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Biochimica et Biophysica Acta 1256 (1995) 175–180

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Michel Clément *, Lan Dinh, Jean-Marie Bourre

INSERM U. 26 Hôpital Fernand Widal, 200 rue du Faubourg Saint Denis, 75475 Paris cedex 10, France

Received 9 November 1994; revised 18 January 1995; accepted 23 January 1995

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BIOCHIMICA ET BIOPHYSICA ACTA

International Journal of Biochemistry and Biophysics
Founded in 1947 by H.G.K. Westenbrink, Managing Editor 1947–1964

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Printed in The Netherlands

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Uptake of dietary RRR-α- and RRR-γ-tocopherol by nervous tissues, liver and muscle in vitamin-E-deficient rats

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INSERM U. 26 Hôpital Fernand Widal, 200 rue du Faubourg Saint Denis, 75475 Paris cedex 10, France

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Abstract

The time course of RRR-α-tocopherol and RRR-γ-tocopherol uptake by liver, muscle and selected nervous tissues was studied in vitamin-E-deficient rats fed diets containing either RRR-α-tocopherol or RRR-γ-tocopherol over a 60 day period. Feeding rats with a RRR-α-tocopherol-supplemented diet induced in brain, cerebellum, sciatic endoneurium and muscle a marked and regular increase in α-tocopherol concentration. In addition, the tocopherol concentration in liver reached a plateau very rapidly. In contrast, feeding rats with a diet containing the same level of RRR-γ-tocopherol induced a very small increase in γ-tocopherol concentration in brain, cerebellum, sciatic endoneurium and muscle, no change in α-tocopherol concentration of brain and muscle and a slight but significant decrease in α-tocopherol concentration in sciatic endoneurium and cerebellum. These results indicate that when γ-tocopherol was supplied continuously in the diet γ-tocopherol accumulated significantly in the tissues but to a much lesser extent than when rats were fed with RRR-α-tocopherol. These results also show that in the tocopherol-deficient rat, γ-tocopherol does not significantly affect the residual α-tocopherol concentrations in brain or cerebellum, except poorly in sciatic endoneurium.

Keywords: Vitamin E; Tocopherol; Uptake; Central nervous system ; Peripheral nervous system; Liver

1. Introduction

Vitamin E, a major lipid-soluble chain-breaking antioxidant in the membranes, is an important factor in the protection of polyunsaturated fatty acids against peroxidative damage. It is well established that vitamin E deficiency is linked with neurological abnormalities in animals and humans [1–4]. An increasing body of literature indicates that vitamin E plays an important role in membrane function. In addition, specific effects of vitamin E that do not involve its antioxidant function and that act upon the architecture of membranes by controlling their lipid profiles have been reported [5].

Vitamin E is a generic term for all tocopherols and tocotrienols (α, β, γ, and δ) which are found especially in dietary vegetable oils. In France, it has been estimated that vegetable oils supply 60–75% of the dietary requirement for vitamin E [6]. Depending on the vegetable oil used in human diet, γ-tocopherol may represent a significant contribution of the total tocopherols. However, many authors have reported that despite a higher intake of dietary γ-tocopherol α-tocopherol is the only antioxidant found in the membranes [7]. Bieri and Poukka Evarts [8] showed that feeding vitamin-E-depleted rats with a mixture of γ- and α-tocopherol (ratio 2:1) induces a non-significant reduction of α-tocopherol and a slight increase in γ-tocopherol concentration of many tissues. In rats fed diets containing low, normal and high levels of tocopherol followed by a single dose of α-, γ- or both tocopherols, Behrens and Madere [9] showed that plasma γ-tocopherol levels varied inversely with the levels of α-tocopherol. Recently, Kayden and Traber [10] reported that in humans, the liver is involved in the discrimination between α- and γ-tocopherol. The α-tocopherol-binding protein, first described by Catignani and Bieri [15] and responsible for this discrimination was recently purified and characterized by Sato et al. [11,12]. These authors have shown that this protein binds preferentially to the α-tocopherol. Investigations into discrimination between α- and γ-tocopherols were carried out either by feeding rats with a mixture of α- and γ-tocopherol or by dosing laboratory animals or humans with single high dose of α- or γ-tocopherol [8,13]. However, to our knowledge, until now no data have been reported on the comparative uptake of dietary γ- and α-tocopherol by liver, muscle and nervous tissues.

