Sources of eicosanoid precursor fatty acid pools in tissues

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Abstract   Tissue arachidonic acid (AA) pools originate from the diet, and from hepatic and extrahepatic desaturation-elongation of dietary linoleic acid (LA). This review summarizes the roles of absorption, transport, and formation of AA in the buildup of tissue AA pools. In humans who ingest 0.2–0.3 g of AA and 10–20 g of LA per day on a Western diet, the formation of AA from LA exceeds the dietary supply of AA. A number of factors favor the partitioning of AA to tissue phospholipids rather than adipose tissue and plasma triglycerides. The characteristics of AA transport with lipoproteins are discussed with focus on the role of lipoprotein lipase, lecithin:cholesterol acyltransferase, hepatic lipase, and the scavenger receptor BI and LDL receptors in tissue uptake of AA. Liver-derived 2-acyl-lysophosphatidylcholine and plasma free AA are two important sources of AA for extrahepatic tissues which exhibit a low rate of uptake of lipoprotein AA. Desaturation-elongation of LA to produce AA occurs both in liver and in extrahepatic tissues, plasma free LA being an important substrate particularly during fasting. The AA preference of the reacylation and transacylation reactions is crucial for the selective retention of AA in phospholipids.—Zhou, L., and Å. Nilsson. **Sources of eicosanoid precursor fatty acid pools in tissues.** *J. Lipid Res.* 2001. 42: 1521–1542.

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INTRODUCTION

Eicosanoids are produced from arachidonic acid (AA), eicosapentaenoic acid (EPA), and dihomo-γ-linolenic acid (20:3n-6) when these fatty acids are released from tissue phospholipids (PL) by phospholipase A_2 (PLA_2). AA is the precursor of the 2-series of prostaglandins. 20:3n-6 and EPA yield prostaglandins of the 1- and 3-series, respectively, which have lower biological activity compared with their homologs derived from AA. Both 20:3n-6 and EPA compete for the prostaglandin synthesis enzyme-binding site with AA and can reduce the production and efficacy of AA derivatives (1). Not only prostaglandins but a variety of biologically active products are formed via cyclo-oxygenase, lipoxygenase, and cytochrome P450-dependent enzymes (**Table 1**). Furthermore the intracellular level of unesterified eicosanoid precursors may itself be an important mediator by its action on the peroxisome proliferator-activated receptor γ (2–8).

The concentration of eicosanoid precursors and DHA in membranes depends on the dietary supply of these fatty acids, and on the desaturation-elongation in the body of ingested precursor PUFA of the n-6 fatty acid series, that is, linoleic acid (LA), and of the n-3 series, that is, α-linolenic acid (ALA). Because carnivores and omnivores but not herbivores ingest C_{20} PUFA, the relative role of the dietary supply of eicosanoid precursors and the desaturation-elongation varies between species, as do the levels of eicosanoid precursors in membrane and plasma lipids. In a comparison between seven mammalian species rat plasma and liver had the highest AA levels in PL, 34% of fatty acids in plasma PL and 29% in liver PL (9). Humans had 10–11% of total fatty acids as AA in plasma PL, and 13% as AA in liver PL (9, 10). Guinea pigs had the highest level of LA and the lowest level of AA. The concentration of PL in plasma also differs in various mammalian species (11). For example, the concentration of PL was 1.2 mg/ml in rat plasma, but only 0.22 mg/ml in guinea pig plasma. A crude estimation based on available tissue lipid data indicates that a 200-g rat contains about 4 mmol (~3 g) of PL, with a total AA content of 0.8–1.0 mmol (250–300 mg), and a 70-kg human contains 50–100 g of AA, distributed between tissue and membrane compartments that vary with regard to turnover rate and physiological function.

Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; CE, cholesteryl ester; CM, chylomicron; CMR, chylomicron remnant; EFA, essential fatty acid; HL, hepatic lipase; LA, linoleic acid; LPC, lysophosphatidylcholine; LRP, LDL receptor-related protein; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PL, phospholipid; PLA_2, phospholipase A_2; PLTP, phospholipid transfer protein; PS, phosphatidylserine; SR-BI, scavenger receptor class B type I.

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TABLE 1. Urine excretion of arachidonic acid metabolites in humans

Products of AA	Main Metabolites in Urine	Excretion[a]
		$\mu g / 24h$
1. Prostaglandin E_2[b]	Tetranor-5,11-diketo-7α-hydroxy-prostane-1,16-dioic acid[c]	21–57
Prostaglandin D_2	9α,11β-PGF2[d]	0.36–0.65
Thromboxane B_2	11-Dehydro-TXB$_2$[e]	0.65–1.29
Prostacyclin	6-Keto-PGF1α and 6,15-diketo-13,14-dihydroPGF1α[f]	0.08–0.16 / 0.45–0.53
2. Leukotrienes[g]	LTE$_4$[h]	0.07–0.14
3. Epoxyeicosatrienoic acids[i]	Dihydroxy derivatives[j]	0.02–0.24
Hydroxyeicosatetraenoic acid	20-HETE	1.01–3.17
4. F_2-isoprostane[k]	8-Epi-PGF$_{2\alpha}$[l]	667.8–1,148.2
Total		0.7–1.2 mg/24 h

[a] Calculated on the basis of the volume of urine (741–1,411 ml/24 h) (300) and/or the excretion of creatinine (1.05–2.1 g/70 kg/24 h) (300, 301) in 70-kg humans.
[b] Cyclo-oxygenase-mediated reaction.
[c] Forstermann and Feuerstein (302).
[d] O'Sullivan et al. (303).
[e] Mizugaki et al. (304).
[f] Forstermann and Feuerstein (302) and Fischer, Scherer, and Weber (305).
[g] Lipoxygenase-mediated reaction.
[h] Mizugaki, Hishinuma, and Suzuki (306) and Hackshaw et al. (307).
[i] Cytochrome P-450-mediated epoxygenase reaction.
[j] Catella et al. (308, 309) and Sacerdoti et al. (310).
[k] Nonenzymatic, free radical-catalyzed peroxidation.
[l] Schwedhelm et al. (311) and Obata et al. (312).

The level of AA in adipose tissue TG is low, the main part being at the 2-position of tissue PL. Both diacyl- and plasmalogenic phosphatidylethanolamine (PE) is rich in AA and DHA, and phosphatidylinositol (PI) has the highest content of AA of all PL (12). The selectivity in tissue distribution of AA is achieved by a number of collaborating mechanisms based on relative specificity of acylation reactions and lipolytic enzymes in combination with the regulation of desaturation-elongation reactions. The metabolism of AA in lipoproteins by enzymes and lipoprotein receptors exhibits important differences from the predominant C_{16}–C_{18} fatty acids. Lipoprotein receptor-independent transport as plasma FFA and as 2-acyl-lysophosphatidylcholine (2-acyl-LPC) represents quantitatively important pathways for the transport of eicosanoid precursors and DHA to tissue compartments that are poorly accessible to lipoproteins. In the liver and several extrahepatic tissues there is a considerable formation of eicosanoid precursors from LA and ALA derived from plasma FFA or from hydrolysis of intracellular lipids. At the cellular level the retention as esters and pools of unesterified eicosanoid precursors is regulated by a distinct balance between the action of PLA$_2$ and reacylating and transacylating enzymes. The result is a continuous metabolism and remodeling of up to 20 AA-containing species of glycerophospholipids (12). The quantitative role of AA utilization for eicosanoid formation in the human body is difficult to estimate. Approximate values can be extrapolated from the daily excretion of main AA metabolites in urine (Table 1) and indicate that only minor portions of the body pools are utilized daily.

A number of excellent reviews concern the metabolism of the highly unsaturated n-3 and n-6 fatty acids (13), the role of the intracellular PL remodeling reactions in AA retention (14), the supply of AA and DHA to the fetus and newborn (15), and the absorption of essential fatty acids (EFA) (16). This review focuses on the roles of absorption, transport, and formation in the supply of AA to the tissues.

ROLE OF INTESTINAL LIPOPROTEINS IN THE TRANSPORT OF DIETARY EICOSANOID PRECURSORS

Supply of AA in diet and bile PL

A number of studies have estimated the AA content of Western diets and in common food constituents. Taber, Chiu, and Whelan (17) examined cooked and raw portions of beef, chicken, eggs, pork, turkey, and tuna and Li et al. (18) examined the AA content of visible fat and meat of beef, lamb, pork, chicken, duck, and turkey. The visible fat of meat contained 20–180 mg of AA per 100 g of fat, whereas the AA content of lean meat was lower, ranging from 30 to 99 mg/100 g. In the Australian diet Mann et al. (19) estimated the average intake of dietary AA as 130 mg/day in males and 96 mg/day in females. The cooking methods may influence the PUFA content of the diet, for example, increasing time of grilling resulted in 20–30% losses of the C_{20} and C_{22} PUFA (20). In a study carried out in a group of subjects on a typical American diet under controlled conditions an average AA intake of 230 mg/day was measured (21). In Japan, the intake of AA is about 300 mg/day (22) with large individual variations. The conclusion is that the average intake is lower than was estimated in earlier studies (23–26), although the individual intake can easily be increased by the ingestion of more animal and marine products.

