Age-Related Changes in Δ6 and Δ5 Desaturase Activities in Rat Liver Microsomes

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Age-related changes in Δ6 desaturation of [1-^{14}C]α-linolenic acid and [1-^{14}C]linoleic acid and in Δ5 desaturation of [2-^{14}C]dihomo-γ-linolenic acid were studied in liver microsomes from Wistar male rats at various ages ranging from 1.5 to 24 mon. Desaturase activities were expressed both as specific activity of liver microsomes and as the capacity of whole liver to desaturate by taking into account the total amount of liver microsomal protein. Δ6 Desaturation of α-linolenic acid increased from 1.5 to 3 mon and then decreased linearly up to 24 mon to reach the same desaturation capacity of liver measured at 1.5 mon. The capacity of liver to desaturate linoleic acid increased up to 6 mon and then remained constant, whereas microsomal specific activity was equal at 1.5 and 24 mon of age. The capacity of liver to convert dihomo-γ-linolenic acid to arachidonic acid by Δ5 desaturation decreased markedly from 1.5 to 3 mon. It then increased to reach, at 24 mon, the same level as that observed at 1.5 mon. Age-related changes in the fatty acid composition of liver microsomal phospholipids at the seven time points studied and of erythrocyte lipids at 1.5 and 24 mon were consistent with the variations in desaturation capacity of liver. In particular, arachidonic acid content in old rats was slightly higher than in young rats whereas contents in linoleic and docosahexaenoic acids varied little throughout the life span. The results suggest that, in liver, the activity of desaturases may be regulated in the course of aging to maintain a constant level of polyunsaturated fatty acids in cellular membranes.
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Arachidonic acid (20:4n-6) and docosahexaenoic acid (22:6n-3), which are the major polyunsaturated fatty acids of phospholipids in mammalian cells, are formed, principally in liver, from the precursors linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3), respectively. The essentiality of these precursors depends on their capacity to be Δ6 desaturated and then transformed to 20:4n-6 and 22:6n-3 by chain elongation and Δ5 desaturation (20:4n-6), and by another elongation and Δ4 desaturation (22:6n-3). Desaturation and elongation are alternative reactions, but the desaturation processes are rate-limiting whereas the elongation steps are rapid (1-3). The hepatic Δ6 desaturase, which is the regulatory enzyme in the pathway involved in the biosynthesis of polyunsaturated fatty acids of the n-6 and n-3 series, converts 18:2n-6 to γ-linolenic acid (18:3n-6) and 18:3n-3 to stearidonic acid (18:4n-3). Another important enzyme, the Δ5 desaturase, is responsible for the biosynthesis of the major precursors of eicosanoids of series 2 and 3, *i.e.*, 20:4n-6 from dihomo-γ-linolenic acid (20:3n-6) and eicosapentaenoic acid (20:5n-3) from eicosatetraenoic acid (20:4n-3). It also controls the balance between the precursors of eicosanoids of series 1 and 2 compounds (20:3n-6 and 20:4n-6, respectively), which have contrasting actions.

Several studies have shown that the *in vitro* fatty acid desaturase activities in liver microsomes are modified with aging. Peluffo and Brenner (4) showed that, in rat liver, Δ6 desaturation of 18:2n-6 and 18:3n-3 was decreased at 12 mon of age, when compared to desaturation at 3 mon. Bordoni *et al.* (5) demonstrated that the Δ6 desaturase activity toward 18:2n-6 decreased with the age of rats (between 1 and 22 mon). A linear correlation was proposed between activity and age. In another study, these authors showed that the decrease in the Δ6 desaturation of 18:3n-3 activity began later than did desaturation of 18:2n-6 (6). These results were obtained on Wistar rats fed a chow diet throughout their life. Choi *et al.* (7) found a significant age-dependent decrease in the Δ6 desaturation activity of 18:2n-6 between young (3-week-old) and adult (8-month-old) rats, but they did not confirm their results in a second study (8). Recently, Biagi *et al.* (9) showed that the Δ6 desaturation rate of 18:2n-6 in Wistar rats of 12 mon was only 44% of that found in young animals (3-month-old) after 1 mon of a semisynthetic diet containing soybean oil. The decrease with age in the rate of 18:3n-3 Δ6 desaturation was much less. Bourre *et al.* (10) found a 40% decrease in the Δ6 desaturation of 18:2n-6 in livers of mice between 4 and 17 mon. In studies using rat liver microsomes, the changes observed in the fatty acid compositions generally correlated with the impairment of Δ6 desaturation, suggesting a possible effect of age on the biosynthesis of prostaglandins and their metabolites.