* Corresponding author. Fax: +33 40 344064.

SSDI 0005-2760(95)00019-4

Table 1

Ingredient	g/kg
Casein (delipidated, vitamin-E-free)	220
Sucrose	218.5
Cellulose	20
Corn starch	435
Peanut oil/rapeseed oil 50:50 [a]	50
Mineral mixture [b]	45
Vitamin mixture [c]	10
DL-Methionine	1.5

[a] Tocopherols were eliminated from peanut oil and rapeseed oil by deodorisation (Medeol, Cappelle-la-Grande, France).

[b] Composition of the mineral mixture (per kg of diet): $CaHPO_4$, $2H_2O$, 17.1; K_2HPO_4, 10.8; $CaCO_3$, 8.1; NaCl, 3.2; MgO, 0.9; $MgSO_4$, $7H_2O$, 4.0; $FeSO_4$, 7H2O, 0.39; $ZnSO_4$, 7H2O, 0.2; $MnSO_4$, H_2O, 0.2; $CuSO_4$, $5H_2O$, 0.05; NaF, 0.04; KI, 0.0032; $CoCO_3$, 0.001; Na_2SeO_3, $5H_2O$, 0.001; $(NH_4)6Mo7O_{24}$,$4H_2O$, 0.001; $CrK(SO_4)2$, $12H_2O$, 0.02.

[c] Composition of vitamin supplements (g/kg tritured in dextrose) United States Biochemicals, Cleveland, OH, USA. 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; thiamine HCl, 1.0; vitamin A acetate, 900000 IU; calciferol (D2), 100000 IU; biotine, 20 mg; folic acid, 90 mg; vitamin B_{12}, 1.35 mg.

This study was undertaken to examine the kinetics of the dietary uptake of RRR-α- or RRR-γ-tocopherols by selected nervous tissues, muscle and liver in tocopherol-deficient rats and thus to compare the respective contribution of the α and γ forms the diet.

2. Materials and methods

Female Sprague-Dawley rats were purchased from Iffa Credo (l'Arbresle, France) and were fed a standard laboratory diet. Animals were maintained under standardized conditions of light (7 am–7 pm), temperature 22° C ± 1, humidity (70%) and received water ad libitum. From the 14th day of gestation, breeding female rats were fed a synthetic vitamin-E-deficient diet (APAE-INRA, Jouy-en Josas, France) (Table 1). Experimental protocols were approved and meet the guidelines of the governmental agency (Ministry of Agriculture, Authorization nº03007; June 4, 1991).

Rats were maintained on this diet during gestation and suckling and pups were fed the same diet for 8 weeks. At the end of the depletion period, male vitamin-E-deficient rats were divided in two groups and fed the vitamin-E-deficient diet supplemented respectively with RRR-α-tocopherol or RRR-γ-tocopherol (0.030 g/kg diet). Six rats of each group were deprived of food for one night and sacrificed under light ether anesthesia at 0, 3, 8, 15, 30, and 60 days. RRR-α-tocopherol and RRR-γ-tocopherol were purchased from Eastman (Rochester, NY, USA).

Blood was collected and serum was separated. Muscle, brain and sciatic nerves were rapidly removed. Cerebrum and cerebellum were dissected on a cold plate. The endoneurium was isolated by microdissection of the sciatic nerve under a dissecting microscope. All the tissues were lyophilized and stored at −30° C until analysis of tocopherols.