In the intestinal lumen bile phosphatidylcholine (PC) is an additional source of AA. The bile PC differs in fatty

acid composition from liver and plasma PC, the proportion of 16:0-AA PC generally being higher (27). AA accounts for 15–20% of the PC fatty acid in the rat bile (28, 29), and for 6–8% in human bile. The secretion in humans of 5–10 g of bile PC per 24 h (30, 31) thus supplies about 150–350 mg of AA to the gut. Adult rats secrete, per 24 h, about 100 mg of PC containing approximately 6 mg of AA (32). The amount of AA entering the gut lumen when mucosal cells are sloughed off during normal cell turnover is not known, but is likely to be less than the amount supplied in bile PC.

Thus more endogenous than dietary AA is supplied to the intestine under most dietary conditions and the total amount of absorbed AA is usually on the order of 0.5–0.8 g/day (**Table 2**). The amount of AA absorbed every day is on the order of 1% of the total body pool and the daily dietary contribution is less than half of 1%.

Supply of linoleic and n-3 fatty acids in diet

Because AA, the n-3 fatty acids, and LA compete for the same transport and acylation pathways it is important to relate the supply of AA to that of other PUFA. In the Western diet the predominant PUFA is LA, with lesser proportions of the long-chain n-3 fatty acids, that is, ALA, EPA, and DHA. The intake of LA is about 10–20 g/day (8 en%), which constitutes >85% of total PUFA intake (19, 22, 25). Dietary ALA is mainly from plant products, fish and other marine products being the main sources of EPA and DHA (33). In other commonly used foods the total n-3 fatty acid level is low, varying from 35 mg/100 g (pork leg meat) to 381 mg/100 g (chicken egg yolk) (19). The intake of n-3 fatty acids was estimated as 0.06–2 g/day (<2 en%) in most Western diets, and as 3.6 g in Japanese diets. The n-6/n-3 ratio was 4.0–8.5 (22). A group of vegetarians ingested 16–31 g of LA per day (7–10 en%) and 1.9 g of ALA per day (0.6–0.8 en%). The n-6 (LA)/n-3 (ALA) ratio was 10–12 (10). The intake of the long-chain, marine n-3 fatty acids was about 7 g/day among Greenland Eskimos (34, 35), and the n-6/n-3 ratio was 0.36.

The conclusion is that attempts to change the n-6/n-3 ratio in humans on a Western diet are done under conditions in which the dietary LA exceeds the n-3 intake severalfold, the adipose tissue contains high levels of LA, and the n-3 fatty acids must compete with a pool of endogenous AA. These factors tend to limit the changes that can be achieved.

Is the dietary supply of AA important?

Studies of humans. Does the amount of AA in the animal products of an ordinary human diet influence the AA level and is it physiologically important? Phinney et al. (23) compared fatty acid composition in vegetarians and omnivorous humans and found relatively small differences in AA level in plasma PL (12.8% vs. 11.1%) and cholesteryl ester (CE) (7.8% vs. 6.5%) and Li et al. (36) reported similar differences. Sinclair et al. (20) fed lean beef together with a low fat diet and increased AA in plasma PL from 11.3% to 14.1% and EPA from 1.4% to 1.8%. Animal products in the diet thus do increase the AA level moderately.

Most evidence supports that ingestion of moderate amounts of AA is not disadvantageous. For example, in a study by Sinclair and Mann (37) prostacyclin but not thromboxane production was increased by feeding kangaroo meat containing 325 mg of AA and 325 mg of n-3 long-chain PUFA per day and male vegetarians had actually higher platelet aggregability than omnivores (10, 38). Even on a vegetarian diet ALA only slightly increases the EPA levels, 70 mg of EPA per day being as effective as 15.4 g of ALA per day (39). In a series of studies humans ingested a diet containing 1.7 g of AA per day for 50 days, and were then extensively studied (21, 40–44). Dietary AA at these levels nearly doubled the AA level in the plasma PL and CE. AA mainly replaced LA, which was reduced by 20%. Some increases in AA in platelet, red blood cell, and tissue lipids were also found but no significant increase in AA was seen in adipose tissue TG and PL. The plasma FFA showed a small but statistically significant rise in the AA level. No harmful effects could be proven during the studies, although an increased production of eicosanoids was ob-

TABLE 2. Human plasma arachidonic acid transport in free fatty acid, lysophosphatidyl choline, and LDL

	Absorbed AA	FFA-AA	LPC-AA	LDL-AA
Diet (mg/day)	100–300			
Bile (mg/day)	150–350			
Sloughing of cells (mg/day)	<200			
Concentration (nmol/ml)		1.2–3.7[a]	4.0[b]	178–198[c]
Pool size (mg)[d]		0.9–2.8	3.0	134–148
Fractional turnover		0.44–0.8/min[e]	0.06–0.33/min[f]	0.3–0.4/day[g]
Mass absorbed/cleared (mg/day)[h]	≅450–800	1,160–2,115	270–1,425	42–57

[a] Croset et al. (178), Hallaq et al. (189), and Deby-Dupont et al. (192).

[b] Croset et al. (178).

[c] LDL-CE, -TG, and -PL concentrations are 1.9–2.2, 0.18, and 0.84 mM, respectively (316, 317), AA is 6.6 mol% of LDL-CE, 1.0 mol% in TG (129), and 2.9 mol% in PL (318).

[d] Calculated from the concentration and with the assumption that the total plasma volume in human is 2.5 liters (1.65 l/m²) (313).

[e] Hagenfeldt, Hagenfeldt, and Wennmalm (199) and Hagenfeldt and Wahren (200).

[f] Half-life of 1-pamitoyl-LPC is 6–11 min in rats (314), and <10 min in squirrel monkeys (315); 2-AA-LPC is 1.07 min in rats (183). Data on the turnover rate of AA-LPC in humans are lacking. In the calculation we postulate the half-life is between 1.5 and 8 min.

[g] Thompson (317).

[h] Calculated from the mass of AA in plasma pool and the fractional turnover.

served. In one early study (45) AA at 6 g/day was given to normal male subjects in the form of ethyl ester. The study was terminated after 3 weeks because of increased ex vivo ADP-induced platelet aggregation.

Animal studies. Animal studies also indicate that low to moderate levels of dietary AA can have significant impact on tissue AA and thus on eicosanoid production. Whelan et al. (26) fed mice diets that were enriched with 6.7% or 18.4% AA for 2 weeks. The AA content in liver increased from 21.3% to 29.6% and 33.6%, whereas increasing the dietary LA content from 20.5% to 39.7% had no effect. Similarly Abedin et al. (46) fed AA- and DHA-enriched diets to guinea pigs and observed substantial increases in liver PL-AA and -DHA. The ability of marine long-chain n-3 fatty acids to influence the AA/EPA ratio by directly competing for acylation into PL, was found to be highly dependent on the AA level of the diet (47).

Conclusion. The conclusion is that feeding moderate amounts of AA to humans or to omnivores and herbivores does increase the AA level in PL, but this has not been shown to be disadvantageous. AA in the diet also influences the effects that can be achieved with n-3 fatty acids.

Specific features of digestion

Although the main course for the absorption of the predominant C_{16}–C_{18} fatty acids and the C_{20}–C_{22} PUFA is held in common, there are also specific features. Briefly, the TG esters of fatty acids containing the C_{20} PUFA are hydrolyzed at a slower rate than the predominant C_{16} and C_{18} fatty acid esters by the colipase-dependent pancreatic lipase (48, 49). The positioning of a double bond at position 5 seems to be crucial. However, because of the excess of colipase-dependent pancreatic lipase and a concerted action with the bile salt-stimulated lipase, TG containing C_{20}–C_{22} PUFA are completely hydrolyzed to monoglyceride (MG) and FFA (50, 51). TG containing AA, EPA, or DHA are thus as efficiently digested to MG and FFA as the more predominant dietary TG, but a more important role can be ascribed to the pancreatic carboxyl ester lipase in the adult and to the milk bile salt-stimulated lipase in the newborn human (52). Ikeda et al. (53) showed that EPA and DHA of fish oil TG rich in these fatty acids at the primary positions were well absorbed despite a slow hydrolysis by pancreatic lipase in vitro. The bile and dietary PC is converted to LPC by the pancreatic PLA_2 before absorption. The AA secreted in bile PC is released by the pancreatic PLA_2 in the gut, like the AA of the dietary PL (54).

The conclusion is thus that the AA esters of diet and bile are efficiently hydrolyzed but the relative role of carboxyl ester lipase and PLA_2 is more important than for other fatty acid esters.

Absorption and metabolism in the intestinal mucosa

Distribution of AA in chylomicron (CM) lipids. Although most of the absorbed PUFA are incorporated into CM TG, the partitioning of PUFA between the chyle lipid classes varies for individual PUFA and with the dietary fat given. Older studies showed that the fatty acid composition of chyle PL varied less than that of TG with the type of dietary fat (55), and in suckling rats ingesting only milk, AA was transported in chyle mainly as PL (56). In another study [^{14}C]LA and [^{3}H]AA were fed in cream, in an LA-rich soybean TG emulsion (Intralipid), or in pure AA (57, 58), and the incorporation of the labeled fatty acids into chyle lipids was studied. With cream a high incorporation of both [^{14}C]LA and [^{3}H]AA into chyle PL was observed, whereas with Intralipid the partitioning of [^{14}C]LA to PL decreased more than that of [^{3}H]AA. Milk fat and Intralipid increased the output of PC and PE, which transported 62% and 59% of the chyle AA mass, 38% and 41% being transported with TG. PE transported 14% of the AA (58), reflecting that both chyle lipoproteins and nascent hepatic VLDL contain more PE than plasma lipoproteins. With pure AA as fat vehicle the intestine produced AA-rich TG that carried 90% of the AA in TG species containing 52% AA. After feeding fish oil TG Chen et al. (59) found that AA and EPA were mainly in TG although overrepresented in PL compared with other fatty acids.

