Commentary

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Fatty acids and Alzheimer's Disease: Evidence on Cognition and Cortical β-amyloid from Secondary Analyses of the Multidomain Alzheimer Preventive Trial

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Fatty acids and the brain

Fatty acids are long-chain hydrocarbons that can be separated into four groups: saturated, monounsaturated, polyunsaturated, and trans fats (1). The brain is highly enriched in fatty acids particularly polyunsaturated fatty acids (PUFAs) with docosahexaenoic acid (an omega 3: n-3 PUFA) and arachidonic acid (an omega 6: n-6 PUFA) being the most abundant (2, 3). Fats control the structure and function of cell membranes and therefore impact upon signal transduction and neurotransmission and PUFAs play a role in inflammatory processes (4). Saturated and monounsaturated fatty acids can be synthesized de novo within the brain, but PUFAs are mainly supplied by the blood (5).

The Multidomain Alzheimer Preventive Trial

The Multidomain Alzheimer Preventive Trial (MAPT) was a large phase III, 3 year, multicentre, randomized, placebo-controlled trial (registration: NCT00672685) (6). The trial had four arms comprising a placebo group and three treatment groups: n-3 PUFA supplementation (docosahexaenoic acid + eicosapentaenoic acid), multidomain intervention (involving nutritional and exercise counselling and cognitive training) and n-3 PUFA supplementation plus multidomain intervention. The trial was designed to assess the efficacy of the interventions in slowing cognitive decline in older adults at risk of dementia (n = 1680) (6). The main analysis of MAPT showed no significant effects of any of the interventions on cognitive function compared to placebo after adjustment for multiple testing (7).

MAPT [18F] Florbetapir Positron Emission Tomography ancillary study

Subjects participated in the MAPT [18F] florbetapir positron emission tomography (PET) ancillary study on a voluntary basis [n = 271: n = 70 (25.8 %) placebo, n = 60 (22.1 %) n-3 PUFA supplementation, n = 68 (25.1 %) multidomain intervention, n = 73 (26.9 %) multidomain intervention and n-3 PUFA]. PET scans were performed using [18F] florbetapir to provide a measure of cerebral β-amyloid (Aβ) load (6, 8). Regional standard uptake value ratios (SUVRs) were generated from semi-automated quantitative analysis with the whole cerebellum as the reference region. Cortical-to-cerebellar SUVRs (cortical-SUVRs) were obtained using the mean signal of the following predefined cortical regions: frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate as previously described (9).

Fats and cognition: evidence from secondary exploratory analyses of MAPT data

Although, in the main analysis of MAPT it was shown that n-3 PUFA supplementation was not effective against cognitive decline (7), subsequent within group analysis has shown that subjects in the placebo group of MAPT with a low omega 3 index (defined as ≤ 4.83 % which represents the lowest quartile of omega 3 index distribution: n = 59 at 3 years) declined significantly on a cognitive composite Z score over 3 years (mean change -0.236, SE 0.072, $p < 0.05$), whereas those on placebo with a higher omega-3 index (upper three quartiles) remained stable (mean change -0.011, SE, 0.037, $p > 0.05$) (10). The mean cognitive decline over three years in the subjects in the lowest quartile of omega 3 index distribution was comparable to the cognitive decline observed in MAPT subjects with a Clinical Dementia Rating (CDR) score of 0.5 (mean change -0.184, SE, 0.052, $p < 0.05$) or carriers of the Apolipoprotein E (ApoE) ε4 allele (mean change -0.208, SE, 0.070, $p < 0.05$ (10).

Further exploratory analysis investigating the effects of n-3 PUFA supplementation in the MAPT subgroup with low omega-3 index (n = 183 including participants in the placebo and n-3 PUFA supplemented groups only) has shown that there was less decline on the Controlled

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Oral Word Association Test (COWAT: number of words/ 2 minutes) in the n-3 PUFA supplementation group compared to placebo (p = 0.009; between group mean difference over 3 years, 2.3; 95 % CI, 0.6,4.0) (11). This suggests that n-3 PUFA supplementation might be beneficial over placebo for the maintenance of executive function (11). Non-memory changes such as changes in executive function are recognised as early cognitive changes in Alzheimer's disease (AD) (12). Collectively these findings from MAPT suggest that n-3 PUFA supplementation might prove therapeutically useful for the combat of cognitive changes in subjects with sub-optimal n-3 PUFA levels in the early stages of AD.

