ALINEA

NUTRITION

APRIL 2020

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Morris MC, Schneider JA, Li H, Tangney CC, Nag S, Bennett DA, Honer WG, Barnes LL. Brain tocopherols related to Alzheimer's disease neuropathology in humans. Alzheimers Dement. 2015 Jan;11(1):32-9.

What We Know, Think We Know, or Are Starting to Know

We know that, amongst factors like exercise, cognitively demanding activities [including years of education], and social interaction, there are strong associations in observational research between diet and healthy brain ageing [1-3]. By 'healthy brain ageing', we also mean reduced risk of neurodegenerative disease, and a number of dietary factors have consistently emerged from the epidemiological literature as conferring a protective effect: long-chain omega-3 fatty acids [DHA in particular], vitamin E, B-vitamins, and polyphenols [flavanoids in particular] [4].

Vitamin E intake has been strongly associated with reduced risk of dementia and Alzheimer's Disease in prospective cohort studies, and in different populations [1-3]. A notable feature of this association is that is has related to dietary intake, not supplemental intake. Based on these data, a number of intervention studies tested the effects of supplemental vitamin E on cognitive outcomes; all came back negative [5,6]. The implication was that 'vitamin E does not improve brain health' [more on this under ***Relevance***, below].

However, a major issue with these studies was the use of synthetic alpha-tocopherol [a-tocopherol]; this is only 1 of 8 different forms of vitamin E, which is comprised of both tocopherols and tocotrienols. We know quite little about the tocotrienols to date, and currently only have in vitro evidence in relation to their potential biological activity. We know that a-tocopherol is the main form in diet, but that gamma-tocopherol [y-tocopherol] is also an important dietary constituent of vitamin E.

Another major issue was that, in subgroup analysis of these intervention trials which found no overall effect, there was an effect in participants with very low baseline levels of vitamin E [<6mg] [7]. However, many nutrition interventions do not screen for baseline levels of nutrients as a factor, and often ethics committees will now allow participants to be included with borderline deficient levels. This can make it hard to detect an effect, where one truly does exist.*

The present study examined brain levels of a-tocopherol and y-tocopherol in relation to clinical assessment of Alzheimer's Disease [AD], using brain autopsy.

*Geek Box: Bertrand's Rule

The French biological scientist and biochemist, Gabriel Bertrand, first published what became known as 'Bertrand's Rule' in 1912. In effect, Bertrand's Rule describes the dose-response bell-curve of biological activity for micronutrients and trace minerals. The rule states that if a nutrient is required for a specific function, this function [effect] will be be low or absent in a deficiency state, and the function will increase with increasing levels of the nutrient from a deficiency. This increase in function is followed by a plateau in the range of adequate intake, then impairment of function if the mechanisms regulating that nutrient are overwhelmed from excessive intake. For each nutrient, therefore, there is a range of intake that is adequate; differences in effect are not likely to be observed comparing levels within this range. An important point in this respect is that the biological activity of nutrients are absolutely specific: deficiency can only be prevented by that element, not by another, even if they are chemically related. E.g., iron and zinc may be metal minerals, but zinc can't prevent/reverse anaemia. Calcium may be crucial for bone health, but only vitamin D adequacy will prevent rickets. Unfortunately, very little heed is given to this fundamental rule of nutrient action outside of the field of nutrition. This tends to manifest as an issue primarily in randomised controlled trials, because the implication of Bertrand's rule is that if nutrient status is within the adequacy range, then relatively optimal biological function will be maintained. Thus, many 'null' effects in RCTs are null by design, not null because there is no effect of the nutrient; it is a biological fact that there is an effect of a nutrient. As the null hypothesis of an RCT on a nutrient supplement is, "Nutrient A has no effect on health outcome B", this is inconsistent with the biological fact that all nutrients have biological activity and influence health status. It is the nutritional status of the participants being compared that may explain the lack of difference between comparison groups.

The Study

The Rush Memory and Aging Project [MAP] study is an ongoing cohort study with participants recruited from retirement communities or subsidised housing in Chicago.

The study began in 1997 with all participants were free from dementia/AD at baseline, and all participants consented to an annual clinical neurological examination, and to brain autopsy at their death.

Clinical diagnosis of AD was made by a neurologist, and the average duration between the last clinical assessment of a participant and death was 10-months.