PL acylation in the gut mucosa. Less [^{3}H]AA than [^{14}C]LA was recovered in chyle during the first 5 h (57) because of retention of [^{3}H]AA (58) in mucosal PC, PE, and PI. Absorbed AA is thus a precursor of mucosal PL. When [^{3}H]EPA and [^{14}C]AA were fed in a fish oil emulsion, less ^{3}H than ^{14}C was retained in mucosal, plasma, and liver PL within 2–4 h (60). EPA thus exhibits a lower preference than AA for incorporation into PL and more appears in TG of intestine, serum, and liver. It was estimated that the EPA in fish oil competed with AA for incorporation into plasma and intestinal PL slightly better than LA (57, 58). Studies of EFA-deficient rats receiving [^{14}C]LA and [^{3}H]AA or [^{3}H]EPA showed an increased retention in the gut of all three fatty acids, again emphasizing the mass dependence of the preferential acylation into PL (61, 62). Little dietary LA and ALA are converted in the mucosa before being incorporated into CM (63).

Considerable amounts of 1-acyl-LPC are formed in the gut lumen during hydrolysis of PC by pancreatic PLA_2. The reacylation of absorbed 1-acyl-LPC is stimulated by dietary fat (64, 65) and accounts for a major part of the chyle PC under physiological conditions (66, 67). The preferential acylation of absorbed 1-acyl-LPC is probably most important for the partitioning of AA into chyle PL. The LPC acyl-CoA acyltransferase utilizes AA more efficiently than other PUFA (68, 69). Viola et al. (70) studied the absorption of AA and found an increased acylation into PC when LPC was given simultaneously. Some of the chyle PL are derived from preexisting pools of mucosal PL (71) and a stimulation of intestinal de novo synthesis of PC (72) occurs during fat feeding. Some AA-containing species may thus be derived from mucosal pools formed by de novo synthesis followed by remodeling reactions. The reason for the preferential incorporation of AA into chyle PE is not known. Among mucosal PL the proportion of retained AA in PE increases with time and that in PC decreases (60, 62, 73, 74). The incorporation into PE may occur by the CDP-ethanolamine pathway selectively utilizing DG species containing AA or DHA for de novo synthesis during fat absorption, or during recycling of these spe-

cies from PC via the reversibility of the phosphotransferase reactions (75–77). Reacylation of lyso-PE and transacylation reactions are the alternatives and the contribution of each pathway has not been studied (78).

Conclusion. In conclusion, eicosanoid precursors are thus selectively partitioned into chyle and mucosal PC and PE, AA with the highest priority. The partitioning is subjected to competition between PUFA and is highly mass dependent, the excess being acylated into TG.

Metabolism of the eicosanoid precursors of the CM

The CM lipids consist of an inner hydrophobic core of TG and CE and a surface layer of PL and protein. Because the TG and PL are metabolized differently the metabolic fate of the CM eicosanoid precursors will depend on their partitioning between these lipids and on the fatty acid preferences of the pathways involved. The role of lipid transfer proteins, enzymes, and receptors involved in the metabolism is summarized in **Figs. 1** and **2**.

AA of the CM triglycerides. The interaction of CM with lipoprotein lipase (LPL) results in the hydrolysis of the major part of the TG (79). Generally LPL does not exhibit any fatty acid preference against different C_{16}–C_{18} fatty acid esters. Esters of AA and EPA of both VLDL (80) and CM-TG (81–83) are, however, released as FFA at a slower rate than LA and other C_{16}–C_{18} fatty acids, and are accordingly enriched in the remaining TG and DG of CM

Fig. 2. Role of hepatic lipoproteins in the transport of AA in the rat. The AA of hepatic VLDL is metabolized in a similar way as the AA of CM in Fig. 1. Rats have high plasma and hepatic AA and low LDL levels. High LCAT and PLTP activities (thick arrows) and lack of CETP activity, in combination with the high preference for AA of LCAT in the rat, results in the accumulation of AA in HDL-CE that is taken up by the SR-BI in liver and steroidogenic tissues (thick arrows). Compared with the secreted VLDL-TG, AA is enriched in the remaining TG of IDL and LDL. Because of the relative resistance of AA esters to LPL, AA is enriched in IDL- and LDL-TG, some of which is transported to HDL in exchange for CE mediated by CETP. The PL, TG, and CE of LDL are thus transport vehicles for AA in the LDL receptor-mediated uptake of this lipoprotein.

Fig. 1. Absorption and transport of AA from the gut. AA is preferentially acylated into mucosal and chyle PL that are transferred to HDL by PLTP, and then metabolized via HL, LCAT, and the SR-BI receptor. The AA esters of CM-TG are relatively resistant to LPL, and thus released as FFA to a limited extent and enriched in CMR-TG. CMR are cleared primarily by the LDL receptor and LRP-mediated uptake in the liver.

remnants (CMR) (Fig. 1). DHA esters were hydrolyzed at a rate in between those of AA-EPA and the C_{16}–C_{18} fatty acids. Using the perfused rat heart, Levy and Herzberg (84) demonstrated that EPA and DHA esters are hydrolyzed by heart LPL at a slower rate than other fatty acids. During the rapid clearance of CM-TG from plasma in vivo AA is eliminated with a slight delay compared with LA, relatively more AA being distributed to the liver and less to muscle and adipose tissue (85). In vitro studies with AA- and EPA-labeled CM supported the idea that LPL and hepatic lipase (HL) may act in a concerted way to hydrolyze TG- and DG-AA (83). Because the CMR are rapidly cleared, mainly by the liver, the quantitative role of HL in vivo may, however, be small, although blockade of HL with antiserum may influence the kinetics of CMR removal under some conditions (86, 87). CM obtained after feeding fish oil, and thus rich in EPA and DHA, were cleared by the rat heart at a similar rate as oleic acid-rich CM (88).

CMR are cleared primarily by the liver (Fig. 1), the uptake being mediated by LDL receptors (89) and/or the LDL receptor-related protein (LRP) (90–93). Hence, AA

of CMR can be metabolized by endocytosis in the hepatocytes and incorporated into membrane PL, reassembled into VLDL, or oxidized for energy. In addition to the hepatic clearance, rat intestine (94) and bone marrow in rabbit (95), marmoset (96), and humans (97, 98) have been postulated to play a role in the catabolism of CM. The uptake of CM-AA in bone marrow and intestine was, however, found to be low in the rat (73). Although the role of CMR in supply of AA to extrahepatic tissues under physiological conditions is difficult to estimate there is an uptake in many tissues, which is, however, much lower than in the liver when expressed per gram of tissue.

AA of the CM PL. The polar surface coat of the CM has a PL/apolipoprotein A-I (apoA-I) ratio that is 3- to 4-fold higher than in circulating HDL (32, 99, 100). During the lipolysis of CM-TG there is a rapid transfer of polar surface material to HDL (Fig. 1). The fundamental role of phospholipid transfer protein (PLTP), which occurs in all examined species (101), in this transfer, has been the subject of reviews (102, 103). Experiments in gene knockout mice have further emphasized its importance (104). At present it is not known whether different molecular species of PL are transferred at different rates, although the transfer rate was shown to be inversely related to chain length in experiments with fluorescent PL analogs in vitro (105). PLTP has a broad substrate specificity and catalyzes the transfer of PC, PE, PI, and sphingomyelin (105). The transfer of PL to HDL in vivo is rapid (106) and the disappearance from blood of ^{32}P-labeled PC and PE of CM and of HDL to which CM-PL had been transferred were similar (107). Although LPL may hydrolyze the 1-ester bond of PL in nascent TG-rich lipoproteins (108), this function may not be quantitatively important in AA transport in vivo, particularly because LPL was less active toward AA-PC than against LA-PC in CM (81).

After transfer to HDL, CM-PL can be metabolized by HL, LCAT, receptors involved in lipid uptake, and by particulate uptake of HDL. The HDL PC, PE, and PI are all substrates for HL (107, 109–111) and LCAT (112, 113). A distinct feature of HL is its high activity against PE (107, 114). The concentration of this PL in plasma is low but it accounts for 12% of the CM-PL (115) and it occurs in similar proportions in nascent hepatic VLDL (116–118). In chyle up to 14% of the AA was transported as PE (58). After intravenous injection of ^{32}P-labeled CM or HDL into rats, antiserum against HL blocked most of the PE elimination (107). The PE thus has a more important role in the transport of PUFA than is apparent from its low plasma concentration, carrying AA to organs containing HL, that is, liver, adrenals, and gonads.

HL also contributes to the catabolism of HDL PC (119) and HDL PI (120) although the quantitative contribution is more difficult to estimate than in the case of PE. In vitro HL hydrolyzes AA-PC and LA-PC at similar rates (121), forming 2-lyso-PL containing PUFA and releasing saturated fatty acids from position 1. Both LPL and HL activities were upregulated in EFA-deficient rats (122, 123) whereas in patients with cystic fibrosis and EFA deficiency HL was lowered (124).

Conclusion. The relative resistance of the eicosanoid precursor esters and the lipoprotein receptor-mediated uptake of CMR enriched in AA are key factors in the metabolism of TG-AA in CM. By its action on PL, HL contributes significantly to the uptake of CM eicosanoid precursors in tissues expressing this enzyme, by a mechanism that does not release these fatty acids as FFA. By interacting with LCAT and with the scavenger receptor class B type I (SR-BI) it also favors indirectly tissue uptake of cholesteryl-arachidonate (CE-AA) and other CE (Figs. 1 and 2) (see the next section).