These previous studies dealt only with Δ6 desaturation of 18:2n-6 or 18:3n-3 and often were limited to few time points. No study involved Δ5 desaturation. Moreover, results were expressed only as specific activity of Δ6 desaturation in liver microsomes. The Δ6 desaturation capacity of whole liver was not determined.

We therefore undertook a more complete survey of the evolution with age of Δ6 and Δ5 desaturation in rat liver. For this purpose, Wistar rats were fed the same balanced semisynthetic diet during their life span. The Δ6 desaturation of 18:2n-6 and of 18:3n-3 and the Δ5 desaturation of 20:3n-6 were determined in liver microsomes at seven time points ranging from 1.5 to 24 mon. Results were expressed both as specific activity and as total capacity of the liver to desaturate. The fatty acid composition of liver microsomal phospholipids was also determined to evaluate whether changes (if any) in the fatty acid profiles with age could be accounted for by modifications in desaturation specific activity or capacity. Data dealing with adult rats (3, 6, 9 mon of age) were reported in a preliminary study (11). The present paper describes the complete study carried out on young, adult and old rats.

MATERIALS AND METHODS

Animals and diet. Weanling male Wistar rats were randomized into groups of three rats and housed in stainless-steel cages in a well-ventilated room maintained at 22°C on a 12-h light/dark cycle. They were fed a balanced diet

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Abbreviation: Prot, protein.

containing (g/kg): casein, 220; DL methionine, 1.6; cellulose, 20; starch, 440; sucrose, 218; mineral mixture, 40; vitamin mixture, 10; oil mixture (50% palm oil plus 50% rapeseed oil), 50. In 100 g of diet, linoleic acid (18:2n-6) and α-linolenic acid (18:3n-3) represented 945 and 188 mg, respectively (n-6/n-3 ratio, 5.0). The fatty acid composition of the diet lipids is shown in Table 1. The diet was stored at 4–6°C, and rats were fed *ad libitum*. Rats were maintained on this diet up to 1.5, 3, 6, 9, 12, 18 and 24 mon of age at the Laboratoire de Nutrition et Sécurité Alimentaire (INRA, Jouy en Josas, France). For the 1.5 mon study, only one group of six rats was used. For the other six ages (3 to 24 mon), two groups of three rats were used at two different periods (generally summer and winter) of the same year or of two different years in order to minimize the effect of season on the desaturation rate (4).

Chemicals. [1-^{14}C]Linoleic acid (58 mCi/mmol, 99% radiochemical purity) was purchased from CEA (Gif sur Yvette, France). [1-^{14}C]α-Linolenic acid and [2-^{14}C]dihomo-γ-linolenic acid (56 mCi/mmol, radiochemical purity, 96%) were purchased from the Amersham Radiochemical Centre (Amersham, United Kingdom). Each substrate was diluted in ethanol with unlabelled fatty acid to a specific activity of 10 mCi/mmol. Coenzymes, biochemicals and other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO).

Preparation of microsomal fractions. All experiments were performed starting at 7:30 a.m. to avoid any circadian variation in desaturase activity (12) and on night-fed animals in order to obtain the maximum desaturation activity (2).

The rats were anesthetized with sodium pentobarbital (6 mg per 100 g of body weight). They were exsanguinated by drawing blood from the abdominal aorta. The liver was excised, rinsed with ice-cold saline solution and weighed. About 3.5 g of liver were homogenized at 4°C in a Potter-Elvejhem homogenizer with 6 vol of 0.25 M sucrose in 0.05 M buffer phosphate (pH 7.4). The homogenate was centrifuged at 13000 × *g* (Model J-21B centrifuge, J-21 rotor, Beckman, Lyon, France) for 20 min to sediment cell fragments, mitochondria and nuclei. The supernatant was recentrifuged (L8-55 Ultracentrifuge, Ti 60 rotor, Beckman) at 105000 × *g* for 60 min, and the microsomal pellet was resuspended in 0.4 mL of supernatant and 0.8 mL of sucrose buffer. The amount of microsomal protein was determined by the method of Layne (13).

