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Relative bioactivity of dietary *RRR*- and all-*rac*- α -tocopheryl acetates in swine assessed with deuterium-labeled vitamin E¹

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ABSTRACT: This study evaluated the relative bioactivities of natural and synthetic stereoisomers of α -tocopherol in swine. Deuterium-labeled vitamin E (150 mg each of *d*₃-*RRR*- [natural] and *d*₆-all-*rac*- [synthetic] α -tocopheryl acetates) was administered orally to adult female pigs (n = 3) with the morning feed. Blood samples were obtained at 0, 3, 6, 9, 12, 36, 48, and 72 h after the dose. The time of maximum plasma *d*₃- α -tocopherol concentration (0.486 μ g/mL) occurred at 12 h, and *d*₆- α -tocopherol peaked earlier (at 9 h) and at a lower ($P < 0.05$) concentration (0.288 μ g/mL). The *d*₃-/*d*₆- α -

tocopherol ratio increased from 1.35 (SD = 0.73) at 3 h after dosing to 2.0 (SD = 0.14) at 72 h ($P = 0.03$). The plasma disappearance rates of *d*₃- and *d*₆- α -tocopherols (post-maximum concentrations) were similar and were estimated to be 0.013 μ g/mL per hour. In summary, swine discriminated between *RRR*- and all-*rac*- α -tocopherols, which resulted in an approximately twofold higher plasma α -tocopherol concentration arising from the *RRR*-form. This 2:1 ratio of *RRR*- to all-*rac*- is higher than the currently accepted USP definition of *RRR*-:all-*rac*- of 1.36:1.00.

Key Words: Absorption, Kinetics, Pigs, Stable Isotopes, Vitamin E

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Introduction

Of the eight naturally occurring forms of vitamin E (α -, β -, γ -, and δ -tocopherols, and α -, β -, γ , and δ -tocotrienols) only α -tocopherol meets human vitamin E requirements (Food and Nutrition Board, and Institute of Medicine, 2000). Importantly, synthetic α -tocopherol (all-*rac*- α -tocopherol [2, 5, 7, 8-tetramethyl-2*RS*-(4'*RS*, 8'*RS*, 12 trimethyltridecyl)-6-chromanol]) is an equimolar mixture of 8 isomers (VERIS, 1997), only one of which is identical to the naturally occurring stereoisomer, *RRR*- α -tocopherol ([2, 5, 7, 8-tetramethyl-2*R*-(4'*R*, 8'*R*, 12 trimethyltridecyl)-6-chromanol]).

Supplemental vitamin E is usually added to animal feed in the form of all-*rac*- α -tocopheryl acetate. The accepted USP biopotency factor for all-*rac*- α -tocopheryl acetate is 1.00, with a third higher factor (1.36) for *RRR*- α -tocopheryl acetate (United States Pharmacopia, 1980). However, this biopotency factor, which

was determined using the rat fetal gestation-resorption assay (Weiser and Vecchi 1981, 1982), does not take into account newer findings in vitamin E metabolism.

When humans were supplemented with a 1:1 ratio of *RRR*- and all-*rac*- α -tocopheryl acetates labeled with different amounts of deuterium, both the plasma and tissues contained twice as much α -tocopherol arising from the labeled *RRR*- as from the all-*rac*- α -tocopherol (Burton et al., 1998). These ratios reflect differences in potency that are thought to arise from differences in the affinity of the hepatic α -tocopherol transfer protein (α -TTP) for the various stereoisomeric forms of α -tocopherol (Hosomi et al., 1997).

In sows, Mahan et al. (2000) also found higher serum α -tocopherol concentrations when the vitamin E supplement was *RRR*- compared with all-*rac*- α -tocopheryl acetate. But there is little other information concerning the bioactivity of natural compared with synthetic stereoisomers of vitamin E in pigs. Therefore, the objective of the present investigation was to evaluate in adult swine the relative efficacy of *RRR*- compared with the all-*rac*- α -tocopheryl acetate, using deuterium-labeled vitamin E.

Materials and Methods

Animals

The protocol for this study was approved by the Institutional Animal Care and Use Committee of Oregon

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State University. The three Yorkshire sows used in this experiment were housed at the Linn-Benton Community College/Oregon State University Swine Research Center. Two sows were littermates, and the third was a half-sibling. Sows were inseminated with semen from the same boar. The sows weighed approximately 250 kg at the time of the experiment. The sows' selenium status was assessed by atomic absorption spectrophotometry and averaged 0.235 $\mu\text{g/mL}$ of plasma. This value was within the range of 0.140 to 0.300 $\mu\text{g/mL}$ that is considered normal for pigs (Puls, 1990).