Fats and cortical Aβ: evidence from secondary exploratory analyses of MAPT data

At a preclinical level we have shown that erythrocyte membrane PUFAs were not associated with cortical Aβ using fully adjusted multiple regression models (13). This exploratory analysis was performed in MAPT subjects in the placebo group with data on cortical Aβ and erythrocyte membrane PUFA levels (n = 61). These findings suggest that n-3 PUFAs might confer their beneficial effects on cognition via Aβ-independent pathways, although it would be interesting to examine whether n-3 PUFAs might be associated with Aβ in subjects with sub-optimal n-3 PUFA levels. However, we did not have sufficient subjects to test this in MAPT.

In our exploratory analyses concerning cortical Aβ, the associations closest to significance were those between erythrocyte membrane arachidonic acid and Aβ (B coefficient, 0.03; 95 % CI, 0.00, 0.06; p = 0.04) and erythrocyte membrane linoleic acid (the precursor to arachidonic acid) and Aβ (B coefficient, -0.02; 95 % CI, -0.04, 0.00; p = 0.09) (13). These findings suggest that n-6 PUFAs might be important in terms of the regulation of amyloidogenesis. Interestingly, arachidonic acid was positively associated with Aβ whereas linoleic acid was inversely associated with Aβ. We hypothesised that low linoleic acid might reflect its increased conversion to arachidonic acid, which in turn might lead to increased pro-inflammatory eicosanoid formation in turn fuelling amyloidogenesis. However, this hypothesis warrants validation. Furthermore, we found that the association between arachidonic acid and cortical Aβ appeared to be specific to ApoE ε4 non-carriers (B coefficient, 0.03; 95 % CI, 0.00, 0.06; p = 0.03) compared to ApoE ε4 carriers (B coefficient, 0.02; 95 % CI, -0.04, 0.08; p = 0.57) (13).

In another exploratory study of MAPT data we have shown that erythrocyte membrane saturated and monounsaturated fatty acids were also not associated with cortical Aβ using fully adjusted multiple linear regression models (14). This analysis was also restricted to MAPT subjects in the placebo group with data on cortical Aβ load and erythrocyte membrane fatty acid levels (n = 61: the same population as described above). In this study the association closest to significance was that between erythrocyte membrane stearic acid (saturated fatty acid) and cortical Aβ (B coefficient, 0.03; 95 % CI, 0.00, 0.05; p = 0.05). This positive association, although statistically non-significant, appeared to be stronger amongst ApoE ε4 carriers (B coefficient, 0.04; 95 % CI, -0.01, 0.09; p = 0.08) compared to ApoE ε4 non-carriers (B coefficient, 0.02; 95 % CI, -0.01, 0.05; p = 0.18), which is in contrast to our findings with arachidonic acid. However, these preliminary findings require further confirmation. Stearic acid has been shown not to modulate α-secretase-dependent cleavage of amyloid precursor protein in cultured neuronal-like cells (15), implying that stearic acid might indirectly facilitate Aβ accumulation over time. Furthermore, at a clinical level, stearic acid has previously been associated with cognitive decline in the elderly (16).

Conclusion

Here we suggest that n-3 PUFA supplementation might be beneficial for the prevention of cognitive decline in the elderly with sub-optimal n-3 PUFA status in the early stages of AD. This might explain the discrepant results seen with clinical trials implementing n-3 PUFAs in the past, which have not focussed on participants with low n-3 PUFA levels at baseline (4). It might be that supplementation restores homeostatic levels thereby preventing cognitive decline and our preliminary findings suggest that this occurs via Aβ-independent mechanisms. In terms of amyloidogenesis, high erythrocyte membrane arachidonic acid and stearic acid and low linoleic acid appeared to be weakly associated with increased cortical Aβ, although it should be noted that statistical significance was not reached in our exploratory studies. Thus, dietary fats might play an important role in the pathophysiology of AD via differing mechanisms. Further studies are warranted to elucidate the roles of fats in Aβ plaque formation, tau phosphorylation and cognitive decline particularly as a function of ApoE ε4 status.

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