REVIEW

Vitamin E and neurological function

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The clinical, neuropathological and electrophysiological evidence that vitamin E (α-tocopherol) is essential for normal neurological function will be reviewed. The possible reasons why neural tissues should be particularly affected by a deficiency of this fat-soluble vitamin and the mechanism(s) involved will be considered.

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1 Introduction

Vitamin E (α-tocopherol) was discovered in 1922 when Evans and Bishop [1] demonstrated the existence of a fat-soluble factor that was necessary for normal reproduction in rats. In the following years, a number of vitamin E deficiency syndromes were produced experimentally in several animal species [2]. These differed in different species and even in some cases within a species depending on age. Despite numerous claims, a well-documented role of vitamin E in human nutrition was not reported until 1967 when it was shown that premature infants fed a formula feed deficient in vitamin E, could develop an hemolytic anemia with edema [3]. Following supplementation of feeds with α-tocopherol, this syndrome disappeared.

It was approximately another decade before evidence began to emerge that vitamin E played an important role in the maintenance of normal neurological structure and function. The evidence came from studying patients with the following:

(i) abetalipoproteinemia, a rare inborn error of lipoprotein metabolism
(ii) other severe and chronic disorders of fat absorption
(iii) a selective deficiency of vitamin E, now known as ataxia with vitamin E deficiency (AVED), and also from
(iv) comparative neuropathological and electrophysiological studies in humans and experimental animals.

This evidence and current studies will now be reviewed and possible mechanisms of action of this fat-soluble vitamin will be considered. This review will not consider the possible beneficial role of vitamin E supplementation in neurological conditions such as Parkinson's disease, Alzheimer's disease and Down's syndrome. It is, however, of interest that vitamin E supplementation could help prevent amyotrophic lateral sclerosis [4].

2 Abetalipoproteinemia

The roles of vitamins and other essential nutrients in human nutrition are typically discovered as a result of deficiency syndromes. As vitamin E is found in numerous foods including vegetable and nut oils, green vegetables, nuts, dairy products, meat and fish [5], it is extremely difficult to make a normal individual deficient in this vitamin. However, as vitamin E is a fat-soluble vitamin, concentrations would be expected to be reduced in chronic fat malabsorptive states. In a study of groups of children with specific defects of fat absorption, it was found that all the groups had mean serum vitamin E concentrations that were significantly reduced below normal [6]. The most severe deficiency of vitamin E was found in patients with abetalipoproteinemia, an inborn error of lipoprotein metabolism involving a defect in the microsomal triglyceride transfer protein, which prevents the appropriate assembly of lipoproteins containing apolipoprotein B [7–9]. All patients with the condition had undetectable serum concentrations of vitamin E from birth [6], which was subsequently confirmed

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Abbreviations: AVED, ataxia with vitamin E deficiency; **αTTP,** α-tocopherol transport protein

by more modern analytical methods using HPLC with fluorimetric detection. The undetectable serum concentrations of vitamin E in this condition result from the absence of chylomicra, which are necessary for its absorption, and the lack of LDL and VLDL necessary for its transport. Abetalipoproteinemia, therefore, provided an ideal model for the study of the effects of a severe and chronic deficiency of vitamin E in humans.

Among the clinical features of abetalipoproteinemia are an ataxic neuropathy and retinal pigmentation, which typically develop during the second decade of life. These features are progressive, leading eventually to crippling and blindness. No cases of spontaneous improvement have been reported. The neurological features are similar to those found in Friedreich's ataxia and comprise loss of reflexes, loss of balance (cerebellar ataxia), loss of position sense, loss of vibration sense, abnormal feet (pes cavus), curvature of the spine, abnormal eye movements, a pigmentary retinopathy and generalized muscle weakness [10].

A number of years ago, we decided to treat our children with abetalipoproteinemia with very large oral doses of vitamin E (100 mg/kg/day all-rac-α-tocopheryl acetate compared with the normal requirements of a total of 10–30 mg/day) [10, 11]. This was done for the following reasons: (i) as discussed above, the vitamin was undetectable in the serum of all patients, (ii) the vitamin E-deficient chick was known to develop a cerebellar disorder with ataxia [12] and (iii) neurological lesions had been described in several other animal species with vitamin E deficiency [2]. We confirmed that some of the very large oral dose was absorbed. First, trace but detectable concentrations of the vitamin could be detected in serum; concentrations never reached the normal range because of the absence of LDL and VLDL. Second, *in vitro* red cell hemolysis, which was abnormally increased before treatment in all the patients in whom it was measured, fell to within normal limits in all patients after supplementation. In addition, Kayden *et al.* [13] reported normal concentrations of vitamin E in adipose tissue in patients with abetalipoproteinemia following similar supplementation.

