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MECHANISMS OF DIGESTION AND ABSORPTION OF DIETARY VITAMIN A*

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■ **Abstract** Mechanisms involved in the digestion and absorption of dietary vitamin A require the participation of several proteins. Dietary retinyl esters are hydrolyzed in the intestine by the pancreatic enzyme, pancreatic triglyceride lipase, and intestinal brush border enzyme, phospholipase B. Unesterified retinol taken up by the enterocyte is complexed with cellular retinol-binding protein type 2 and the complex serves as a substrate for reesterification of the retinol by the enzyme lecithin:retinol acyltransferase (LRAT). The retinyl esters are then incorporated into chylomicrons, intestinal lipoproteins containing other dietary lipids, such as triglycerides, phospholipids, and free and esterified cholesterol, and apolipoprotein B. Chylomicrons containing newly absorbed retinyl esters are then secreted into the lymph. Although under normal dietary conditions much of the dietary vitamin A is absorbed via the chylomicron/lymphatic route, it is also clear that under some circumstances there is substantial absorption of unesterified retinol via the portal route. Evidence supports the idea that the cellular uptake and efflux of unesterified retinol by enterocytes is mediated by lipid transporters, but the exact number, identity, and role of these proteins is not known and is an active area of research.

CONTENTS

ABBREVIATIONS

ARAT, acyl-CoA:retinol acyltransferase; CEL, carboxyl ester lipase; CEL KO, CEL knockout; CRBP, cellular retinol-binding protein; KO, knock out; LRAT, lecithin:retinol acyltransferase; PLRP, pancreatic lipase-related protein; PTL, pancreatic triglyceride lipase; RE, retinyl ester; REH, retinyl ester hydrolase; WT, wild type.

INTRODUCTION

Vitamin A deficiency affects more than 100 million children throughout the world (51, 66). Thus, knowledge about the mechanisms of absorption of vitamin A can lead to better approaches for enhancing its absorption and could be helpful in ameliorating some of the deficiencies. The major sources of vitamin A in the human diet are the provitamin A carotenoids in fruits and vegetables and retinyl esters (REs) found in foods of animal origin. In humans, carotenoids either are cleaved to generate retinol or are absorbed intact. In contrast, REs are completely hydrolyzed in the intestinal lumen and free retinol is taken up by enterocytes. The intestinal absorption and metabolism of dietary carotenoids has been the subject of recent reviews (12, 17, 86). This review focuses on the biochemical and molecular mechanisms involved in the digestion of REs in the intestinal lumen, the uptake and reesterification of retinol in enterocytes, and the incorporation of the resulting REs into chylomicrons and secretion of these lipoproteins from the enterocytes. Li & Tso (46) have recently published an excellent review of these issues. The present review also focuses on the possible role of lipid transporters in the uptake and/or efflux of unesterified retinol in enterocytes.

VITAMIN A METABOLISM AND TRANSPORT: OVERVIEW

Capability for the de novo synthesis of compounds with vitamin A activity is limited to plants and microorganisms (23, 24). Thus, higher animals must obtain vitamin A from the diet, either as the preformed vitamin or as a provitamin carotenoid such as ß-carotene. In the intestinal mucosa, carotene is converted (via two enzymatic steps) to retinol (59). The major dietary forms of preformed vitamin A are long-chain fatty acid esters of retinol (60). These esters must be hydrolyzed prior to intestinal absorption. Hydrolysis of the esters can be catalyzed both by enzymes secreted by the pancreas into the intestinal lumen and by those associated directly with intestinal cells.

Following the hydrolysis of dietary REs, the free retinol is then taken up by the mucosal cell (15), where it is reesterified with long-chain, mainly saturated, fatty

acids by the enzyme lecithin:retinol acyltransferase (LRAT), which is membrane-bound (49, 58). The resulting REs are incorporated with other neutral lipid esters (i.e., triacylglycerols and cholesteryl esters) into chylomicrons and absorbed via the lymphatics (28, 35). In the vascular compartment, much of the chylomicron triacylglycerol is hydrolyzed by lipoprotein lipase in extrahepatic tissues, resulting in the production of a "chylomicron remnant" that contains most of the newly absorbed REs (29, 37). In the rat, the chylomicron remnants are taken up by the liver rapidly and almost quantitatively, and there is evidence that the REs are rapidly hydrolyzed and reesterified during this process (7, 27, 41). The reesterification in liver is also thought to be catalyzed by LRAT (50, 87).

