THE ROLE OF FATTY ACIDS IN COGNITIVE DECLINE

The subject of cognitive decline has received much attention over the last few years. ***Satu Henson****, student at CNELM, explains why fatty acids play such an important role in preserving cognitive health.*

Nutrient imbalances are increasingly recognised as a contributing factor to early cognitive decline. Research suggests that among other nutrients, fatty acids and their biosynthesis in the liver play a critical role in the progression of cognitive decline.

It is likely that the pathological progress that leads to cognitive decline starts years, even decades, prior to the diagnosis, but it is not a done deal that we all end up suffering from dementia. Our diet and lifestyle are something that we can influence to maintain our memory and independence for longer.

Pharmaceutical advances to delay the onset of cognitive decline have been slow due to several factors:

- the complex and evolving pathophysiological understanding of this disease progress
- the lack of reliable biomarkers
- the delays caused by the extensive timeline
- the costs required to develop and approve the drugs.

The drugs that do exist are largely aimed at modifying the pathways leading to Alzheimer's Disease (AD), the most common form of dementia, but the effectiveness of these available drugs is still very limited.

In addition to key pathways leading to AD, cognitive decline can have multiple other causes. Comorbidities such as metabolic syndrome and vascular disease may all lead to cognitive decline, and stroke, high blood pressure, hyperlipidemia, diabetes mellitus, male gender and smoking are all recognised risk factors of vascular dementia.[2,3] Additionally, genetic factors such as Apolipoprotein E (ApoE) with the ε4 allele increases the risk of AD but does not cause it.[4]

WHAT IS COGNITIVE DECLINE?

Cognitive decline, more commonly described as dementia, is characterised by a progressive global deterioration of cognitive abilities in multiple domains including memory and in at least one additional area – learning, orientation, language, comprehension, and judgment – severe enough to interfere with daily life.[1]

PATHWAYS TO COGNITIVE DECLINE

The characteristic symptoms of AD and related brain atrophy occur as the neocortex suffers neuronal, synaptic and dendritic losses, and amyloid plaques and neurofibrillary tangles proliferate.[5] While the amyloid and tau pathologies are the hallmarks of Alzheimer's Disease, neuroinflammation and oxidative stress are integral within both pathologies and also in the early stages of cognitive impairment, which does not necessarily lead to AD.

Fats are important during the initial brain development, but beyond this the Essential Fatty Acids (EFA), also known as Polyunsaturated Fatty Acids (PUFA), are involved in the synthesis and function of brain neurotransmitters. Nearly 60 per cent of the human brain is made of fat, and the phospholipid pools within the neuronal membranes are involved in the synthesis of lipid messengers that promote either neuroprotection or neuronal injury.[6] The inflammatory and oxidative stress pathways are a critical addition when considering the mechanism of action in cognitive decline, particularly due to the high fatty acid content in the brain and the potential they provide for preventive strategies available to the therapists and the individuals.

Amyloid pathology

Generation of amyloid peptides Aß40 and Aß42, and the subsequent amyloid fibrils form the amyloid plaques. Amyloid oligomers are considered the most toxic of all beta amyloids (Aß).[7,-9] Amyloid plagues lead to synaptic failure, causing neuronal cell death, while Aß oligomers lead to disruption of a number of cell receptors, dysregulation of which may lead to dysfunction of synaptic mitochondria and excessive formation of Reactive Oxygen Species (ROS) and increase of neuronal calcium levels.[10,11] Disruption of calcium, zinc and other ion homeostasis within neuronal membrane may further accelerate neurodegeneration, including formation of free radicals and phosphorylation of tau.[12,13]

Tau pathology

The neurofibrillary tangles are formed of tau proteins that are phosphorylated into abnormally twisted filaments, destroying the scaffolding-type structure in the normally functioning nerve cells.[5] Toxic Aß increase the activity of tau kinases, as does the Aß oligomer-induced increase of tau protein.[14] Tau kinases and an increase in tau protein lead to tau phosphorylation.

