Dietary Linoleic Acid and Polyunsaturated Fatty Acids in Rat Brain and Other Organs. Minimal Requirements of Linoleic Acid

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Starting three weeks before mating, 12 groups of female rats were fed different amounts of linoleic acid (18:2n-6). Their male pups were killed when 21-days-old. Varying the dietary 18:2n-6 content between 150 and 6200 mg/100 g food intake had the following results. Linoleic acid levels remained very low in brain, myelin, synaptosomes, and retina. In contrast, 18:2n-6 levels increased in sciatic nerve. In heart, linoleic acid levels were high, but were not related to dietary linoleic acid intake. Levels of 18:2n-6 were significantly increased in liver, lung, kidney, and testicle and were even higher in muscle and adipose tissue. On the other hand, in heart a constant amount of 18:2n-6 was found at a low level of dietary 18:2n-6. Constant levels of arachidonic acid (20:4n-6) were reached at 150 mg/100 g diet in all nerve structures, and at 300 mg/100 g diet in testicle and muscle, at 800 mg/100 g diet in kidney, and at 1200 mg/100 g diet in liver, lung, and heart. Constant adrenic acid (22:4n-6) levels were obtained at 150, 900, and 1200 mg/100 g diet in myelin, sciatic nerve, and brain, respectively. Minimal levels were difficult to determine. In all fractions examined accumulation of docosapentaenoic acid (22:5n-6) was the most direct and specific consequence of increasing amounts of dietary 18:2n-6. Tissue eicosapentaenoic acid (20:5n-3) and 22:5n-3 levels were relatively independent of dietary 18:2n-6 intake, except in lung, liver, and kidney. In several organs (muscle, lung, kidney, liver, heart) as well as in myelin, very low levels of dietary linoleic acid led to an increase in 20:5n-3. Dietary requirements for 18:2n-6 varied from 150 to 1200 mg/100 g food intake, depending on the organ and the nature of the tissue fatty acid. Therefore, the minimum dietary requirement is estimated to be about 1200 mg/100 g (i.e., the level that ensures stable and constant amounts of arachidonic acid).

***Lipids 25,* 465–472 (1990).**

There have been many studies of essential polyunsaturated fatty acids since the first report by Burr and Burr (1). Linoleic acid is now universally recognized to be an essential nutrient. On the other hand, α-linolenic acid was considered non-essential until recently. The effects of polyunsaturated fatty acid deficiency have been extensively studied; prolonged deficiency leads to death in animals. This deficiency is partially corrected in cellular structures by the endogenous synthesis of polyunsaturated fatty acids from oleic acid, which can itself be synthesized *de novo*. However, the resulting fatty acid has only 20 carbon atoms and 3 double bonds (2–4).

Polyunsaturated fatty acid deficiency alters the composition and structure of membranes in all types of cells, including those of the nervous system. The presence of α-linolenic acid, as well as various dietary, hormonal, or toxic factors, can affect linoleic acid metabolism (5–7). Essential fatty acid deficiency affects all nerve functions, including conductivity, and there are changes in the electroretinogram and in behavior (8,9). The effects of deficiency have also been described in man and can result from maternal or perinatal deficiency, undernutrition in the adult, or unsuitable enteral or parenteral feeding (10,11).

The polyunsaturated fatty acids in membranes are not the same as the dietary precursors (linoleic and α-linolenic acids), but have longer and more highly unsaturated chains (mainly arachidonic and cervonic acids). These acids, in particular arachidonic acid, are the precursors of important hormonal substances (prostaglandins and leukotrienes), but their structural role is also important (4) since they play a major role in the structure, enzymatic activities, and function of the membrane (12–15).

Studies carried out in man and in animals have suggested that the minimal dietary requirement of linoleic acid is probably about 3–5% of calories (i.e., 1.5–2.5 g/100 g food intake). The variability in requirements of different organs has not been studied. Our previous results showed that the minimal α-linolenic acid requirement (i.e., to maintain a constant amount of 22:6n-3 in the various organs) in the developing rat is 0.4% of calories (200 mg/100 g food intake) in all organs studied (16). A deficiency in α-linolenic acid is reflected in a decrease in cervonic acid (22:6n-3) in all cerebral cells and organelles, and this is compensated for by an increase in 22:5n-6 (16,17).

The objective of this work was to determine the linoleic acid requirement of the brain and other organs when the requirement in α-linolenic acid was concurrently satisfied. Requirements are defined as the minimal amount of linoleic acid that maintains a constant amount of 20:4n-6 in all tissues, and the minimal amount of dietary α-linolenic acid to obtain a constant amount of 22:6n-3 in all tissues being 0.4% of calories (16).

MATERIAL AND METHODS

A strain of Wistar rats was given a semi-synthetic diet containing 2% sunflower oil for at least two generations to stabilize fatty acid content in all tissues. The diet was prepared in our laboratory. The overall composition of the diet is given in Table 1. It includes a vitamin supplement containing vitamin E as an antioxidant. Three weeks before mating, 12 groups of 8 females were fed one of 12 diets differing in their linoleic and α-linolenic acid content (six groups were fed a diet containing 150 mg/100 g α-linolenic acid, the other six received a diet containing 300 mg/100 g). Three days after parturition, the litters were adjusted to 10 animals.

In each of the 12 diets (containing 5% lipids), the

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Abbreviations: ANOVA, analysis of variance, EPA, eicosapentanoic acid.

linoleic acid content was obtained by mixing different quantities of rapeseed, soybean, linseed, or hydrogenated palm oil (Table 2). The fatty acid contents of the diets are given in Table 3. The n-6/n-3 ratio ranged from 1 to 10, and the maximum dietary linoleic acid content was 3000 mg/100 g. A 13th diet, containing 10% lipids, consisted of a mixture of soybean and sunflower oil so as to supply 6200 mg linoleic acid and 300 mg α-linolenic acid.