Desaturation assays. Incubations were performed in open flasks at 37°C for 15 min using a shaker water bath with a total volume of 2.1 mL incubation medium containing 72 mM phosphate buffer, pH 7.4, 4.8 mM $MgCl_2$, 0.5 mM coenzyme A, 3.6 mM adenosine 5′-triphosphate, 1.2 mM reduced nicotinamide adenine dinucleotide phosphate and 120 nmol, 120 nmol and 80 nmol of labelled 18:3n-3, 18:2n-6 and 20:3n-6 (30 μL of ethanolic solution), *i.e.*, about 57, 57 and 38 μM, respectively. At time 0, 5 mg of microsomal protein was added to the incubation medium. Incubations were stopped after 15 min by adding 15 mL of chloroform/methanol (1:1, vol/vol). Lipids were transmethylated in methanolic BF_3 according to Slover and Lanza (14).

The substrate and desaturation product were separated by high-performance liquid chromatography as described by Narce *et al.* (15), using a Waters Chromatograph Model 6000A and a Model 401 differential refractometer (Waters Associates, Milford, MA). The 250 × 4 mm i.d. column packed with LiChrospher 100 RP-18 (4 μm particles), protected by a LiChrosorb RP-18 precolumn, was purchased from Merck (Darmstadt, Germany). The fatty acid methyl esters were collected at the detector outlet, and their radioactivity was measured directly in the solvent by liquid scintillation counting with a Packard Model A 3000CD spectrometer (Packard Instruments, Rungis, France). The conditions permitted a good separation of the different polyunsaturated fatty acid methyl esters, and the desaturation product was eluted before its substrate, avoiding its contamination by the highly radioactive substrate.

Specific activity was expressed as pmol of radioactive fatty acid converted to desaturation product per min and per mg microsomal protein. For each animal, the desaturation capacity of whole liver was calculated by taking into account the total amount of microsomal protein in liver. It was expressed as nmol of substrate converted per min and per whole liver.

Preparation of erythrocytes. Erythrocytes were isolated from blood according to Rao *et al.* (16). Blood was collected from the abdominal aorta using heparin mixed with buffered saline solution (NaCl, 141 mM; KCl, 10 mM; $MgCl_2$, 1 mM; $CaCl_2$, 1.3 mM; NaH_2PO_4, 5 mM) in the proportion 1:5 (vol/vol). The suspension was gently shaken and centrifuged at 2500–3000 × *g* for 7 min. The pellet was resuspended in the saline solution and recentrifuged. The operation was repeated three times.

Fatty acid analysis. Lipids from an aliquot of liver microsomes and from the remaining pellet containing erythrocytes were extracted with dimethoxymethane/methanol (4:1, vol/vol) according to Delsal (17). Microsomal phospholipids were obtained by silicic acid column chromatography according to Hirsch and Ahrens (18). Fatty acids were transmethylated (14), and the fatty acid methyl esters were analyzed by gas-liquid chromatography using a Packard Model 417 chromatograph equipped with a laboratory made 30 m × 0.3 mm i.d. glass capillary column coated with Carbowax 20M. Analyses

TABLE 1

Fatty Acid Composition of Dietary Lipids[a]

Fatty acids	Mole %
14:0	0.2
16:0	7.7
16:1n-7	0.3
18:0	2.9
18:1n-9	57.3
18:1n-7	2.3
18:2n-6	20.1
18:3n-3	4.0
20:0	1.1
20:1n-9	1.5
22:0	1.8
24:0	0.8
Saturated	14.5
Monounsaturated	61.4
Polyunsaturated	24.1
n-6/n-3 ratio	5.0

[a]Mixture of rapeseed and peanut oils.

were carried out at 180°C at a nitrogen flow rate of 1 mL/min. The esters were detected with a flame-ionization detector. Peak areas were measured using a Delsi Model Enica 21 computing integrator (Delsi Instruments, Suresnes, France). Results are expressed as mole % of total fatty acids of the lipid fraction.

Statistical analysis. The results are expressed as means ±SD of six rats (1.5 mon) or of three rats in two different groups (3 to 24 mon). The graphs were traced using the means of the six rats for each age. After analysis of variance using the Fischer multiple range test, means were compared in the seven groups of age according to the least significant difference and classified in decreasing order. Means assigned different superscript letters were significantly different ($P < 0.05$). The fatty acid compositions of erythrocyte lipids and liver microsomal phospholipids were compared at 1.5 and 24 mon by means of Student's *t*-test.

