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Long Chain Polyunsaturated Fatty Acid Metabolism and Cellular Utilization: Regulation and Interactions

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The unique presence of the long chain highly unsaturated fatty acids (HUFA) of the linoleic (LA) and the α linolenic (LNA) acid series in the animal kingdom underlines the existence of specialized mechanisms for the incorporation and maintenance of these compounds, which are present in biological systems mainly as esters of glycerol in phospholipids, as structural components of biomembranes. The fact that the 18-carbon polyunsaturated fatty acids (PUFA), LA and α LNA, are present in large excess in modern food, when compared with the trace concentrations of the HUFA, has led to the concept that the major process responsible for the availability of HUFA in higher organisms is their metabolic formation from the 18-carbon PUFA of dietary origin. Biochemical studies have shown that enzymatic desaturation and elongation of LA and α LNA occur in tissues, the liver being the most relevant site of fatty acid metabolism. In addition, nutritional studies carried out mostly on laboratory animals have shown that modifications of the absolute amounts and relative proportions of LA and α LNA in the diet induce changes of HUFA profiles in lipids of various tissues that can be attributed to the fatty acid desaturation and elongation reactions disclosed in biochemical investigations.

On the other, studies carried out in various types of cells show that data on the desaturation and elongation of unsaturated fatty acids do not quantitatively account for the accumulation of selected PUFA in different tissues nor for the incorporation of specific HUFA in selected lipid pools. Hence, metabolic studies do not allow an accurate prediction of the effects of manipulations of dietary fatty acids on the fatty acid profiles of different cells (1). A number of integrated processes, in cells and in their membranes, responsible for the continuous remodeling of structural lipids, appear to be involved in the maintenance of selected fatty acid profiles, while allowing a turnover of the lipid components.

In addition, the intake of preformed HUFA in the diet plays important physiological and metabolic roles. For instance, tissue and organ development in

physiological states, such as intrauterine growth of the embryo and fetus and the early postnatal growth of the suckling newborn, are highly dependent upon the availability of preformed HUFA obtained from the mother. Also, the presence of appreciable levels of HUFA of the n-3 and n-6 series in foods obtained from marine animals and from lean muscles of terrestrial animals, respectively, indicates that under various dietary conditions in the past and at present, the intake of preformed HUFA has contributed and is contributing to the availability of these structural components for organ development and function. The intake of appreciable amounts of long chain PUFA (LCPUFA) is typical of animal species that are predators, and this may have represented an important process for the development of specialized functions in organs requiring an adequate availability of HUFA, and, more generally, for the evolution of species endowed with more developed organs and functions (2).

It appears, thus, that the maintenance of the proper amounts and proportions of HUFA in biological systems is based on a number of processes, such as 1) metabolic conversion of the major polyunsaturated fatty acids of the diet, LA and α LNA, to HUFA; 2) intake of preformed HUFA with the diet; 3) phospholipid biosynthesis coupled with membrane formation; 4) uptake and incorporation of selected fatty acids in tissue lipids and in lipid classes; 5) and remodeling of glycerophospholipids in biomembranes through reactions (deacylation, reacylation) involving hydrolysis and re-esterification of these compounds within the membrane.

These combined processes will ultimately affect levels of HUFA in biomembranes and, as a result, their physicochemical properties, the availability of substrates for eicosanoid synthesis, and the activity of enzymes involved in lipid metabolism and in the generation of lipid-derived mediators.

This chapter is devoted to a brief discussion of some of the factors which appear to modulate HUFA profiles in tissues (dietary intake; differential tissue responses to fatty acid intakes with particular relevance to the relationships between liver and extrahepatic tissues; relations between the intake and incorporation of HUFA into plasma and cell lipids and the dietary energy intake; interactions between fatty acid series and between HUFA and antioxidants). We also discuss the influences of modified HUFA profiles in various cells on functional parameters, assessed in response to cell activation.