ROLE OF LIVER IN SECRETION AND TRANSPORT OF EICOSANOID PRECURSORS

Transport by liver-derived lipoproteins

Liver is essential in the eicosanoid precursor traffic in several respects. Much of the AA absorbed in the intestine reaches the liver via uptake of CMR, HDL-PL, and HDL-CE. Liver-derived lipoproteins and 2-acyl-LPC supply other tissues with AA, and the uptake of LDL and HDL lipids returns PL and cholesterol to the liver to be reutilized in lipoprotein and bile secretion. Eicosanoid precursor fatty acids are transported in blood mainly in PL and CE, in low concentration in TG, as 2-acyl-LPC, and as a small pool of FFA-AA. VLDL compete with CM for the same catabolic pathway (125, 126) and are converted to LDL via progressive lipolysis. Both VLDL and LDL provide fatty acids for tissues and organs (127, 128). AA is preferentially incorporated into VLDL-PL and the roles of LPL, PLTP, and HL are similar for CM and hepatic VLDL. Because of the relative resistance of AA ester bonds to LPL, IDL- and LDL-TG formed during the lipolysis of VLDL contain larger proportions of AA than does VLDL-TG (129). LCAT and CETP remodel lipoprotein particles by the formation of CE primarily in HDL and by transfer of CE to LDL and TG-rich lipoproteins. Whereas CE of secreted CM and VLDL contains mainly oleic acid, the fatty acid composition of plasma CE reflects mainly the action of LCAT on plasma PC.

Role of LCAT and the SR-BI. HDL originates as neutral lipid-poor discoidal particles secreted from the liver and intestine, which are converted in the plasma to spherical particles with a neutral lipid core. The key events in this transformation are the PLTP-mediated addition of polar surface material from CM and VLDL and the release of cholesterol and PL from cells mediated by the ATP-binding cassette transporter 1 (ABC1) (130–132). The particles are continuously modified by HL, LCAT, CETP if present, and selective lipid uptake via the SR-BI. PLTP and LCAT are fundamental to HDL metabolism in all examined mammalian species (101, 133, 134), independent of the LDL and CETP levels. The major substrate of LCAT is HDL-PL and cholesterol.

AA PREFERENCE OF RAT LCAT. The role of LCAT in AA transport is most easy to envision in animals with a high AA level in their plasma lipids (Fig. 2). The rat has high LCAT and PLTP activity, low LDL, and no CETP activity.

Furthermore, rat LCAT has a pronounced AA preference that can be demonstrated both in vitro in fresh whole plasma, with the purified enzyme, and in vivo as judged from the high incorporation of AA into plasma CE (133, 135–137). EPA has the same preference as AA (138, 139). Oschry and Eisenberg (140) found that AA contributed 56.7% and 72.3% of the total CE fatty acid in HDL$_1$ and HDL$_2$, respectively, but only 7.9% and 27.3% in VLDL and LDL. AA oil feeding to rats increased the cholesterol level in HDL but not in LDL (141). HDL-CE is thus a major carrier of AA in the rat and the AA preference of rat LCAT is fundamental to its formation.

SR-BI. It is now recognized that the metabolism of HDL-CE in the liver and in steroidogenic tissues such as adrenals, testes, and ovaries is mediated mainly by the SR-BI (142, 143). This receptor must thus also mediate uptake of AA as CE in these tissues although studies of the SR-BI have so far been focused on its role in cholesterol transport. In SR-BI knockout mice, the bile cholesterol output and the uptake of CE by steroidogenic tissues are decreased (144) whereas overexpression of the SR-BI lowered HDL and increased biliary cholesterol output (145). It was reported that human macrophages transfected with cDNA for the human SR-BI efficiently took up PC, PE, and sphingomyelin of HDL and IDL (146), indicating that the SR-BI may also transfer PL from lipoproteins to cells. SR-BI and HL mRNA are both expressed in rat and human liver and steroidogenic organs (147) and may collaborate in the metabolism of HDL-PUFA. The hydrolysis of HDL-PL by HL was shown to favor the uptake of HDL-CE (148–150) and deficiency of HL decreased the hepatic uptake of CE in mice in vivo (151). The SR-BI in adrenal gland is upregulated in HL knockout mice (152), and acute in vivo inhibition of HL activity increased rat adrenal SR-BI expression and uptake of HDL-CE (153). Substitution of PUFA in the diet of hamsters increases SR-BI expression and lowers plasma HDL-CE concentrations (154), indicating that PUFA in the diet in addition to steroids and hypophyseal hormones (155) may regulate the SR-BI. Because in contrast HL is upregulated by EFA deficiency this further support the reciprocal regulation and the complementary action of HL and the SR-BI in the transport of PUFA.

Several pieces of information that would be relevant to the role of the SR-BI in AA transport are, however, at present missing. For example, it is not known whether the SR-BI exhibits any fatty acid selectivity in the transport of CE or other lipids and studies of the fatty acid composition of plasma CE and PL in SR-BI knockout mice have not been reported. It is also unknown whether SR-BI-mediated AA transport has a distinct physiological function. Interestingly, SR-BI knockout female mice had lowered fertility, despite normal estrogen and progesterone production (144), and estrogen treatment of humans, which suppresses the SR-BI (155, 156), increases the AA level in plasma CE and PL (157–159).

The quantitative role of the SR-BI in AA transport to tissues other than the liver and the steroidogenic tissues is at present unknown. Different tissue pools of AA equilibrate with the plasma lipoprotein and liver pools at different rates. Melin, Qi, and Nilsson (73) studied the time course for the change of isotope ratios in different tissues after injection of [^{3}H]AA-labeled CM and [^{14}C]AA-FFA in rats. The conclusion was that AA pools of plasma, liver, bile, and upper small intestine mix within a few hours whereas, for example, the stomach and colon mucosa and the bone marrow cells are semiclosed compartments to which lipoprotein-AA has limited access. These tissues must therefore have other important pathways for supply of AA that do not depend on lipid uptake from HDL or LDL or a long turnover time for their AA pools.

CONCLUSION. The conclusion is that in AA-high HDL animals such as the rat and mouse, LCAT and the SR-BI in collaboration with HL form an important delivery system for AA as CE and PL to the liver and steroid hormone-producing tissues. Other catabolic pathways for HDL may contribute as well (160), but evidence of a major role of HDL in the supply of AA to other extrahepatic tissues is lacking.

Role of LDL. Humans have much higher LDL levels than rats and high CETP activity. Neither in human whole plasma nor in experiments with purified human LCAT can any preference for AA or EPA be shown and the activity against DHA is low (133, 134, 136, 138, 139). Wang et al. (137), in examining a number of mutations of human LCAT, were able to ascribe the difference between rat and human LCAT to a difference at amino acid residue 149. In contrast to studies carried out under different conditions (133, 161) these authors could not demonstrate a shift in the positional specificity of human LCAT when the substrate was PC with AA or DHA at the 2-position. Although human LCAT does not prefer eicosanoid precursors AA is enriched in LDL-CE and PL compared with the TG-rich lipoproteins, and it has been suggested that LDL-AA is an important source of AA and eicosanoids in tissues. In cultured fibroblasts the cellular content of AA as well as the rate of prostaglandin formation may be influenced by addition of LDL to the medium and Habenicht et al. (162, 163) showed that AA in LDL can act as a precursor of eicosanoids in cells stimulated by platelet-derived growth factor.

Quantitative studies of the role of the LDL receptor in the supply of AA to extrahepatic tissues in vivo are lacking although one may hypothesize that an uptake of AA occurs that is proportional to the LDL receptor-mediated cholesterol uptake by different tissues and to the AA content of the LDL lipids. A study of mouse by Osono et al. (164) emphasized the relative role of local cholesterol synthesis in several tissues and the important role of LDL receptor-mediated hepatic uptake rather than supply to extrahepatic tissues of cholesterol via the LDL receptor. Existing data on cholesterol transport can thus not be extrapolated to indicate that the LDL receptor is an important source of AA for extrahepatic tissues. On the basis of known turnover rates, AA content, and AA pool size, it was calculated that the particulate catabolism of LDL in humans is expected to transport 42–57 mg of AA per day to tissues (Table 2). If one postulates that most of this amount is accounted for by the hepatic uptake the trans-

port of AA to extrahepatic tissue will be on the order of 20 mg/day or less. The main conclusion is therefore that LDL is a much less important source of AA for extrahepatic tissues than is FFA and LPC (Table 2).

Do high and low AA animals transport AA differently? The interesting phenomenon that the AA level correlates inversely with the susceptibility to arteriosclerosis of different species (134) has been emphasized. The reason for this inverse correlation is unknown. In comparing the LCAT activity in plasma of 14 species, it was concluded that those who were susceptible to atherosclerosis had significantly higher 16:0/20:4 ratios in their plasma CE and this could be explained by differences in the properties of LCAT (134). Studies show that transgenic mice overexpressing LCAT become more tolerant to development of arteriosclerosis (165–167). One possibility is that the AA preference of LCAT simply correlates with high total LCAT activity. Furthermore, it has been suggested that the uptake of CE-AA is correlated with eicosanoid synthesis in the cells (168) in a manner that may be protective, for example, stimulate the clearance of CE from the cultured arterial cells (169). The high AA group includes several carnivorous and omnivorous species, which normally eat food containing cholesterol as well as AA. One may speculate that in carnivore lipid transport a high AA level in CE is linked to a preference of LCAT for AA (134), a rapid PL transfer to HDL (101), and an efficient SR-BI system for return of cholesterol to the liver (Fig. 2, thick arrows). When the SR-BI was overexpressed in LDL receptor knockout mice the LDL and VLDL cholesterol was lowered and the degree of atherosclerosis decreased (170).