RESULTS

Body weights, liver weights and liver microsomal protein concentrations at the seven time points studied are reported in Table 2. Body weight increased from 1.5 to 9 mon without any great difference between the two groups of three rats at 3, 6 and 9 mon of age. However, for the subsequent time points (12, 18 and 24 mon), body weight varied greatly between the two groups at each age. Liver weights also increased with age from 1.5 to 9 mon but more slowly than did body weights. As a consequence, the ratio of liver weight to body weight decreased from 1.5 to 6 mon. In the older rats, liver weight increased proportionally to body weight so that the liver weight/body weight ratio remained constant. The microsomal protein concentration was relatively constant, even in the two different groups (of the same age) of old rats so that the microsomal protein content of whole liver followed roughly the increase in liver weight.

The age-related specific activity of liver microsomes and capacity of whole liver to convert α-linolenic acid (18:3n-3) to stearidonic acid (18:4n-3) by Δ6 desaturation are reported in Figure 1. Both specific activity and liver capacity increased from 1.5 to 3 mon, but the latter increased more (2.8-fold) than did the former (1.3-fold). After 3 mon, the two parameters decreased with age but the specific activity decreased more rapidly than did liver capacity. At 24 mon, the specific activity of Δ6 desaturation of 18:3n-3 was 60% of that observed at 1.5 mon, while the liver capacity had returned to the initial level.

The parameters for the Δ6 desaturation of linoleic acid (18:2n-6) to γ-linolenic acid (18:3n-6) are reported in Figure 2. The specific activity of microsomes showed some variations with age, with relatively large differences occurring between groups at each age. However, the desaturation rate remained essentially constant between 1.5 and 24 mon. Paralleling the increase in total microsomal protein content, the liver capacity to desaturate linoleic acid increased from 1.5 to 6 mon, reaching a plateau between 6 and 24 mon. At 24 mon, the capacity was twice that measured at 1.5 mon.

The age-related specific activity of liver microsomes and the capacity of whole liver to convert dihomo-γ-linolenic acid (20:3n-6) to arachidonic acid (20:4n-6) by Δ5 desaturation are reported in Figure 3. The specific activity decreased markedly (6.5-fold) between 1.5 and 3 mon and then increased very slightly up to 24 mon to reach a value 2.5-fold lower than that at the earliest age studied. The capacity of the liver to desaturate also decreased between 1.5 and 3 mon but more slowly (2.4-fold) than did specific activity. From then on it increased, and, at 24 mon, the capacity of the liver to desaturate 20:3n-6 to 20:4n-6 was not significantly different from that found at 1.5 mon.

Figure 4 illustrates the age-related percentages of linoleic acid, of arachidonic acid, its product of Δ6 and Δ5 desaturations, and of docosahexaenoic acid in liver microsomal phospholipids. The percentage of 18:2n-6 did not change between 1.5 and 24 mon. The percentage of 20:4n-6 increased slightly, with some variations, reaching a higher value at 24 mon (32.2%) than at 1.5 mon (26.2%). Consequently, the 20:4/18:2 ratio increased from 3.4 (1.5

TABLE 2

Age-Related Changes in Body Weight, Liver Weight and Liver Microsomal Protein[a]

Age (mon)	n	Body weight (g)		Liver weight (g)		Microsomal protein (mg/g liver)	
1.5	6		150 ± 7[f]		6.8 ± 0.6[e]		16.1 ± 1.7[c]
3	3	340 ± 35		11.8 ± 0.8		18.6 ± 4.5	
	3	313 ± 9	327 ± 27[e]	11.2 ± 0.5	11.4 ± 0.7[d]	19.1 ± 5.4	19.1 ± 3.4[b]
6	3	393 ± 28		11.7 ± 0.7		19.3 ± 0.6	
	3	430 ± 5	411 ± 27[d]	13.7 ± 0.4	12.7 ± 1.2[c,d]	13.4 ± 0.1	15.4 ± 2.2[c]
9	3	448 ± 5		13.1 ± 0.4		15.1 ± 1.5	
	3	510 ± 36	479 ± 40[c,d]	15.3 ± 1.2	14.2 ± 1.5[b,c]	19.1 ± 2.3	17.1 ± 2.8[c]
12	3	600 ± 54		18.2 ± 1.3		17.5 ± 1.3	
	3	410 ± 23	505 ± 110[b,c]	12.4 ± 1.3	15.3 ± 3.6[b]	18.9 ± 2.7	18.2 ± 2.0[b,c]
18	3	563 ± 7		14.6 ± 1.0		17.4 ± 2.4	
	3	491 ± 37	527 ± 57[b,c]	13.2 ± 2.1	13.9 ± 1.7[b,c]	17.9 ± 1.9	17.9 ± 2.0[b,c]
24	3	608 ± 57		15.6 ± 1.3		17.3 ± 3.2	
	3	474 ± 21	540 ± 82[b]	12.6 ± 0.2	14.1 ± 1.9[b,c]	14.5 ± 0.9	15.8 ± 2.7[b,c]

