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Invited Review

Activities, bioavailability, and metabolism of lipids from structural membranes and oils: Promising research on mild cognitive impairment

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ABSTRACT

Concomitant with increased lifespan, large segments of the population are experiencing cognitive decline, which might progress to Alzheimer's disease (AD). Currently, there is no cure for AD and, once the neurodegenerative disorders are established, patients use pharmacologic therapy to slow the progression of the symptoms and require appropriate care to manage their condition. The preclinical stage of neural degeneration that progress through mild cognitive impairment (MCI) before the onset of AD is when it might be possible to introduce behavioral changes and pharma-nutritional interventions that modify the risk factors of MCI conversion to AD. Some food components accumulate in brain tissues, where they play essential roles. Among them, polar lipids, omega 3 fatty acids, and carotenoids appear to work additively or synergistically. Therefore, there is an opportunity to formulate nutraceuticals/functional foods to slow the progression of MCI. In this paper, we review the biochemical bases and recent interventions with bioactive lipids-rich formulations. Based on accumulated evidence, we propose that appropriate large-scale trials are warranted.

1. Introduction

Life is challenging, with commitments and incentives influenced and, sometimes, determined by multiple physiological and psychological factors. Hence, starting from the second year of life, interacting genetic and environmental issues contribute to both corporal and cognitive development and function [1]. Modulation of such aspects (namely, the genetic ones) is still limited and, indeed, most therapies and medical treatments of severe degenerative disorders only provide symptomatic relief. Conversely, nutritional intervention strategies may augment physiological conditions, promote cognitive development, and contribute to a healthier life span [2]. Various observations indicate that macro- and micro-nutrients play pivotal roles in the proper management of cognition [2,3] and might be exploited therapeutically [4,5]. However, it is important to note that the success of dietary interventions is often impaired by the very nature of such interventions. The first hurdle to overcome is that dietary components play multiple physiological functions and activities; hence, robust correlations between individual ingredients and observed effects are difficult to establish. The second hindrance is that successful outcomes are possible only through constant and sustained proper diets and their combination with other aspects of lifestyle such as physical exercise is indispensable. To overcome these constraints, it is necessary to precisely define the target population and select the moment when the start of proper dietary intervention would be successful. Then, we need to combine those interventions with the selection of a target function/objective specifically influenced by few dietary ingredients.

Alzheimer's disease (AD) is the most common form of dementia, affecting 48 million people in the world [6]. It is a progressive neurodegenerative disorder characterized by the formation of amyloid beta (Aβ) plaques, which are released by sequential proteolytic cleavage of the amyloid precursor protein (APP), and the appearance of intracellular neurofibrillary tangles in the brain [7]. Currently, there is no cure for AD and its diagnosis in its preclinical stage is not easy, although there is knowledge of its clinical and pathological patterns. Therefore, once neurodegenerative disorders are established, patients use pharmacologic therapy to slow the progression of the symptoms and require appropriate care to manage their AD condition.

There is a preclinical stage of neural degeneration that progress through mild cognitive impairment (MCI) before the onset of AD.

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Precisely at this stage it might be possible to introduce behavioral changes and pharmacological interventions that modify the risk factors of MCI conversion to AD [8,9]. Convincing evidence is available for vascular risk factors (hypertension, diabetes mellitus, smoking, obesity [10] and lifestyle and psychosocial factors (depression, social isolation, psychosocial stress [11] that increase the risk of dementia when present in midlife. Finally, appropriate dietary habits with the inclusion of potentially protective nutrients, e.g. omega-3 fatty acids, other unsaturated fats and polar lipids, vitamins, polyphenols, and compounds contained in traditionally recognized healthy foods function in synergy to decrease the risk of MCI conversion to AD [12–15]

2. Nutrition and neurodegeneration

Although nutritional requirements are the same as those of younger adults, food intakes in the elderly are frequently inadequate, both qualitatively and quantitatively [16]. It is noteworthy that micronutrient intakes are often below the recommended levels even when energy intake is appropriate [17,2]. Other factors that contribute to the risk of malnutrition in the elderly are the impairments in sensory perception of foods, including vision as a flavor-related component, contributing to an altered perception and liking of foods and leading to a monotonous diet and/or to an overall reduction in food intake [18]. Under- and malnutrition prevalence can be as high as 5–10% of seniors and this percentage reaches 35% in those with different pathological conditions. There is now a substantial body of literature indicating that plasma and tissue contents of bioactive lipids in patients with mild cognitive impairment is significantly low when compared with control subjects [19]. This difference should be attributed to an inadequate nutrient intake, resulting either from the substitution of food sources rich in polyunsaturated fatty acids (PUFAs) by a high dietary intake of saturated and hydrogenated fats [20,21] or to a compromised nutritional status due to the intake of non-fat dairy products, that yields lower levels of circulating bioactive lipids and antioxidants [22]. These issues create a milieu with increased levels of redox-mediated processes, which are found in cognitive impairment conditions. In turn, the low intake of antioxidants might lessen circulating PUFAs, which is not contrasted by their dietary intake [23]. Therefore, specific recommendations have been proposed for this age group, with sources of special foods which must be not only nutritious, but also adapted to the different feeding needs and surpassing the common difficulties at this age [24]. Thus, the concept of senior-friendly foods has started to emerge and include reference meals and nutrient sources that meet the above-mentioned criteria; dairy products are among them.