Animal species with a higher arteriosclerosis susceptibility, for example, rabbits, pig, and chicken, tend to have higher CETP activity and LDL levels, and more HDL-CE is transferred to LDL (101). The CETP catalyzes transfer of TG from TG-rich lipoproteins to HDL and CE from HDL to apoB-containing lipoproteins in plasma. The IDL and LDL that have received CE are taken up by the hepatic LDL receptor (Fig. 2). The HDL_2 is enriched with TG that is hydrolyzed by HL. There are few studies of the fatty acid specificity of CETP. Sugano, Makino, and Yanaga (171) observed that in plasma of hypercholesterolemic rabbits fed fish oil, CETP transferred CE containing ALA, AA, or EPA faster than CE containing other fatty acids.

In conclusion, the HDL-SR-BI-HL system and the LDL receptor system collaborate both in cholesterol and AA transport. From an AA point of view the HDL-LCAT-HL-SR-BI system is an efficient way of returning AA of PL from the polar surface coat of TG-rich lipoproteins and from cells to the liver, particularly in "high AA species." LDL fills a similar function in species with high CETP levels and may be a less efficient SR-BI system.

Role of plasma LPC

LPC is one of the prevalent PL in plasma, representing 5–20% of total PL, depending on the mammalian species (11). Albumin-bound LPC can be readily taken up from the plasma both by the liver and a variety of extrahepatic tissues and reacylated to PC (172). Thus it can provide extrahepatic tissues with a source of choline and PUFA that is independent of lipoprotein metabolism (173).

LPC can be formed by the action of LCAT (**Fig. 3**), a reaction that is responsible for most saturated LPC (133). Rat LCAT utilized mostly the *sn*-2-acyl group from either 1-palmitoyl 2-AA-PC or from 2-LA-PC to form unsaturated CE and saturated 1-acyl-LPC. However, human LCAT was found to utilize fatty acids derived from the *sn*-1-position of 2-AA-PC or 2-DHA-PC and thus release 2-AA-LPC or 2-DHA-LPC (133, 161). LPC can also be secreted from liver by the hydrolysis of hepatic PC (172, 174–176) (Fig. 3). The major portion of fatty acids in LPC secreted from perfused rat liver and hepatocytes is polyunsaturated, and the most prevalent PUFA was AA followed by LA. The secretion of LPC from hepatocytes occurs mainly by the action
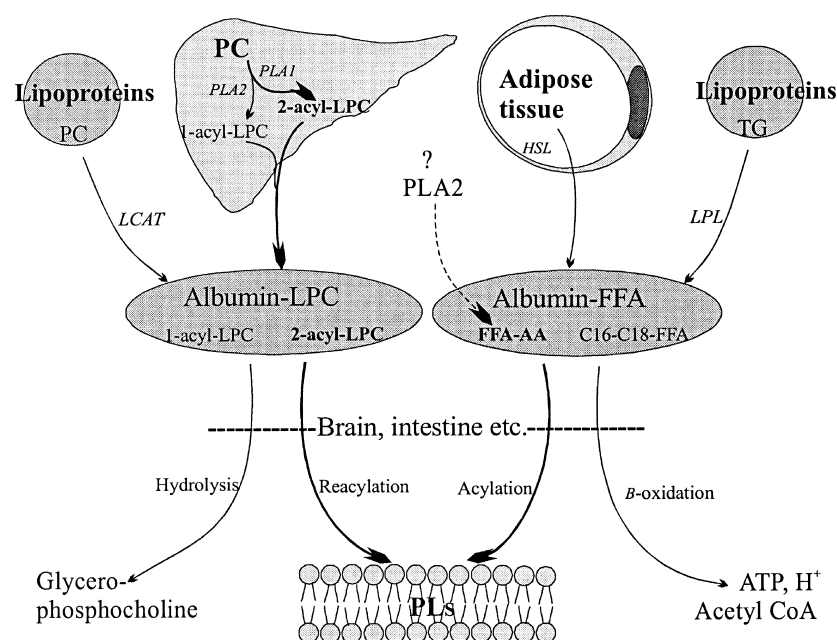

Fig. 3. Role of lysophosphatidylcholine and unesterified AA. 2-Acyl-LPC is released by PLA1 from the liver in some species, and is also formed by HL. 1-Acyl-LPC is formed in plasma by LCAT and in tissues by phospholipase A_2, and acts as an acceptor for AA-CoA in tissues by which it is taken up. Plasma FFA-AA may be formed by phospholipase A_2 (PLA_2) action in cells and blood, and to some extent by the action of LPL and hormone-sensitive lipase. 2-Acyl-LPC and FFA-AA are two important transport forms for AA in plasma with access also to the tissue compartment which takes up few lipoproteins. Tissue AA acquired from plasma 2-acyl-LPC and FFA-AA are mainly acylated into tissue membrane PL.

of phospholipase A$_1$ with some participation of PLA$_2$ (173, 175). The concentration of plasma LPC remains relatively high in human patients with hereditary deficiency of LCAT (177).

In human and rat plasma, the PUFA concentration in LPC was 25.9 and 14.2 nmol/ml, respectively, which is comparable with PUFA in plasma FFA. The AA content in LPC was 2-fold (human) and 5-fold (rat) higher than that in plasma FFA (178). In human and rat plasma, unsaturated LPC was associated mainly with albumin rather than lipoproteins (178). [^{13}C]DHA-FFA and [^{13}C]DHA-LPC were found to appear in plasma of humans and rats after ingestion of [^{13}C]DHA-labeled TG (179–181). Unesterified [^{13}C]DHA bound to albumin was rapidly produced after ingestion of [^{13}C]DHA-TG in humans, as a result of the hydrolysis of VLDL-TG plus CM-TG (179, 180). The labeling in FFA was highest at 2 h, and reached its minimal value by 6 h, at which time the labeling was maximal in LPC. The labeled LPC was suggested to be of hepatic origin. Despite the fast migration of the 2-acyl group to the 1-acyl position at physiological pH, approximately 50% of the PUFA of LPC was located at the 2-acyl position of LPC present in human and rat plasma (178).

Morash, Cook, and Spence (182) examined the fate of exogenous 1-acyl- and 2-acyl-LPC specifically radiolabeled with choline and/or fatty acid in NIE-115 neuroblastoma and C6 rat glioma cells in culture. They found that both species were taken up at similar rates. The 2-acyl species was acylated to PC faster than the 1-acyl species in both cell lines, possibly because 1-acyl-LPC is a better substrate for hydrolysis to glycerophosphocholine. It was suggested that the 2-acyl-LPC may be an important transport system for carrying AA, DHA, and other PUFA to extrahepatic tissues that are rich in these fatty acids such as gastrointestinal tract and brain (Fig. 3). When [2-^{14}C]AA-LPC was injected intravenously into rats, a substantial amount of AA was retained in extrahepatic tissues (183). Although the highest uptake was observed for the liver, as much as 15% of the recovered radioactivity was found in the small intestine and the retention of AA-LPC was calculated to be 25 nmol/min in the gastrointestinal tract. In kidneys and lungs the radioactivity per gram of tissue amounted to 30–40% of the hepatic radioactivity. In the liver and gastrointestinal tract a high reacylation of LPC into PC was observed whereas in other organs it proceeded at a slower rate. Other studies (184) found that doubly labeled 2-acyl-LPC can be taken up by brain tissues without prior hydrolysis and reacylated at the 1-acyl position to form membrane PC. It was also found that the brain uptake of 2-acyl-LPC increases with the degree of unsaturation and was 6- to 10-fold higher than that of the corresponding unesterified fatty acid. The ability to take up and acylate albumin-bound 2-acyl-LPC thus is a general feature of many tissues. Although there are still few quantitative studies, 2-acyl-LPC has a rapid turnover and may transport substantial amounts of AA and DHA. Calculations based on available plasma concentration and turnover data in humans indicated that the daily transport of AA with plasma LPC is 270–1425 mg, that is, severalfold more

than is transported with LDL (Table 2). Furthermore, 1-acyl-LPC takeup from blood can be an important acceptor of AA in its selective acylation into PC.

The main conclusion is thus that LPC is a quantitatively important vehicle for the transport of AA. It provides AA also to tissues to which lipoproteins have poor access, without the need to release AA as FFA in blood.