A subgroup of the MAP study began in 2004 to specifically investigate brain levels of tocopherols. Tocopherol levels in the brain were measured in two brain regions, the inferior temporal and midfrontal cortical regions, both of which are affected by AD. Tocopherol levels were also measured in subcortical regions - the posterior putamen and ventromedial caudate - which are involved in motor function and cognitive behaviour, respectively.

The relationship between brain levels of a-tocopherol and g-tocopherol levels was analysed using linear regression models adjusted for age at death, sex, years of education, and APOE-4*, and time from death to autopsy.

*Geek Box: ApoE-4

Apolipoprotein E [ApoE] is a protein expressed in tissues throughout the body, but with particularly high expression in the liver and in the brain. The e4 variant of the ApoE gene [ApoE-e4] is strongly associated with Alzheimer's Disease. The mechanisms identified to date is the influence of this gene on metabolism of amyloid-beta [AB] protein in the brain. The high metabolic activity - and therefore waste generation - by the brain results in the production of amyloid-B precursor protein [APP]. APP can be metabolised through a number of pathways: the gamma-secretase pathway is strongly implicated in the build up of AB and plaque formation in the brain. Mechanistically, high cholesterol levels contribute to this abnormal processing of AB protein. The ApoE-e4 genetic variant may increase risk for Alzheimer's by resulted in disordered AB metabolism in the brain, either through impaired clearance of AB or through influencing disordered cholesterol metabolism [the two may interact]. While the mechanistic processes remain to be fully elucidated, there is compelling evidence supporting a significantly increased Alzheimer's risk with the ApoE-e4 genetic variant. Those with this variant are generally advised to follow a diet very low in saturated fat, lower in total fat, and low in dietary cholesterol.

Results: The present study included 115 brains from participants who had died since enrolment in 2004. 75 deceased participants exhibited no clinical evidence of AD/dementia, while 40 had a clinical diagnosis of AD/dementia. 29.5% of deceased participants expressed the ApoE-e4 gene.

The predominant tocopherol in brain tissue was a-tocopherol, which constituted 62-72% of tocopherol concentrations in the 4 brain regions analysed. However, there was no significant association between brain a-tocopherol levels and amyloid plaque load or neurofibrillary tangles.

There was a significant and linear association between y-tocopherol levels and lower amyloid plaque load and less severe neurofibrillary tangles.

a-tocopherol supplement use positive correlated with brain levels of a-tocopherol, but increasing supplemental a-tocopherol intake correlated with decreased y-tocopherol levels.

Adjusting for clinical diagnosis of AD did not alter the significant associations between y-tocopherol and amyloid load.

The Critical Breakdown

Pros: This was the first analysis to specifically quantify brain tocopherol levels by autopsy. In addition, the sample was free from dementia or AD at baseline, when recruited to the study. 115 brains were analysed, and around 2/3' s of the overall sample had no dementia at time of death, providing a strong comparison between healthy brains vs. brains with clinical diagnosis of neurodegenerative disease. Brain levels of tocopherols were measured in specific regions known to be affected by AD. The laboratory analysts were blinded to whether brains clinically diagnosed with AD or healthy.

Cons: The main limitation is that dietary intake of tocopherols was not available from this analysis, only data on a-tocopherol supplement use. The cross-sectional design - comparing brains between disease free vs. dementia/AD - is a comparison at that time only, and does not provide insight into the relationship between vitamin E status and the outcome over time [i.e., longitudinal]. Thus, while the data suggests dietary intake is the reason for brain tocopherol levels, we cannot make that conclusion or comparison from this study. Finally, participants in residential homes or subsidised housing may differ in risk profile and nutrient status than the wider general population, thus caution is warranted in assuming generalisability of the findings.

Key Characteristic

The key feature of this study is the use of autopsy to investigate the respective contributions of tocopherols. Prospective cohort studies generally provide an association between an exposure [diet, or nutrients] and outcome, but without the capacity to look specifically at underlying pathology. The MAP study thus provided a unique observational study design in which, through examination of brains of deceased participants by autopsy, an objective look at the extent of neurodegenerative disease severity could be undertaken, and precise quantifications of brain tocopherol levels obtained.

Thus, this study provides a very precise assessment of two variables: disease status and severity, and brain tissue levels of tocopherols. While it is a limitation of this study that a more comprehensive dietary assessment of vitamin E was not completed, this study provides important insight into the relationship between objective pathology and brain tissue levels of tocopherols.

Interesting Finding

The fascinating result of this study is that y-tocopherol was primarily associated with protective effects.