[a]Results are means ± SD for n = three or six animals in each group. After analysis of variance (Fisher multiple range test), means of the six rats per age were compared in each column according to the least significant difference and classified in decreasing order. Means assigned different superscript letters (b–f) were significantly different ($P < 0.05$).

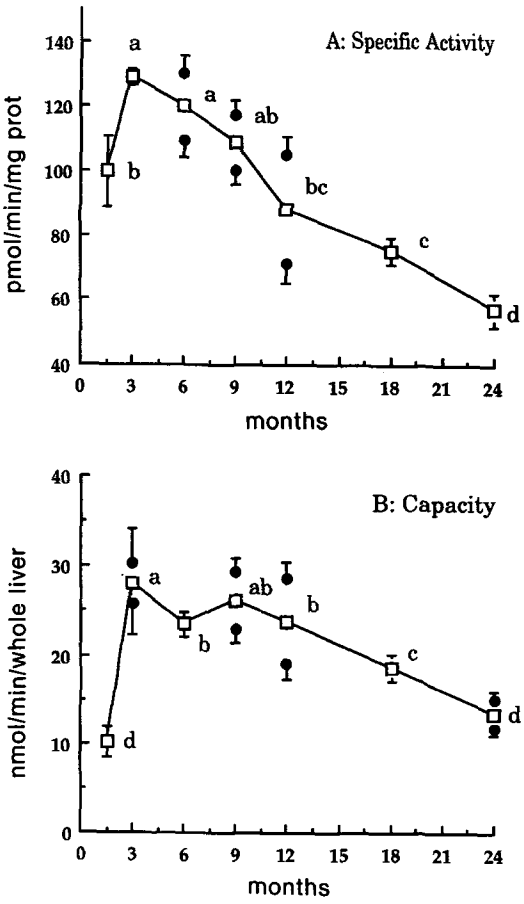

FIG. 1. Age-related changes in Δ6 desaturation of α-linolenic acid (18:3n-3) in liver microsomes expressed both as specific activity of liver microsomes (A) and activity of whole liver or capacity (B). Results are means ±SD obtained from one group of six rats (1.5 mon) or two groups of three rats at all other ages. After analysis of variance using the Fisher multiple range test, means of the six rats for each age were compared according to the least significant difference and classified in decreasing order. Means assigned different superscript letters were significantly different ($P < 0.05$). Prot, protein.

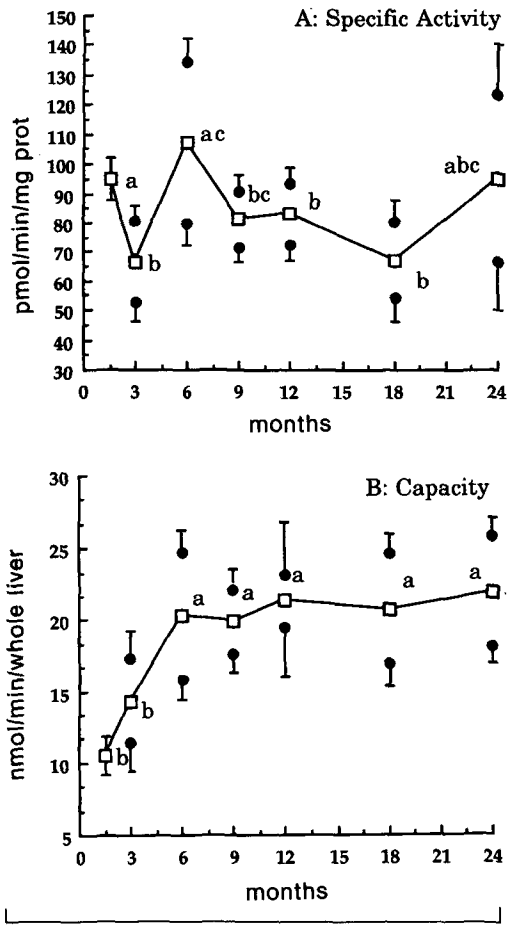

FIG. 2. Age-related changes in Δ6 desaturation of linoleic acid (18:2n-6) in liver microsomes expressed both as specific activity of liver microsomes (A) and activity of whole liver or capacity (B). Results are means ±SD obtained from one group of six rats (1.5 mon) or two groups of three rats at all other ages. After analysis of variance using the Fisher multiple range test, means of the six rats for each age were compared according to the least significant difference and classified in decreasing order. Means assigned different superscript letters were significantly different ($P < 0.05$). Prot, protein.