Under conditions of adequate vitamin A nutriture, the liver is the main site of vitamin A storage, with more than 95% of the total neutral retinoid being present as REs, predominately retinyl palmitate and stearate (9, 19, 26, 47). Although chylomicron remnants (and the REs they contain) initially are taken up exclusively by the hepatocytes in liver, the REs are then transferred largely to the perisinusoidal stellate cells (7, 8). In vitamin A–adequate rats, the stellate cells account for approximately 80% of the total RE store; the remainder of the store is in hepatocytes (4, 8, 50). In both cell types the REs are stored in cytoplasmic lipid droplets along with other neutral lipids. Prior to mobilization from the liver, the REs are hydrolyzed, and free retinol is complexed to serum retinol-binding protein for secretion from the liver (67).

DIETARY SOURCES AND FORMS

As mentioned above, vitamin A activity in the diet derives from two sources: preformed vitamin A as REs in foods of animal origin and provitamin A carotenoids, such as β-carotene, α-carotene, and β-cryptoxanthin, found in plant-derived foods. Stoichiometric conversion of one mole of β-carotene (with two β-ionone rings) would give rise to two moles of retinol (via retinal), whereas conversion of a mole of either β-cryptoxanthin or α-carotene (each with only a single β-ionone ring) would give rise to a single mole of retinol.

Foods in the U.S. diet with the highest concentrations of preformed vitamin A are avian and mammalian livers (4–20 mg retinol/100 g), instant powdered breakfast drinks (3–6 mg/100 g), ready-to-eat cereals (0.7–1.5 mg/100 g), and margarines (about 0.8 mg/100 g) (76). Note that other than liver, the other sources derive their high RE contents from fortification. The highest concentrations of vitamin A as provitamin A carotenoids are found in carrots, sweet potatoes, pumpkin, kale, spinach, collards, and squash (roughly 5–10 mg retinol activity equivalents per 100 g) (76). A retinol activity equivalent (RAE) is equal to 1μg retinol or 12 μg β-carotene, or 24 μg of α-carotene or β-cryptoxanthin (78). Analysis of the National Health and Nutrition Examination Survey (NHANES) 2000 data for food consumption in the United States shows that the major contributors to the intake of preformed vitamin A are milk, margarine, eggs, beef liver, and ready-to-eat cereals, whereas the major sources of provitamin A are carrots, cantaloupes, sweet

potatoes, and spinach. Analysis of recent NHANES data (77), for both genders and all age groups, showed that the mean intake of vitamin A in the United States was about 600 μg RAE/day from food and that 70% to 75% of this was as preformed vitamin A (retinol).

DIGESTION OF RETINYL ESTERS

Solubilization

The digestion of REs requires catalysis by lipases, enzymes that hydrolyze water-insoluble substrates. The fundamental distinction between esterases and lipases is the involvement of a lipid-water interface in the catalytic process for the latter class of enzymes. Esterases function on water-soluble substrates and hence catalyze reactions in which the enzyme, substrate, and products are homogeneously distributed in a single (aqueous) phase. With lipases and water-insoluble substrates like REs, this is not the case. The presence of heterogeneous phases per se, and the fact that they change in composition during the course of the lipolytic reaction, makes the interpretation of enzyme kinetic data much more complicated than for homogeneous catalysis. A full discussion of lipase kinetics is beyond the scope of the present review, and the reader is referred to the excellent monograph edited by Borgstrom & Brockman (11). However, a few points of particular relevance to the study of the hydrolysis of highly apolar lipids such as REs should be made. The composition and packing of nonsubstrate molecules at the interface (the "quality" of the interface) plays a large role in the binding of the enzyme and the rates of substrate hydrolysis observed. Obviously, the availability of substrate molecules is also important. The point is that the observed kinetic "preference" for one substrate over another may reflect more its interactions with other lipids that allow it to achieve a high concentration at the interface than preferential binding to the enzyme itself. In other words, the apparent specificity of a lipolytic enzyme may reflect mostly the physical availability of the substrate at the interface. The physiological relevance of this is that the detailed composition of luminal lipids has a major impact on the digestion and absorption of dietary vitamin A.