Animals were housed in plastic cages, humidity and temperature were kept constant (65% and 21°C, respectively) and a 12-hr day-night cycle was maintained. There were no significant differences in food intake or body weight between groups.

Twenty-one-day-old rats were killed by decapitation followed by exsanguination. Organs were removed and any remaining blood washed out. Myelin and nerve endings (synaptosome) were prepared as previously described and their purity determined by electron microscopy, enzyme marker assay, and characterization of specific proteins by electrophoresis and radioimmunoassay (17).

Total lipids were extracted using a modification of Folch's method and methyl esters were obtained according to Morisson and Smith (18) and analyzed by capillary column gas chromatography as previously reported (17). Statistical analyses were performed using Students t-test or analysis of variance (ANOVA). Data are given as means, and S.D. were always less than 15%.

Analyses on whole organs were performed on at least six individual animals from at least three different litters. Six retinas from three animals were pooled and three pools were analyzed. Myelin and nerve endings were prepared from four pooled animals and five preparations from five different litters were used in the experiments.

TABLE 1

Diet Constituents[a]

	Sunflower oil (g/kg)	Experimental 5% Lipid (g/kg)	Experimental 10% Lipid (g/kg)
Delipidated casein	220	220	220
DL-methionine	1.6	1.6	1.6
Cellulose	20	20	20
Starch	463.4	443.4	405.4
Saccharose	225	215	203
Oil	20	50	100
Vitamin supplement	10	10	10
Mineral supplement	40	40	40

[a]The diet containing sunflower oil was fed to the rats before the animals received the experimental diet. The experimental diet contained a mixture of various oils (see Table 2). Composition of the vitamin supplement (United State Biochemical Corp., Cleveland, OH; mg/kg, triturated in dextrose) was as follows: α-tocopherol (1000 i.u./g), 5.0; L-ascorbic acid, 45.0; choline chloride 75.0; D-calcium pantothenate, 3.0; inositol, 5.0; menadione, 2.25; niacin 4.5; para-aminobenzoic acid, 5.0; pyridoxine HCl, 1.0; riboflavin, 1.0; thiamin HCl, 1.0; retinol acetate , 900,000 i.u.; ergocalciferol (vitamin D_2), 100,000 i.u.; biotin, 20 mg; folic acid, 90 mg; vitamin B_{12} 1.35 mg. The caloric density was 3780 Kcal/kg.

TABLE 2

Oil Content of Diets Varying in Linoleic Acid[a]

n-6/n-3 ratio	n-3 = 300 mg/100 g		n-3 = 150 mg/100g	
1	Rapeseed	25.40	Rapeseed	9.48
	Linseed	7.38	Linseed	4.10
	Hydrogenated palm	67.22	Hydrogenated palm	86.42
2	Rapeseed	66.80	Rapeseed	30.64
	Linseed	2.06	Linseed	1.38
	Hydrogenated palm	31.14	Hydrogenated palm	67.98
4	Rapeseed	56.03	Rapeseed	41.32
	Soybean	27.25	Sunflower	7.30
	Hydrogenated palm	16.67	Hydrogenated palm	51.38
6	Rapeseed	19.02	Rapeseed	41.08
	Soybean	64.78	Sunflower	17.18
	Hydrogenated palm	16.20	Hydrogenated palm	41.74
8	Soybean	83.70	Rapeseed	40.72
	Sunflower	9.62	Sunflower	27.16
	Hydrogenated palm	6.68	Hydrogenated palm	32.12
10	Linseed	9.76	Rapeseed	40.48
	Sunflower	90.24	Sunflower	37.36
			Hydrogenated palm	22.16

[a]Experimental animals were fed a 5% lipid diet.

TABLE 3

Fatty Acid Composition of Diets Varying in Linoleic Acid[a]

Fatty acids	n-3 = 300 mg						n-3 = 150 mg					
14:0	1.1	0.5	0.3	0.3	0.2	0.1	1	1	0.7	0.6	0.5	0.4
16:0	27.5	16.5	13	14.1	11.5	6.1	39.9	33.3	25.6	21.5	17.5	14.4
18:0	8.1	6	4.8	5.2	4.4	3.8	14.9	10.5	9.6	8.3	7.0	5.9
18:1n-9	48.2	57.4	46.2	31.8	23.2	21.3	37.7	39.8	47.4	46.2	44.2	42.7
18:1n-7	1.3	—	3.4	2.6	1.7	1.4	—	—	—	—	—	—
18:2n-6	6.7	12.6	25	38.8	51.7	60.6	3	6.9	12.7	19.3	26.2	32.1
18:3n-3	6.6	5.8	6.1	6.3	6.5	5.9	3	3.6	3.1	3.1	3.2	3.3
20:0	0.3	0.4	0.4	0.4	0.3	0.2	0.4	0.3	0.4	0.4	0.4	0.4
20:1n-7 + n-9	0.2	0.6	0.6	0.3	0.2	0.1	0.1	0.3	0.4	0.4	0.4	0.5
22:0	—	0.2	0.2	0.2	0.3	0.5	—	—	0.1	0.2	0.2	0.3
n-6/n-3 ratio	1.0	2.2	4.1	6.2	7.9	10.3	1	1.9	4.1	6.2	8.2	9.7

[a]Results are expressed in mg/100 mg fatty acids.