Tocopherols were determined by HPLC in serum and lyophilized tissues according to Ueda and Igarashi [14]. For HPLC determination, a 12.5 cm Lichrosphere RP 18 column containing 4 μm particles was used (Merck-Clévenot, Nogent-sur-Marne, France). The eluant, methanol/water 95:5, was pumped at a rate of 1 ml/min with a 2150 LKB pump (Pharmacia LKB, Saint Quentin en Yvelines, France). Tocopherols were detected by their native fluorescence (excitation 295 nm, emission 320 nm) using a fluorometer (Merck-Hitachi, Nogent-sur-Marne, France) to eliminate the UV absorbing compounds that migrate close to α-tocopherol. The concentrations of α- and γ-tocopherols were calculated with a 2500 Chromato-Integrator (Merck-Hitachi, Nogent-sur-Marne, France) using δ-tocopherol as internal standard. Results are expressed as μg/ml for serum and μg/g fresh weight for tissues except for endoneurium which was expressed as μg/g dry weight (because endoneurium was separated from whole sciatic nerve to avoid contamination by perineurium and fat cells).

Data were expressed as means ± S.D. Statistical comparisons of means were made using analysis of variance (ANOVA) with the Bonferroni correction for multiple comparisons. Differences were considered significant at $P < 0.05$ using the dBSTATS program package (Ashton-Tate, Torrance, USA).

3. Results

Table 2 shows the concentrations of α- and γ-tocopherol in serum, liver, muscle and nervous tissues in rats after 8 weeks of tocopherol deprivation and after 8 weeks of α- and γ-tocopherol repletion. Feeding rats with a vitamin-E-deficient diet for 8 weeks induced a dramatic reduction in the concentrations of α-tocopherol in serum, liver, and muscle. In contrast, significant concentrations of α-tocopherol were observed in all nervous tissue samples from these rats. Curiously, sciatic endoneurium was the only tissue where a significant level of γ-tocopherol was found. Table 2 also shows that the α/γ-tocopherol ratio was higher in forebrain and cerebellum than in the other tissues.

Fig. 1 shows the time course of the concentrations of α- and γ-tocopherol in the serum of rats fed diets enriched with either RRR-α-tocopherol or RRR-γ-tocopherol for 8 weeks. Although the diets supplied the same amounts of tocopherols, the concentrations of α-tocopherol in serum were higher than those found in serum of rats fed a diet supplemented with RRR-γ-tocopherol. Consequently, the time course of the concentrations of α- and γ-tocopherol in liver displayed a similar pattern (Fig. 2A and 2B).

Table 2

	Time	
	Day-0	Day-60
Serum		
α	ND	4.77 ± 0.71
γ	ND	1.45 ± 0.24
α/γ		3.30
Liver		
α	0.48 ± 0.22	8.75 ± 1.35
γ	0.46 ± 0.06	1.48 ± 0.19
α/γ	1.15	5.9
Muscle		
α	0.50 ± 0.01	7.55 ± 1.13
γ	0.31 ± 0.07	2.00 ± 0.34
α/γ	1.70	3.7
Forebrain		
α	3.75 ± 0.35	14.70 ± 0.91
γ	0.33 ± 0.07	1.65 ± 0.20
α/γ	11.70	8.9
Cerebellum		
α	2.57 ± 0.16	10.50 ± 1.31
γ	0.18 ± 0.01	1.30 ± 0.18
α/γ	14.50	8.1
Sciatic endoneurium		
α	9.61 ± 0.97	26.94 ± 3.41
γ	3.86 ± 1.02	6.42 ± 0.93
α/γ	2.65	4.2

Serum and tissue levels of α- and γ-tocopherol in rats fed a vitamin-E-deficient diet for 8 weeks (Day-0) and in vitamin-E-deficient rats fed a diet supplemented with either α- or γ-tocopherol for 8 weeks (Day-60). Values are expressed as μg of tocopherol/g of fresh tissue except serum (μg/ml) and sciatic endoneurium (μg/g dry tissue). Each value represent the mean ± S.D. of six animals.