TRANSPORT OF AA AS PLASMA FFA

Sources of plasma unesterified AA

Plasma FFA are derived by selective mobilization of fatty acids from TG in adipose tissue (185) and derived from the hydrolysis of lipoprotein TG by LPL and HL (186) (Fig. 3). The concentration and composition of plasma FFA are therefore influenced both by the absorption of dietary fat and/or release of individual fatty acid from adipose tissue during fasting and ranges from 0.4 to 0.8 mM in humans. AA accounts for a small proportion of both lipoprotein and adipose tissue TG and regulation of the plasma FFA-AA level may be different than for other FFA. When isolated adipocytes from humans or rats were incubated with lipolytic agents, EPA and AA were preferentially mobilized (185, 187). Adrenocorticotropic hormone-stimulated lipolysis in weaning rabbits showed that the relative mobilization of fatty acids from adipose tissue occurs in the following order: EPA > AA > ALA > DHA > LA. However, during fasting, selective retention of LA and AA in PL was found in brown adipose tissue (188). The level of FFA-AA does not vary with feeding-fasting and physical exercise in parallel with the predominant FFA (189). Differences in the regulation of the small adipose tissue pools as well as other sources of AA than mobilization from adipose tissue TG are possible explanations. Some FFA-AA might originate from the action of PLA$_2$ succeeded by release to surrounding albumin in any tissue, for example, from endothelial cells (190) and by the action of secretory PLA$_2$ on lipoproteins (191) (Fig. 3). The concentration of AA in plasma FFA is 1.2–3.7 nmol/ml (178, 189, 192). It accounts for 2.0–2.8 wt% and EPA for 0.1 wt% of the plasma FFA in Americans (23, 193). Accordingly, it is estimated that the FFA-AA pool is about 0.9–2.8 mg in plasma in humans (Table 2). The average EPA/AA ratio in plasma FFA is 0.15 in healthy Japanese (194). The AA level in FFA was slightly increased after dietary supply of AA (193). It was noticed that in stressed humans with various diseases values of FFA-AA about 10 times higher than normal can be observed (192).

Fate of plasma unesterified AA

Albumin-bound FFA are rapidly cleared from blood to undergo oxidation, acylation, or interconversion reactions in the tissues. It is thus both a major source of energy, and an important precursor for synthesis of membrane PL (195–198). The fractional rate of turnover of FFA is rapid, 20–40% of the total mass being utilized every minute. The plasma pool of AA in men was 75% higher

than in women and the fractional turnover of plasma FFA-AA was 0.47/min in men and 0.8/min in women (199). It was shown that the fractional turnover of plasma FFA-AA was 50% higher than that of oleic acid (200). The turnover of AA was not significantly increased during physical exercise, in contrast to the turnover of oleic acid. The fractional uptake of FFA-AA in the splanchnic region was about 60% higher than for oleic acid (200). From the turnover and concentration data it can be calculated that 1.1–2.1 g of AA is cleared from FFA in human plasma every day (Table 2). Plasma FFA-AA can be taken up by several tissues and is preferentially acylated in PL (Fig. 3), mainly in PC (73, 201).

Conclusion

The conclusion is that despite the low concentration of AA as FFA in blood this transport form contributes significantly to the supply of AA to tissue PL, including pools to which lipoproteins have poor access.

BIOSYNTHESIS OF THE EICOSANOID PRECURSOR FATTY ACIDS IN TISSUES

Desaturation elongation reactions

Δ^6-*Desaturase.* The sequential interconversion of LA to AA and of ALA to EPA is catalyzed in mammals by the activity of desaturases, which varies broadly with the kind of tissue and species considered. High hepatic Δ^6- and Δ^5-desaturase activity in rats and mice, and low activities in the livers of rabbit, guinea pig, as well as humans were reported (202). Δ^6- and Δ^5-desaturases are microsomal enzymes and have been cloned (203, 204). The open reading frames of the human Δ^6-desaturase and Δ^5-desaturase are identical in size, encoding a 444-amino acid peptide, and share 61% identity. There is a common opinion that the activity of Δ^6-desaturase is low in most tissues except the liver and the central nervous system in the fetus and young animals (205). Consequently, the liver has been considered the primary site for the production of PUFA (202, 206). However, Δ^6- and Δ^5-desaturase activities have also been found in brain, testis, kidney, and in several types of primary cell cultures and cell lines. Rat small intestine also possesses Δ^6-desaturase activity to convert LA to γ-linolenic acid (18:3n-6) (207). Northern analysis revealed that many human tissues express Δ^6- and Δ^5-desaturase mRNA, which are most abundant in the liver, brain, heart, and lung. The human brain can contain several times more Δ^6-desaturase mRNA than is found in other tissues including the liver, which may be regulated by nutrition or aging (203, 204).

In liver, Δ^6-desaturase activity can be influenced by a number of nutritional, hormonal, and metabolic factors (202, 208–212). The process of Δ^6 desaturation slows with aging in the liver (213). In addition to being affected by fasting and feeding, hepatic Δ^6-desaturase activity is highly dependent on the composition of dietary fat (202, 214, 215). Both dietary ALA and EPA inhibit conversion of LA and reduce the AA content in serum and liver PL, but the

AA level was not affected when n-3 fatty acids were fed together with high levels of LA (216). In EFA-deficient rats an increased hepatic interconversion of LA to AA has been demonstrated in vivo (61) and in vitro (217). Δ^5-Desaturase is also influenced by diet and hormonal changes, but does not respond as rapidly as the Δ^6-desaturase. Like Δ^6-desaturase, Δ^5-desaturase activity is depressed in diabetes and reactivated by insulin treatment. The abundance of Δ^5-desaturase mRNA was much lower than that for Δ^6-desaturase in all tissues in humans (204). Hepatic and extrahepatic desaturase enzymes are regulated differently in response to physiological states. For example, short-term fasting increased Δ^6-desaturase activity in jejunum and ileum homogenates 3-fold and 1.7-fold, respectively, in rats (218) whereas the Δ^6-desaturase activity in the liver decreased. Dietary enrichment of LA (209) and ALA (219) inhibit Δ^6-desaturase activity in liver. In contrast, Δ^6-desaturase activity in jejunum was increased by feeding a diet high in LA, and was not significantly affected by feeding a diet high in ALA (218). Δ^6-Desaturase is thus expressed in several tissues and may be differently regulated at the various sites.

In vivo studies in humans. Emken et al. (43, 220–223) observed a significant interconversion of dietary deuterium-labeled LA and ALA to AA, EPA, as well as other n-6 or n-3 long-chain metabolites in adult humans. On the basis of analysis of interconversion products of dietary deuterated LA in human plasma lipids over 96 h, it was concluded that the percentage interconversion to AA corresponded to a daily formation of 677 mg of AA and an accumulation of 805 mg of n-6 long-chain metabolites with a daily dietary intake of 20 g of LA (43, 223). Dietary AA significantly inhibited the accumulation of n-6 long-chain metabolites from the conversion of deuterium-labeled LA. Feedback inhibition by dietary AA at 1.5 g/day was estimated to reduce accumulation of newly synthesized AA from 677 to 326 mg/day and dietary DHA at 6.5 g/day was estimated to reduce accumulation of n-3 long-chain metabolites from 121 to 32 mg/day (by ~66%) and reduced the accumulation of n-6 long-chain metabolites from 805 to 186 mg (by ~70%) with a daily dietary intake of 2.5 g of ALA and 20 g of LA. The results indicated that an unphysiologically high AA intake does inhibit the interconversion reaction, but moderate fluctuations in dietary AA intake have no major effect on LA metabolism and total accumulation of AA in the body. Dietary AA actually increased the interconversion of 20:3n-6 to AA, indicating that the regulation of the reaction sequence is a complex function of substrate availability, enzyme level, and competition for acylation sites (44).

Conclusion. Formation of AA from LA is an important source of AA in all herbivores and omnivores, desaturating-elongating enzymes being present in many tissues. In humans interconversion of 1–3% of the normal dietary LA (10–20 g) equals the intake of AA in normal Western diets (100–300 mg). The available human data therefore indicate that the amount of AA formed by interconversion normally exceeds the dietary intake of AA.

Uptake and interconversion of plasma unesterified LA

The FFA of normal human plasma contains many PUFA, LA accounting for about 15% (mol/mol) (224). The concentration of LA in plasma FFA is about 24–30 nmol/ml (178, 189), and the pool size is approximately 18–23 mg of LA in plasma FFA. The fractional turnover of FFA-LA is equal to or higher than 0.31/min in humans (225). Thus 8–10 g of LA can be cleared from the albumin-bound FFA fraction in human plasma every day.

When albumin-bound [^{14}C]LA was injected intravenously in rats (195) and guinea pigs (226, 227) it was shown that a significant proportion of LA taken up from blood as FFA is interconverted to Δ^6-desaturase products not only in the liver but also in the gastrointestinal tract, bone marrow, spleen, kidney, and lungs. In heart the two species differed. It was earlier found that there is no desaturation-elongation in isolated rat cardiac myocytes and in the perfused heart (228) and negligible desaturation-elongation in the heart was observed after intravenous injection of [^{14}C]LA (195). However, the guinea pig (226, 227) produces significant amounts of Δ^6-desaturase products also in the heart. A significant proportion of ALA taken up from blood as FFA is also interconverted to Δ^6-desaturase products in the liver and in the gastrointestinal tract in rats (229). Most of the interconversion occurred within 5 min after injection, that is, soon after uptake into cells. The acyl-CoAs formed at this stage were thus available for the desaturating-elongating enzymes. A question was therefore raised concerning whether fasting that increases the plasma concentration of FFA, more than 2-fold in healthy humans (230) and more than 5-fold in guinea pigs (227), also increases the production of Δ^6-desaturase products due to increased substrate availability. The uptake and the total formation of Δ^6-desaturase products from plasma FFA-LA in guinea pigs were found to be severalfold higher in all organs in the fasted state (227). For example, the formation of Δ^6-desaturase products was 3.8-fold higher in liver, 7.2-fold in upper small intestine, 6.5-fold in bone marrow and 6.0-fold in colon (226, 227). Although Δ^6-desaturase is generally considered to be the key regulatory step in the interconversion sequence significant proportions of the interconversion products were intermediaries, that is, 18:3n-6 and 20:3n-6. These proportions were much higher in the guinea pig, particularly in the liver, than in the rat. This may be caused by differences in the ratio between Δ^6- and Δ^5-desaturase activities in the tissues as well by differences in acylation kinetics.