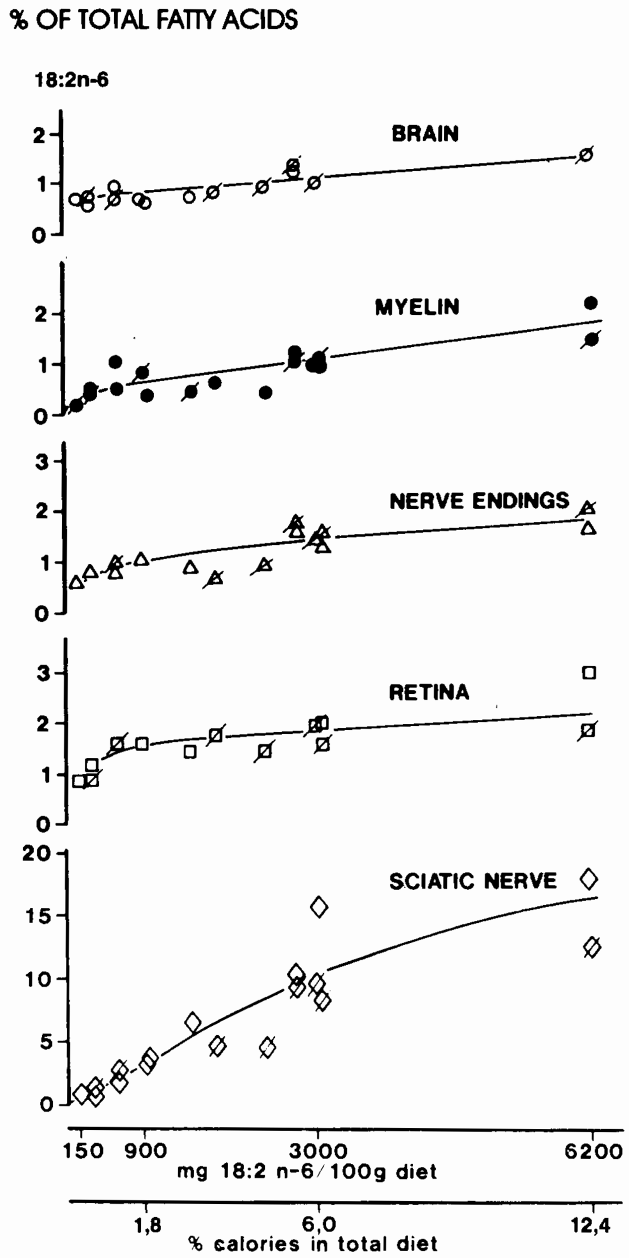

FIG. 1. Relationship between dietary content and concentration of linoleic acid in nervous tissues. Values are % of total fatty acids. All variations were statistically significant between 150 and 6200 mg linoleic acid/100 g diet ($p < 0.05$ for brain, myelin, nerve endings; $p < 0.01$ for sciatic nerve). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

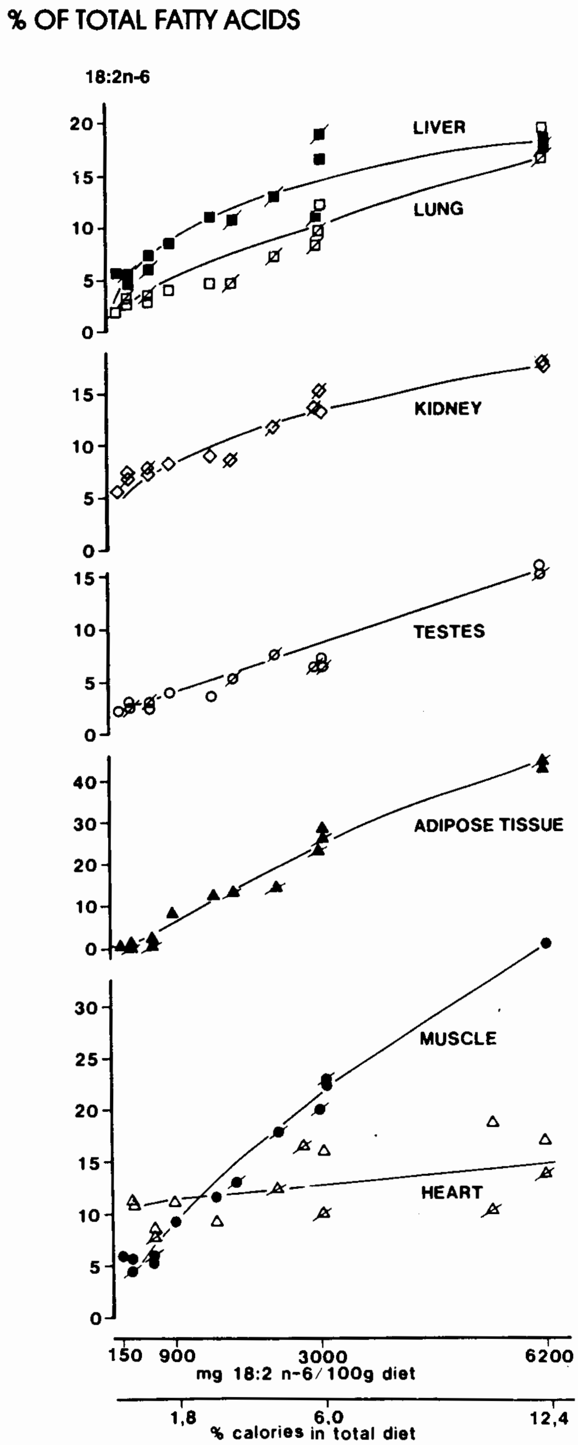

FIG. 2. Relationship between dietary content and concentration of linoleic acid in various organs. Values are % of total fatty acids. Except for heart, all variations were statistically significant ($p < 0.01$). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

RESULTS

Linoleic acid. In the nervous system (Fig. 1), the level of 18:2n-6 was very low (about 1% of fatty acids in brain, retina, synaptosomes, and myelin). Increasing dietary 18:2n-6 resulted in only a small increase in levels in brain, retina, synaptosomes and myelin; a 41-fold increase in dietary 18:2n-6 increased tissue levels to a maximum of 2% of total fatty acid. On the other hand, peripheral nerve (sciatic nerve) responded in a linear manner to increasing amounts of dietary 18:2n-6; a 41-fold dietary increase resulted in a nearly 20-fold increase of 18:2n-6 in sciatic nerve. At 6200 mg/100 g food intake, the amount of 18:2n-6 found in sciatic nerve represented 15% of total fatty acids.