The clinical results following treatment with vitamin E can be summarized as follows: (i) the patients who were treated from the age of 16 months did not develop any of the neurological and retinal features and (ii) the progression of the signs and symptoms in the older patients, who already showed some neurological dysfunction before commencing supplementation with the vitamin, was either halted or in some cases reversed [10, 11]. Others have reported similar findings [14–17].

Initially there was discussion in the literature as to whether the retinal abnormalities seen in abetalipoproteinemia resulted from solely a deficiency of vitamin E or from both vitamins A and E. It is now, however, generally agreed that a severe deficiency of vitamin E alone can cause retinal abnormalities. Treatment with vitamin E can also prevent the development of the retinopathy, or if present halt its progression [16].

3 Other fat malabsorptive conditions

Although, as indicated above, vitamin E deficiency can occur in any chronic disorder of fat absorption, it is likely to be particularly severe in cholestatic liver disease. This is because bile salts, which are synthesized in the liver, are essential for the solubilization and absorption of the vitamin [18]. Neurological features very similar to those found in abetalipoproteinemia have been described in a number of studies of patients with cholestatic liver disease [19–22]. The typical spinocerebellar syndrome associated with severe and chronic vitamin E deficiency has also been described in patients with extensive intestinal resection [23, 24] and cystic fibrosis [19, 25]. Neurological sequelae are, however, rarely seen in patients with cystic fibrosis and tend only to occur in those patients with added complications such as liver disease or intestinal resection. Retinal involvement, similar to that seen in abetalipoproteinemia, has also been reported in patients with cholestatic liver disease [21] and ileal resection [24].

Improvement in neurological function following treatment with appropriate supplements (dose and type) of vitamin E has been reported in patients from all these groups [19, 20, 22–24]. In cholestatic liver disease, it is necessary to overcome the problems of solubilization by either giving intramuscular injections of the vitamin [18, 20, 22] or oral supplements of vitamin E in a water-soluble form such as α-tocopheryl polyethylene glycol-1000 succinate, which does not require bile salts for solubilization and absorption [26, 27].

The majority of the patients reported in the literature with neurological syndromes associated with vitamin E deficiency have had a greatly reduced vitamin E status from birth or infancy. It has, therefore, been suggested that the developing neurological system is particularly at risk from a deficiency of the vitamin. A few adults have, however, been reported who have developed a deficiency of vitamin E following massive ileal resection for conditions such as Crohn's disease or intestinal pseudo-obstruction [23, 24] and gone on to develop the typical neurological sequelae. These patients did not develop neurological symptoms until 10 years or more after the onset of the gastrointestinal disease, which is a similar delay to that seen in patients with abetalipoproteinemia. These observations in adults with intestinal resection, therefore, suggest that the mature neurological system is also at risk from a deficiency of this vitamin.

4 AVED

The most convincing evidence that a chronic and severe deficiency of vitamin E can result in a characteristic neurological syndrome comes from patients with familial isolated vitamin E deficiency, now known as AVED. The condition was first described in the early 1980s [28, 29] and

has been reviewed by Cavalier *et al.* [30]. As the name of the condition suggests, patients have a severe deficiency of vitamin E without generalized fat malabsorption. Subjects with AVED develop neurological and retinal features very similar to those described above in patients with severe vitamin E deficiency as a consequence of fat malabsorption and Friedreich's ataxia.

The underlying defect causing AVED was elucidated by a series of elegant studies by clinical neurologists, biochemists, geneticists and molecular biologists. Traber *et al.* [31] showed, using deuterated tocopherols, that absorption of vitamin E was normal in AVED but that disappearance from plasma was more rapid than in controls. They suggested that these patients lacked a functional hepatic binding protein for α-tocopherol which was necessary for the transfer of α-tocopherol to VLDL and its subsequent transport from the liver. The gene for AVED was localized to chromosome 8q [32] and then the gene for an hepatic α-tocopherol transfer protein (αTTP) which had been described in rat and human liver was also assigned to the same chromosome [33]. This, therefore, became the likely candidate gene for AVED and its involvement was confirmed when mutations in the gene for αTTP were independently described by two groups in patients with AVED [34, 35]. The αTTP protein has been reported to be present in human brain [36] and its mRNA in a number of tissues including brain, where it was found predominantly in the cerebellar cortex [37]. For a recent review of studies in AVED, the αTTP knockout mouse and the three-dimensional structure of αTTP, see Manor and Morley [38].