Inflammation

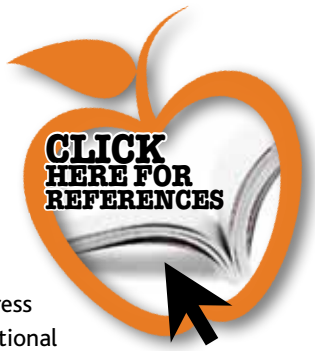
Inflammatory markers, such as nitric oxide, IL-6, IL-1, and TNF-α, generated either through the deposition of Aß within the amyloid pathway or other comorbidities, are linked to neuroinflammation,[15,16] which in turn leads to an increase in tau phosphorylation and neuronal cell death.

Oxidative stress

Combining unsaturated lipids with high oxygen utilisation, high redox metal ions, and a compromised antioxidant system makes the brain very vulnerable to oxidative damage.[17] Increased ROS is linked to neuronal cell death and is associated with dysfunctional ion transport leading to neurotoxicity, whereas lipid peroxidation may cause degradation of the cell membrane phospholipids.[18] The PUFA oxidation product Malondialdehyde (MDA) has been linked to reduced activity of antioxidant enzyme Superoxidase Dismutase (SOD).[19] Multiple in vitro and in vivo studies have shown the negative impacts on neuronal integrity and function due to lipid peroxidation and protein oxidation.

PUFA TO RESCUE

Multiple studies show how PUFA and particularly Docosahexaenoic Acid (DHA) can positively impact the pathways that result in the accumulation of Aß and even directly reduce Aß.[20-22] The reduction in Aß and therefore amyloid fibrils reduces the risk of amyloid plaque formation, synaptic failure, and highly toxic Aß oligomers, the latter of which have far-reaching consequences resulting in increased tau phosphorylation and ROS and subsequent



oxidative stress and dysfunctional cell membrane integrity. DHA has been also been directly linked to multiple other pathways, including inflammatory and oxidative stress pathways, improving the cell membrane fluidity and ion homeostasis, and reducing the cell permeability.

There is an agreement across the in vitro, in vivo and human studies showing reduced levels of omega-3 and increased levels of omega-6 in the brains of the subjects with Alzheimer's disease and Mild Cognitive Impairment (MCI). Additionally, aged-related cognitive impairment has also been linked to increased levels of omega-6 Arachidonic Acid (AA), and reduced levels of omega-3 DHA and Eicosapentaenoic Acid (EPA).[23,24] Increased AA contributes to increased inflammation, while the benefits of a PUFA-rich diet has shown direct reduction of neuroinflammation by increasing the levels of DHA and EPA. This gives us yet another reason to consider the dietary intake of essential fatty acids and a healthy omega-6:omega-3 ratio.

In addition to obtaining DHA from dietary sources, humans can synthesise DHA in the liver from shorter chain omega-3 fatty acid precursors, α-linolenic acids and eisosapentaenoic acid, which are available from green plant leaves. There is evidence that even in the absence of overt liver pathology, a subtle molecular liver dysfunction is associated with AD.[25] As a result, this lack of available DHA could be caused by a defect in the last step of DHA biosynthesis in the liver, rather than from a nutritional deficiency of DHA.

INTAKE OF OMEGA-3

Consumption of fish high in omega-3 PUFA and daily intake of omega-3 PUFA supplements has been shown to significantly lower the risk of cognitive

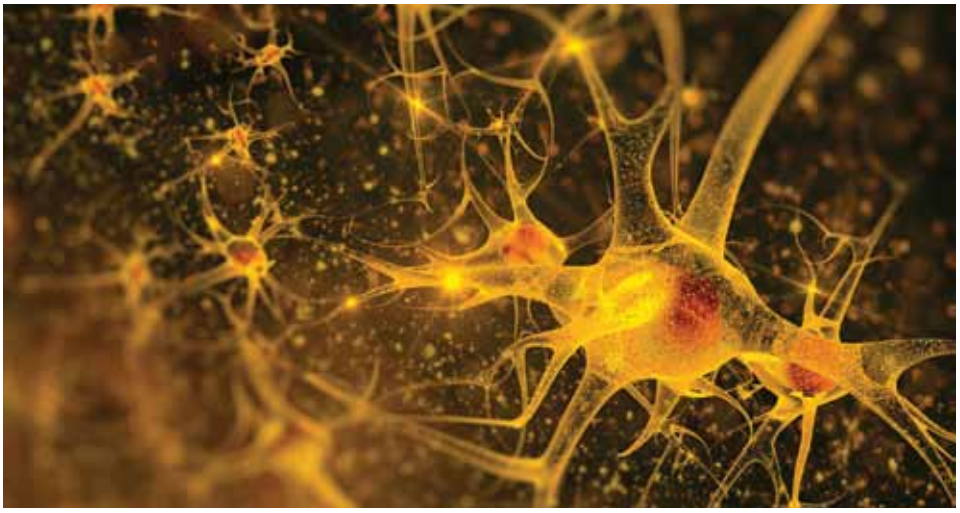
impairment and decline; this reduction being particularly significant in those with oxidative stress-related conditions such as hypertension and dyslipidaemia.[26-30]