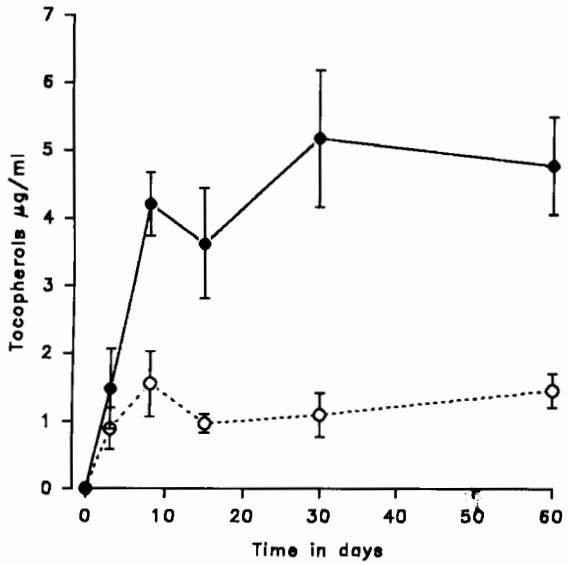

Fig. 1. Kinetics of α- and γ-tocopherol repletion in serum. Rats previously fed a vitamin-E-deficient diet for 8 weeks were fed for 8 weeks with diets containing either RRR-α-tocopherol (30 mg/kg diet) or RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. ●, α-tocopherol; ○, γ-tocopherol.

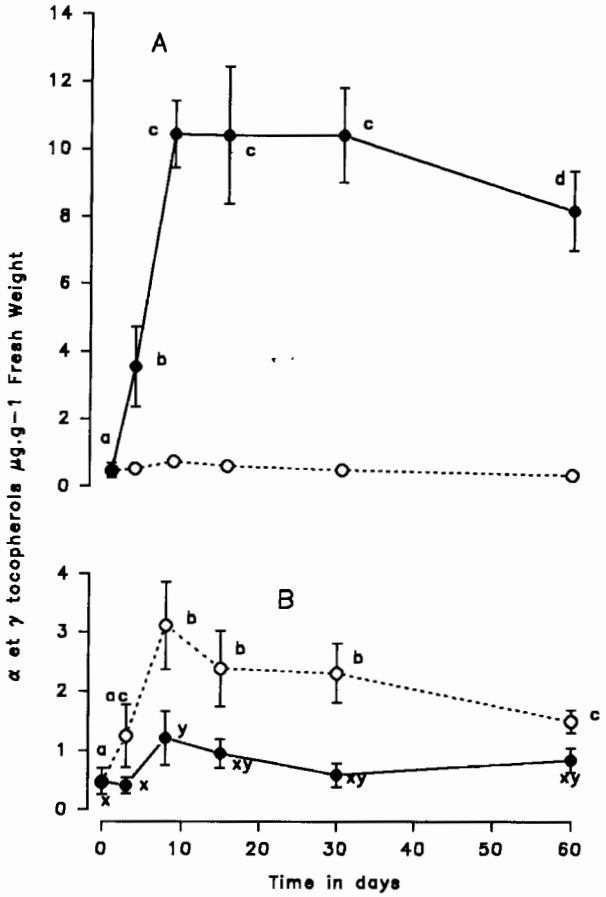

Fig. 2. Kinetics of α- and γ-tocopherol repletion in liver. Rats previously fed a vitamin-E-deficient diet for 8 weeks were fed for 8 weeks with diets containing either (A) RRR-α-tocopherol (30 mg/kg diet) or (B) RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. Values not bearing the same superscript letter are significantly different at $P < 0.05$. ●, α-tocopherol; ○, γ-tocopherol.

In rats fed a diet enriched with RRR-α-tocopherol, the α-tocopherol concentration in each tissue increased with time and at a different rate. The concentrations of α-tocopherol in muscle, forebrain and cerebellum increased linearly with time and did not plateau before the end of the experiment (Figs. 3A, 4A and 5A). In contrast, the non-linear increase in the α-tocopherol concentration in sciatic endoneurium reached a maximum after 2 weeks (Fig. 6A). Liver accumulated α-tocopherol at a faster rate than any of the other tissues. After only 8 days of repletion with RRR-α-tocopherol, α-tocopherol concentrations in liver reached a plateau. The concentrations of γ-tocopherol in each tissue were below the limit of detection during the repletion with RRR-α-tocopherol (Figs. 3A, 4A and 5A).