Sows were individually penned and feed was provided twice daily in equal amounts during the experiment (72 h in total). The diet was a commercial diet obtained from Purina Mills (St. Louis, MO). The chemical composition of the diet was determined according to the AOAC procedure (1990), and the enzyme digestibility of organic matter was determined according to Boisen and Fernandez (1997). The dry matter content of the diet amounted to 89.5% and contained 17% crude protein, 5.4% crude fat, 5.6% ash, and 4.9% crude fiber. The enzyme digestibility of organic matter was 84.4%. The amount of vitamin E (all-*rac*- α -tocopheryl acetate) that was added by the manufacturer to the sow diet was 17.5 IU/kg. The analyzed amount of dietary vitamin E, which was determined as described below, is provided in the Results section.

Protocol

At d 81 after insemination, the sows were restrained in individual crates and a local anesthetic (lidocaine) was injected into the ear at the proposed catheter insertion site. A 7.6-cm, 16-gauge i.v. catheter was inserted into the lateral ear vein, and the venous catheter was sutured in position. Blood samples were taken from the external jugular vein by inserting a 35.6-cm, 22-gauge, i.v. catheter into the 16-gauge catheter and threading it into the vein, so that the tip was positioned in the jugular vein. Blood sampling occurred at 0, 3, 6, 9, 12, 24, 36, 48, and 72 h after each sow had consumed deuterated vitamin E with its morning meal. The dose contained an equimolar mixture of 150 mg each of *RRR*- and all-*rac*- α -tocopheryl acetate labeled with different amounts of deuterium (d_3 -*RRR*- and d_6 -all-*rac*- α -tocopheryl acetate, respectively). Blood samples were collected in evacuated tubes containing EDTA and kept on ice until centrifugation ($500 \times g$ for 10 min at 4°C) to obtain plasma. Plasma was stored at -80°C until later analysis.

The deuterated vitamin E was a gift from the Natural Source Vitamin E Association and had been synthesized by Eastman Kodak, Rochester, NY. The isotopic purities of the deuterated compounds (d_3 -*RRR*- and d_6 -all-*rac*- α -tocopheryl acetate) at their nominal level of deuteration were 84% (d_0 : 4.0%; d_1 : 2.0%; d_2 : 9.7%) and 86% (d_0 , d_1 : < 0.1%; d_2 : 0.1; d_3 : 0.8%; d_4 : 1.3%; d_5 : 11.2%), respectively, and the *RRR*/all-*rac* ratio was determined

by gas chromatography-mass spectrometry to be 0.98, as described by Traber et al. (1998).

Laboratory Analyses

The concentrations of α - and of γ -tocopherols and of α - and γ -tocotrienols in plasma and feed were determined after extraction and analysis by HPLC with electrochemical detection as described by Podda et al. (1996). Quantification of the deuterated and unlabeled α -tocopherol in plasma samples was accomplished by liquid chromatography-tandem mass spectrometry as described by Lauridsen et al. (2001). Plasma concentrations of triglycerides were determined using enzymatic hydrolysis of triglycerides with a subsequent determination of liberated glycerol by colorimetry (Sigma Diagnostics, St. Louis). Plasma concentrations of cholesterol were determined after oxidation to cholestenone and hydrogen peroxide (Sigma Diagnostics).

Statistical and Mathematical Analyses

For each sow i , blood samples were drawn at various times t , which resulted in a two-dimensional response, $Y_{it} = (Y_{it1}, Y_{it2})$, where Y_{ite} is the recording of α -tocopherol of type e (d_3 -*RRR*- or d_6 -all-*rac*- α -tocopherol) on sow i . Hence, the only factor in the experiment is time. The model used for analyzing occurrence of deuterated vitamin E in plasma was $Y_{ite} = \alpha_e + \beta t + \beta_e t + U_{ie} + \varepsilon_{ite}$, where U_{ie} refers to a random animal effect accounting for repeated measurements being made on the same sow and α_e and βt are the effects of deuterated vitamin E and time, respectively ($\beta_e t$ refers to the regression of deuterated vitamin E vs time) (Ramon et al., 1996). It is assumed that $U_{ie} \sim N(0, \sigma_u^2)$ and $\varepsilon_{ite} \sim N(0, \sigma_\varepsilon^2)$. Apart from the fact that time is regarded as a covariate rather than a factor, the model corresponds to the model commonly used for analyzing a split-plot experiment in which e is regarded as the whole-plot treatment and t as the split-plot treatment. Data were analyzed with the MIXED procedure of SAS (SAS Inst. Inc., Cary, NC).