Interestingly, a Mediterranean diet has shown similar improvements, as has the consumption of olive oil, both of which have reduced the occurrence of MCI, reduced the progression from MCI to AD, and delayed the onset of age-related cognitive decline.[31-33] The Mediterranean diet is characterised by a high intake of fish, vegetables, legumes, fruits, cereals and unsaturated fatty acids (particularly olive oil), and low intake of dairy products, meat and saturated fatty acids, with a regular but moderate intake of alcohol. High adherence to a Mediterranean diet has been found to reduce the risk of MCI by 28 per cent and deliver a 48 per cent risk reduction in progressing from MCI to Alzheimer's disease,[32] providing us with a very achievable and sustainable method to reduce risk of memory impairment.

OTHER INTERVENTIONS

Multiple other nutrients, such as antioxidant nutrients, vitamin D and B-vitamins, are key areas of research in relation to cognitive impairment, as are many lifestyle factors. Elevated homocysteine and low levels of folate and vitamin B12 have been associated with AD. The VITACOG study showed benefits in improved cognitive function and decreased cerebral atrophy by combining folic acid, vitamin B12 and vitamin B6.[34] The combination of vitamin E and C has been associated with a decrease in prevalence and incidence of AD,[35] whereas lower concentrations of 25-hydroxyvitamin D has been associated with cognitive decline,[36] but further studies are required to understand if vitamin D could help preventatively.

Caloric restriction is also being considered as a therapeutic intervention for those with Alzheimer's disease,[37] and only last month the media spread the word about how regular physical activity can increase the size of the prefrontal



cortex and hippocampus, areas that are linked to memory function. This could all lead to improved brain function and a delay in onset of senile dementia. Physical exercise has also previously been found to improve fitness, physical function, cognitive function and positive behaviour in people with dementia,[38] improving the quality of life of those suffering from dementia and their caregivers.

WHAT'S THE VERDICT?

Lipid layers with sufficient PUFA content maintain the cell fluidity, integrity and ion transport homeostasis. Combining this functional cell integrity with healthy biosynthesis of DHA in the liver, reduced inflammation and efficient antioxidant defences, the brain is protected from an imbalanced omega-6 to omega-3 ratio, dysfunctional ion transport and increased membrane permeability. If these defences were to break, increases in omega-6 fatty acids and other toxins, such as zinc and calcification of cell membranes, would contribute to neuronal injury. These mechanisms are common in age-related cognitive impairment and in Alzheimer's disease pathology.

A personalised, preventative, pleiotropic intervention and approach is the key to success when aiming to delay the onset of cognitive impairment. The approach should consider the multiple aetiologies, including inflammation, oxidative stress, homocysteine, ion homeostasis and liver function, as well as pleiotropic nutrient and lifestyle interventions that aim for optimal nutrient balance and the correct omega-6 to omega-3 ratio from early on.

Based on an extensive review of current research, it is evident that omega-3 PUFA, particularly DHA, delays the onset of cognitive decline only if the brain DHA levels and supply were brought to and maintained at sufficient levels in the early stages of cognitive impairment, such as MCI, not when Alzheimer's disease is already diagnosed and more advanced. This places the responsibility on individuals to manage their diet and lifestyle years, even decades before they reach their 60s, after which the early signs of cognitive impairment commonly surface. ●

THE KEY TO LONG-TERM COGNITIVE HEALTH

- Eat oily fish at least twice a week, including wild salmon, trout, sardines, mackerel, herring and anchovies.
- Eat plenty of green leafy vegetables.
- Follow a Mediterranean-style diet.
- Exercise minimum of 150 min/week.
- Keep your brain active socially and intellectually.

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