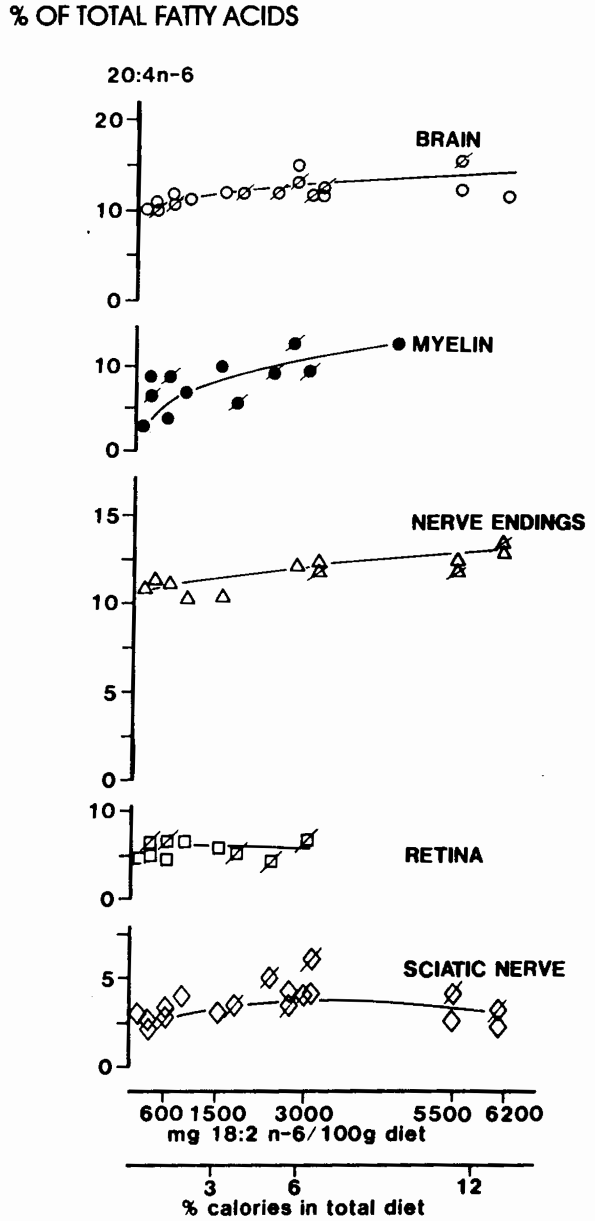

FIG. 3. Arachidonic acid concentration in nervous tissues in relation to dietary linoleic acid content. Values are % of total fatty acids. Except for myelin ($p < 0.05$), no significant variations were found. Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

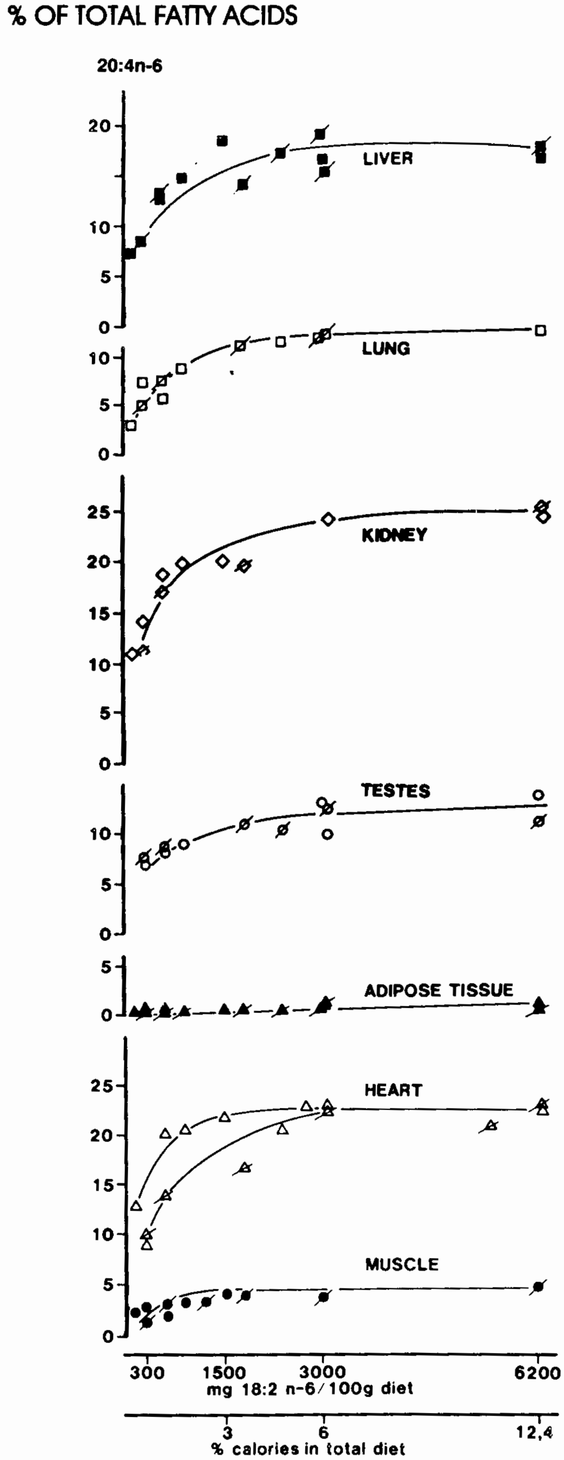

FIG. 4. Arachidonic acid concentration in various organs in relation to dietary linoleic acid content. Values are % of total fatty acids. Except for muscle and adipose tissue, all variations were statistically significant ($p < 0.05$ for testes, $p < 0.01$ for liver, lung, kidney, and heart). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

Accumulation of 18:2n-6 in nerve structures was independent of dietary α-linolenic acid (18:3n-3), both when dietary 18:3n-3 remained close to the optimal value (150 or 300 mg/100 g food intake, this study), or when dietary intake was very low (down to 20 mg/100 mg food, unpublished results).

