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Deletion of apolipoprotein E gene modifies the rate of depletion of alpha tocopherol (vitamin E) from mice brains

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ABSTRACT

Our previous reports show that apolipoprotein E (apoE) influences the dynamics of alpha tocopherol (vitamin E) in brain. In this investigation, the patterns of depletion of alpha tocopherol from tissues of apoE deficient and wild type mice were compared after the animals were fed vitamin E deficient diets. Alpha tocopherol concentrations in specific regions of the brain and peripheral tissues at different times were determined by HPLC with electrochemical detection. ApoE deficiency significantly retarded the rate of depletion of alpha tocopherol from all regions of the brain. In addition, comparison of the rates of depletion of alpha tocopherol in both apoE deficient and wild type animals showed that cerebellum behaved differently from other areas such as cortex, hippocampus and striatum. This reinforces the uniqueness of cerebellum with regard to vitamin E biology. Patterns of depletion of tocopherol from peripheral tissues were different from brain. Serum tocopherol was higher in apoE deficient animals and remained higher than wild type during E deficiency. Depletion of liver tocopherol also tended to be unaffected by apoE deficiency. Our current and previous observations strongly suggest that apoE has an important role in modulating tocopherol concentrations in brain, probably acting in concert with other proteins as well.

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1. Introduction

Many experimental and clinical reports indicate that vitamin E has an impact upon the incidence and treatment of Alzheimer's disease (AD) even though some aspects have been somewhat controversial. Behl et al. [1] have found that vitamin E in the culture medium protected PC12 cells (that are used as models of peripheral neurons) from the cytotoxic effects of amyloid beta protein. A study on experimental animals also tends to support a role for vitamin E in altering learning behavior. Ichitani et al.[2] found that vitamin E had an effect on a step-through passive avoidance response task and found that the vitamin E deficient animals showed significantly lower and vitamin E supplemented animals significantly higher rates of passive avoidance response than the control animals. Investigations conducted at Chicago, USA [3] and Rotterdam, Netherlands [4] suggest that higher intakes of antioxidants, especially vitamin E, are associated with a lower risk of incidence of AD. However, a randomized trial of dietary supplementation of vitamin E did not find any beneficial effects on cognitive function in healthy older women [5]. In a controlled clinical trial in humans Sano et al.[6] showed that vitamin E treatment slows the progression of AD. It should be noted, however, that a recent review examining the clinical use of vitamin E in AD could only conclude that this practice "may be" of some benefit [7]. Thus there is need for additional information on the potential relationships between vitamin E and other factors that may influence cognition.

Numerous studies have shown that apolipoprotein E (apoE) has an important role in the pathophysiology of AD. Genetically, the presence of the apo E4 allele is associated with the late-onset, sporadic form of AD [8]. This observation has led to a large number of studies on the functions of apoE in brain. Some of the neuropathological features of AD that have been replicated in transgenic mice overexpressing apo E4 gene include reduced numbers of presynaptic terminals, increased plaque deposition, increased phosphorylation of tau, and impaired learning and memory (see review [9]). Even though most investigations deal with the impact of apoE on lipid metabolism in peripheral tissues, apoE also plays an important role in lipid metabolism in brain. Studies indicate that apoE mediates sulfatide trafficking and metabolism in the CNS, alters phospholipid molecular species in some membranes, and influences cholesterol dynamics (see review [10]).

We have observed that there is biological interaction between vitamin E and apoE. Firstly, the steady state levels of alpha tocopherol in different brain regions were lower in apoE deficient mice compared with the wild type [11]. The changes in tocopherol concentration were dependent upon age and were also specific for different regions of the brain. Secondly, we observed that when radioactive vitamin E was

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injected into the lateral ventricles the levels of uptake of the radioactivity by different brain regions of apoE deficient animals were different from that of the wild type brain [12]. The focus of the current investigation is to compare the rates of depletion of vitamin E from different brain areas of apoE deficient and wild type animals on vitamin E deficient diets.

2. Materials and methods

2.1. Chemicals

The chemicals used were of reagent grade purity from standard sources. Solvents for chromatography were HPLC grade from Fisher Scientific, Itasca, IL., U.S.A. Standard alpha tocopherol was purchased from Kodak Laboratory Chemicals, Rochester, NY, USA. Absolute ethanol was obtained from Aaper Alcohol and Chemical Company, Shelbyville, Kentucky, U.S.A., and was redistilled prior to use. Most of the other reagent grade chemicals were from Sigma Chemicals, St. Louis, MO, USA.