Studies of the enzymatic hydrolysis of retinyl esters generally have been conducted under conditions in which the interfacial concentration of substrate (and other lipids or detergents) is undefined. This does not preclude making certain operational comparisons of the rates of hydrolysis of different potential substrates. It does mean, however, that it is problematic to conclude that the higher rate of hydrolysis of one ester over another tells much about the enzyme's specificity. This is especially true when one considers that even fairly well characterized substrate forms (i.e., micelles, liposomes, or monolayers of defined composition) probably do not closely resemble the physical forms adopted by REs in vivo (e.g., the complex emulsions, micelles, and vesicles in the intestinal lumen).

It is worth pointing out, too, that there is almost no detailed information on the physical forms or "phases" that REs adopt in the intestinal lumen. Much more detailed information on these issues is available for other major dietary lipids such

as triglycerides, phospholipids, and cholesterol (31, 68). Nonetheless, it is clear from studies both in experimental animals and in humans that the co-ingestion of dietary fat markedly enhances the intestinal absorption of dietary vitamin A (8, 55, 74). The presence of dietary fat in the intestine can stimulate RE digestion by (*a*) stimulating pancreatic enzyme secretion, (*b*) stimulating the secretion of bile salts, which serve to form mixed micelles of lipids, and (*c*) providing products of lipid digestion (i.e., lysophospholipids, monoglycerides, and free fatty acids), which themselves can serve as components of micelles. Finally, fat ingestion promotes vitamin A absorption by providing the lipid components for intestinal chylomicron assembly, a process discussed in more detail below.

Pancreatic Enzymes

More than three decades ago Erlanson & Borgström (18) reported the partial separation of two different pancreatic RE hydrolase (REH) activities in the rat using a Sephadex G100 column. These two activities hydrolyzed different physical forms of the retinyl palmitate substrate. The early peak mainly hydrolyzed retinyl palmitate, which was dispersed in millimolar concentrations of taurodeoxycholate [a condition known to stimulate carboxylester lipase (CEL) and to inhibit pancreatic triglyceride lipase (PTL) (10)], whereas the subsequent peak was more effective in hydrolyzing dispersed retinyl palmitate in the absence of bile salt. These two different REH elution patterns were consistent with CEL and PTL, respectively.

Pancreatic carboxylester lipase catalyzes the hydrolysis of cholesteryl esters, triglycerides, and lysophospholipids. It was thought to hydrolyze retinyl esters also in the intestine. CEL knockout (KO) mice were generated to study the functions of CEL (80, 83). Though neither CEL KO nor wild-type (WT) mice absorbed nonhydrolyzable cholesteryl ether, CEL KO mice absorbed about half the amount of cholesterol provided as cholesteryl ester compared with WT mice. These data indicated that hydrolysis of cholesteryl esters is necessary prior to absorption, and that CEL plays an important role in cholesterol absorption. In contrast to the results for cholesteryl ester, CEL KO mice absorbed the same amount of retinol, when provided as RE, as did WT mice. On the other hand, neither mouse absorbed the nonhydrolyzable retinyl hexadecyl ether. These data suggested that RE hydrolysis was required for absorption and that CEL was not the responsible enzyme (at least under conditions where the amount of dietary RE was in the ug range, as used in this study). Triglyceride absorption was also comparable between CEL KO and WT mice, indicating that absence of CEL does not affect triglyceride hydrolysis. Therefore, if intestinal RE absorption is unaffected in CEL KO mice, one or more other RE hydrolytic enzymes must be present in the gut lumen or on the enterocyte surface.

Studies were then conducted to identify the non-CEL pancreatic REH activity that appeared to be present in CEL KO mice, as well as to investigate this activity in WT mice and in rats. Several lines of evidence suggest that this activity is due to PTL (79). First, the dependence of pancreatic REH on different types of