FACTORS AFFECTING HUFA PROFILES IN TISSUES

Fatty Acid Metabolism

The major site of the metabolism of PUFA is the liver, where, in the endoplasmic reticulum, dietary unsaturated fatty acids are modified through desaturation and elongation reactions. These types of reactions are discussed in detail in Dr. Sprecher's chapter. Although data on desaturation and elongation rates may be useful for appreciating the rates of fatty acid metabolism under various conditions, as has been pointed out by Sprecher (1), they do not allow us to predict the effects of

supplementation with unsaturated fatty acids on the fatty acid profiles of cell membranes. Other parameters, such as specificity for acylation processes, may prevail in determining the preferential incorporation of certain fatty acids in phospholipids. Rates of acylation reactions are undoubtedly much higher than those for desaturation and elongation (see Dr. Sprecher's chapter) and thus acylation processes may play a more important role in modulating the incorporation of fatty acids in selected phospholipid pools.

Coupling of the metabolism of PUFA to membrane lipid biosynthesis appears also to be an important process in modifying tissue fatty acid composition, at least in the liver (1). Metabolic studies carried out in various laboratories by incubating liver microsomes with labeled substrates have shown different rates of conversion for fatty acids with different degrees of unsaturation and belonging to different series. Metabolic data coupled with data obtained in animal experiments carried out by feeding different fatty acids have also led to the concept of competition between substrates for the desaturation steps. More specifically, the well-known accumulation of 20:3 n-9 during essential fatty acid (EFA) deficiency (3) and that of 22:5 n-6 during a deficiency of n-3 fatty acids (4) are usually explained as a consequence of the released inhibition in the desaturation and elongation of oleic acid and 20:4 n-6, respectively. However, alternative explanations which have been proposed (1) are that competition between PUFA of the different series occurs in phospholipid acylation processes, or that different turnover rates of phospholipids with different types of PUFA may result in accumulation of certain fatty acids.

A generally accepted concept concerning fatty acid metabolism is that the liver is the major site of formation and that extrahepatic cells and tissues take up fatty acids from plasma for further modification by metabolic conversion and by additional processes.

The types of mechanisms which control the fatty acid profiles in cells (for an overview, see ref. 5) are listed in Table 1. Reactions taking place in the endoplasmic reticulum appear to predominate in the liver, whereas reactions in the plasma membranes and other organelles are relevant in extrahepatic tissues and especially in circulating cells.

TABLE 1. *Enzymes involved in maintenance of fatty acyl group composition*

Reactions occurring in endoplasmic reticulum
Elongation and desaturation of precursor fatty acids
Formation of phosphatidate and other phosphoglycerides
Phospholipid exchange enzymes
Membrane synthesis
Transport of lipids and proteins to plasma membrane
Reactions taking place in plasma membrane and other organelle membranes
Phospholipase action
Acylation
Transacylation
Headgroup exchange

HUFA in Liver and Extrahepatic Tissues

An understanding of the role of liver as key organ for fatty acid metabolism and as a store of PUFA for supply to other tissues comes from nutritional and metabolic studies. In rats born to mothers fed an EFA-deficient diet during pregnancy and lactation, and subsequently fed the EFA-deficient diet after weaning (6), levels of arachidonate in liver (mg/g tissue) decline within a few weeks, reaching at 40 days a value of about 10% of the values at birth (Fig. 1). This value was not subsequently reduced any further. Levels of 20:3 n-9 increased very slowly during the same period of time. In brain, in contrast to the situation in liver, arachidonate continued to accumulate after birth, though reaching, at 40 days, a value about 20% lower than in EFA-supplemented animals. After 40 days of age, when the concentration of arachidonate in liver reached its minimum value, 20:3 n-9 started to accumulate in brain. These results indicate that during EFA deficiency the liver supplies arachidonate to the brain, where it accumulates until liver stores are available. After the liver is depleted of n-6 PUFA, the brain starts accumulating n-9 PUFA. The central role of the liver in synthesizing and providing arachidonate to extrahepatic tissues for membrane synthesis has been confirmed in a more recent study (7), showing decline of arachidonate in liver lipids, but conservation in heart and kidney cortex phospholipids in EFA-deficient mice. In the same study it was shown that labeled arachidonate, which was rapidly taken up in the liver, was released over a period of time by this organ, being mobilized for acylation into heart and kidney phospholipids. In this and other studies on the effects of EFA deficiency on tissue fatty acids it was shown that the total level of unsaturation (unsaturation index) of individual phospholipids was not modified in extrahepatic tissues such as the brain, due to the replacement of HUFA of the n-6 series (mainly arachidonate) by 20:3 n-9, whereas reduction of total unsaturation occurred in liver as a consequence of the marked decrease of arachidonate compensated by only a modest accumulation of the n-9 PUFA.