Comparisons of the concentrations of the two forms of vitamin E (d_3 - and d_6 - α -tocopherols) at various time points were made using the paired values obtained simultaneously for each sow. Similarly, the concentrations of the various forms of plasma vitamin E at the various time points were made using paired values. The experimental unit was the individual sow.

Results

Deuterated Vitamin E

Pig plasma concentrations of d_3 - α -tocopherol were greater ($P < 0.05$) than those of d_6 - α -tocopherol over the 72-h period (Figure 1). The maximum observed plasma concentration (c_{max}) of d_3 - α -tocopherol (mean [SD]) was 0.49 (0.10) $\mu\text{g/mL}$, which occurred at h 12 postprandially, whereas d_6 - α -tocopherol reached a maximum con-

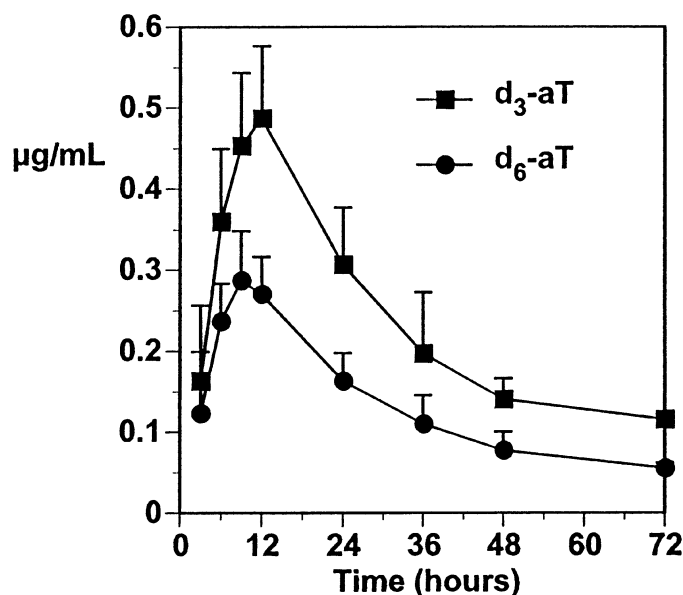


Figure 1. Plasma concentrations ($\mu\text{g/mL}$) of d_3 -RRR- α -tocopherol (d_3 -aT) and d_6 -all-*rac*- α -tocopherol (d_6 -aT) in sows following oral administration of d_3 -RRR- α - and d_6 -all-*rac*- α -tocopheryl acetates. To convert to nmol/mL multiply by 0.43.

centration of 0.29 (0.06) $\mu\text{g/mL}$ at h 9. Both d_3 - and d_6 - α -tocopherol concentrations subsequently declined in an exponential manner. The post-peak rates of decline of d_3 - and d_6 - α -tocopherols were not different and averaged 0.013 (0.001) $\mu\text{g}\cdot\text{mL}^{-1}\cdot\text{h}^{-1}$. In contrast, the estimated maximum plasma concentrations (intercept with the y-axis) of d_3 - α -tocopherol were higher (0.61 [0.08] $\mu\text{g/mL}$, $P < 0.001$) than those of d_6 - α -tocopherol (0.33 [0.08] $\mu\text{g/mL}$). These values, estimated from the regression equations, are in the same range as those actually observed (at h 12 d_3 - α -tocopherol 0.49 [0.10] $\mu\text{g/mL}$ plasma and at h 9 d_6 - α -tocopherol 0.29 [0.06] $\mu\text{g/mL}$ plasma).