It is very important to be able to make the diagnosis of AVED and distinguish it from Friedreich's ataxia, as patients with AVED respond to treatment with vitamin E in a similar way to those with severe vitamin E deficiency secondary to chronic fat malabsorption [29, 30, 39]. Thus, vitamin E supplementation can halt the progression of the neurological signs and symptoms and in some cases improve them. Normal serum concentrations of vitamin E and clinical improvement can be achieved with a dose of 800 mg/day, which compares with the much larger dose of 100 mg/kg/day recommended for patients with abetalipoproteinemia.

5 Comparative neuropathological and electrophysiological studies

The final line of evidence linking a severe and chronic deficiency of vitamin E to neurological sequelae comes from comparative neuropathological and electrophysiological studies in humans and experimental animals. Thus, the neuropathological features found in vitamin E-deficient rats [40–43], monkeys [44] and humans [45–47] are very similar. In general, the central nervous system is more severely affected than the peripheral, with sensory axons more involved than the motor axons. The neuropathology of both the central and peripheral nervous system is suggestive of a dying back process [44] which is caused by a primary damage to the axon of the neuron with secondary demyelination [48, 49].

An accumulation of organelles is seen at the distal ends of nerves [42, 43], which strongly suggests an abnormality of ''turnaround.'' This is the mechanism whereby materials that have descended the axon in the anterograde transport system are packaged into lysosomes for their return to the cell body in the retrograde transport system. This conclusion was further supported by the finding of a reduction in the velocity of both fast anterograde and retrograde transport of endogenous acetylcholinesterase in the vitamin E-deficient rat [43].

Detailed electrophysiological studies have been reported in vitamin E-deficient humans (see [50]) and similar studies have been carried out in a vitamin E-deficient rat model [51–55]. The results in humans and the rat model are essentially similar. Hayton *et al.* [55] also carried out repletion studies in the rat model and reported significant improvements in electrophysiological parameters of neural and visual function.

6 The uptake and retention of vitamin E by neural tissues

The mechanism(s) of uptake of α-tocopherol by tissues including neural tissues is poorly understood. It has been suggested from *in vitro* studies that the apolipoprotein B/E receptor pathway for LDL may be involved [56, 57]. To investigate the role of this pathway *in vivo*, the transport and uptake of α-tocopherol by tissues in the Watanabe heritable hyperlipidemic rabbit, which lack functional apolipoprotein B/E receptors [58] was investigated. From this study, it was concluded that there were several different mechanisms for the tissue uptake of α-tocopherol. These included receptor-dependent and independent pathways, independent and co-transport of α-tocopherol and LDL, and uptake from a number of different lipoproteins [59]. Recent studies in the mouse have shown that apolipoprotein E may be involved in the transport and/or retention of α-tocopherol in the brain [60, 61].

There have been a number of studies describing the effects of prolonged vitamin E deficiency on the vitamin E status of various tissues from different animal species (see [62]). There is also information regarding vitamin E concentrations in neural tissues of control and vitamin E-deficient animals such as the mouse [63], guinea pig [64] and rat [64–69] and also vitamin E-deficient humans [70]. A detailed longitudinal study in the rat was undertaken [69], where the loss of α-tocopherol from neural and other tissues was examined during the course of vitamin E deficiency from weaning to 1 year of age. The decrease in α-tocopherol concentrations was less rapid in neural tissues (brain, cord and nerve) than in non-neural (serum, liver and adipose)

tissues. Similar results were observed in the mouse [63]. They were also consistent with the observations of Ingold *et al.* [71], who estimated the half-life of natural (RRR) α-tocopherol in various tissues by sequentially feeding rats unlabeled and deuterated RRR-α-tocopherol. All these studies, therefore, suggest that neural tissues preferentially conserve vitamin E and that this may reflect a reduced rate of turnover compared with other tissues.

All tissues appear to show two phases of depletion, an initial rapid loss during the first 4–8 wk of deficiency, followed by a second phase of slow prolonged depletion. Bieri [72] suggested that the first phase corresponded to a rapidly mobilized pool of labile vitamin E and that the second represented vitamin E bound to sub-cellular or membranous structures. It is possible that this latter phase relates to the loss of the functional and more critical component of tissue vitamin E. It may, therefore, be significant that neural tissues appear to maintain a greater proportion of α-tocopherol in the second less labile pool. Further evidence that neural tissues conserve vitamin E and that during vitamin E deficiency there is a redistribution of tocopherol from non-neural to neural tissues was obtained using deuterated tocopherol [73].