When rats were fed the diet supplemented with RRR-γ-tocopherol, significant concentrations of γ-tocopherol were found in all tissues, but these concentrations were much lower than the α-tocopherol concentrations determined in rats fed the α-tocopherol supplemented diet (Figs. 2B, 3B, 4B, 5B and 6B). The α-tocopherol concen-

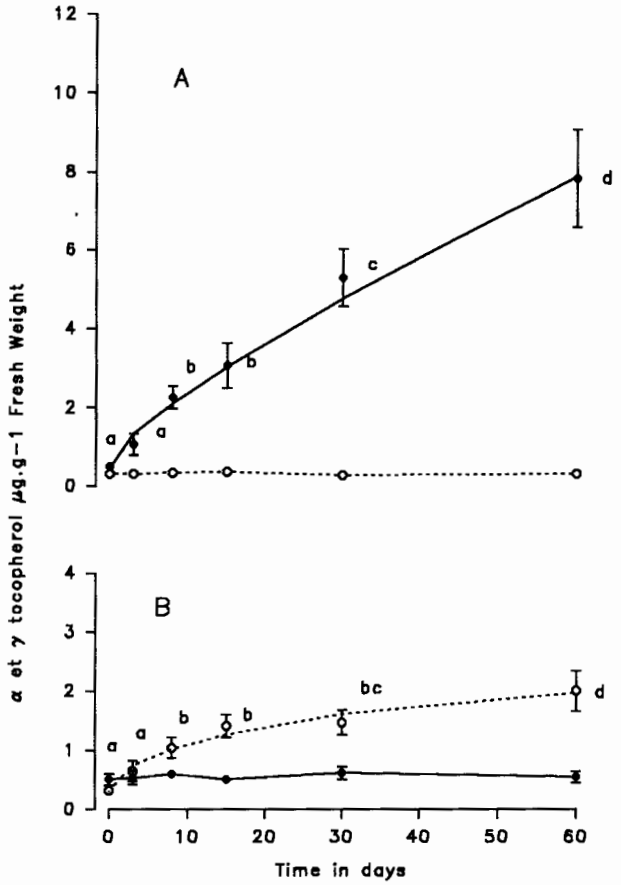

Fig. 3. Kinetics of α- and γ-tocopherol repletion in muscle. Rats previously fed a vitamin-E-deficient diet for 8 weeks were fed for 8 weeks with diets containing either (A) RRR-α-tocopherol (30 mg/kg diet) or (B) RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. Values not bearing the same superscript letter are significantly different at $P < 0.05$. ●, α-tocopherol; ○, γ-tocopherol.

trations in forebrain were maintained for 8 weeks although the diet enriched with γ-tocopherol was devoid of α-tocopherol (Fig. 4B). Furthermore, the γ-tocopherol concentration in forebrain did not reach the residual α-tocopherol level even after 8 weeks of repletion with a diet enriched with RRR-γ-tocopherol (Fig. 4B). In contrast, the α-tocopherol concentration decreased significantly in cerebellum and sciatic endoneurium and γ-tocopherol increased very slightly (Figs. 5B and 6B).

4. Discussion

This study demonstrates that when RRR-γ-tocopherol was provided continuously in the diet, RRR-γ-tocopherol accumulated significantly in the tissues but to a much lesser extent than when rats were fed a RRR-α-tocopherol diet. Furthermore, marked differences in the tissue uptakes were observed.

In 1977, Catigniani and Bieri demonstrated that rat liver cytosol contains a protein that binds α-tocopherol with high affinity and specificity [15]. In recent years many authors have emphasized the role of this α-tocopherol binding protein in the transfer of α-tocopherol between membranes [15–17]. It was shown by Berhens and Madère [9] that the uptake of γ-tocopherol varies inversely with the levels of α-tocopherol. In addition, Traber et al. [13] have reported that α-tocopherol as compared with γ-tocopherol is preferentially incorporated and secreted in lipoproteins. In 1987, Ingold et al. [19] reported the synthesis and utilization of deuterium-labeled α-tocopherol to examine the uptake of natural RRR-α-tocopherol and the biodiscrimination between RRR-α- and SRR-α-tocopherol in various rat tissues under normal dietary conditions. Then, using these deuterium-substituted tocopherols, Traber et al. [20] have shown that the nascent very low density lipoproteins of monkeys fed a mixture of RRR-α- and SRR-α-tocopherol have higher levels of RRR-α than SRR-α-tocopherol. All these results suggest that α-