2.2. Treatment of animals

All procedures with animals were approved by the Subcommittee on Animal Studies of the Minneapolis Veterans Affairs Medical Center. Mice with the Apo*e* gene knocked out (C57BL/6J-Apo$e^{tm1/unc}$) were obtained commercially from Jackson Laboratories, Bar Harbor, Maine. Control mice (C57 BL/6J) were also purchased from the same source. The animals obtained after weaning were placed on control or vitamin E deficient diet for a period of 9.5 months. The diets were custom manufactured by Dyets Inc., Bethlehem, PA 18017 (catalog numbers 119614 and 119615) according to the specifications of AIN 93 purified diets for laboratory rodents [13] and slightly modified for production of vitamin E deficient formulations. The lipid source was tocopherol-stripped lard (10%). The control diet was obtained by the addition of 75 IU of vitamin E as alpha tocopherol acetate per kg diet.

After different times on the control or vitamin E deficient diet the animals were anesthetized and perfused with cold isotonic saline via a catheter inserted into the left cardiac ventricle. The brain was then taken out and lightly rinsed with cold isotonic saline. The different brain regions were dissected out according to the method of Glowinski and Iversen [14]. The tissues were weighed, homogenized in 0.32 M sucrose, 10 mM HEPES, 1 mM EDTA at pH 7.4 and stored at −70 °C and were used later for the various assays.

2.3. Determination of tocopherol

The method for determination of tocopherols by liquid chromatography has been published [15]. Briefly, 2 ml ethanol containing 0.025% (w/v) butylated hydroxytoluene (BHT) and 0.1 ml of 30% (w/v) ascorbic acid were pipetted into tubes containing samples for tocopherol analyses. The mixture was saponified at 60 °C for 30 min after the addition of 1 ml of 10% potassium hydroxide solution. Sample tubes were cooled and 2 ml of water was added followed by 2 ml of hexane containing 0.025% (w/v) BHT. Tocopherols were extracted into the hexane phase by vortexing the samples for 1 min. The hexane phase was separated out and evaporated down under a stream of nitrogen. The residue was redissolved in mobile phase and analyzed by reverse phase liquid chromatography using the following conditions: column=ultrasphere ODS, 5 μm, 4.6×150 mm (Beckman Instruments, Fullerton, CA, USA); mobile phase=methanol : water, (94.5 : 5.5) with 7.5 mM sodium dihydrogen phosphate (final concentration); flow rate=2.7 ml/min. The tocopherols were detected electrochemically: Coulochem 5100 A detector, 5011 analytical cell with detector 1 at −0.25 V and detector 2 at +0.65 V and 5021 conditioning cell at −0.75 V.

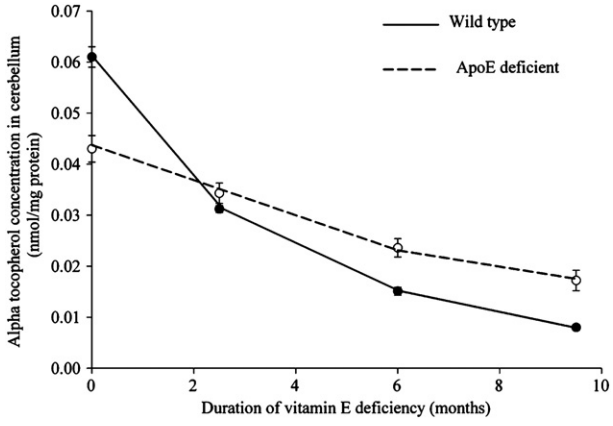

Fig. 1. Rates of decline of alpha tocopherol in cerebellum of apoE deficient and wild type mice that were fed vitamin E deficient diet for 9.5 months. At the indicated times the animals were sacrificed, perfused with cold isotonic saline, and tissues were dissected out. Alpha tocopherol concentrations were determined in the tissue samples by HPLC with electrochemical detection using procedures described. Each point represents mean of values obtained from four different animals in this and the rest of the figures. Error bars are S.E.M.