7 Mechanism(s) of action

A number of fundamental questions arise from the clinical, pathological, electrophysiological and biochemical observations described above. Why, for example, should nerves be particularly affected by a deficiency of this fat-soluble vitamin and what are the mechanisms involved?

Cavanagh [74] pointed out that neurons with long axons have logistical problems, as the cell body has to maintain a very large surface area of axonal membranes. As a result, it is possibly not surprising that the distal ends of the longest fibers are likely to be the first affected, resulting in the observed dying-back axonopathy. There is also the possibility that the membranes of neural intracellular structures such as the neurotubules, neurofilaments and mitochondria may also be at risk from a deficiency of vitamin E. Disruption of any of these structures could impair axonal transport and thereby result in neural dysfunction.

Essentially, two types of mechanism have been suggested to explain the function of vitamin E in neural tissues, *i.e.* that it is acting as a fat-soluble antioxidant or by more specific mechanisms.

7.1 Antioxidant function

From theoretical considerations, the nervous system including the retina is likely to be particularly vulnerable to a deficiency of this fat-soluble antioxidant and thereby to the deleterious actions of increased concentrations of oxygen-derived free radicals. Thus, the brain contains high concentrations of PUFAs, which are susceptible to lipid peroxidation, receives a disproportionately large percentage of oxygen, is relatively deficient in antioxidant systems (with almost no catalase, a reduced activity of glutathione peroxidase and a reduced concentration of glutathione) and specific regions contain high concentrations of iron, which is able to catalyze free radical production (see [75]). The retina is also served with a plentiful supply of oxygen, has an abundant supply of mitochondria and an unusually high rate of oxidative metabolism [76]. The retinal rod outer segments are particularly vulnerable to lipid peroxidation as more than 65% of the membrane fatty acids are polyunsaturated, which is the highest proportion found in any vertebrate tissue examined to date. The retina is also frequently exposed to intense light, which can be phototoxic.

The effect of vitamin E deficiency on lipid peroxidation of neural tissues has been investigated [77]. All tissues from rats kept on a vitamin E-deficient diet for 1 year showed evidence of increased lipid peroxidation compared with controls. The increases were, however, greater in peripheral tissues such as liver, muscle and heart than neural tissues (brain and spinal cord). When neural tissues and fractions from the myelinated axons of the brainstem of 1-year-old vitamin E-deficient animals were stressed *in vitro* with oxygen derived free radicals, the following order of susceptibility to lipid peroxidation was observed: brain$\gg$spinal cord$>$nerve, and the fraction containing intracellular membranes and organelles$>$axolemma-enriched fraction$>$whole homogenate$>$myelin. These latter results are consistent with the neuropathology of vitamin E deficiency and the hypothesis regarding impaired axonal transport and turnaround.

If vitamin E is acting principally as an antioxidant in neural tissues, then the characteristic neuropathology of vitamin E deficiency in the rat should be prevented by the addition of alternative antioxidants. This was reported by Nelson, who was able to prevent the characteristic neuropathology by the addition of ethoxyquin and promethazine [78]. Further evidence was provided by the study of Southam *et al.* [43], who first confirmed that ethoxyquin could prevent the development of the neurological features and second, that the addition of excess peroxidisable substrate in the form of polyunsaturated fat markedly accelerated the rate of development of the neurological syndrome in vitamin E-deficient rats.

It was postulated that peroxidation of mitochondrial membranes might be specifically implicated. Mitochondria contain a high proportion of polyunsaturated fatty acyl chains [79] and may, therefore, be particularly susceptible to damage in vitamin E deficiency. In addition, there is an increased production of oxygen-derived free radicals in mitochondria as a by-product of oxidative phosphorylation. If the axonal mitochondria are functionally impaired this might be expected to lead to abnormalities in fast anterograde and retrograde transport, which are energy dependent, and thus to defective turnaround. The resultant

accumulation of organelles could then plug off the terminal axons so that they become isolated from the cell body and ultimately degenerate. This process could then spread in a dying back manner.

Support for this hypothesis comes from studies of muscle mitochondria from vitamin E-deficient rats [80], where significant decreases in the activities of complexes I and IV of the respiratory chain, a reduction in the respiratory control ratio (indicative of membrane damage) and increased membrane fluidity were reported. An altered membrane lipid environment, possibly secondary to a higher level of lipid peroxidation, could result in the inhibition of complexes I and IV. This could also be caused by oxidative damage to the complexes themselves or to mitochondrial DNA.