mon) to 3.8 (24 mon). The percentage of 18:3n-3 remained very low (*ca.* 0.3%) (unreported results) and constant, while that of 22:6n-3 decreased between 1.5 and 3 mon and then increased slightly to reach, at 24 mon, what had been the 1.5-mon value.

The fatty acid composition of erythrocyte lipids (mostly phospholipids) in 1.5- and 24-month-old rats is reported in Table 3, together with the composition of liver microsomal phospholipids at the same ages. The proportion of 18:2n-6 in erythrocytes was the same at the two ages studied, whereas the proportion of 20:4n-6 was higher in older rats. The percentage of 22:6n-3 in erythrocyte lipids was slightly lower in 24-month-old rats, but the level of total n-3 fatty acids was not significantly different at the two ages studied. The most striking difference in the fatty acid profiles of erythrocyte lipids and microsomal phospholipids is the higher percentage of 22:6n-3 and a lower percentage of palmitic acid (16:0) in the latter. Differences in the n-6 fatty acids were not pronounced.

DISCUSSION

The aims of this study were to investigate age-related changes in various desaturase activities of rat liver microsomes and to determine if these changes in turn induced alterations in the phospholipid fatty acid composition of erythrocytes and liver microsomes. The latter support the different desaturases and their associated proteins, and the former are rich in arachidonic acid.

Our data on the effects of age on Δ6 desaturation rates with 18:2n-6 and 18:3n-3 as substrates conflict with those reported by Hrelia *et al.* (6). These authors observed a decrease of 55% in the specific activity of Δ6 desaturase for 18:2n-6 between 1 mon and 22 or 25 mon. However, the Δ6 desaturation rate of 18:3n-3, much higher than that of 18:2n-6 at all ages, decreased from the end of 12 mon until 25 mon. We observed a pronounced decrease in the Δ6 desaturation of 18:3n-3 between 9 and 24 mon, whereas the Δ6 desaturation of 18:2n-6 was modified little through-

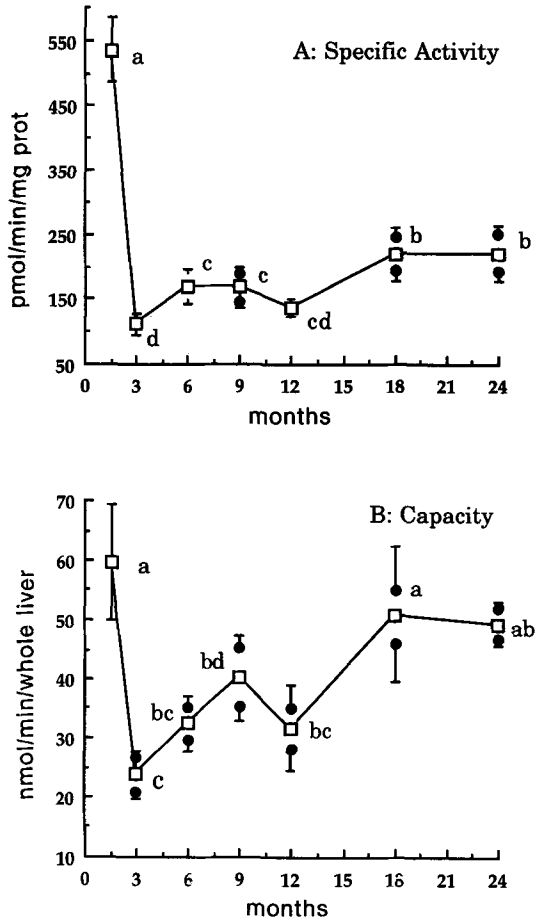

FIG. 3. Age-related changes in Δ5 desaturation of dihomo-γ-linolenic acid (20:3n-6) in liver microsomes expressed both as specific activity of liver microsomes (A) and activity of whole liver or capacity (B). Figures are means ±SD obtained from one group of six rats (1.5 mon) or two groups of three rats at all other ages. After analysis of variance using the Fisher multiple range test, means of the six rats for each age were compared to the least significant difference and classified in decreasing order. Means assigned different superscript letters were significantly different ($P < 0.05$). Prot, protein.