In contrast to nervous tissue, all the other organs examined (Fig. 2) showed an increase in 18:2n-6 that was parallel to dietary 18:2n-6. This increase was marked in muscle (from 5% to 32% of fatty acids) and adipose tissue (from trace level to nearly 40%). In liver, lung, kidney, and testicle the increase was smaller; in heart a plateau was reached at 150 mg/100 g food intake.

Arachidonic acid (20:4n-6). The amount of 20:4n-6 was tightly controlled by the organism and was independent of dietary 18:3n-3. For nervous tissue, the constant level was reached at 150 mg 18:2n-6/100 g food intake

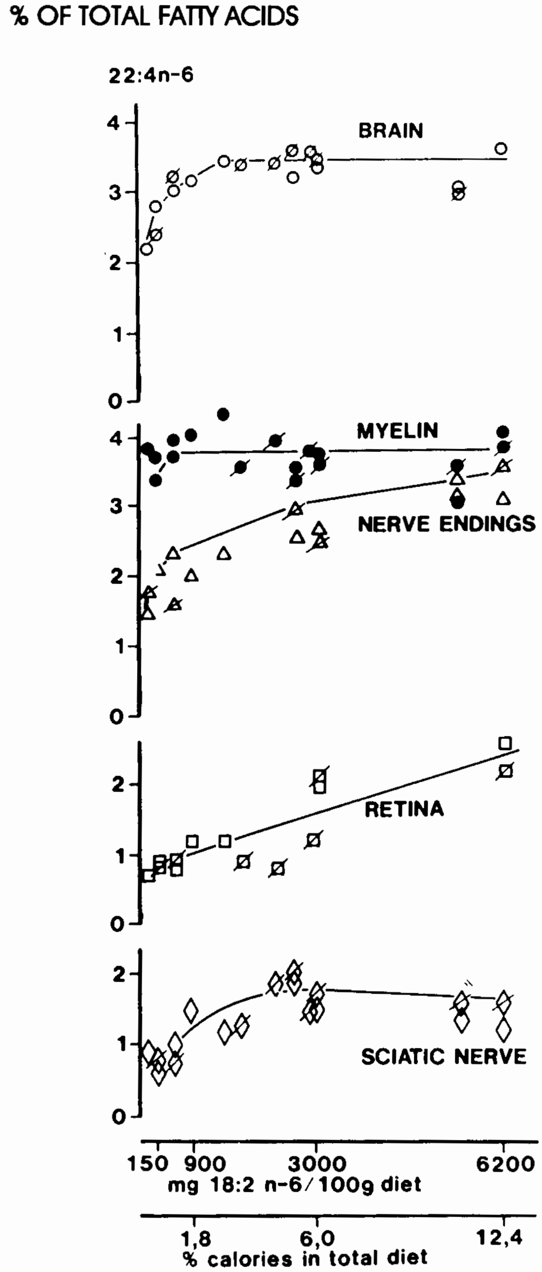

FIG. 5. Adrenic acid concentration in nervous tissues in relation to dietary linoleic acid content. Values are % of total fatty acids. Except for myelin, all variations were statistically significant ($p < 0.01$ for retina, nerve endings and brain; $p < 0.05$ for sciatic nerves). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

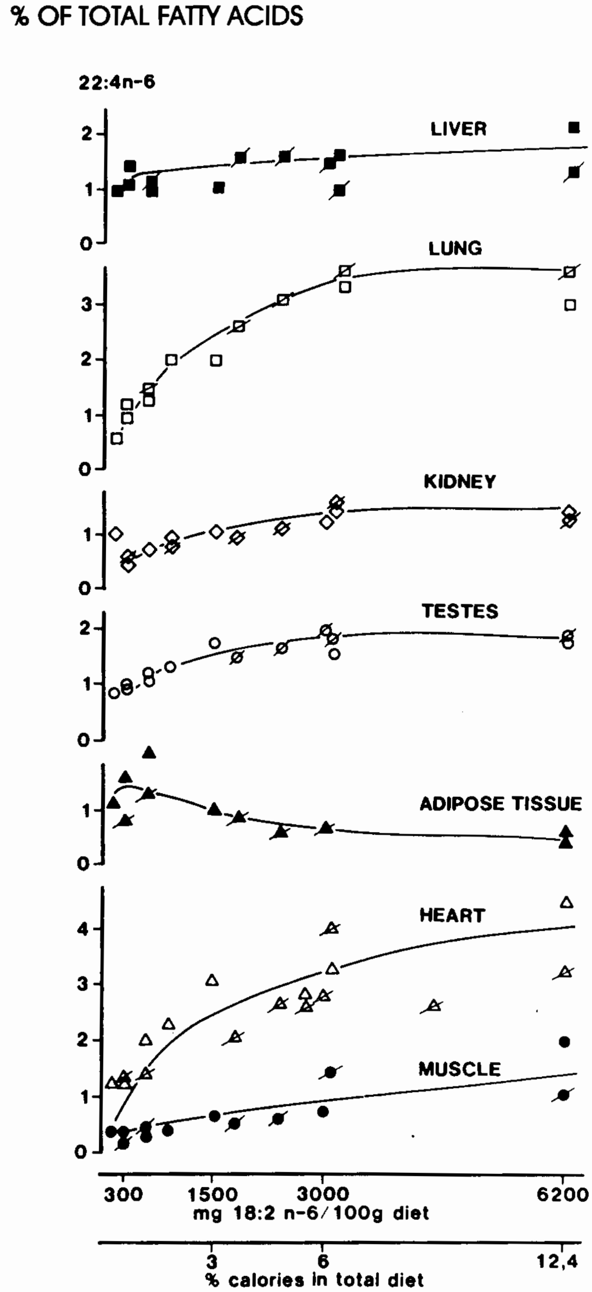

FIG. 6. Adrenic acid concentration in various organs in relation to dietary linoleic acid content. Values are % of total fatty acids. Except for liver and kidney, all variations were statistically significant ($p < 0.05$ for testes, adipose tissue and muscle, $p < 0.01$ for lung and heart). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