In conclusion, FFA-LA is abundant, it has access to most tissues, and the LA-CoA formed soon after uptake is available for interconversion. Accordingly the LA level in the adipose tissue from which FFA is mobilized as well as nutritional factors regulating FFA mobilization must be important determinants of AA formation in addition to the desaturase levels.

ROLE OF REACYLATION AND TRANSACYLATION REACTIONS

It is well recognized that after uptake into cells AA is selectively retained in PL. Leyton, Drury, and Crawford (196) studied the rates of oxidation of saturated and unsaturated fatty acids in vivo in rats and found that AA was oxidized at the slowest rate. The role of intracellular reacylating and transacylating enzymes in the selective build-up of AA-containing PL species has been the subject of earlier excellent reviews (14, 231) and is discussed only briefly in this article.

DG containing unsaturated fatty acids are rather unselectively used for de novo synthesis of PC, whereas there is a preferential use of DG containing AA or DHA for PE synthesis. The fatty acid pattern is then modified by selective remodeling. For example, in liver cells the major de novo synthesized molecular species of PC were 16:0–18:2, 16:0–18:1, 16:0–22:6, and 18:1–18:2. Remodeling occurs mainly by replacing fatty acids at position 1 with stearic acid and fatty acids at position 2 with AA (69). It is believed that the selective acylation of 1-acyl-LPC with AA-CoA (68, 69, 232) is most important. 1-Lyso-PC-acyl-CoA-acyltransferase has been shown to select AA-CoA with a relatively high preference, when present in a mixture of acyl-CoA (233). The properties of this important enzyme, originally discovered by Lands (234) and Lands and Crawford (235), has been reviewed (236). In most tissues a high initial incorporation of AA into PC is seen, succeeded by an increased proportion in PE and PI with time (60, 62, 73, 74). The proportion that is retained in PL and particularly in PE increases in EFA deficiency (61, 237–239). The enrichment of AA and DHA in PE with time depends on transacylating and reacylating reactions as well as the selective recycling into PE of DG containing AA and DHA at position 2 (240, 241).

The relative importance of each pathway is to some extent tissue specific. In many cell types, for example, neutrophils, plasmalogen-linked PE is a major store of AA. Exogenous AA is initially incorporated into 1-acyl-linked PL and is believed to be transferred to the 1-ether-linked PL via the action of a CoA-dependent acyltransferase (242). Similar findings have been made in platelets and in endothelial and smooth muscle cells. Interestingly, macrophages with a mutation causing a defect plasmalogen synthesis had normal AA levels but a decreased ability to retain DHA (243).

The control of AA levels within inflammatory cells has been the subject of a review (14). The metabolism of AA in these cells reflects a carefully balanced series of reactions, where the key enzymes are AA-CoA-synthetase, the CoA-dependent acyltransferases, CoA-dependent transacylase, and CoA-independent transacylase. The selective action of these enzymes guarantees an effective initial acylation of AA into PC as well as a selective acyl transfer and exchange reactions involving up to 20 diacyl- and 1-ether-linked molecular PL species.

In summary, the selectivity of the reacylating and transacylating enzymes is of key importance in regulating the AA and DHA content of the PL subclasses and molecular species. It is notable that the selective DG utilization for de novo synthesis of PE provides a complementary pathway by which these fatty acids can be enriched in PE without competing for the same selective acylation site.

REGULATION OF THE N-6/N-3 RATIO OF TISSUE PL

The basis for many dietary studies is the intention to lower the long-chain n-6/n-3 ratio in tissues to achieve beneficial medical effects. For coverage of more recent dietary studies the reader is referred to reviews (15, 244). The relation between n-3 and n-6 PUFA is based on a series of reactions that aim to regulate both AA and DHA levels within distinct limits under all normal dietary conditions.

In a purely vegetarian diet LA and ALA compete for the desaturating-elongating enzymes, ALA being the preferred substrate. The selective partitioning of ALA to oxidation limits, however, the proportion of n-3 interconversion products because of the high LA/ALA ratio of the available substrate pools. Of dietary unsaturated fatty acids studied in humans, ALA was the most rapidly oxidized, linoleate being oxidized at a much slower rate (245) and in guinea pigs the modest effect of a high ALA diet on the EPA and DHA levels was ascribed to increased oxidation (246). Although ALA is initially well incorporated into PL of several cells and tissues it is not well retained (246, 247). Why this is so is at present poorly understood. The possibility that ALA is not as effectively retained because of selectivities of PL-remodeling enzymes needs further study. Regardless of the mechanism behind the sorting out of ALA for oxidation, the result is that among the fatty acid pools from which the substrates of Δ^6-desaturase are derived the concentration of LA greatly exceeds that of ALA.

In an omnivorous diet EPA and DHA will compete for acylation into PL, both with the dietary and endogenous AA and with the large amount of LA in the diet, both in the intestine and liver and in the tissue to which the fatty acids are transported. Sinclair et al. (20) found that diets rich in lean beef increased AA, 20:3n-6, and long-chain n-3 PUFA levels (including EPA) in human plasma PL. However, a high level of LA in the diet prevented the rise in plasma PL levels of 20:3n-6 and EPA. Thus dietary LA, AA, EPA, and DHA compete for acylation with the interconversion products or might exert a feedback regulation of the interconversion. Chilton et al. (248) examined the effects of dietary n-3 fatty acids on neutrophil lipid composition and mediator production. The feeding of 2.8 g of EPA and 1.2 g of DHA per day for 1 week decreased the AA/EPA ratio from 49:1 to 8:1 but then no further change occurred during another 6 weeks.

In conclusion, the abundance of LA in the diet, the preferential oxidation of ALA, and the high affinity of AA for PL acylation and remodeling reactions are key factors that limit changes in the n-3/n-6 ratio that can be achieved by dietary supply of n-3 fatty acids.

SOURCES OF EICOSANOID PRECURSORS IN CERTAIN EXTRAHEPATIC TISSUES

The liver has a central position in the traffic of PUFA absorbed from the diet, returned to the liver via HL or via the LDL or SR-BI or as FFA. Not unexpectedly the liver AA pool seems to equilibrate more rapidly with the plasma AA pools than does the AA of other tissues and cells, each of which has common as well as unique features in their turnover of AA. This is exemplified by platelets, in which eicosanoid formation is a key regulator of cell function; the gastrointestinal mucosa and the bone marrow, which have a rapid cell turnover; and the brain, which has uniquely high levels of AA and DHA.

Platelets

Platelets are unable to synthesize AA from the precursor LA (249). Incorporation of AA into platelet PL must either be an integral part of platelet formation in bone marrow cells, or the result of transfer from plasma lipoproteins (250), or uptake of FFA (251) and/or 2-AA-LPC (173) in blood circulation.

Platelets can take up or bind the different lipoprotein classes (250, 252–254) and the existence of PC exchange between HDL and platelets was suggested (250). In agonist-stimulated platelets PE can be selectively taken up from added LDL (255). However, no distinct evidence of the presence of the LDL receptor in platelets has been reported and platelets do not express LRP (256). A low uptake of CMR and a lack of net degradation of CMR-CE and [^{3}H]AA-TG were observed during incubation of CMR with platelets (257). This finding also supports the idea that no significant LDL receptor or LRP-mediated endocytosis of CMR occurs in platelets. Although CMR contains high levels of AA and the interaction with CMR potentiated the aggregation and the serotonin release of platelets induced by ADP and thrombin (258), the uptake of CMR by platelets is unlikely to modify the AA content of platelets.

Megakaryocytes are the nucleated bone marrow progenitor cells of platelets. The PL distribution in megakaryocytes and platelets was similar and the content of fatty acids in the individual platelet PL reflected those of the megakaryocyte counterparts, with increased AA and decreased oleic acid levels (259). The increase in AA in platelets is similar for all four major glycerophospholipids. Megakaryocytes contain a high level of AA (259, 260). PE, the second predominant PL in megakaryocytes and platelets, contains half the AA of the cells (259).

Albumin-bound FFA can be incorporated into platelet PC and PI in vitro (261–263), the incorporation of AA into platelet PE being small (264). The transfer of LA and AA from lipoprotein-associated PC into platelets involved only 3% of platelet PC (265). During incubation of isolated megakaryocytes with radiolabeled AA, AA is preferentially incorporated by immature megakaryocytes (266). It was suggested that AA is concentrated into the membranes that are destined to become part of certain granule membranes of platelets (259, 266).

Human (249) and guinea pig (260) platelets do not interconvert LA to AA. However, bone marrow and spleen of young rats (195) and guinea pigs (226, 227) form AA by uptake and interconversion of blood unesterified LA. Bone marrow had the highest rate of interconversion observed in any tissue in guinea pig and the highest rate

among extrahepatic tissues in the rat. Autoradiography after injection of [^{14}C]LA intravenously showed that mega-karyocytes accumulated ^{14}C (226). Thus, platelets have a limited capacity to alter structural pools of AA contained primarily in PE and PS (260). Megakaryocytes can, however, form and regulate the pools of platelet AA either by uptake or synthesis of AA.

The conclusion is that the formation AA pools in platelets is an integral part of the formation of cell membranes during platelet proliferation in the bone marrow. Some modification in blood probably occurs by uptake of unest-erified AA or AA-LPC, but not via LDL receptor- or LRP-mediated lipoprotein uptake. The selective transfer of PL-AA from LDL remains an interesting possibility (255).