bile salt was investigated in pancreatic homogenates of WT mice and rats. When assayed utilizing different bile salt conditions, cholesteryl ester hydrolase activity was detected only in the presence of trihydroxy bile salts, consistent with previous results (25, 84). Pancreatic REH activity, however, was not absolutely dependent on trihydroxy bile salts. RE hydrolysis not only was detected in the presence of trihydroxy bile salts, but also in the presence of dihydroxy bile salts and CHAPS, a bile salt analog, as well as in the absence of bile salts. The finding that REH activity was supported by dihydroxy bile salts is consistent with PTL-mediated hydrolysis. Second, when total pancreatic homogenates obtained from rats, WT mice, and CEL KO mice are used to assay REH activity, a considerable stimulation of the REH activity by colipase was observed; this indicates that PTL was at least partially contributing to the pancreatic bile salt–dependent REH activity. Third, when pancreatic homogenates from rats, WT mice, and CEL KO mice were applied to diethylaminoethanol chromatography, the majority of REH activity co-eluted with PTL activity in the unbound fraction. In contrast, a minor peak eluted with CEL activity during the KCl gradient elution in both species. This further supports the notion of PTL-mediated RE hydrolysis. Fourth, because of the possibility that multiple proteins are involved in pancreatic RE hydrolysis, the enzymatic characteristics of purified human PTL, using either triolein or retinyl palmitate as a substrate, were studied. Both REH and triglyceride hydrolase activities of the enzyme were completely dependent on the presence of colipase. In addition, identical patterns of bile salt inhibition were observed using either triolein or retinyl palmitate as a substrate. Based on these data, PTL may be the main REH activity in the intestinal lumen of both mice and rats.

Although these data strongly suggest that PTL may be a major REH in rat and mouse intestinal lumen, they do not provide final proof for this concept. In addition, other enzymes synthesized and secreted by the pancreas may also play a role in the lumenal hydrolysis of REs. For example, some triglyceride hydrolysis was observed in the absence of colipase in pancreatic homogenates from both rats and mice, which may point to the presence of other related enzyme activities, such as pancreatic lipase-related protein 2 (PLRP2). It is possible that the triglyceride hydrolase activity observed in the absence of colipase is due to endogenous colipase present in the pancreatic homogenates. Nonetheless, PLRP2 is 65% identical to PTL and hydrolyzes phospholipids and shows activity toward triglycerides in the classical PTL assay (39). At present, the percentage of PLRP2's contribution to pancreatic bile salt–dependent REH activity is not known. In addition, yet another pancreatic lipase-related protein (PLRP1) has been cloned that is 68% homologous to PTL but for which the substrate is still unknown (20). Thus, more than one enzyme may be responsible for the complete hydrolysis of REs in the intestinal lumen.

Intestinal Enzymes

In addition to pancreatic bile salt–dependent REH activities, an REH activity that is intrinsically located in the brush border membrane of the absorptive enterocytes

was shown in rat and human intestines (64, 65). It was suggested that this enzyme activity is due to an intestinal phospholipase B (63). These authors showed that rat brush border membrane isolated from rats in which the common pancreatic duct had been ligated for two days (thus prohibiting contamination of brush border membrane with any enzymes secreted by the pancreas, such as CEL or PTL) had a greatly decreased hydrolytic activity against short-chain REs (in the presence of trihydroxy bile salts) and a smaller (30%) decrease in the activity against long-chain REs (such as retinyl palmitate) as compared with sham-operated rats. Therefore, they suggested that short-chain REH was mainly due to enzymes of pancreatic origin (and could be due to CEL), whereas the majority (70%) of long-chain REH was intrinsic to the brush border. The remaining 30% of REH activity, however, could be due to PTL, as this REH activity was detected in both the presence of trihydroxy and dihydroxy bile salts. It is important to point out, however, that the relative activities observed in vitro may not reflect the relative contributions of the various enzymes in vivo. It is likely that both PTL and phospholipase B contribute to RE digestion. In order to determine their relative roles in intestinal RE digestion and absorption, it will become essential to perform RE absorption experiments in the appropriate KO mice strains and in mice deficient in more than one enzyme. The enzymes potentially involved in hydrolysis of dietary REs are outlined in Table 1 and Figure 1.