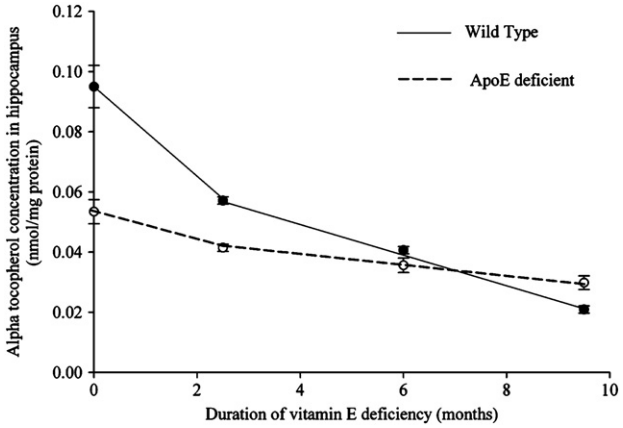

Fig. 2. Alpha tocopherol concentrations in the hippocampus of wild type and apoE deficient mice fed vitamin E deficient diets. The tissues were dissected out as described and tocopherol concentrations determined by HPLC with electrochemical detection.

2.4. Other biochemical assays

Concentration of total protein was determined by the Lowry technique as modified by Markwell et al [16].

2.5. Statistical methods

SPSS (version 15, Chicago, Illinois) was used to determine multiple regressions as estimates of the linear and curvilinear effects of the duration of dietary regimen upon alpha tocopherol concentrations in tissue. In addition, standard ANOVA as well as student *t*-tests were also used as indicated.

3. Results

Data from our lab and those of other investigators have shown that the characteristics of handling of tocopherols are different among various regions of the brain. For example, cerebellum is an area of special interest with regard to the metabolism and utilization of vitamin E. Hence we determined the changes in concentrations of alpha tocopherol in different brain regions such as cerebellum, hippocampus, cerebral cortex and others. Fig. 1 shows the rate of decline of alpha tocopherol in the cerebella of apoE deficient and wild type animals.

As we have reported before [11], cerebellar alpha tocopherol levels are lower in the apoE deficient animals than the wild type at the beginning of the dietary regimen. However, vitamin E deficiency results in a sharper decline in tocopherol levels in the wild type animals. At the end of the study the apoE deficient animals have slightly higher levels of alpha tocopherol in cerebellum than the wild type. Alpha tocopherol concentration as a function of time on the vitamin E deficient diet was subjected to statistical analysis. The data showed significant curvilinear effect with R^2 of 0.964. The curvilinear interaction term (group×time^2) was highly significant indicating that the two groups (wild type and apoE deficient) were significantly different with regard to the patterns of decline of alpha tocopherol levels over time ($P<0.001$). In general, the rate of decline of vitamin E was slower in the apoE deficient than in the wild type animals.

Next, we examined data from hippocampus, an area that plays a critical role in memory function. The results would be useful for understanding the potential importance of tocopherols in disorders of memory such as Alzheimer's disease. The declines in alpha tocopherol levels as a function of the duration of vitamin E deficiency are shown in Fig. 2.

Hippocampal alpha tocopherol levels were lower in the apoE deficient animals at the beginning of the study, as we reported earlier.