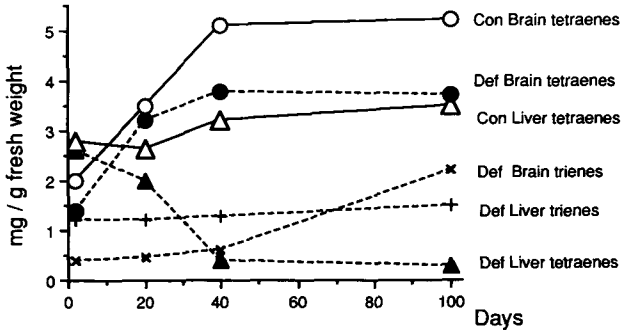


FIG. 1. Time course of the levels (mg/g fresh weight) of tetraenoic fatty acids (20:4 + 22:4 n-6) and of trienoic fatty acids (20:3 + 22:3 n-9) in brain and liver of control and EFA-deficient rats. Con, control; Def, deficient.

Although the uptake of fatty acids by various types of cells from plasma is a generally recognized process, limited information is available concerning the incorporation into tissues of fatty acids mobilized from the liver. In fact, the mechanisms responsible for the delivery from plasma to extrahepatic cells of linoleic acid, which is not synthesized by animal cells, and of arachidonic acid, which is not easily formed from its precursor, have not been fully elucidated. It has been recently shown, however, that low density lipoproteins (LDL) deliver arachidonate for prostaglandin synthesis to fibroblasts through high affinity receptor-mediated mechanisms (8). This is, possibly, a general mechanism for arachidonate delivery to cells expressing high numbers of LDL receptors and also a high activity of PGH synthetase.

The liver plays also a central role in supplying the long chain n-3 fatty acids—e.g., docosahexaenoic acid (DHA), which is primarily generated in this organ from dietary α linolenic acid (18:3 n-3) through desaturation and elongation reactions—to the brain and the retina (9). The highly unsaturated n-3 fatty acids are utilized for the synthesis of phospholipids which are released from the liver in the bloodstream in the form of lipoproteins. It has been proposed that the uptake of the n-3 HUFA in the retina operates through an apolipoprotein E LDL receptor, which has been found in developing photoreceptor cells (10).

Liver-Extrahepatic Tissue Relationships in Feeding Studies

The different balance between the reactions listed in Table 1 (mainly FA metabolism *vs.* phospholipid remodeling in membranes) in liver and extrahepatic tissues, explains why the patterns of tissue fatty acids are changed in different ways in the liver and in other tissues after feeding PUFA. For instance, after feeding diets (11) with high (10% of energy) (HL) or low (2.5%) (LL) LA content to rabbits, it was observed, when comparing the HL with the LL group, that both LA and arachidonate accumulated in livers of the HL group, as expected, but in platelets, in contrast, arachidonate was depleted, being replaced by LA. Somewhat similar findings were observed in human studies (12) in which elevation of the LA content in the diet resulted in a lower arachidonate/linoleate ratio in platelets. In addition it was found that the unsaturated index (UI) of platelet lipids was not affected in either study by the change in the LA content in the diet, whereas in the animal study it appeared that this index was affected by the diet in liver. These data indicate that the prevailing process concerning PUFA metabolism in liver is the conversion of LA to arachidonate; so after high LA, the more LA that enters the liver, the more is converted to arachidonate, with only slight effects on the arachidonate/linoleate ratio. The accumulation of both PUFAs in liver also results in elevation of the UI. In platelets, by contrast, the prevailing process appears to be replacement of arachidonate by LA, the total level of PUFA and the UI of lipids remaining constant.