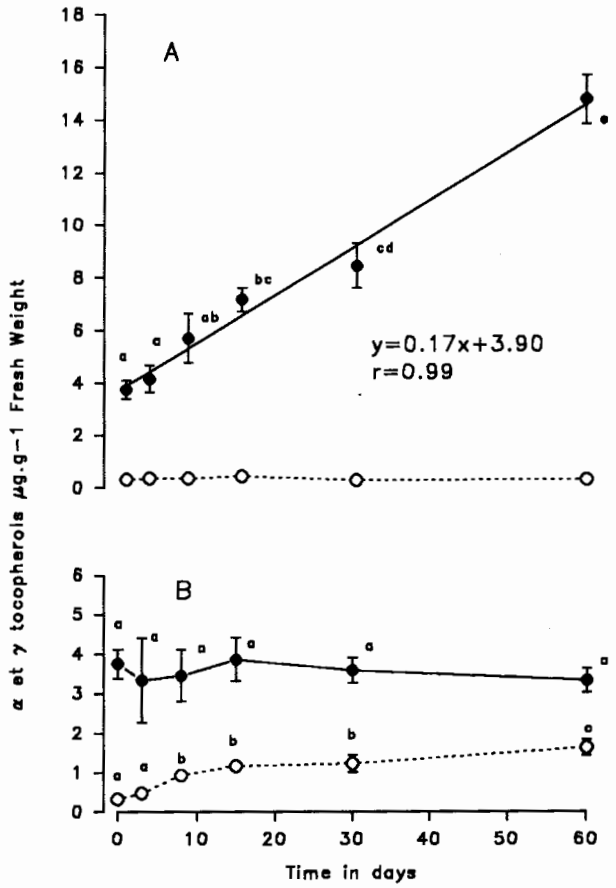

Fig. 4. Kinetics of α- and γ-tocopherol repletion in forebrain. Rats previously fed a vitamin-E-deficient diet for 8 weeks were fed for 8 weeks with diets containing either (A) RRR-α-tocopherol (30 mg/kg diet) or (B) RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. Values not bearing the same superscript letter are significantly different at $P < 0.05$. ●, α-tocopherol; ○, γ-tocopherol.

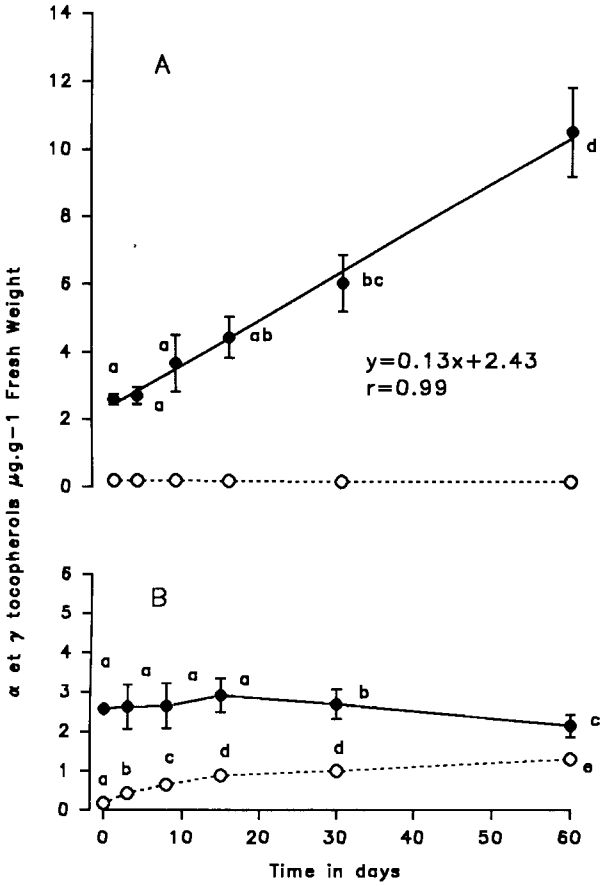

Fig. 5. Kinetics of α- and γ-tocopherol repletion in cerebellum. Rats previously fed a vitamin-E-deficient diet for 8 weeks, were fed for 8 weeks with diets containing either (A) RRR-α-tocopherol (30 mg/kg diet) or (B) RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. Values not bearing the same superscript letter are significantly different at $P < 0.05$. ●, α-tocopherol; ○, γ-tocopherol.