TABLE 1 Proteins involved in the digestion, absorption, and transport of retinol

1. Retinyl ester hydrolysis	a. Lumen	Pancreatic triglyceride lipase
		Pancreatic lipase-related protein 1 (?)
		Pancreatic lipase-related protein 2 (?)
		Carboxyl ester lipase (probably NOT involved)
	b. Brush border membrane	Phospholipase B
2. Retinol uptake, transfer, and efflux		
	Retinol transporters (CD36, SRB1, NPC1L1, ABCA1, etc.) (?)	
	Cellular retinol binding protein I (?)	
	Cellular retinol binding protein II	
3. Retinyl ester synthesis		
	Lecithin:retinol acyltransferase	
	Acyl-CoA:retinol acyltransferase (probably NOT involved)	
4. Chylomicron assembly		
	Apolipoprotein B	
	Microsomal triglyceride transfer protein	

INTESTINAL ABSORPTION OF VITAMIN A

Mechanisms of Cellular Uptake and Efflux of Unesterified Retinol in Enterocytes—Portal Secretion

Studies concerning the uptake of retinol by the human intestinal cell line, Caco-2, indicated that retinol at physiologic and pharmacologic concentrations was taken up by saturable carrier-mediated processes and nonsaturable diffusion-dependent processes, respectively (61). The retinol taken up by these cells was esterified, and the REs mainly contained palmitic and oleic acids (43, 61). Studies showed that retinol uptake is a rapid process with a half-life of minutes (52). This uptake was not affected by the presence of high concentrations of free fatty acids.

Recent experiments in the author's laboratory have further examined the role of transporters in retinol flux in Caco-2 cells (16). When cells were incubated with 3 μM retinol for varying times up to 24 hours, cellular retinol plateaued within 2 hours, whereas there was continuous formation of REs. Both retinol and REs secreted in basolateral medium increased linearly with time (up to 20 hours). REs were associated with chylomicrons and retinol with the nonlipoprotein fraction. After incubation with retinol concentrations of 0.5–130 μM, cellular uptake of retinol was directly proportional to initial retinol concentration. However, the kinetics of efflux of retinol into basolateral medium revealed two processes. Retinol secretion showed saturation at concentrations <10 μM, which suggests a mediated transport out of the cell, and linearity with higher concentrations, which suggests passive diffusion. One interpretation of these data is that free retinol enters into intestinal cells by simple diffusion, whereas its secretion may require a facilitated transport at physiological doses. This notion is supported by other experiments in which glyburide, a known inhibitor of the ABCA1 transporter, caused marked inhibition of the efflux of free retinol into basolateral medium (but not cell uptake). Of course, it is also possible that cellular uptake at the apical membrane is also facilitated, but that the rapid esterification of retinol after uptake makes it difficult to demonstrate kinetically that the transport is rate limiting.

Early studies using intestinal segments also suggested that the unesterified retinol was taken up by protein-mediated facilitated diffusion and passive diffusion mechanisms at physiologic (150 nM) and pharmacological (450 nM–2700 nM) concentrations, respectively (33, 34). Other evidence for protein-mediated uptake of retinol has been presented using intestinal segments (15). However, no protein has yet been identified and characterized that might be involved in the uptake of retinol.

There is an enormous amount of current interest in the role of membrane-bound lipid transporters in the cellular uptake and efflux of fat-soluble molecules. For example, three different membrane-bound proteins—CD36, membrane-bound fatty acid–binding protein, and a fatty acid transport protein—that might be involved in fatty acid uptake have been identified (for review, see 1, 21). In the case of cholesterol, SRB1, CD36, NPC1L1, and a variety of ABC transporters have been

implicated in its uptake and/or efflux from various cells (2, 13, 14, 75, 81, 82). It is possible that these or other proteins play a role in the transport of retinol across cell membranes. Defining the exact mechanisms of cellular uptake of retinol (or other lipids) is complicated by the fact that, as indicated above, multiple mechanisms (both facilitated and passive) may exist in a single cell. An additional problem is that much of the work in this area relies on the use of membrane transporter inhibitors, and there is increasing evidence that some of these compounds inhibit multiple transporter types (54). A final complication is that some of the transport inhibitors also affect the expression of transporter genes and, thus, exert effects on transporter number and function simultaneously.

The general perception that retinol is efficiently absorbed and quantitatively transported on chylomicrons may need reevaluation (for review, see 5, 6). First, it should be pointed out that the recovery of ingested retinol into lymph varies between 20% and 60% (6, 22, 35). Second, Hollander showed that approximately 60% and 30% of the absorbed retinol is secreted into lymph and portal circulation, respectively (32). Furthermore, he showed that secretion of retinol into lymph was modulated by the presence of different concentrations of taurocholate and different fatty acids (32). Third, oral supplementation of retinol into abetalipoproteinemia patients, who do not assemble and secrete chylomicrons, results in partial recovery from symptoms of retinol deficiency (40). Fourth, cell culture studies showed that free retinol or its metabolized products are transported across the cells independent of the assembly and secretion of lipoproteins (52). Thus, much of the absorbed retinol is secreted into lymph in esterified form. However, a significant amount is also secreted into portal circulation, probably as free retinol. The transport of free retinol to the portal circulation is expected to be physiologically significant in pathologic conditions that affect the secretion of chylomicrons. Thus, the transport of free retinol may be an essential back-up mechanism for the homoeostasis of vitamin A under some conditions.