The link between cognitive function in the elderly and dietary interventions is that several basic cerebral functions are determined by some food components that specifically accumulate in brain tissues, where they play essential roles [25]. Such food components are mainly omega-3 PUFAs, i.e. eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, polar lipids, i.e. phospho- and sphingolipids, and xanthophylls, e.g. lutein [26–28]. They are key membrane components involved in the proper neuronal and brain function through a range of potential mechanisms related with neurogenesis and neuronal function [29], including increase of new synapses formation [30], effects on synaptic function, integrity and neurochemistry, and synaptic plasticity [31,32]. All of this contributes neuroplasticity, which it is finally associated with the enhancement of cognitive activity [33]. Other important processes modulated by those bioactive polar lipids are related to inflammation and cardiovascular disease [34] as well as antiproliferative activity [35].

3. Influence of milk fat globule membrane (MFGM)'s structure in digestive dynamics and lipids bioavailability

The available evidence shows that the specific assembly of different lipid domains, proteins and enzymes proper of the milk fat globule membrane (MFGM), is advantageous for the nutritional efficacy of its characteristic polar lipids, independent of the different models that have been proposed to describe MGFM's structure [36]. *A priori*, the complex structural constitution of the MFGM may represent a handicap for the digestion and absorption of those lipids and lead to decreased bioavailability [37]. Thus, the interfacial phenomena that take place during lipids' digestion by pancreatic enzymes, which necessary bind to the interphase of the lipid-containing structures to catalyze the hydrolysis of ester linkages [38], could be debilitated by the very architecture of the MFGMs. Actually, this interfering effect of the interfacial composition in the anchoring of lipases has been observed for the bioavailability of lipids from subcellular organelles of vegetal origin when raw and unprocessed green vegetables are consumed [39]. Different treatments including mincing, pureeing, or heating are applied to homogenize the natural matrix and enhance the release of lipids from where they are embedded, hence increasing their bioavailability and the nutritional value. However, the tri-layer of polar lipids surrounding the fat globules behaves in a different fashion during digestion. Indeed, it has been shown that the physico-chemical phenomena of the anchoring of lipases to the surface of the MFGM are mediated by rearrangement processes of the membrane lipids and proteins at the surface, resulting in an efficient enzymatic hydrolysis of the lipids from the fat globules [40,41]. Even the strategies mentioned above, e.g. to homogenize the food matrix, lower bioavailability of lipids when they are applied to native milk. Thus, the homogenization of milk by high pressure leads to a reorganization of the surface of MFGM, and occasionally to their total disruption. The different physico-chemical characteristics of the interface occurring after that processing impair the enzymatic activity of pancreatic secretions, because of the lower stability of the milk fat globule surface or due to the incorporation of milk proteins (casein and serum proteins) that were not initially present in the MFGM structure [42,43]. Consequently, the improved kinetics performance of lipases during digestion of milk lipids when the native MFGM structure is preserved introduces a second element on their functional properties; in other words, the value of MFGMs is not limited only to their composition in lipids associated with cognitive function but also to facilitated lipid digestion and higher bioavailability. This issue is gaining traction in the development of specific dairy products containing intact MFGMs to optimize the digestion of lipids by the elderly and a maximal delivery of nutrients [36].

As specifically regards omega 3 fatty acids, namely the long-chain ones no data are available on their bioavailability when supplied via MFGMs. However, it is noteworthy that different formulations, e.g. triacylglycerols vs. ethyl esters differentially impact their plasma concentrations [44]. It is unfortunate that this issue is very often neglected when clinical trials of DHA and EPA in, e.g. cardiovascular prevention are performed [45]. In short, we reiterate the need to assess the omega 3 fatty status (by lipidomic techniques) in patients or healthy subjects before and after intervention trials are carried out.

4. Milk fat globule membrane lipids

As mentioned, dietary interventions could be effective to promote better quality of life and prevent age-related cognitive deficits. Some bioactive lipids (omega-3 PUFAs, phospho- and sphingolipids, and xanthophylls) are also foremost components implicated in cognitive function [46]. These compounds are the essential blocks of synaptic membranes and function as modulatory agents in inflammation and oxidative stress [47,33]. Their concentrations in serum, retina, and brain of patients with cognitive impairment and visual dysfunction are low, while dietary interventions successfully increase those levels. Such compounds might also be useful in mild cognitive impairment, by restoring synaptic functions and membrane remodeling and protect from oxidative and inflammatory processes occurring in the brain and the eyes [48]. Of particular interest is the clear correlation between mild cognitive impairment and visual dysfunction and the success of dietary