A more detailed picture of the differences in fatty acid accumulation in liver *vs.* other tissues after feeding, e.g., increasing levels of LA, is presented in Fig. 2, which shows the relationships between relative LA and arachidonate levels in liver and in

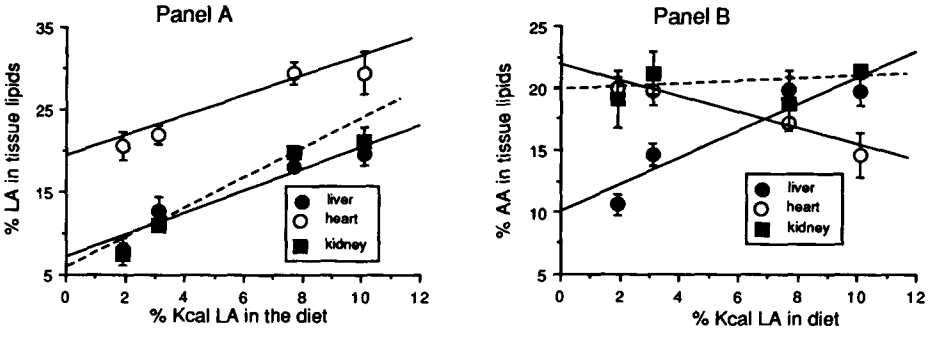


FIG. 2. Relationships between levels of linoleic acid (LA) in the diet as % of energy intake and levels, as % of tissue fatty acids, of LA (*Panel A*), and of arachidonic acid (AA) (*Panel B*) in liver, heart, and kidneys.

other organs of rats fed isoenergetic, semisynthetic diets containing from 2% to 10% of energy as LA (from 9% to 48% of dietary fatty acids). It is evident that, while LA increased as percentage of total fatty acids in liver, heart, and kidney with increasing intake of LA in the diet, changes of arachidonate levels followed very different trends in the various organs. Arachidonate was increased in the liver, whereas it was not modified in kidney and tended to decrease in heart. Similarly, with increasing dietary LA, the total level of saturation (now shown) increased in liver and, somewhat less, in kidneys, but it decreased in heart. We have already mentioned that in EFA deficiency the UI is not modified in brain phospholipids, whereas it is reduced in liver phospholipids. The different types of interactions between PUFA in liver and other tissues, e.g., the heart, are also apparent when, in the above study with increasing amount of LA in the diet, we considered the relationships between dietary LA and the levels of n-3 fatty acids in liver and heart (Fig. 3). The levels of EPA and DHA in liver were not affected by dietary LA, whereas DHA levels, similar to those of arachidonate, were reduced with increasing dietary LA. This again

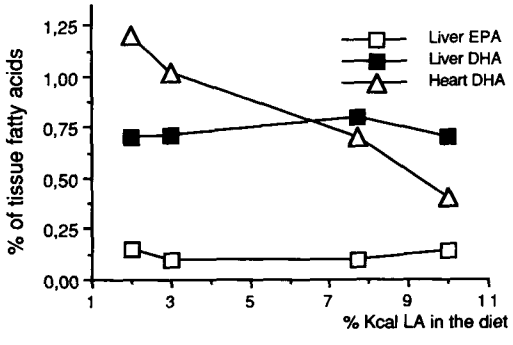


FIG. 3. Relationships between levels of linoleic acid (LA) in the diet as % of energy intake and levels of EPA and DHA, as percentage of tissue fatty acids, in liver and heart.

indicates that in heart, displacement of n-3 fatty acids by increasing dietary LA was the major process, whereas in liver, the enhanced LA pool did not interfere with n-3 fatty acid pools.

As shown by these examples, the different responses of PUFA profiles in liver and other tissues to changes of the intake of unsaturated fatty acids with the diet make it rather difficult to predict the impact of dietary manipulations on tissue fatty acids, and, indirectly, on functional parameters that are dependent upon or correlated with fatty acid pools. In addition, the metabolic relationships between liver and extrahepatic tissues may play a role in inducing alterations in the fatty acid profiles in tissues as a consequence of liver diseases. In liver cirrhosis (13), for instance, levels of arachidonate in platelet lipids are reduced, possibly as a result of impaired synthesis in the damaged organ.