tocopherol binding protein plays an important role in the biodiscrimination between α and γ-tocopherol and between the C2 epimers of α-tocopherol. It is well accepted that α- and γ-tocopherols are equally absorbed by the intestine and secreted in chylomicrons at a similar rate [8,10,21]. Then, following uptake by liver the RRR-α is preferentially incorporated into nascent very low density lipoproteins [20], while the γ-tocopherol is eliminated in the bile [13]. This suggests that the discrimination between α- and γ-tocopherol takes place in the liver. Vitamin E deficiency has been described in patients consuming normal dietary amounts of vitamin E without abnormalities in lipid absorption and lipoprotein metabolism. In these patients, using deuterated tocopherols, Traber et al. [22] suggested that the low α-tocopherol levels were linked to an impairment of hepatic α-tocopherol binding protein activity.

In our experiments the kinetics of the dietary uptake of RRR-α- and RRR-γ-tocopherol were investigated in vitamin-E-deficient rats because, firstly the α-tocopherol transfer activity is higher in vitamin-E-deficient rats than in control rats [17,18] and secondly in order to determine accurately the increase in RRR-α- or RRR-γ-tocopherol. After 8 weeks of vitamin E deprivation the α-tocopherol concentrations in serum and tissues were similar to those previously reported by our laboratory [23] and by Vatassery et al. in deprived rats [24].

The low plasma γ-tocopherol levels resulting from chylomicron catabolism and exchange between the lipoproteins and the faster rate of γ-tocopherol decrease in cells reported by Tran et al. [25] may contribute to the low γ-tocopherol concentrations in the tissues.

Our study shows, although the two diets contained the same amount of either α- or γ-tocopherol, that the γ-tocopherol concentrations in serum and liver were always much lower than the concentration of α-tocopherol determined at the same time in rats fed the diet supplemented with RRR-α-tocopherol. Our results are in agreement with

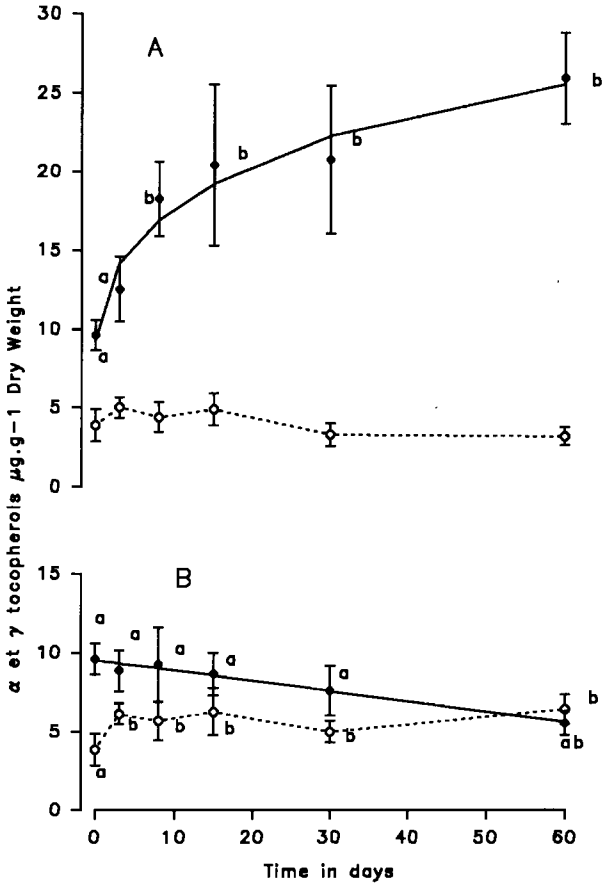

Fig. 6. Kinetics of α- and γ-tocopherol repletion in sciatic endoneurium. Rats previously fed a vitamin-E-deficient diet for 8 weeks, were fed for 8 weeks with diets containing either (A) RRR-α-tocopherol (30 mg/kg diet) or (B) RRR-γ-tocopherol (30 mg/kg diet). Animals were sacrificed at different times after repletion. Each point represents the mean ± S.D. of 6 rats. Values not bearing the same superscript letter are significantly different at $P < 0.05$. ●, α-tocopherol; ○, γ-tocopherol.