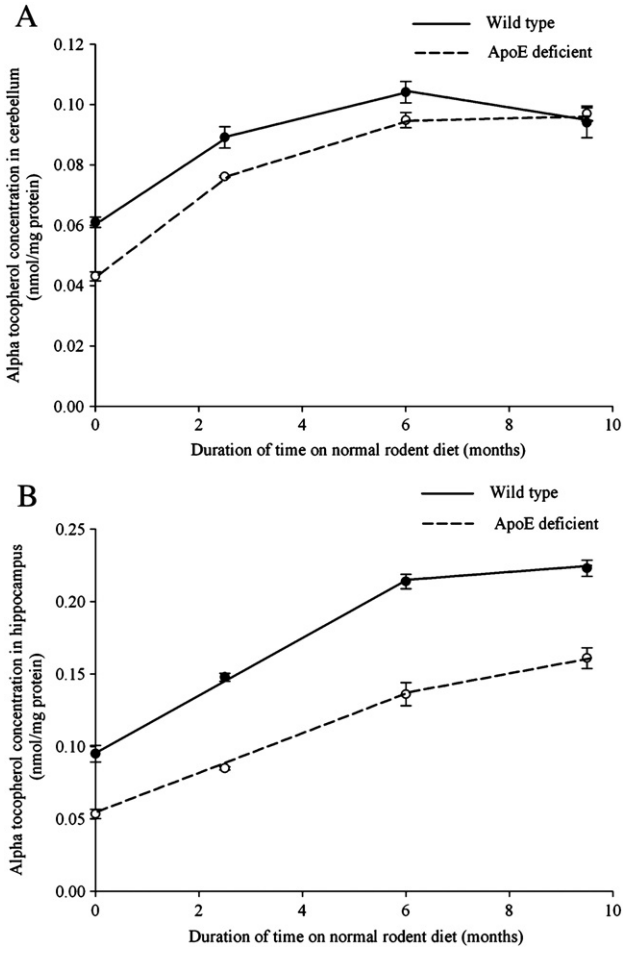

Fig. 3. Changes in alpha tocopherol concentrations in two brain regions of wild type and apoE deficient mice that were fed normal rodent diets. A. Cerebellum and B. Hippocampus. Dietary treatment of the mice were identical to the vitamin E deficient study except for the addition of normal levels of vitamin E.

Furthermore, the rate of decline of alpha tocopherol concentration was slower in apoE deficient animals compared to the wild type. As observed with cerebellum, the curvilinear group interaction term was significant ($P<0.001$). Thus, the rate of decline of alpha tocopherol from the hippocampus of apoE deficient mice was also significantly slower than that of the wild type animals.

In order to calculate the half lives for alpha tocopherol depletion from the cerebellum and hippocampus the alpha tocopherol concentrations were converted to logarithmic values and fitted to linear equations. Using these equations the calculated half lives for tocopherol depletion were as follows. a) Cerebellum: wild type=2.91 months; apoE deficient=6.86 months. b) Hippocampus: wild type=4.24 months; apoE deficient=11.6 months. The half lives for tocopherol were increased by 2.36-fold in the cerebellum and 2.74-fold in the hippocampus of the apoE deficient animals when compared with the wild type confirming that apoE deficiency results in slowing of tocopherol turnover in the brain. It is also interesting to note that Burton et al. [17] calculated the half lives of deuterium labeled alpha tocopherol in various tissues and reported that the half lives of the compound in brain are 107 and 40 days in guinea pigs and rat, respectively. These values are comparable to the half lives in the wild type animals in the current study.

Since this study involved feeding of mice with vitamin E deficient diets for considerable lengths of time it is important to examine whether there are any changes in brain alpha tocopherol concentrations when mice are fed normal diets for the same length of time. Therefore, mice were fed normal diets and brain samples were removed as described under Materials and methods and the tissues analyzed for alpha tocopherol by HPLC. The results for cerebellum and hippocampus are shown in Fig. 3A and B. The figures show that the alpha tocopherol concentrations in both brain regions increase during the course of the experiment when the animals were fed normal diets irrespective of the apoE deficiency status.

We examined the depletion of alpha tocopherol from several other regions of the brain such as pons, hypothalamus, midbrain, and cortex of mice fed vitamin E deficient diets. Statistical examination of data from all these regions showed that the two groups (apoE deficient and wild type) were significantly different with regard to the rates of decline in alpha tocopherol when the animals were fed vitamin E deficient diets. The patterns of decline in alpha tocopherol levels were nearly identical in all cases suggesting that the underlying mechanism(s) responsible for the differences in the rates of depletion of alpha tocopherol were the same in all cases.

A few selected peripheral tissues were also analyzed. It should be emphasized that the initial levels of alpha tocopherol in peripheral tissues are not lower in the apoE deficient animals compared with wild type, unlike brain concentrations. Alterations in serum concentrations are of special interest since tocopherols have to be transported to the brain via serum. The data are shown in Fig. 4.