(Fig. 3). Above this concentration, 20:4n-6 levels remained stable in brain, retina, sciatic nerve, and synaptosomes. There was a slight increase in myelin. For other organs (Fig. 4), the quantity of 20:4n-6 increased parallel to dietary 18:2n-6 content until this reached 300 mg for testicle and muscle, 800 mg for kidney, and 1200 mg for liver, lung and heart. These values were independent of dietary 18:3n-3 content (150 or 300 mg/100 g diet), except for heart.

In adipose tissue, the increase was very small; excess dietary 18:2n-6 resulted in increased 18:2n-6 and not 20:4n-6.

Adrenic acid. In brain, myelin, and sciatic nerve, optimal levels of 22:4n-6 were attained at dietary 18:2n-6 levels of 1200 mg, 150 mg, and 900 mg/100 g food intake, respectively. For retina, there was a change in the slope at 150 mg (Fig. 5) and for synaptosomes at 900 mg. Tissue 22:4n-6 levels were independent of dietary 18:3n-3 (150

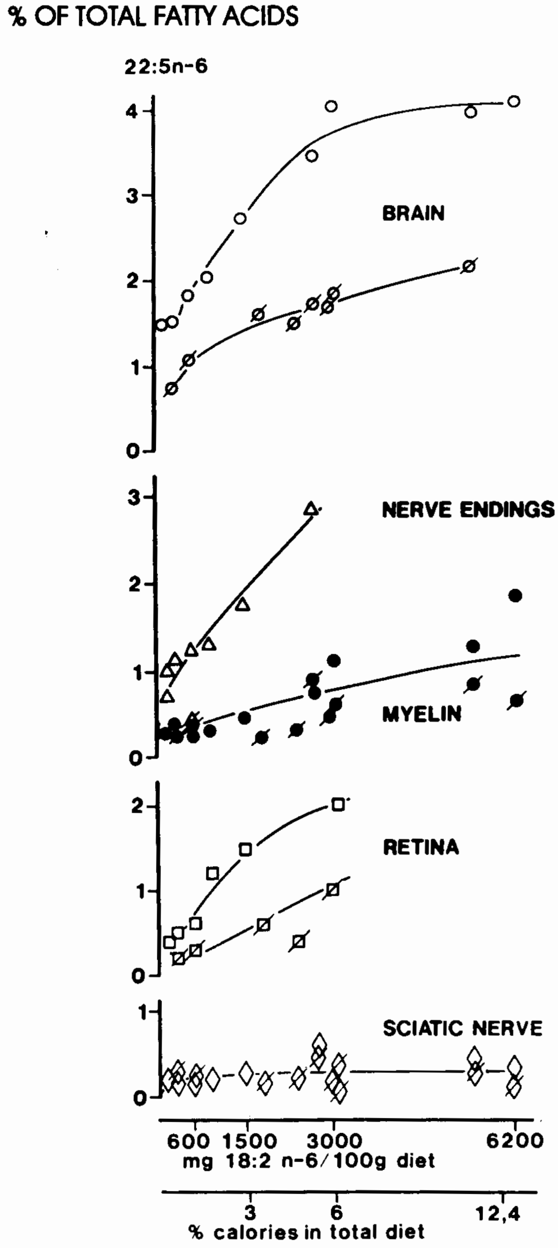

FIG. 7. Concentration of 22:5n-6 in nervous tissues as a function of dietary α-linolenic acid. Values are % of total fatty acids. Except for sciatic nerve, all variations were statistically significant ($p < 0.01$). Except for sciatic nerve values obtained with the 150 or 300 mg 183n-3/100 g diet are statistically significant ($p < 0.01$). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