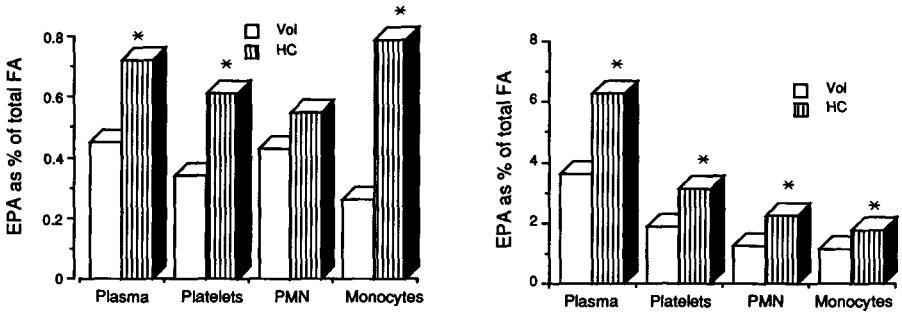
ACCUMULATION OF HUFA IN PLASMA AND CELL LIPIDS IN HYPERCHOLESTEROLEMIA AND IN RELATION TO FAT INTAKE

Data on the favorable effects of dietary n-6 and/or n-3 fatty acids on plasma lipids and thrombotic parameters in animal and human studies have led to the generally accepted recommendation that the intake of these compounds should be increased in order to prevent a rise in serum cholesterol and its vascular complications. Limited information is, however, available on the status and metabolism of LCPUFA in hypercholesterolemic subjects. We have found that the levels of arachidonic acid in platelet phospholipids of type IIa hypercholesterolemic patients were higher than in normocholesterolemic subjects (14), suggesting that the processes responsible for uptake, incorporation, or utilization of this fatty acid are affected by altered lipoprotein metabolism.

In addition, we have treated both normocholesterolemic subjects (five healthy volunteers with serum cholesterol ranging from 165 to 220 mg/dl, and on a typical Western diet, with fat contributing about 36% of energy and about 2,400 kcal/day), and eight moderately hypercholesterolemic patients (type IIa with average serum cholesterol of 290 mg/dl, on a prudent diet with 1,700 kcal/day and 30% fat), for a period of 6 weeks, with highly enriched preparations of EPA + DHA ethyl esters (2.7 and 1.6 g/day, respectively). We found that, in the hypercholesterolemics, levels of EPA and DHA in plasma and circulating cells were considerably higher than in controls both before and after treatment (Fig. 4). This suggests that some aspect of n-3 fatty acid metabolism (e.g., plasma transport, incorporation into cells) is also modified by hypercholesterolemia. It should be borne in mind, however, that in the above treatment schedule, the patients were on a relatively low fat intake and this might have affected n-3 fatty acid incorporation in plasma and cell lipids, especially after supplementation.

PUFA AND ANTIOXIDANTS

Highly unsaturated fatty acids are susceptible to oxidative alterations, which are blocked by natural lipid-soluble compounds with antioxidant properties such as the



* Significantly different from volunteers

FIG. 4. Levels of EPA in plasma, monocyte, and polymorphonuclear leukocyte lipids in hypercholesterolemic (HC) subjects on a low fat diet or in normocholesterolemics (Vol) on a regular diet treated with 2.7 g/day of EPA and 1.6 g/day DHA for 6 weeks.

tocopherols, and, in biological systems, by enzymatic processes cooperating with lipid antioxidants in the prevention of and protection from oxygen-generated radicals.

In nature, fats rich in PUFA also contain high levels of lipid antioxidants, such as the tocopherols and other compounds, but in the preparation of oils and fats and in their use for cooking, some loss may occur. Adequate levels of vitamin E in the diet are recommended in order to control lipid peroxidation processes and to prevent cell damage resulting from generation of lipid peroxides. Dietary requirements for vitamin E are obviously dependent upon the intake of PUFA, and thus the use of preparations enriched with HUFA of the n-3 series, with five and six double bonds, may result in shortage of vitamin E in tissues.