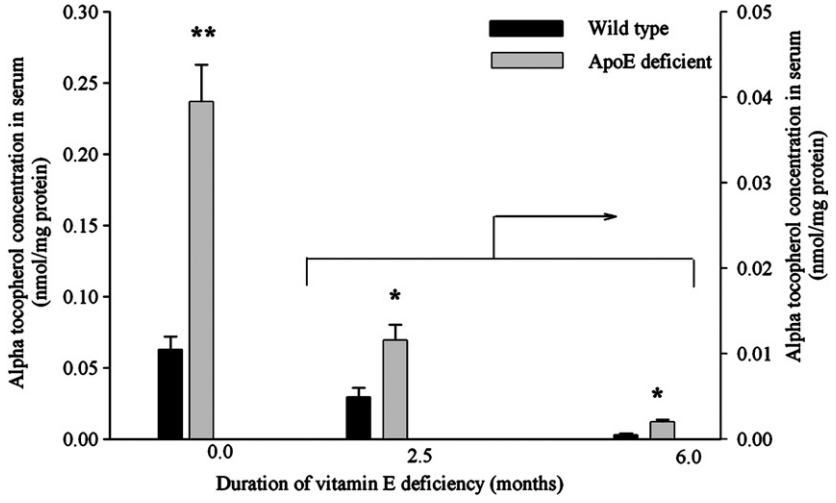

Fig. 4. Alpha tocopherol concentrations in sera of wild type and apoE deficient mice that were fed vitamin E deficient diets. Blood samples were collected at the time of sacrifice and sera obtained after centrifugation of clotted blood. Alpha tocopherol concentrations were assayed by HPLC. Note that the concentrations at 2.5 and 6 months are very low and this is indicated by the arrow within the Figure along with a different *Y*-axis. Statistical comparisons: *P* values **<0.01; *<0.03.

Upon feeding of vitamin E deficient diets, serum alpha tocopherol concentrations undergo very steep declines such that the levels are below limits of measurement at 9.5 months and hence data are shown only until six months of feeding of vitamin E deficient diets. In sharp contrast with brain, tocopherol was depleted dramatically in serum even within two and half months of deficiency. The data are shown as bar graphs with concentration values after 2.5 and 6.5 months of vitamin E deficiency being depicted on a separate *Y*-axis. It is noteworthy that the serum alpha tocopherol concentrations were significantly higher in the apoE deficient animals at the beginning of the study when compared with wild type animals. This relationship was maintained throughout the study. Thus, apoE deficiency did not alter the mode of depletion of alpha tocopherol in serum, in sharp contrast to brain.

Liver plays a critically important role in the metabolism and processing of tocopherols [18]. Hence changes in alpha tocopherol levels in livers of both types of mice raised on vitamin E deficient diets are of special interest. The data from this experiment are shown in Fig. 5.

Liver alpha tocopherol concentrations at the start and after 2.5 months of dietary treatment tended to be higher in the apoE deficient animals than in wild type. This effect is similar to that observed in the serum and opposite of that in brain. However, the alpha tocopherol levels in the apoE deficient liver were not significantly different from that of wild type animals throughout the study. The contrast in the rates of tocopherol depletion within the brain and liver (for example, compare Figs. 1 and 5) suggests that apoE may be involved specifically in the uptake and handling of tocopherol within brain cells such as neurons and glia.

We have reported that the patterns of change in alpha tocopherol concentrations with age in the apoE deficient animals were different among specific regions of the brain [11]. In addition, we have reported earlier that the rate of decline of alpha tocopherol from the cerebellum of mice is strikingly different from those of other areas of the brain [19]. Both of these reports demonstrate that vitamin E processing in the cerebellum has some unique features. Therefore, we compared the declines in alpha tocopherol concentrations in cerebellum with those from other brain regions as a function of the duration of vitamin E deficiency. The results from different brain regions are shown in Fig. 6A and B with changes graphed as percent of original value.

It can be seen that the data formed two regional groups consisting of cerebellum at the bottom and cerebral cortex, hippocampus and striatum as a separate group at the top. The two groups were compared using matched pair *t*-tests and were found to be significantly different ($P<0.01$at each time point for both wild type and apoE deficient animals). Thus, cerebellum exhibits a different rate of tocopherol depletion compared with cortex, hippocampus and striatum. This is very similar to our observation in an earlier study where the animals were on normal diet and the changes in alpha tocopherol at different