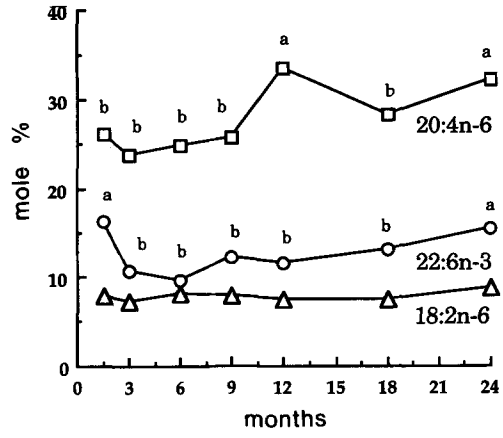

FIG. 4. Age-related changes in percentages of major polyunsaturated fatty acids in liver microsomal phospholipids. Results are means from six rats at each age. After analysis of variance using the Fisher multiple range test, the means were compared according to the least significant difference and classified in decreasing order. Means assigned different superscript letters were significantly different ($P < 0.05$).

out the life span. Moreover, the 18:2n-6 and 18:3n-3 Δ6 desaturation specific activities we observed at 1.5 mon (*ca.* 100 pmol/min/mg microsomal protein) were similar. Several differences between the experimental conditions used may in part explain these discrepancies. Hrelia *et al.* (6) used rats fed a chow diet throughout their life span and the liver microsomal preparations were frozen until use. Bourre *et al.* (10) also found a decrease with aging in Δ6 desaturation, but mice were used and desaturation measurements were done on liver homogenates. In our experiments, rats received a semisynthetic diet, and incubations were done immediately using fresh microsomes. In addition, we used a higher substrate concentration (57 μM instead of 40 μM used by Hrelia *et al.* (6)).

The differences in desaturation activities we observed between the two series of three animals, between 3 and 24 mon, were due in part to seasonal variations, as was previously shown for 6-month-old rats (11). To compensate for the seasonal variations of desaturation (4), we used two groups of animals at two different periods of the year. However, in the course of the experiment, another factor of variation appeared between the two groups: the liver weight in relation to the body weight. The desaturation rates varied in reverse order to the liver weight. So in 2-month-old rats, the amount of 18:2n-6 transformed by Δ6 desaturation was found equal to 71 ± 11 and 93 ± 4 pmol/min/mg microsomal protein in liver weighing 18.2 and 12.4 g, respectively. At certain ages, the effects of season and liver weight added and caused great variations between groups. At other ages, they compensated and the deviations were low. But within each group the variations between animals were not great.

No study has yet been reported on the age-related changes in Δ5 desaturase activity. Only data relative to the 20:3n-6/20:4n-6 ratio in liver lipids as a function of age have been reported, suggesting depressed Δ5 desaturase activity (19) or, on the contrary, a possible increase of this activity (20). Our results demonstrate that the specific Δ5 desaturase activity toward 20:3n-6 was 5.5 times higher than the Δ6 desaturase activity toward 18:2n-6 or 18:3n-3 at 1.5 mon.

The fatty acid composition of liver microsomal phospholipids and erythrocyte lipids reflected desaturation activities. The constant levels of 18:2n-6 and 20:4n-6 in liver microsomes after 3 mon are in agreement with the unchanged desaturation capacity of liver relative to 18:2n-6 and the increased capacity relative to 20:3n-6 in adult and aged animals. Despite some variations in desaturation activities, the 20:4n-6/18:2n-6 ratio varied little with age (3.4 to 3.8) except at 12 mon (4.5). These ratios were consistent with the observed changes in both Δ6 and Δ5 desaturation capacities. The changes in desaturation rates associated with the development of animals occur principally in the early stages of life.