Gastrointestinal tract

A supply of PUFA is required for mucosal cell mem-brane biogenesis because mucosal cells in stomach, small intestine, and colon exhibit a rapid rate of cell turnover with a half-life of 2–4 days (218). Intestinal mucosal PL contain large amounts of LA and AA (267). The most abundant PC species of rat gastric mucosa were 16:0/18:1, 16:0/LA, 16:0/AA, and 18:0/AA (268). The AA level was 6.8 mol% in the intact mucosa in human colon (269), and AA increased to 12.5 mol% in inflamed colonic mucosa from patients with active ulcerative colitis (269). Cell membrane AA is also increased in rat colorectal tumor cells (270). Unesterified AA in cells is a signal for induc-tion of apoptosis and the cellular level of AA is inversely correlated with the reduction of cell death (271). Cyclo-oxygenase 2 (COX-2) and fatty acid ligase, which both are AA-utilizing enzymes, are upregulated in colon adeno-carcinomas (271). Nonsteroidal anti-inflammatory drug treatment of colon tumor cells, which inhibits COX-2 activity, results in a dramatic increase in AA that may mediate apoptosis (272). After fasting, the AA content of microsomal total PL increased in the jejunum with a con-comitant decrease in LA content. AA and LA concentra-tions remain unchanged in ileal microsomes after short-term food withdrawal. Feeding a diet containing n-3 fatty acids lowered the content of AA and increased EPA and DHA levels in both jejunal and ileal microsomes (218). Dietary EPA reduced the number and size of tumors in male Apc$^{min/+}$ mice, and this effect was associated with re-ductions in tissue AA content and prostaglandin levels (273). As mentioned previously the retention of AA in di-etary and bile PL in small intestine is an important source of mucosal PL-AA, which is, however, limited to the ab-sorptive villous cells of the upper small intestine. Mans-bach and Dowell (94) suggested that a significant uptake of CMR carrying AA to the intestinal mucosa may occur. Our group could confirm that some uptake of AA as CMR in the intestine and bone marrow occurs after injection of moderate doses of AA-labeled CM. The labeled AA trans-ferred as CM-PL to HDL equilibrated slowly with the co-lon, ileum, and gastric AA pools and the uptake of labeled AA injected as FFA was 2- to 3-fold higher (73). The 2-AA-LPC pathway is a quantitatively more important source of AA in the rat small intestine, which was found to supply

21.6 nmol/min to the small intestine of rats (183). Local interconversion of plasma unesterified LA to AA is an-other pathway, which supplies AA at 0.8 nmol/min to the small intestine of nonfasted rats and 5- to 7-fold more in the fasted state (195). Similar data were obtained for stomach and colon. The total formation of Δ^6-desaturase products in the intestine amounted to 8% of that in the liver in rats. Both villus and crypt cells are sites for the interconversion (226).

The conclusion is thus that AA in 2-acyl-LPC and inter-conversion of LA taken up from blood as FFA are impor-tant sources of eicosanoid precursors in the gastrointesti-nal tract. Some uptake of FFA-AA from blood occurs. In the upper part of the small intestine absorption of bile and dietary AA is an exclusive source for the absorptive cells and for CM-PL formation. Absorbed LA and ALA are rapidly acylated into CM, with little being interconverted in the mucosa.

Central nervous system

The adult mammalian brain contains approximately 10% of the fresh weight and 50–60% of its dry weight as lipid, mostly PL. The major PL are PC (35.5%), PE (34.1%), PS (12.2%), sphingomyelin (5.7%), and PI (3.1%) (274). DHA and AA are the main PUFA (274). DHA represents roughly 15% of the total fatty acids in the brains of most animals and humans (275), and is acylated mainly in PS and PE with exceptionally high levels found in the retina (276). DHA is required for the development of visual acuity and learning in young animals and hu-mans (277, 278). Throughout its growth, the brain utilizes large amounts of PUFA for biosynthesis of rapidly expand-ing neural plasma membranes. A rapid quantitative accre-tion of both DHA and AA occurs during the last trimester of pregnancy (279), and the fetal brain acquires about 21 g of DHA per week during the last trimester of pregnancy (280). There is also a DHA accretion "spurt," which coin-cides with the peak of neurogenesis in the rat fetus (276). The long-chain PUFA concentrations are higher in the fetal than maternal circulation, and at birth DHA and AA concentrations among the total fatty acids in cord plasma is doubled, but ALA and LA concentrations in newborns is only half that in maternal plasma (281–284).

All EFA and most PUFA in fetus must originate from fatty acids in the maternal diet. The transfer of FFA across the placenta occurs by the dissociation of the albumin-bound FFA to the cell surface via a process involving plasma membrane fatty acid-binding proteins and/or pas-sive diffusion (285). The ranking of transfer rates from a physiological mixture of fatty acids was DHA > ALA > LA > oleic acid > AA from the maternal to the fetal circula-tion in human placenta (286). A placenta plasma mem-brane fatty acid-binding protein, which preferentially bound with EFA and long-chain PUFA over non-EFA, was identified (287, 288). This transfer mechanism would allow the preferential transfer of DHA and EFA to the fetal circulation during fetal development.

It has been suggested that DHA is synthesized mainly in the liver and then is redistributed into the brain (206).

However, the developing brain itself can metabolize ALA to DHA, thus contributing to the accumulation of DHA during its development (205, 276, 289–291). Some studies also demonstrated that the developing rat brain takes up preferentially DHA, AA, and other PUFA esterified in LPC, compared with the unesterified form, both being delivered bound to albumin (184, 292). This preferential uptake of DHA-LPC was specific to the brain, as it was not observed in the liver, heart, or kidney. The role of the different cells involved in LPC metabolism and transport of PUFA carried by LPC to the brain was studied in vitro by using an in vitro model of the blood-brain barrier, by growing brain capillary endothelial cells on the upper side of a filter insert lying on culture medium covering an astrocyte culture (293). It was found that DHA-LPC is preferentially transferred and taken up by astrocytes over the unesterified DHA, a process that may be facilitated by molecules released by the in vitro blood-brain barrier. Injection of different labeled nonesterified fatty acids into the rat fetus showed a substantial uptake in brain (289) and after intravenous infusion of albumin-bound FFA-AA in anesthetized rats labeled AA was shown to enter a pool of FFA-AA in brain that had 5-fold lower specific activity (294). Similarly labeled FFA-DHA was taken up by brain and entered a pool of PL-DHA with a comparatively rapid turnover (295).

The quantitative role of the lipoprotein receptors is at present difficult to evaluate. LDL receptor is expressed on both brain endothelium and in glial cells (296, 297), and coculture of endothelial cells and astrocytes increased the expression on endothelial cells (298). Bile drainage that is known to induce the LDL receptor increased LDL uptake in brain (299).

The conclusion is that FFA-AA and 2-acyl-LPC can enter the brain in both the fetal and adult state and are important sources of AA. A considerable local interconversion occurs during the early stages of life. The role of lipoprotein receptors is not fully characterized. The selective use of AA and DHA containing DG for PE synthesis may be especially important in brain.

CONCLUSIONS

Buildup of eicosanoid precursor pools depends on the transport of preformed AA and EPA to tissues, and on the local formation of these fatty acids from the precursor C_{18} PUFA. AA is transported in lipoproteins by mechanisms that minimize the appearance of unesterified AA as plasma FFA and in adipose tissue TG. The preferential incorporation into lipoprotein PL, the positional specificity of HL for the 1-ester bond of PL, the transfer of AA by LCAT from PL to HDL-CE, the relative resistance of AA esters to LPL, and the functions of the LDL receptor and the SR-BI are all instruments that can be used for this purpose. The quantitative role of the SR-BI and LDL receptor in supplying AA to extrahepatic tissues is uncertain. Albumin-bound unesterified AA and 2-acyl-LPC are two important, lipoprotein receptor-independent transport

pathways that have access to most tissue compartments. Interconversion of LA both in the liver and in several extrahepatic tissues is important in herbivores and omnivores. Fasting increases the interconversion severalfold in most tissues, emphasizing the importance of the plasma FFA-LA in supplying the substrate. The composition and size of the plasma FFA pool, the nutritional state, and the regulation of Δ^6- and Δ^5-desaturase are thus important determinants of this pathway.

The relative importance of the pathways used is species and tissue specific. Obligate carnivores do not produce AA by desaturation-elongation and depend on supply of AA in the diet. One may speculate that FFA-AA and AA-LPC must be key transporters of AA to most extrahepatic tissues in these species whereas herbivores tend to favor local production of AA in extrahepatic tissues. The rat, being an omnivore with a high AA level, utilizes the LPC pathway and has high AA production in the liver. The guinea pig exhibits low levels of plasma LPC, lacks HL, and has a high rate of AA formation in extrahepatic tissues. On a speculative basis one might place humans in between rats and guinea pigs on a carnivore-omnivore scale, as an omnivore with a high LA intake who produces most of its AA but ingests dietary AA as well and utilizes AA transport as FFA and 2-AA-LPC as major pathways to supply AA to tissues.

The systems for eicosanoid precursor supply are subjected to competition between n-3 and n-6 fatty acids. The sorting out of ALA for oxidation and the lower affinity of long-chain n-3 PUFA, compared with AA, for the saturable pathways for selective acylation into PL as well as the AA selectivity of PL-remodeling enzymes limit the effects that can be achieved by dietary n-3 PUFA.

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