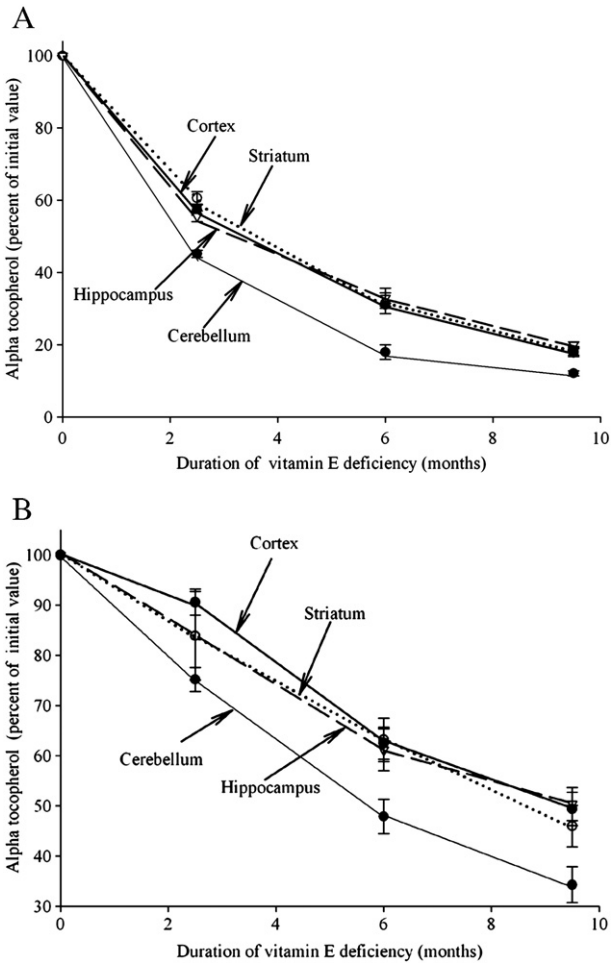

Fig. 6. Comparison of the rates of loss of alpha tocopherol from four regions of the brains of wild type and apoE deficient animals that were fed vitamin E deficient diets. The alpha tocopherol concentrations are expressed as percent of the initial values. A) Wild type B) ApoE deficient.

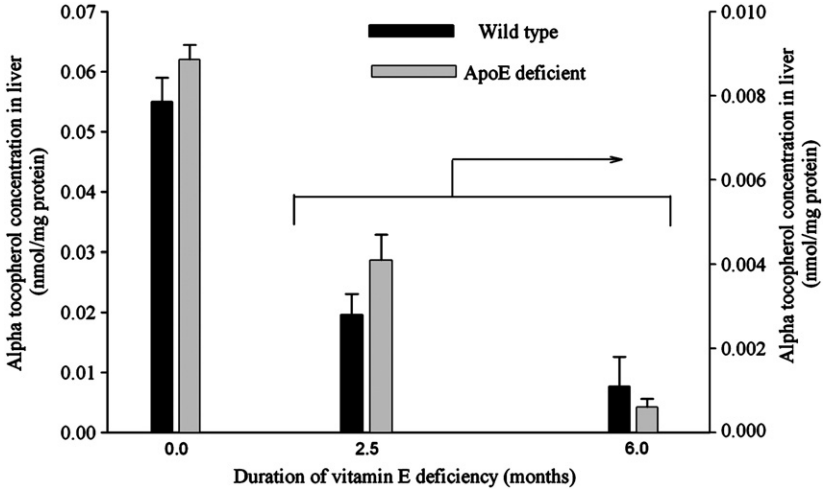

Fig. 5. Alpha tocopherol concentration in liver of wild type and apoE deficient mice fed vitamin E deficient diets. The liver samples were collected and analyzed for alpha tocopherol by HPLC with electrochemical detection as detailed under Materials and methods. Note that the concentrations at 2.5 and 6 months are very low and this is indicated by the arrow within the Figure along with a different *Y*-axis.

ages were investigated [11]. The latter report and the current studies point to differences in the mechanism and/or rate of handling of tocopherol in different regions of the brain. Cerebellum tends to be unique in this and other functional parameters related to tocopherol handling and metabolism (see Discussion).

4. Discussion

4.1. Accumulation of alpha tocopherol in the cerebellum and hippocampus of wild type and apoE deficient mice placed on normal diets

We observed that alpha tocopherol concentrations increased in brain regions when mice were fed normal diets over the same length of time as the vitamin E deficiency study (Fig. 3A and B). Our data (Fig. 3A) also show that alpha tocopherol concentration in the cerebellum of apoE deficient animals became equal to the wild type at the oldest age studied. Thus the changes in alpha tocopherol levels with age when mice were fed normal diets were dependent upon the anatomic site and this has already been discussed in detail [11]. It can also be noted that the observed increase in alpha tocopherol with age agrees with the data from Ramassamy et al [20]. In any case, the dynamics of the rate of depletion of alpha tocopherol after vitamin E deficiency seem to differ from the rate of increase of the compound when animals were fed normal diet in that the patterns of increase in alpha tocopherol levels are similar in both wild type and apoE deficient animals.

4.2. Overview of the main finding of the vitamin E deficiency study

One of our main findings is that the rates of decline of alpha tocopherol in brain regions of apoE deficient animals are slower compared with those from brains of wild type animals when both groups were fed vitamin E deficient diets. ApoE deficiency results in slower rates of processing of vitamin E within brain. Such slower rates could result from simple retardation of removal of tocopherol and/or decline in rate of utilization of tocopherol. The modes of transport of alpha tocopherol between brain cells and extracellular fluid will determine the rate of depletion of brain tocopherol.