Intracellular Transport by Cellular Retinol-Binding Protein (II)

After cellular uptake, free retinol is probably immediately sequestered by cellular retinol-binding proteins (CRBPs) (Table 1). Two CRBPs, CRBP(I) and CRBP(II), have been purified and characterized extensively. They have considerable sequence identity and belong to a family of fatty acid–binding proteins. Both of the proteins are highly conserved during evolution, which indicates their physiologic importance. These proteins share considerable structural, genetic, and biochemical properties. However, the cellular expression pattern of these proteins is very different. The CRBP(I), a 14.6 kDa polypeptide, is expressed in many tissues, whereas CRBP(II), a 16 kDa polypeptide, is expressed primarily in the absorptive cells of the small intestine. The CRBP(II) is one of the most abundant proteins and accounts for approximately 1% of the total soluble proteins recovered from the jejunal mucosa. The tissue distribution and abundance indicate that it must

be uniquely suited for retinol absorption by the intestine (for reviews, see 45, 53, 56, 57).

In vitro studies indicate that CRBP(II) can play several functions in the trafficking of retinol. It has been speculated that it can bind to specific transporters on the brush border membrane and permit facilitated diffusion. It can serve as a reservoir to keep the concentrations of free retinoids very low and protect cells from their detergent-like properties. More important, it may present retinoids to different enzymes and direct their metabolism (56, 57).

In vivo studies showed that CRBP(II) mRNA levels are increased in the small intestine of retinoid-deficient rats (62) and rats fed with long-chain fatty acids (70). In Caco-2 cells, CRBP(II) mRNA was shown to be increased (two- to threefold) after treatment of the differentiated cells with retinoic acid. More importantly, this resulted in increased absorption and intracellular esterification of radiolabeled retinol. Furthermore, absorption and esterification was also increased after the overexpression of CRBP(II) in these cells (48). These studies indicate that changes in CRBP(II) expression results in the modulation of retinol metabolism (44, 69, 71). However, it is not known whether the increased expression of CRBP(II) results in increased secretion of REs in chylomicrons.

Recent characterization of the CRBP(II) knockout mouse has clarified that CRBP(II) plays an important, but not absolutely essential, role in the intestinal absorption of vitamin A (85). Using the methodology originally described by Dew & Ong (15), Li & coworkers showed that the saturable component of retinol uptake by jejunal segments was reduced to about half that of tissue from WT littermates (85). The CRBP(II) knockout mice, when maintained on a vitamin A–enriched diet, also had reduced (about 40%) hepatic stores of vitamin A, which suggests that the incomplete impairment of retinol processing in the intestine nonetheless affects whole-body vitamin A status.

Reesterification and Incorporation into Chylomicrons—Lymphatic Secretion

Early studies in intact rats and humans clearly demonstrated that after uptake of newly absorbed retinol, the retinol was largely reesterified with long-chain fatty acids (mostly palmitate) and secreted into the lymphatics along with other dietary lipids in chylomicrons. Caco-2 cells have been used to study mechanisms of vitamin A absorption that are difficult to study in intact animals. The differentiated Caco-2 cells were shown to express CRBP(II), ARAT, LRAT, and retinal reductase (43, 61). Studies on retinol secretion revealed that Caco-2 cells supplemented with no fatty acids secreted only free retinol. However, cells incubated with oleic acid were shown to secrete REs in addition to free retinol (43). Based on these observations, it has been suggested that lipoprotein particles secreted by these cells may contain retinol and REs (43). However, no data about the secretion of either free or esterified retinol as part of different lipoprotein particles were reported in these studies.