The capacity of liver to convert 18:3n-3 to 18:4n-3 by Δ6 desaturation decreased with age, whereas the level of 22:6n-3 in microsomal phospholipids increased between 3 and 24 mon. An explanation for this may be that the decrease in Δ6 desaturase could be compensated for by

TABLE 3

Fatty Acid Composition (mole %) of Erythrocyte Lipids and Liver Microsomal Phospholipids at 1.5 and 24 Months of Age[a]

Fatty acids	Erythrocytes		Microsomes	
	1.5 mon	24 mon	1.5 mon	24 mon
14:0	1.0 ± 0.2	1.0 ± 0.2	0.6 ± 0.1	0.4 ± 0.1
16:0	27.2 ± 0.8	25.0 ± 0.2[b]	18.6 ± 1.0	16.2 ± 0.9[c]
16:1n-7	2.0 ± 0.9	2.1 ± 0.6	2.5 ± 0.6	2.0 ± 0.3
18:0	12.1 ± 0.5	15.6 ± 0.1[d]	13.6 ± 0.9	13.2 ± 2.5
18:1n-9	13.9 ± 0.7	12.1 ± 1.0[c]	9.7 ± 1.0	9.3 ± 1.2
18:2n-6	6.2 ± 0.1	5.9 ± 0.4	7.8 ± 0.9	8.6 ± 0.8
18:3n-6	0.6 ± 0.1	0.7 ± 0.3	0.3 ± 0.1	0.4 ± 0.1
18:3n-3	—	—	0.2 ± 0.1	0.2 ± 0.1
20:0	0.6 ± 0.1	0.5 ± 0.2	—	—
20:2n-6	0.6 ± 0.1	—	1.1 ± 0.3	0.3 ± 0.1[d]
20:3n-6	0.5 ± 0.1	0.8 ± 0.1[b]	1.3 ± 0.2	1.2 ± 0.2
20:4n-6	24.9 ± 1.2	26.9 ± 0.7[c]	26.2 ± 1.9	32.3 ± 1.3[d]
20:5n-3	0.4 ± 0.1	0.7 ± 0.4	1.2 ± 0.2	1.3 ± 0.4
22:0	0.7 ± 0.1	0.4 ± 0.2[c]	—	—
22:4n-6	1.8 ± 0.2	1.5 ± 0.1[b]	0.3 ± 0.1	0.2 ± 0.1
22:5n-6	—	—	1.1 ± 0.3	0.4 ± 0.2[d]
22:5n-3	1.7 ± 0.1	2.2 ± 0.2[c]	0.9 ± 0.2	0.4 ± 0.2[c]
22:6n-3	4.6 ± 0.4	3.3 ± 0.9[c]	12.9 ± 1.2	12.5 ± 1.1
24:0	0.5 ± 0.1	0.4 ± 0.2[c]	0.4 ± 0.4	—
total n-6	34.5 ± 1.1	35.8 ± 0.8[c]	38.0 ± 1.0	43.4 ± 2.0[d]
total n-3	6.7 ± 0.4	6.3 ± 1.5	15.2 ± 1.5	14.4 ± 1.5
n-6/n-3	5.2 ± 0.1	5.8 ± 1.0	2.5 ± 0.4	3.0 ± 0.4[c]

[a]In erythrocytes and microsomes means ± SD for n = six rats were compared between 1.5 and 24 mon using the Student's *t*-test.
[b]$P < 0.05$.
[c]$P < 0.01$.
[d]$P < 0.001$.

an increase in the Δ5 desaturation rate, as observed in the n-6 series, and/or by an increase in Δ4 desaturation and elongation rates, as reported recently by Mimouni *et al.* (21). On the other hand, an age-dependent decrease in the peroxisomal 22:6n-3 retroconversion, a decreased turnover rate and an increased incorporation into phospholipids may also explain that the 22:6n-3 levels in liver microsomes and in erythrocytes are maintained, despite a decrease in the Δ6 n-3 desaturation rate.

Although Δ6 and Δ5 desaturation activities are low in human liver (22–24), several studies indicated that few differences exist between elderly and young subjects with respect to the n-6 and n-3 fatty acid composition of serum (25,26), erythrocyte (27) and platelet (28) phospholipids. It can thus be assumed that in humans, as in rats, the desaturation activities are regulated to maintain constant the polyunsaturated fatty acid levels in membrane phospholipids. In particular, the desaturation rate could be increased to compensate for an increase, with aging, in peroxidation reactions in membranes. However, this compensation might disappear in different pathophysiological situations such as hypercholesterolemia or diabetes or modifications of nutritional conditions, leading to a decrease in polyunsaturated fatty acid content in tissue lipids and impairment of eicosanoid production.

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