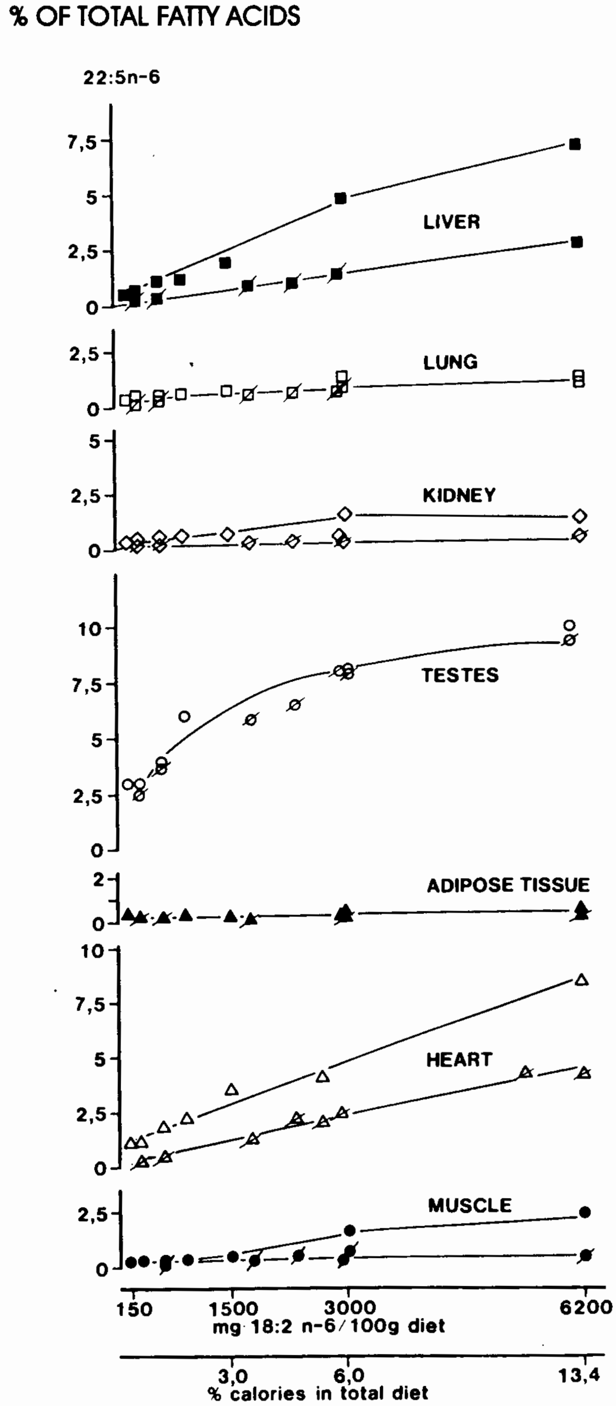

FIG. 8. Concentration of 22:5n-6 in various organs as a function of dietary α-linolenic acid. Values are % of total fatty acids. Except for adipose tissue and muscle (symbols with a bar), variations were statistically significant ($p < 0.01$). Except for testes, lung, and adipose tissue, values obtained with the 150 or 300 mg 18:3n-3/100 g diet were statistically different ($p < 0.01$) for dietary content of 18:2n-6 being equal or superior to 1500, 3000, 150, or 3000 mg 18:2n-6/100 g diet, in liver, muscle, heart, and kidney, respectively. Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

or 300 mg/100 g diet). In other organs, the amounts of 22:4n-6 present were very small (Fig. 6).

Docosapentaenoic acid. In nervous tissue, this fatty acid accumulated when dietary 18:2n-6 was increased (Fig. 7). This accumulation depended on dietary 18:3n-3 content for brain and retina but not for sciatic nerve and myelin. With increasing amounts of dietary 18:2n-6, the other organs accumulated both 18:2n-6 (Fig. 2) and 22:5n-6 (Figs. 7 and 8). This accumulation depended on dietary 18:3n-3 content for liver, heart and muscle, but not for testicle (for lung and adipose tissue, values were too low to show a statistical difference).

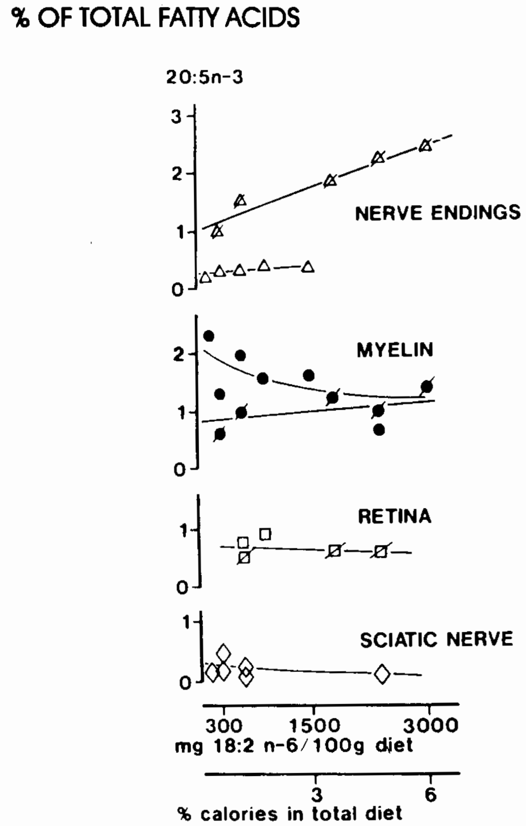

FIG. 9. Concentration of EPA in nervous tissues in relation to dietary linoleic acid content. Values are % of total fatty acids. Variations were statistically significant for nerve endings and myelin ($p < 0.05$) but not for retina and sciatic nerve. For nerve endings, all values obtained with 150 or 300 mg 18:3n-3 were statistically different ($p < 0.05$); for myelin it was statistically different only for 150 and 300 mg 18:2n-6/100 g diet. Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

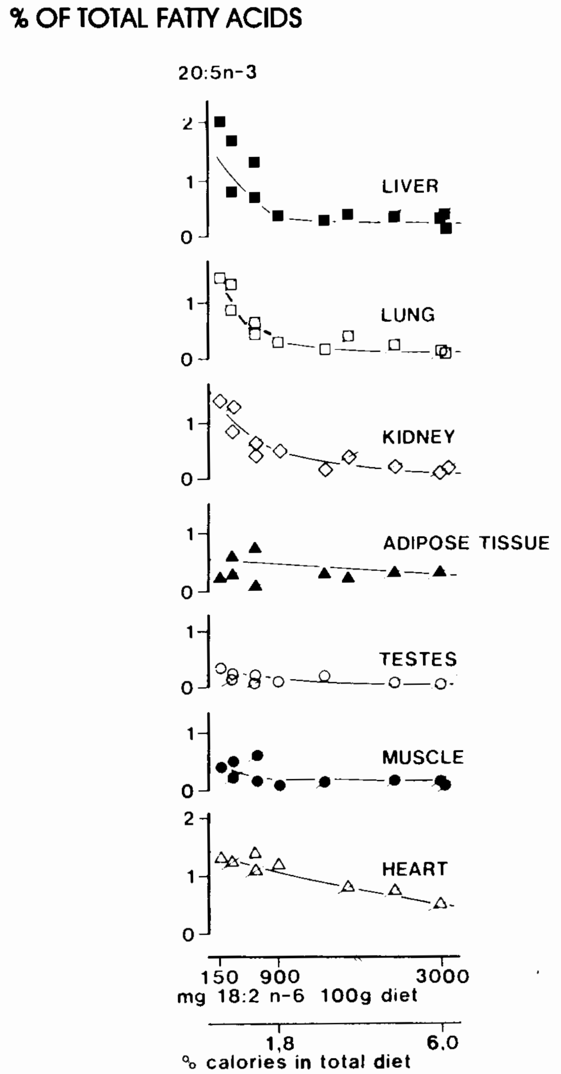

FIG. 10. Concentration of EPA in various organs in relation to dietary content of linoleic acid. Values are % of total fatty acids. Variations were statistically significant for liver, lung, kidney, heart ($p < 0.01$). Open symbols, the dietary content of α-linolenic acid was 150 mg/100 g diet. Symbols with a bar, the dietary content of α-linolenic acid was 300 mg/100 g diet.