In the cells, the free retinol can remain associated with its cellular retinol binding proteins. However, much of the retinol is usually esterified and stored. In enterocytes, two enzymes—LRAT and ARAT—have been identified that can catalyze the esterification of free retinol in vitro (30, 49). It has been suggested, but not shown, that REs formed by LRAT and ARAT may be targeted for secretion with chylomicrons and storage, respectively (5, 6). The recent characterization of the LRAT knockout mouse has largely resolved the question of whether enzymes other than LRAT play any physiological role in retinol esterification. Given that the LRAT knockout mouse has no detectable tissue REs (3), it is unlikely that other enzymes such as ARAT are physiologically involved in retinol esterification in intestine. Obviously, this issue warrants further investigation. It is possible, and even likely, that other acyltransferases can catalyze the acyl-CoA-dependent esterification of retinol in vitro. It is also possible that other enzymes are involved in the esterification of retinol if given to animals in very large quantities.

It is generally believed that retinol is mainly secreted into the lymph as retinyl palmitate. During metabolic studies, analysis of the plasma revealed that most of the REs are present in small chylomicrons (42). Significant amounts of REs are also found in large chylomicrons, followed by smaller amounts in very-low-density lipoproteins (42). In contrast to triglycerides, cholesterol esters, and other lipids, REs are not present in other lipoproteins such as intermediate-density lipoproteins, low-density lipoproteins, or high-density lipoproteins. These studies indicate that REs are mainly present in large and small chylomicrons and behave very differently from other neutral lipids, such as triglycerides and cholesterol esters.

To understand the mechanism of secretion of RE by the intestine under the fasting and postprandial states, studies were conducted in which differentiated Caco-2 cells were supplemented with radiolabeled retinol under conditions that support (postprandial) or do not support (fasting) chylomicron secretion (52). These cells assimilated vitamin A by a very rapid uptake mechanism under both conditions. After uptake, the cells stored retinol in both esterified and unesterified forms. Under fasting conditions, the cells mainly secreted variable amounts of free retinol unassociated with lipoproteins. However, under postprandial conditions, these cells secreted significant amounts of REs, mainly with chylomicrons. The secretion of RE with chylomicrons was independent of the rate of uptake of retinol, intracellular free, and esterified retinol levels, and was dependent on the assembly and secretion of chylomicrons. The secretion of RE was correlated with the secretion of chylomicrons and not with the secretion of total apoB. Inhibition of chylomicron secretion by Pluronic L81 decreased the secretion of RE and did not result in their increased secretion with smaller lipoproteins. These data strongly suggest that RE secretion by the intestinal cells is a highly specific and regulated process that is dependent on the assembly and secretion of chylomicrons. These data also indicate that the incorporation of RE into chylomicrons is not a passive process but rather is an exquisitely orchestrated event. RE secretion does not occur at all times. It is induced when cells can assemble and secrete chylomicrons. Thus, it

appears that intestinal cells may have a specific mechanism for the targeting of REs to nascent chylomicrons.

As discussed above, Caco-2 cells do not secrete REs under conditions simulating a fasting state. In recent work on the kinetics of retinol uptake by Caco2 cells, a five-day "washout" experiment was conducted in which cells were incubated with retinol for 16 hours to accumulate cellular retinol and REs, followed by incubation with retinoid-free medium (containing fatty acids and thus mimicking the "fed" state) that was changed every 24 hours (16). This resulted in the release of the free retinol but not the accumulated REs. This implies that only newly synthesized REs are incorporated into chylomicrons and that preformed REs cannot be used for chylomicron assembly. Thus, the synthesis of REs and their incorporation into chylomicrons appear to be concerted processes.

Due to the specificity of the secretion of REs, it was proposed that REs could be used as signposts to study chylomicron assembly (36, 38). Two different mechanisms have been proposed for the assembly and secretion of chylomicrons (for review, see 36–38). First, in the independent pathway, very-low-density lipoproteins and chylomicrons have been proposed to be synthesized by two independent mechanisms (72, 73). If chylomicron assembly occurs by an independent pathway that is induced during the postprandial state, REs may be used to differentiate between chylomicron and very-low-density lipoprotein assembly pathways. The second, sequential assembly mechanism suggests that the assembly of chylomicrons and very-low-density lipoproteins involves a common first event resulting in the synthesis of primordial lipoproteins. Another important event hypothesized for the assembly of chylomicrons and other lipoproteins is the formation of different-sized lipid droplets. Subsequently, the larger lipid droplets are proposed to fuse with primordial lipoproteins, resulting in the "core expansion" of primordial lipoproteins (36, 37). If this is true, REs may be incorporated at the terminal stages of lipoprotein assembly. Both of these mechanisms can be distinguished by studying the presence of REs in different intracellular lipoproteins. It is clear that RE synthesis and the incorporation and secretion of REs in chylomicrons are concerted processes.