The percentage of deuterated α -tocopherol [% deuterated α -tocopherol = $100 \times (\text{d}_3 + \text{d}_6\text{-}\alpha\text{-tocopherols}) / (\text{d}_0 + \text{d}_3 + \text{d}_6\text{-}\alpha\text{-tocopherols})$] reached a maximum of 30.1% (3.6%) at h 12 then decreased to 8.9% (0.2%) at h 72 (Figure 2). The ratio of d_3 -/ d_6 - α -tocopherols increased from 1.35 (0.73) at h 3 to 2.0 (0.14) at h 72 ($P < 0.03$).

Dietary Vitamin E

The concentrations of α - and γ -tocopherols in the pig feed were 23.2 (4.1) and 29.0 (0.3) mg/kg feed (or 54 [9.5] and 70 [0.6] $\mu\text{mol/kg}$), respectively. Additionally, tocotrienols were detected in the pig feed. Concentrations of α - and γ -tocotrienols were 8.8 (0.6) and 15.6 (0.5) mg/kg feed (or 21 [1.3] and 38 [1.2] $\mu\text{mol/kg}$), respectively.

Figure 3 shows plasma concentrations of total α - and γ -tocopherols and of α - and γ -tocotrienols, as well as the concentrations expressed in relation to plasma cho-

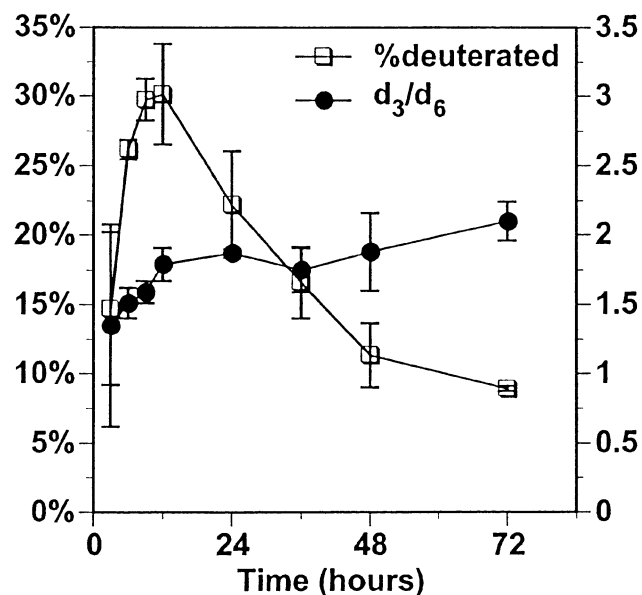


Figure 2. The mean percentage of deuterated α -tocopherol (% deuterated) and the ratio of d_3 -RRR- α -tocopherol to d_6 -all-*rac*- α -tocopherol (d_3/d_6) in plasma of pigs following oral administration of d_3 -RRR- and d_6 -all-*rac*- α -tocopheryl acetates.

lesterol and total lipids at the different time points during blood sampling. Other vitamin E forms (e.g., β - and δ -tocopherols and tocotrienols) were not detected in the plasma samples.

The concentration of total α -tocopherol increased ($P = 0.03$) from its initial value of 0.51 (0.09) nmol/mL plasma at h 0 to 0.80 (0.12) nmol/mL at h 12 after feeding the deuterated α -tocopherols, and by h 72 it had returned to baseline levels (0.55 nmol/mL [0.07]). When expressed in relation to plasma lipid content, there was an increase ($P = 0.03$) in the ratios of total α -tocopherol to either cholesterol or to total lipids from h 0 to 12, then these ratios declined ($P = 0.01$) from h 12 to 36 and then became nearly constant.

Plasma γ -tocopherol concentrations increased ($P = 0.05$) from h 3 to 12 h, decreased ($P = 0.02$) from h 12 to 24, and then remained nearly constant. When the concentration of γ -tocopherol was expressed in relation to the lipid content of the plasma, the ratio of γ -tocopherol/cholesterol increased ($P < 0.04$) from h 0 to 12 and returned to baseline levels by 24 h. The ratio of γ -tocopherol/total lipids did not change over the course of the study. Lipid concentrations are shown in Figure 4. Average cholesterol concentrations were 3.1 (0.2) mmol/L (or 119 [8] mg/dL) and triglycerides were 0.55 (0.09) mmol/L (or 44 [7] mg/dL).