The administration of fish oil concentrates has, indeed, been shown to induce a depletion of circulating levels of α-tocopherol (15). Furthermore we have observed (16) that the administration of n-3 fatty acids (MaxEPA) supplemented with additional α-tocopherol, up to 10 mg/ml *vs.* the original 1 mg/ml of the preparation, to rats fed a standard laboratory chow, induced a significant change in the proportion of n-6 PUFA in plasma and circulating cells, when compared to the n-6 fatty acid profiles obtained with the administration of MaxEPA without the vitamin supplement. In fact, levels (Table 2) of LA were significantly higher in plasma and those of arachidonate significantly higher in platelets, red blood cells, and especially in polymorphonuclear leukocyte lipids, after 8 weeks of administration with 3.2 ml/kg/day MaxEPA containing the α-tocopherol supplement. In contrast, vitamin E supplementation did not affect the levels of 20:5 and 22:6 in the same samples. It appears, thus, that the effects of n-3 fatty acids on the profile of n-6 in plasma and cells are modulated by the availability of lipid antioxidants, and this represents an additional type of interaction between dietary fatty acids, on the one hand, and the metabolism and accumulation of PUFA in cells and tissues on the other.

TABLE 2. *Levels of n-6 and n-3 PUFA in plasma and cell lipids*[a]

Fatty acids	Plasma		Platelets		Red blood cells		PMN	
	−Vit E	+Vit E	−Vit E	+Vit E	−Vit E	+Vit E	−Vit E	+Vit E
18:2	25.6	**28.7**	11.3	10.5	11.9	11.8	10.0	10.1
20:4	9.4	**10.7**	19.8	**20.9**	18.4	**19.6**	11.2	**17.4**
20:5	1.2	1.0	4.4	3.9	1.9	1.8	2.0	1.7
22:6	3.0	3.0	2.6	2.6	4.1	4.0	6.2	6.4

[a] Values in bold differ from the corresponding values in regular typeface.
PUFA, polyunsaturated fatty acids; PMN, polymorphonuclear leukocytes.

PUFA AND CELL FUNCTION

This aspect is discussed by other authors in this volume. However, some consideration should be given in this chapter to the type of relationship between HUFA in cell lipids and functional parameters, which can be studied, for instance, during cell activation.

The impact of diet-induced modifications of the fatty acid profiles in cells on cell functions is generally attributed to alterations of the eicosanoid pathway, as a consequence of variations of the fatty acid precursor levels. Modified formation of metabolites derived from arachidonate and/or formation of compounds derived from EPA, when this fatty acid accumulates in cell lipids, have been shown as a consequence of manipulation of dietary fatty acids. It becomes, however, evident from various studies that other processes, in addition to those mediated by the eicosanoid system, are affected by diet-induced changes in cell fatty acids. Furthermore, different types of cells are differently affected by modifications of dietary fatty acids.

Among the processes involved in cell activation which have been reported to be modified by changes of the fatty acid composition of the diet, we wish to highlight in particular those concerning the formation of inositol phosphates by stimulated cells. The administration of isoenergetic diets enriched in either n-9 (olive oil), or n-6 (corn oil), or n-3 (MaxEPA) fatty acids to rabbits for a period of 5 weeks resulted in corresponding changes of the fatty acid profiles in plasma and platelet lipids (17). The formation of total inositol phosphates (IP) and the proportions among the various components (IP_3, IP_2, and IP) by platelets stimulated with thrombin were also significantly modified by the types of fatty acid in the diet. The lowest accumulation of IP_3, the product which is involved in the activation of calcium mobilization in the stimulated cell, was observed in platelets enriched in the n-3 fatty acids. This modification, which in the particular dietary conditions of the study was independent of changes in thromboxane formation by stimulated platelets, indicates that the phospholipase C pathway was affected by dietary fatty acids in a way which was not directly related to the eicosanoid system. We have also observed a reduction in total inositol phosphate production by thrombin-stimulated platelets and a change in the balance among the various products, in male volunteers treated for 6 weeks, while

remaining on a conventional diet, with EPA plus DHA ethyl ester preparations (6 capsules/day containing a total of 2.7 g EPA and 1.6 g DHA) (18).

In another recent study, the incorporation of EPA or arachidonate in cultured myocardial cells resulted in gross differences in the fluctuations of cytosolic free calcium concentrations and of the changes in amplitude and frequency of contraction following exposure to ouabain (19). These, and other examples indicate that the proportions of HUFA in cell lipids, which can be modified by diet, influence a number of incompletely explored functional parameters. An additional point concerning the influence of diet-induced modifications of cell fatty acids on cell function is that different cells may be differently affected. In the above study carried out by administering EPA and DHA ethyl esters to volunteers, we have observed, for instance, that after treatment the production of superoxide anion by stimulated monocytes, but not from polymorphonuclear leukocytes, was significantly reduced.