PROSPECTIVE

The literature reviewed above suggests that the intestinal digestion and absorption of vitamin A is a highly complex process, and that a number of enzymes and other proteins participate in the process. Table 1 and Figure 1 summarize some of the proteins described in this review. Given the complexity of the process, caution is urged in attempts to define a single enzyme or protein that is the physiologically relevant one in a given step. Several of the proteins studied may be relevant, and certainly, a number will be found that are involved in the overall process. Further use of techniques such as overexpression of specific proteins or gene ablation might ultimately lead to a definition of which proteins play which roles in vitamin

A absorption. In addition, the development of highly specific inhibitors could also shed light on these issues.

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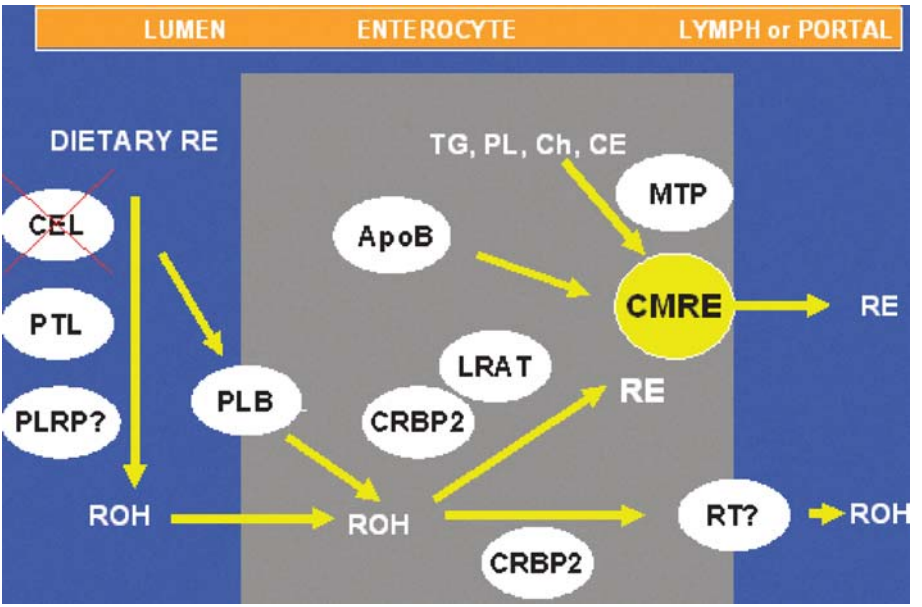

Figure 1 Overview of digestion and absorption of vitamin A. Dietary retinyl esters (REs) are hydrolyzed in the lumen by the pancreatic enzyme pancreatic triglyceride lipase (PTL) and intestinal brush border enzyme phospholipase B (PLB). Studies of the carboxylester lipase (CEL) knockout mouse suggest that CEL is not involved in dietary RE digestion. The possible roles of the pancreatic lipase-related proteins (PLRPs) 1 and 2 and other enzymes require further investigation. Unesterified retinol (ROH) is taken up by the enterocyte, perhaps facilitated by a yet unidentified retinol transporter. Once in the cell, retinol is complexed with cellular retinol-binding protein type 2 (CRBP2) and the complex serves as a substrate for reesterification of the retinol by the enzyme lecithin:retinol acyltransferase (LRAT). The REs are then incorporated into chylomicrons, intestinal lipoproteins containing other dietary lipids such as triglyceride (TG), phospholipid (PL), cholesterol (Ch) and cholesteryl esters (CEs), and apolipoprotein B (apoB). The incorporation of some of these lipids is dependent on the activity of microsomal triglyceride transfer protein (MTP). Chylomicrons containing newly absorbed retinyl esters (CMRE) are then secreted into the lymph. Unesterified retinol is also absorbed into the portal circulation and its efflux from the basolateral cell membrane may also be facilitated by retinol transporter (RT) proteins.

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CONTENTS