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Review

Dietary fatty acids in dementia and predementia syndromes: Epidemiological evidence and possible underlying mechanisms

Vincenzo Solfrizzi [a], Vincenza Frisardi [a], Cristiano Capurso [b], Alessia D'Introno [a], Anna M. Colacicco [a], Gianluigi Vendemiale [b,c], Antonio Capurso [a], Francesco Panza [a,*]

[a] Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy
[b] Department of Geriatrics, University of Foggia, Foggia, Italy
[c] Internal Medicine Unit, IRCSS Casa Sollievo dalla Sofferenza, San Giovanni Rotondo, Foggia, Italy

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ABSTRACT

Drugs currently used in the treatment of cognitive impairment and dementia have a very limited therapeutic value, suggesting the necessity to potentially individualize new strategies able to prevent and to slow down the progression of predementia and dementia syndromes. An increasing body of epidemiological evidence suggested that elevated saturated fatty acids (SFA) could have negative effects on age-related cognitive decline (ARCD) and mild cognitive impairment (MCI). Furthermore, a clear reduction of risk for cognitive decline has been found in population samples with elevated fish consumption, high intake of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), particularly $n-3$ PUFA. Epidemiological findings demonstrated that high PUFA intake appeared to have borderline non-significant trend for a protective effect against the development of MCI. Several hypotheses could explain the association between dietary unsaturated fatty acids and cognitive functioning, including mechanisms through the co-presence of antioxidant compounds in food groups rich in fatty acids, via atherosclerosis and thrombosis, inflammation, accumulation of b-amyloid, or via an effect in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes that thereby regulate neuronal transmission. However, recent findings from clinical trials with $n-3$ PUFA supplementation showed efficacy on depressive symptoms only in non-apolipoprotein E (APOE) ε4 carriers, and on cognitive symptoms only in very mild Alzheimer's disease (AD) subgroups, MCI patients, and cognitively unimpaired subjects non-APOE ε4 carriers. These data together with epidemiological evidence support a possible role of fatty acid intake in maintaining adequate cognitive functioning and possibly for the prevention and management of cognitive decline and dementia, but not when the AD process has already taken over.

1. Introduction

Dementia is estimated as affecting approximately 6% of the population aged 65 and older, the prevalence increasing exponentially with age, being 40–70% at the age of 95 years and over (Qiu et al., 2007). In Western countries, the most common forms of dementia are Alzheimer's Disease (AD) and vascular dementia (VaD), with respective frequencies of 70% and 15% of all dementias (Whitehouse et al., 1997). The number of people suffering from AD, that currently affects more than 26 million people worldwide with an expected increase to more than 106 million by 2050 (Brookmeyer et al., 2008), is rising quickly because there are no effective treatments for the disorder available. Therefore, clinical and epidemiological research has also focused on the identification of risk factors that may be modified in predementia syndromes, at a preclinical or early clinical stage of dementing disorders. The umbrella term "predementia syndromes" include all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive of early stages of dementia (Panza et al., 2005, 2006a). Such predementia syndromes have been defined for AD and partly for VaD, but have not yet been operationalized for other specific forms of dementia. Therefore, the term "predementia syndromes" includes different conditions and, among them, MCI is at present the most widely used term to indicate non-demented aged persons with no significant disability and a mild memory or cognitive impairment which cannot be explained by any recognized medical or psychiatric condition (Petersen et al., 1999, 2001; Winblad et al., 2004). There is now ample evidence that MCI is

* Corresponding author. Tel.: +39 080 5473685; fax: +39 080 5478860.
E-mail address: geriat.dot@geriatria.uniba.it (F. Panza).