The changes in the plasma concentrations of α - and γ -tocotrienols from h 0 to 72 mirrored those of γ -tocopherol (Figure 3). Increases (h 0 to 12) in the plasma ratio of α -tocotrienol:total lipids were observed ($P = 0.02$). Both α - ($P = 0.02$) and γ - ($P = 0.01$) tocotrienol/lipids decreased from h 12 to 24. No differences ($P \geq 0.05$) in

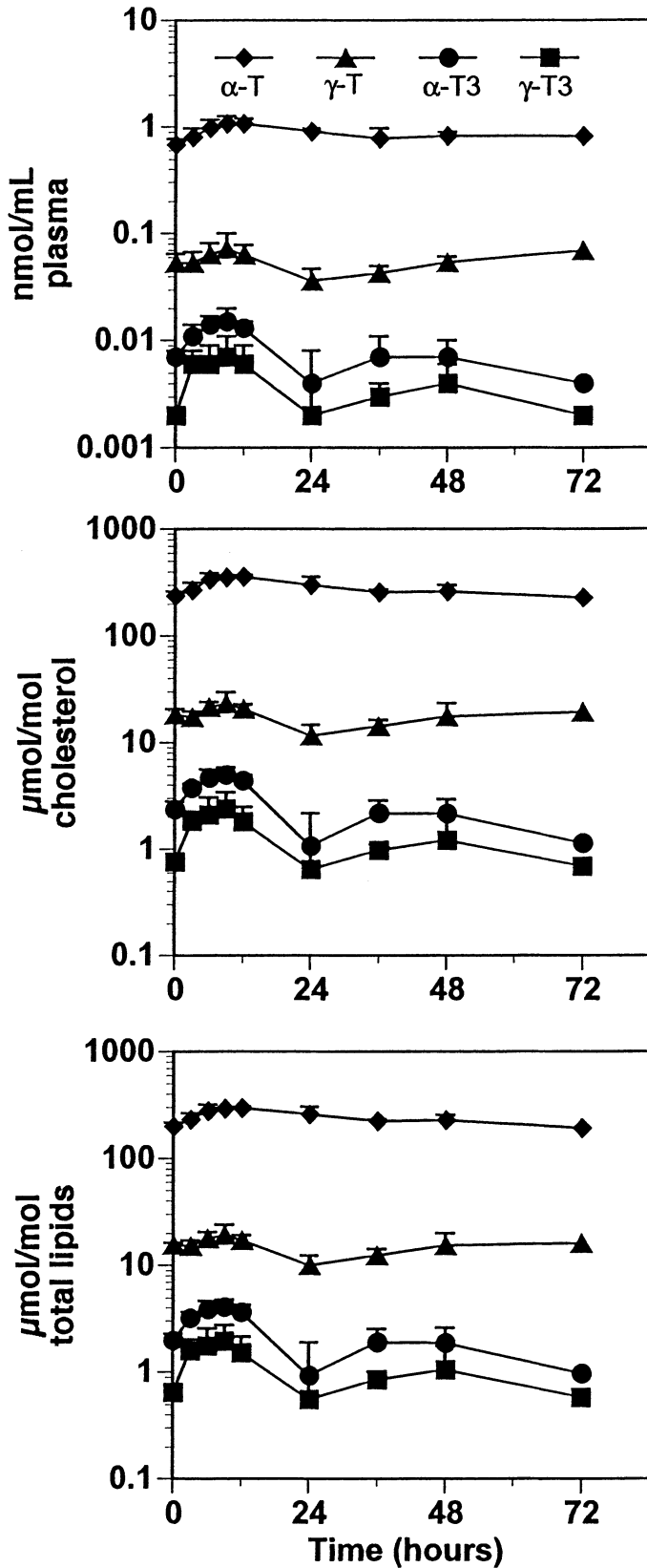


Figure 3. Plasma total α - (α -T) and γ -tocopherol (γ -T) and α - (α -T3) and γ - (γ -T3) tocotrienol concentrations (nmol/mL) (top), expressed per cholesterol (mmol/mol) (middle) or expressed per total lipids (bottom).