Information on proteins that can be involved in the transport and processing of tocopherol within brain can be derived from studies of lipoproteins in cerebrospinal fluid which exist in equilibrium with brain extracellular fluid. ApoE is the primary lipoprotein in cerebrospinal fluid and therefore this molecule could have a critical role in lipoprotein-mediated transport. In addition, it is known that HDL enriched in apoE is a predominant lipoprotein in CSF [21,22]. Reports also show that alpha tocopherol bound to HDL is transferred to pneumocytes [23] and brain capillary endothelial cells [24], It is possible that tocopherol transport between cells in the brain is mediated by a pathway facilitated by apoE in HDL. Such a pathway would not be operating efficiently in apoE deficient animals. An alternate explanation for the slower movement of tocopherol in the apoE deficient animals is that other molecules that normally participate in the cellular uptake of alpha tocopherol may have been altered in concentration, composition or structure in response to apoE deficiency.

4.3. Cellular uptake and transport of tocopherol in brain: possible importance of proteins other than apoE

Both VLDL and LDL are important in the delivery of tocopherol to extrahepatic tissues. The process involves the LDL-receptor mediated pathway as well as an independent pathway utilizing lipoprotein lipase or phospholipids transfer protein (see review Hacquebard and Carpentier [25]). It has been suggested that tocopherol uptake could involve the binding of HDL particles (containing alpha tocopherol) to the SR-BI receptor followed by the entry of tocopherol into cells [26]. Interestingly, a deficiency of SR-BI receptor led to declines in tocopherol levels in various tissues including brain [27]. Studies by Kostner et.al. [28] have shown that phospholipid transfer protein from lipoprotein-free plasma can also facilitate transfer of tocopherol from lipoproteins to cells. Lipoprotein lipase should also be considered. When lipoprotein lipase was overexpressed specifically in muscle, concentrations of tocopherol increased in this tissue whereas no changes in tocopherol levels were observed in the brain where lipase levels were unaltered [29]. Another protein of interest is afamin which is a glycoprotein with a large binding capacity and multiple binding sites for both alpha and gamma tocopherol. Afamin occurs in significant amounts in both blood plasma and cerebrospinal fluid and may play a role in transporting tocopherol to the brain [30,31]. The relative importance of apoE when compared with the above proteins as a mediator of alpha tocopherol transport needs further investigation.

4.4. Depletion of tocopherol from liver

ApoE deficiency did not have a significant impact upon liver concentrations of alpha tocopherol since the decline in liver vitamin E upon treatment with vitamin E deficient diets was not affected by apoE deficiency (Fig. 5). ApoE has well-known functions in the binding, uptake and catabolism of lipoproteins. Hence, one would expect apoE to have a significant impact upon lipoprotein metabolism and transport of lipids in general. Furthermore, liver is critical for the handling of vitamin E [18]. Alpha tocopherol transfer protein plays a very important role in loading of VLDL with tocopherol in the liver for transport to other tissues (see review [26]). Liver is also important for the metabolism of vitamin E via the cytochrome P450 system [32]. These and other unknown proteins may have dominant effects on the dynamics of alpha tocopherol in liver with apoE playing a much less crucial role in this organ. This may explain the relative lack of effect of apoE deficiency on liver concentrations of alpha tocopherol.

4.5. Depletion of serum tocopherol

Our data show that apoE deficient animals have very high levels of serum alpha tocopherol and the latter was depleted quite fast in both wild type and apoE deficient animals (Fig. 4). The serum depletion pattern is different from that of the brain with serum alpha tocopherol remaining high in apoE deficient animals compared to wild type throughout the study (Compare Figs. 1 and 4). A number of proteins such as lipoprotein lipase and PLTP may be involved in the transport and uptake of tocopherol in serum and peripheral tissues [33]. Thus, apoE may only be playing a minor role in controlling tocopherol levels in serum.

4.6. Neuroanatomical considerations and the uniqueness of cerebellum

Our data show that the rates of depletion of alpha tocopherol from the cerebellum are significantly faster than those from cortex, hippocampus and striatum (Fig. 6). In our previous study the rates of accumulation of alpha tocopherol with age also showed the same grouping of the different brain regions with cerebellum being different from the others [11]. The current data reinforces the conclusion that cerebellum is unique with regard to processing of alpha tocopherol.