the data previously reported by Bieri and Poukka Evarts [8] in rats fed a diet containing a mixture of α- and γ-tocopherol (ratio in the diet 1:2). Our results suggest also that the α-tocopherol binding protein binds to γ-tocopherol but to a lesser extent than to α-tocopherol. Determination of the transfer activity of the α-tocopherol binding protein indicates that γ-tocopherol is a poor substrate [12].

Berhens and Madère [26] reported a linear rate of repletion of α-tocopherol in liver. On the contrary, our results in liver show a rapid and non-linear kinetic of repletion. The plateau was reached for liver in 8 days. In liver the slope calculated from the linear part of the curve is 1.25 μg^{-1} day^{-1}. In addition in rats maintained under a normal laboratory diet Ingold et al. [19] reported that the half-life of α-tocopherol for liver was about 10 days. The last time point of Fig. 2A may indicate that the amount of α-tocopherol supply by the diet is insufficient to compensate for the requirement of α-tocopherol needed by growing liver. Of interest was the repletion of the nervous tissues by α- and γ-tocopherol. The kinetics of repletion of α-tocopherol in forebrain and cerebellum were linear and no plateau was seen during the experiment. The slopes calculated from the linear regression between RRR-α-tocopherol concentrations over time in forebrain and cerebellum were, respectively, 0.17 μg^{-1} day^{-1} and 0.13 μg^{-1} day^{-1}. These results mean that the rate of uptake of α-tocopherol is similar in forebrain and cerebellum although the α-tocopherol concentrations in brain and cerebellum are different [7,27]. The capillary endothelial cells of the blood-brain barrier would restrict and regulate the passage of molecules from blood to the brain. The uptake of α-tocopherol by peripheral tissues may occur via the activity of lipoprotein lipase [28], via the low density lipoprotein receptor or by a non specific uptake [29,30]. The presence of both lipoprotein lipase activity [31] and low density lipoprotein receptors [32] in brain microvessels suggest that the delivery of tocopherol to the brain may involve different mechanisms.

In our experiments, γ-tocopherol was poorly taken up by brain and cerebellum in contrast to α-tocopherol. Firstly, in rats fed a diet enriched exclusively with γ-tocopherol, the concentration of γ-tocopherol in serum was low, secondly it was reported recently that the uptake in brain consists mainly of RRR-α-tocopherol [19,33], and thirdly that the α-tocopherol remaining after depletion could inhibit uptake of the γ-tocopherol. Among the nervous tissues, the uptake of α-tocopherol by the sciatic endoneurium reached a plateau after 2 weeks of repletion and suggests a limiting level of α-tocopherol repletion.

As in the case of brain and cerebellum, the uptake of α-tocopherol by muscle was linear. The α/γ ratio in muscle was the highest among the tissues tested.

Finally, these results show that γ-tocopherol was poorly incorporated into tissues but could contribute to antioxidant activity when the diet does not contain α-tocopherol.

Acknowledgements

This work was supported by INSERM and LESIEUR company. The authors are grateful to A. Strickland for reviewing this manuscript.

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US mailing notice – Biochimica et Biophysica Acta (*Lipids and Lipid Metabolism*) (ISSN 0005-2760) is published monthly except semimonthly in Jan., Mar., Apr., Jun., Aug. and Oct. (total 18 issues) by Elsevier Science B.V. (Molenwerf 1, Postbus 211, 1000 AE Amsterdam, The Netherlands).
Annual subscription price in the USA US$ 1355.00 (valid in North, Central and South America), including air speed delivery. Second class postage paid at Jamaica, NY 11431.
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