7.2 Other novel functions

In recent years, novel functions of α-tocopherol have been described, which can influence enzyme activities, signaling cascades and gene regulation. Any or all of these functions could be involved in the nervous system (for a review, see [81]).

A number of enzymes have been identified that can be specifically regulated by α-tocopherol. These include the inhibition of protein kinase C, 5-lipoxygenase and phospholipase A_2, and the activation of protein phosphatase 2A and diacylglycerol kinase (see [82]). It is of interest and possible significance that in general α-tocopherol does not have a direct action on these enzymes but requires them to be either bound to membranes or activated by membrane components.

A number of genes can be regulated by α-tocopherol (see [83]). These include genes encoding proteins involved in apoptosis, cell cycle regulation and lipoprotein receptors. Roy *et al.* [84] were the first to use microarray analysis to investigate the effect of vitamin E on genes in neural tissues. They investigated rat fetal brain after feeding mothers the vitamin and identified a set of vitamin E sensitive genes. Subsequently, microarray analyses have been carried out on neural tissues in the α-TTP knockout mouse [85, 86] and vitamin E-deficient rats [87].

The α-TTP knockout mice were shown to have a systemic deficiency of vitamin E [88] and a severe deficiency of α-tocopherol in multiple regions of the brain [89]. As in humans with AVED, these α-TPP knockout mice are ataxic and show abnormal electrophysiology [90]. Differential analysis of the transcription profiles of the brain and liver of these mice showed that the cerebral cortex had an increased sensitivity compared to the liver, with 90 genes downregulated and 50 upregulated [85]. Among the genes downregulated were a number involved with transport. A 13-fold decrease in the expression of retinoic acid receptor-related orphan receptor-α was also reported. Transgenic mice deficient in retinoic acid receptor-related orphan receptor-α have a number of defects including a failure to develop a normal cerebellum, which results in an ataxia [91], and this could account for the ataxia in the α-TTP-deficient mice. The repression of some genes involved in synaptic plasticity and neuronal development was also reported.

Hyland *et al.* [87] examined cerebral cortical gene expression in the vitamin E-deficient rat and also found more genes were downregulated than upregulated. An increased expression was seen in the genes encoding for catalase and the axon guidance molecule tenascin-R1, whereas the expression of genes encoding protein components of myelin and determinants of neuronal signal propagation were decreased. These results were consistent with the observed neurological and electrophysiological changes previously reported in this animal model [55, 92]. None of the differentially regulated genes was identical in the two different animal models used by Gohil *et al.* [85] and Hyland *et al.* [87], but similarities were found at the level of gene families.

Nell *et al.* [93] examined the expression profiles of liver from mice fed different amounts of vitamin E and their findings were in general complementary to those of Gohil in the vitamin E-deficient brain [85]. Thus a number of transport-related genes, which were upregulated in the liver following the feeding studies of Nell *et al.* [93], were downregulated in the cerebellar cortex of the α-TTP-deficient mice.

It has been suggested that taken together, the results of these studies indicate that α-tocopherol may be involved in membrane fusion processes including the assembly of biological membranes, vesicular transport and cellular trafficking [81]. This in turn could affect turnaround in long axons as described above. Another possible mechanism could involve membrane stabilization particularly of the mitochondrion, which as described previously might be an organelle particularly implicated in the abnormalities of neural function associated with vitamin E deficiency.

8 Concluding remarks

Despite the fact that it is now almost 90 years since the discovery of vitamin E and over 30 years since neurological abnormalities were first associated with a severe and chronic deficiency of the vitamin, progress in our understanding of the precise role(s) of vitamin E *in vivo* in humans has been slow and rather disappointing. At present, two functions for the vitamin have been proposed: that it is acting solely as an antioxidant [94] or that it has more specific functions [95]. These views have tended to polarize opinion in the field but there is no reason why they need be mutually exclusive. It is also important and relevant to note that α-tocopherol does not appear to be evenly or randomly distributed throughout biological membranes but forms complexes with specific membrane constituents (see [81, 96]) and could, therefore, interact with specific proteins in these membrane areas.

There is, therefore, still much work to be done to elucidate the mechanism(s) of action of vitamin E *in vivo* and I believe it is necessary to concentrate our efforts on its role(s) in neural function as this is its only well-documented biological function in humans.

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9 References

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