Eicosapentaenoic acid. Levels of 20:5n-3 fatty acid were very low in all tissues examined (Figs. 9 and 10). An increase in dietary 18:2n-6 up to 900 mg/100 g decreased 20:5n-3 levels in liver, lung, and kidney. Above 900 mg, the decrease was small (Fig. 9). In heart, levels decreased in a linear manner. In retina, sciatic nerve, testicle, and muscle, the decrease was small. In total brain, the amount of 20:5n-3 was extremely low.

Docosapentaenoic acid and docosahexaenoic acid. Levels of 22:5n-3 were very low in all tissues examined, and the amount was independent of dietary 18:2n-6 content (data not shown). In contrast, a 4300% increase in dietary 18:2n-6 resulted in a slight decrease in 22:6n-3 levels in brain, synaptosomes, and retina (44, 25, 36%, respectively). On the other hand, myelin and sciatic nerve 22:6n-3 levels did not depend on dietary 18:2n-6 content. In liver, kidney, heart, muscle, lung, and testicle, the levels of 22:6n-3 were independent of dietary 18:2n-6 content (16).

DISCUSSION

Polyunsaturated fatty acids of the n-9 family were never detected in animals. This suggests that rats fed a low amount of linoleic acid in the presence of adequate amounts of α-linolenic acid are not deficient in essential fatty acids.

It was surprising to find that low levels of dietary linoleic acid (0.3% of calories, 150 mg/100 g food intake) did not have any effect on reproduction, gestation, perinatal mortality, body weight increase, or overall mortality. In fact, as long as the minimal quantity of α-linolenic acid (200 mg/100 g) was supplied, a linoleic acid intake of 150 mg/100 g covered the minimal requirements of certain organs and of certain fatty acids (meaning, for instance, that the level of arachidonic acid was constant and did not increase at a higher dietary content of linoleic acid). However, the minimal requirement of the organ most dependent on linoleic acid (the liver) was 1200 mg/100 g food intake (2.4% of calories). The level of the n-6 series polyunsaturated fatty acids in the brain varied with dietary linoleic acid content (19). The figure of 2.4% of calories is higher than that previously proposed (20) for male (1.3% of calories) or female rats (0.5% of calories), but is the level generally accepted in human nutrition (21-24). In the human male adult, 1.3% of calories (25), in children 3% of calories (26), and in pigs 0.7% of calories (27) are the levels considered sufficient.

Brain linoleic acid requirements are very high in man during the perinatal period (28,29). However, it should be noted that high concentrations of linoleic acid during total parenteral nutrition in newborns alter the liver fatty acid profile as well as that of brain (30).

Excess dietary linoleic acid leads to a specific accumulation of 22:5n-6 which depends on the dietary linoleic acid levels. A deficiency of dietary α-linolenic acid leads to an accumulation of 22:5n-6, which then replaces the deficient 22:6n-3 (16,17). Dietary linoleic acid deficiency results in a reduction in arachidonic acid levels as well as in the level of 22:4n-6. There is a linear relationship between dietary linoleic acid content and the concentration of 20:4n-6 in membranes and other tissues up to a certain threshold. Above that level, the concentration of these fatty acids is constant regardless of dietary linoleic acid. It should be noted that in several organs (muscle, lung, kidney, liver, heart) as well as in myelin, a low level of dietary linoleic acid led to an incease in 20:5n-3. When dietary linoleic acid falls below the minimum requirement, 20:5n-3 (but not 22:5n-3 or 22:6n-3) increases. The 20:4n-6 deficiency is partially compensated for by 20:5n-3.

Mean fatty acid levels in human brain differ little from those of similar regions in rat brain. Human development involves a greater daily increase in brain mass over a longer period, and the ratio brain weight-to-total body weight is greater in man, even taking the 2/3 coefficient into account. Consequently, the minimal requirements in rat are *a fortiori* those in man. In any case, for obvious ethical reasons, it will not be possible to determine the effects of increasing dietary fatty acid levels on the composition of human cerebral membranes. Our study is the first to measure simultaneously the variations of all the polyunsaturated fatty acid levels in several organs as a function of variations in dietary linoleic acid content, while minimal α-linolenic acid requirements are being satisfied. In contrast to α-linolenic acid requirements, which are the same for all organs [200 mg/100 g food intake (16,17)], the linoleic acid requirement differs according to organ. The minimal requirements in man may, therefore, be taken as 1200 mg/100 g food intake (2.4% of calories) for linoleic acid and 200 mg/100 g food intake (0.4% of calories) for α-linolenic acid.

It should be noted that cultured nerve cells differentiate, multiply, the up and release neurotransmitters only if the medium contains 20:4n-6 and 22:6n-3, but not if it contains 182n-6 and 18:3n-3 (31,32). Hepatic desaturase must be functional for transformation of dietary precursors into longer chains. $\Delta 6$ Desaturase activity decreases very quickly after birth (33,34) and this might explain certain aspects of aging (35).

ACKNOWLEDGMENTS

This work was suppoted by I.N.S.E.R.M., I.N.R.A., O.N.I.D.O.L. and C.E.T.I.O.M.

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[Received January 23, 1989; Revision accepted June 13, 1990]