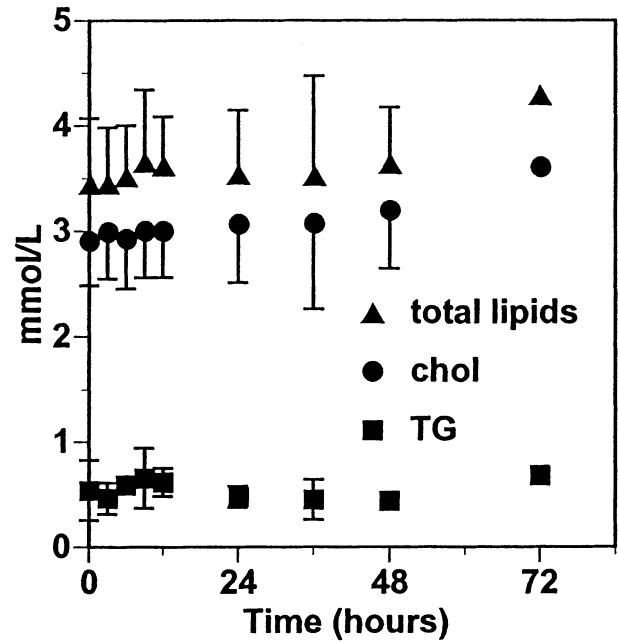


Figure 4. Plasma concentrations (mmol/mL) of cholesterol, triglycerides, and total lipids during the course of the study.

the ratios of tocotrienols to lipids were found between baseline and the fasting blood samples taken on d 1, 2, and 3 (i.e., h 0, 24, 48, or 72).

Discussion

This study demonstrates that α -tocopherol with natural stereochemistry is twice as effective at maintaining plasma α -tocopherol concentrations in pigs than is synthetic α -tocopherol that contains eight different stereoisomers. Oral administration of a 1:1 mixture of *RRR*- and all-*rac*- α -tocopheryl acetates, labeled with different amounts of deuterium, resulted in a 2:1 ratio of pig plasma α -tocopherol arising from the *RRR*- α -tocopherol compared to the all-*rac*- α -tocopherol.

Burton et al. (1998) noted that one of the advantages with using deuterated vitamin E forms is that the newly absorbed vitamin can readily be distinguished from the unlabeled vitamin E already present in the body. In addition, the deuterated vitamin E technique allows the direct and simultaneous comparison of two distinctly labeled *RRR*- and all-*rac*-forms in the same subject, whereby most of the variation attributable to differences between individuals, and factors that change with time, can be eliminated. A disadvantage of this technique is that all-*rac*- α -tocopherol is a mixture of eight stereoisomers (*RRR*, *RSR*, *RRS*, *RSS*, *SRR*, *SSR*, *SRS*, *SSS*), but the mass spectrometer detects d_6 - α -tocopherol, not the chirality of the carbons at positions 2, 4', or 8' in the α -tocopherol molecule. Thus, some interpretation of the results based on previous work in humans using *RRR*- and *SRR*- α -tocopherols (labeled with different amounts of deuterium) is necessary. Unlike *RRR*-

and all-*rac*- α -tocopherols, *RRR*- and *SRR*- α -tocopherols differ only at the 2-position where the chromanol ring and the phytyl tail meet. When humans consumed a 1:1 mixture of d_3 -*RRR* and d_6 -*SRR*- α -tocopherols, both stereoisomers were absorbed, and a 1:1 ratio was found in the intestinally derived, triglyceride-rich chylomicrons up to 12 h after the dose (Traber et al., 1990a). However, 24 h after administration of the deuterated tocopherols, the plasma was preferentially enriched in d_3 -*RRR*- α -tocopherol (Traber et al., 1990a).

Several lines of evidence illustrate that plasma enrichment with *RRR*- α -tocopherol depends upon the hepatic α -tocopherol transfer protein (α -TTP). First, humans with a defect in the α -TTP gene (Cavalier et al., 1998) spontaneously become vitamin E-deficient because their plasma α -tocopherol concentrations are less than 1/10 of normal and any absorbed α -tocopherol rapidly disappears from the plasma compartment (Traber et al., 1990b; Traber et al., 1994). Moreover, they are unable to discriminate between d_3 -*RRR* and d_6 -*SRR*- α -tocopherols (Traber et al., 1993b). Similarly, α -TTP-knockout mice are vitamin E-deficient (Terasawa et al., 2000). Additionally, purified α -TTP in vitro preferentially transfers *RRR*- α -tocopherol between liposomes and microsomes; *SRR*- α -tocopherol, as well as other tocopherols and tocotrienols, are poor competitors (Hosomi et al., 1997). Taken together, these data indicate that of the eight stereoisomers (*RRR*, *RSR*, *RRS*, *RSS*, *SRR*, *SSR*, *SRS*, *SSS*) in all-*rac*- α -tocopherol, only the four 2*R*-forms (*RRR*, *RSR*, *RSS*, *RRS*) are recognized by α -TTP and maintained in the plasma. Indeed, the Food and Nutrition Board (Food and Nutrition Board and Institute of Medicine, 2000) has defined that only α -tocopherol, specifically the 2*R*-forms of α -tocopherol, can fulfill the human requirement for vitamin E. Thus, all-*rac*- α -tocopherol has only half the activity of *RRR*- α -tocopherol.