4.7. Mechanistic considerations

We do not have sufficient information to propose a definitive mechanism for the modulation of brain tocopherol dynamics by apoE. However, some speculations can be entertained. Our published data show that the steady state levels of alpha tocopherol in nearly all brain regions of apoE deficient mice are lower that those in the wild type [11]. A biological interaction between apoE and vitamin E is also reinforced by other lines of evidence showing that oxidative damage in the central nervous system of apoE deficient animals is modulated by dietary administration of vitamin E [34] or by the combined dietary

deficiency of folate and vitamin E [35] Furthermore, the current study found that the half life of tocopherol is slower in the apoE deficient mice. Nonetheless, it should be noted that alpha tocopherol concentrations in the brains of apoE deficient animals are at least 40% of wild type levels [11] suggesting that other proteins are also involved in tocopherol handling in the brain. Our current hypothesis is that apoE along with one or more other proteins is involved in the trafficking of tocopherol in the brain. Many molecules or lipoproteins can be suitable as apoE partners. Some of these proteins have already been discussed. Alpha tocopherol transfer protein has been the object of many investigations on tocopherol dynamics. However, we feel that alpha tocopherol transfer protein may not play a major role in this process since we and others have not observed significant levels of this protein in the brain [36,37] even though specific cell types contain alpha tocopherol transfer protein that can be demonstrated by immunohistochemical methods [38]. Nonetheless, a recent study by Yoshida et al. [39] using mice deficient in both apoE and alpha tocopherol transfer protein genes found that vitamin E modulates oxidative stress markers in this model indicating a possible interaction between apoE and alpha tocopherol transfer protein. Hence the involvement of the latter protein in tocopherol trafficking in brain should be left open for further studies. As mentioned earlier, other species such as lipoprotein lipase, scavenger receptor SR-BI and HDL are worthy of experimental investigations (see review by Mardones [26]) as potential partners in a complex with apoE that may facilitate the movement of alpha tocopherol between neurons and glia.

4.8. Impact of our findings for the therapeutic use of vitamin E

The observed interaction between vitamin E and apoE can be postulated to have at least two possible consequences. **A).** The clinical efficacy of vitamin E may depend upon the level of biological activity of apoE which in turn can be modulated by apoE molecular structure and environmental factors. Support for this idea comes from a number of studies. The fact that serum cholesterol is different among carriers of apolipoprotein E2, E3 and E4 genes is the most established property of apoE. Interestingly, Ortega et al. [40] found that alpha tocopherol levels in each plasma lipid class vary according to apoE genotype suggesting an analogous influence of apoE genotype upon serum alpha tocopherol. In addition, dietary or environmental factors could also play important roles. For example, Corella et al. [41] observed that the effect of alcohol intake on LDL cholesterol was influenced by apoE polymorphism. **B).** Vitamin E may have efficacy only in the presence of specific disease-related pathology. Studies of the effectiveness of drugs as a function of apoE isoforms support this idea. For instance, carriers of apo E2 were found to be more responsive to statins than those carrying E3 or E4 [42]. Another investigation demonstrated that qualitatively the response of subjects with Alzheimer's disease to the cholinesterase drug rivastigmine was different among E4 carriers compared with others [43]. In short, factors that influence the biological function of apoE such as presence of specific isoforms as well as environmental factors and the disease process would be expected to modulate the interaction between apoE and vitamin E and in turn influence the clinical efficacy of vitamin E.

4.9. Conclusions

Our investigation shows that apoE deficiency retards the depletion of alpha tocopherol from different regions of mouse brain. The characteristics of depletion of brain tocopherol are very different from those in peripheral tissues like liver where the depletion of tocopherol was not modulated by apoE deficiency. This could be due to the function of other proteins (such as tocopherol transfer protein) that may play dominant roles in tocopherol processing within the liver and not in the brain. Tocopherol dynamics in the serum compartment is quite different since apoE deficiency alone results in substantial increase in serum alpha tocopherol concentrations. In this case also other proteins such as phospholipid transfer protein and afamin may have dominant roles in maintaining serum alpha tocopherol concentrations. The data presented here, along with our previous reports, suggest that apoE is an important protein taking part in alpha tocopherol processing within brain. It is quite likely that a complex of apoE with other proteins may be involved in this process.

Acknowledgments

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