CONCLUSION

In conclusion, the relationships between dietary PUFA and the fatty acid profiles of different cells and tissues are complex and appear to be dependent upon various factors and processes. Among them, the following appear to be relevant: 1) in the diet, the absolute amounts, the relative proportions among different PUFA, and their relationships with the energy intake and with dietary antioxidants; 2) in the body, the combined effects of desaturation and elongation reactions (mainly occurring in the liver) with processes at the membrane level, predominant in extrahepatic tissue, responsible for phospholipid remodeling and based upon deacylation-reacylation reactions, and coupled with membrane lipid synthesis. The relationships between the supply of PUFA by the liver to extrahepatic tissues, through poorly studied mechanisms, and the processes at membrane level, dictate the fatty acid profile in lipids of different cell types.

Alterations in lipid and lipoprotein transport, such as the hyperlipemias, appear to affect the metabolism and turnover of n-6 and n-3 PUFA. This aspect deserves investigation since supplementation of the diet with high levels of these fatty acids is recommended as an important step for the prevention of atherosclerosis and cardiovascular diseases.

Finally, modified HUFA levels in cell membranes affect functional parameters through mechanisms which indicate that fatty acids in membranes modulate processes in the transduction of stimuli and in the early activation phase in response to various agents.

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DISCUSSION

Dr. Strandvik: When you presented the data about the different fatty acids in different organs in relation to the linoleic acid contained in the diet, did you look at lipids of different polarity, and have you looked at different phospholipid classes? There could be tremendous changes in these in the absence of major changes in the lipid contents of different fatty acids.

Dr. Galli: An important point. We have found very different relationships between the accumulation of linoleic acid and arachidonic acid in plasma and liver following increased

dietary intake of linoleic acid. In plasma, linoleic acid accumulates mainly in triglycerides and arachidonic acid mainly in cholesterol esters, whereas in liver, arachidonic acid mainly enters in phospholipids. The accumulation of arachidonic acid in the cholesterol ester pool may be mediated by the plasma LCAT activity, which transfers arachidonic acid from phospholipids to cholesterol esters. There are also differences when the incorporation of exogenous fatty acids in lipid pools is studied in cell culture.

Dr. Jeremy: You showed that there was a change in lipid profiles in the heart and you mentioned that this may relate to functional changes. What functional changes?

Dr. Galli: I am referring to data showing that n-3 fatty acids in heart muscle have antiarrhythmic properties. It appears that the higher the 22:6 content in the heart the less sensitive is the organ to arrhythmogenic agents (1,2). When 22:6 is decreased in the heart, as occurs during high dietary linoleic acid intake, the heart muscle may become more sensitive to arrhythmogenic conditions. The effects of n-3 fatty acids appear to be mediated by changes in Ca^{2+} mobilization within the cell.

Dr. Jeremy: PUFA have also been shown to inhibit calcium-linked potassium channels.

Dr. Crawford: We have been studying the effects of GLA-rich oils on heart and liver tissue over time. In the first 1–8 days the concentrations of arachidonic acid increase in the choline phosphoglycerides and later in the ethanolamine phosphoglycerides, though not as much as in the choline. What is interesting is that in the first 8 days you don't see any change in heart tissue phosphoglycerides, although the liver has already responded during this time. So there is a distinct delay in the way in which the heart takes up these fatty acids, which is quite consistent with your data.

Dr. Strandvik: In rats with essential fatty acid deficiency we have found tremendous differences in uptake of labeled arachidonic acid and linoleic acid in the heart compared with control rats. The uptake was very different in the different fractions, the most significant increase being in phosphatidylethanolamine. There are profound changes in cardiolipin in the heart. We followed the incorporation for 4 hours after giving labeled essential fatty acids orally or in chylomicrons. The increase occurs within 4 hours and the proportion of linoleic is 22% compared with 2% in controls.

Dr. Crawford: You are looking at a situation where there is severe arachidonic acid deficit in the cell membranes. We are looking at something quite different—that is, the effect of increasing the levels of arachidonic acid in different membrane fractions in animals receiving a normal diet. This is a different situation from essential fatty acid deficiency.

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