There are a number of layers to this finding in the study which make it compelling. First, increasing supplemental a-tocopherol use correlated to decreased brain g-tocopherol levels; this suggests a delicate balance in the homeostatic mechanisms [think about Bertrand' s Rule above!] regulating vitamin E.

In addition, high levels of a-tocopherol were associated with increased amyloid load except when y-tocopherol levels were also concomitantly high. This suggests a protective effect of y-tocopherol independent of a-tocopherol.

Finally, when clinical diagnosis of AD was adjusted for in the analysis for a-tocopherol, it appeared there was a significant association between a-tocopherol and neurofibrillary tangles; however, once this was adjusted for y-tocopherol, the association became non-significant. This suggests that the association between a-tocopherol and neurofibrillary tangles was in fact confounded by y-tocopherol.

Thus, all roads of statistical analysis and adjustment in this study lead to the conclusion that the protective effect of 'vitamin E' in the brain, and specifically in relation to AD/dementia severity, is attributable to y-tocopherol.

Relevance

The discord between the epidemiological findings relating dietary vitamin E to improved cognitive outcomes, and the RCTs finding ' null' effect, has been interpreted to assume that vitamin E does not improve brain health, or protect against AD/dementia. This is flawed reasoning.

It is often incorrectly assumed that disconnect between observational research and RCTs has to be reconciled in favour of the RCT results: this is naive and over-simplistic thinking*.

In The Rotterdam Study, a cohort of 5,295 participants aged >55yrs and free from dementia at baseline, those with the highest level of dietary vitamin E intake at 18.5mg/d had a 25% reduced risk of dementia compared to those in a range of 9-13.5mg/d after 10yrs follow-up [(2)]. Over 13.5mg was a threshold at which significant protective effects were most evident.

In the Chicago Health and Ageing Project [CHAP] study, conducted by the same research group as the present study, each 5mg/d increase in dietary vitamin E was associated with a 26% reduced risk for AD after 6yrs follow-up [(1)]. This study also provided evidence for separate effects of both a-tocopherol and g-tocopherol.

The present study lends support to a particular effect of of y-tocopherol, and, to paraphrase a 2001 paper in the American Journal of Clinical Nutrition, gamma-tocopherol deserves more attention [(8)]. The objective measures of disease severity and brain tocopherol levels provide significant weight to both

- the wider observations of a protective effect of dietary vitamin E against AD/dementia, and;
- a potential explanation for why the supplemental a-tocopherol trials failed to find an effect.

The real relevance, therefore, is that if we are to be skeptical of any results and inclined to favour one line of evidence over the other, in this nutritional example, it is the observational data which currently appears more consistent.

*Geek Box: The Famous HRT Example

Any medical student likely knows this by heart at this stage. In a cohort study published in 1996, an association was found between post-menopausal women taking hormone-replacement therapy and reduced risk of cardiovascular disease. Following this study, a subsequent randomised controlled trial in fact found that post-menopausal women taking HRT were at increased risk of cardiovascular disease. Because of the differential status in 'standard' of evidence applied to cohort studies vs. RCTs, the discrepancy between the two studies was reconciled in favour of the RCT: the RCT result was deemed to be the "right" result, because it was assumed the observational study result was invalid if the RCT found otherwise. However, understanding of the relationship between the timing of menopause and cardiovascular disease ultimately indicated that the discrepancy in the results related to the timing of menopause relative to when HRT was initiated. Women with early-onset menopause tend to be at higher risk for CVD. Thus, when both studies were analysed through this lens - age of menopause onset relative to initiation of HRT - both studies were 'right': their answers were correct for their respective population subgroups who had been studied. While this famous example has historically been taught as a reason for why observational research can't be trusted, in fact it can be taught as as example for why over-simplistic rejection of the observational finding in favour of the RCT finding in the first place is not true scientific thinking. As I've said before, there is more to scientific thinking than, "was the trial randomised."

Application to Practice

The main take-home from this study may be that caution may be warranted with excessive a-tocopherol supplementation from a brain health perspective. It appears that for vitamin E intake, as it relates to brain health [and cardiovascular health], it is a case of 'food first'. In particular, all roads appear to be pointing toward g-tocopherol as the main vitamin E form implicated in reduced neurodegenerative disease risk. Rich dietary sources of g-tocopherol include rapeseed oil, pecan nuts, walnuts, and peanuts. Simple, easy-to-include foods for any diet [anaphylaxis aside!].

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