effect study, the significant association between changes in weight and apoA-IV levels suggests a possible effect of apoA-IV on food intake reduction and weight loss in humans. ApoA-IV KO mice could provide a powerful tool to further demonstrate the importance of apoA-IV in mediating the effect of RYGB, including determining whether the improvement of obesity and diabetes is blunted by a deficiency of apoA-IV.

Evidence in the literature adds apoA-IV to the list of gastrointestinal hormones whose plasma concentrations rise after RYGB, including peptide tyrosine-tyrosine (PYY) and GLP-1 (65). Notably, changes in gastrointestinal hormones following RYGB typically occur within days to weeks (65). Further studies are needed to examine the time course of changes in apoA-IV levels after surgery and to see whether apoA-IV participated in the early amelioration in metabolic abnormalities of obese patients. Whether the response of apoA-IV to fasting and feeding (which is lost after a chronic high-fat diet) is recovered after RYGB is another question that warrants further investigation.

How apoA-IV is regulated by RYGB is unclear. ApoA-IV is most highly expressed in the duodenum and the first part of the jejunum, the parts of the gastrointestinal tract bypassed by the RYGB procedure (83). It is possible that the fast gastric emptying with passage of nutrients directly into the jejunum might stimulate apoA-IV secretion in the lower gut. However, intestinal secretion of apoA-IV is also stimulated by an ileal factor, probably PYY, which is increased following RYGB (7). Intravenous infusion of physiological doses of PYY elicits significant increases in both apoA-IV synthesis and lymphatic transport through translation in rats, which probably acts centrally via the vagus nerve to send a signal to the gut to stimulate apoA-IV synthesis (39). Current data are unable to ascertain whether the observed increases in apoA-IV after bypass surgery arise from the action of PYY. This interesting hypothesis deserves further study.

In conclusion, ApoA-IV plays a variety of important physiological roles and seems to link dietary lipid absorption with cardiovascular disease risk, diabetes, and obesity. This underscores the potential for apoA-IV to serve as a therapeutic target for the treatment of these diseases and emphasizes the importance of exploring the precise molecular details of apoA-IV.
APOA-IV: ROLE IN LIPID METABOLISM, GLUCOSE HOMEOSTASIS, AND SATIETY