It is thus not surprising that pig plasma d_3 -*RRR*- α -tocopherol concentrations were consistently greater than those of d_6 - α -tocopherol and that given sufficient time to allow the hepatic mechanism to clear unpreferred forms of vitamin E, the ratio of d_3 : d_6 was 2:1. These results are in accordance with previous studies carried out in humans (Burton et al., 1998), rats (Ingold et al., 1987), and dogs (Traber et al., 1993b).

The estimated maximum d_3 - α -tocopherol concentration was double that of d_6 - α -tocopherol, yet the post-peak disappearance rates did not differ. These findings fit with the hypothesis that once both forms are absorbed and the synthetic non-2*R*- α -tocopherol forms are removed from the plasma, only the 2*R*-forms are recognized by the α -TTP and preferentially re-secreted from the liver into the plasma. The fate of the synthetic non-2*R*- α -tocopherol forms is not known with certainty. However, some is preferentially metabolized by humans to α -CEHC (2,5,7,8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman), a urinary vitamin E metabolite (Traber et al., 1998).

Supporting our findings are those of Mahan et al. (2000). They provided sows equivalent IU of natural and synthetic vitamin E but found 17% higher serum α -tocopherol concentration in sows (at d 70 post coitum) fed *RRR*- α -tocopheryl acetate as compared with all-*rac*- α -tocopheryl acetate.

Despite their relatively high concentrations in the feed, sow plasma γ -tocopherol and α - and γ -tocotrienol concentrations were low compared to α -tocopherol concentrations. Previous studies in pigs (Engberg et al., 1993) showed that increasing dietary amounts (up to 1,000 mg/kg diet) of *RRR*- α -, γ -, and δ -tocopheryl acetates (with the relative distribution of 40.4, 41.1, and 18.3%, respectively) increased the plasma concentrations of the corresponding tocopherols during experimental periods of 6 to 8 wk. However, the plasma γ - and δ -tocopherol concentrations were considerably lower than α -tocopherol concentrations. Using a similar vitamin E enrichment in feed given to broilers, Jakobsen et al. (1995) found that the relative proportion of α -, γ -, and δ -tocopherol in plasma was 89:10:1. Similarly, α -tocopherol supplements given to humans depress plasma γ -tocopherol concentrations (Handelman et al., 1985; Baker et al., 1986). However, in sows serum concentrations of γ -tocopherol at d 80 post coitum was not influenced by supplemental α -tocopheryl acetate (Mahan, 1991).

In humans, all forms of vitamin E are similarly absorbed, but the plasma becomes preferentially enriched in α -tocopherol after passage through the liver as a result of the specific selection of α -tocopherol by α -TTP (Traber and Sies, 1996). The absorption process does allow some of the non- α -tocopherol forms to enter the circulation. During the present study in pigs, increases in the plasma α - and γ -tocopherols and α - and γ -tocotrienols were found during the first 12 h after a meal. Blood samples taken at h 24, 48, and 72 were prior to the morning meal. It is noteworthy that at h 24, all of the plasma vitamin E forms, except α -tocopherol, were lower or the same as at baseline, suggesting that the preceding increases reflect absorption of these forms from the diet, but subsequently these forms were not maintained in the plasma, when α -tocopherol in fact displaced them.

Implications

This study on vitamin E bioactivity in pigs has demonstrated that pigs not only have a preference for the α -tocopherol form of vitamin E compared with other dietary forms, but they also discriminate between *RRR*- and all-*rac*- α -tocopherols with a preference for natural, *RRR*- α -tocopherol. The results also demonstrated that the natural vitamin E has roughly twice the activity of synthetic vitamin E in maintaining plasma concentrations. This 2:1 ratio of *RRR*:all-*rac* is higher than the currently accepted *RRR*:all-*rac* ratio of 1.36:1.00.

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