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often a pathology-based condition with a high rate of progression to AD (Panza et al., 2005, 2006a). Therefore, MCI has also been identified as the predementia syndrome for AD. The more recently proposed multiple subtypes of MCI were intended to reflect the heterogeneity of different types of dementia. Actually, there are at least three different subclassifications of MCI according to its cognitive features (Winblad et al., 2004), clinical presentation (Luis et al., 2003), and probable etiology (Gauthier et al., 2006). Furthermore, different diagnostic criteria have been proposed for other predementia syndromes, and the terms age-related cognitive decline (ARCD) (American Psychiatric Association, 1994) and aging-associated cognitive decline (AACD) (Levy, 1994) have been recently proposed to distinguish individuals with mild cognitive disorders associated with aging, also non-pathological-based, from non-cognitively unimpaired individuals. In particular, ARCD is defined by the DSM-IV as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age", but there are no defined diagnostic criteria, and few epidemiological studies using this definition have been conducted (Panza et al., 2005).

AD involves aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of paired helical filaments of hyperphosphorylated tau protein [neurofibrillary tangles (NFTs)], and extracellular protein aggregates [senile plaques (SPs)]. According to the "amyloid cascade hypothesis" (Hardy and Allsop, 1991; Hardy and Selkoe, 2002), SPs are the result of misprocessing of the amyloid precursor protein (APP), a type 1 transmembrane protein, by β- and γ-secretase, to form a toxic Aβ peptide of 40–42 amino acids (Walter et al., 2001) which aggregates and initiates a pathogenic self-perpetuating cascade, ultimately leading to neuronal loss and dementia.

The causes of predementia and dementia syndromes are at present unknown. However, some studies have suggested that these conditions may be prevented (Coley et al., 2008; Kivipelto and Solomon, 2008; Solfrizzi et al., 2008a). The role of the diet in cognitive decline has not been extensively investigated, with a few data available on the role of macronutrient intake in the pathogenesis of predementia and dementia syndromes (Grant, 1997, 1999; Solfrizzi et al., 2003, 2006a; Panza et al., 2004a,b; Luchsinger and Mayeux, 2004; Luchsinger et al., 2007). Since several dietary factors affect the risk of cardiovascular disease, it can be assumed that they also influence the risk of dementia (Panza et al., 2004a). Some recent studies have suggested that dietary fatty acids may play a role in the development of cognitive decline associated with aging or dementia (Solfrizzi et al., 2005; Cunnane et al., 2009). This concept is further supported by recent evidence that certain diets have been associated with a lower incidence of AD (Grant, 1997, 1999). In fact, antioxidants, dietary fatty acids, and micronutrients appear to have a role, and evidence is at least suggestive that diets rich in fruits and vegetables and other dietary approaches may permit a beneficial effect on the risk of dementia (Coley et al., 2008; Solfrizzi et al., 2008a).

Fatty acids can be categorized briefly into saturated fatty acids (SFA) and unsaturated fatty acids (UFA). SFA, such as stearic acid, are present in products such as meat, dairy products, cookies and pastries. Monounsaturated fatty acids (MUFA) are most frequently consumed in olive oil. The principal series of polyunsaturated fatty acids (PUFA) are $n-6$ (i.e., linoleic acid) and $n-3$ [i.e., α-linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)]. In our Mediterranean dietary pattern the main sources of $n-6$ PUFA are vegetable oils, while the principal sources of $n-3$ PUFA are fatty fish (salmon, tuna, and mackerel). In fact, olive oil contains 70–80% MUFA (oleic acid) and 8–10% PUFA (6–7% linoleic acid and 1–2% α-linolenic acid) (Solfrizzi et al., 2005). The aims of this article was to examine the possible role of dietary fatty acids in modulating the risk of age-related changes in cognitive function, predementia syndromes, and dementia as well as the possible mechanisms behind the observed associations. Furthermore, we briefly reviewed current evidence on dietary fatty acid supplementation in predementia and dementia syndromes.

2. Dietary fatty acids in ARCD and other predementia syndromes

2.1. Cross-sectional studies

At present, an increasing number of epidemiological and clinical studies have addressed the link between UFA intake and cognitive function, most being cross-sectional (Solfrizzi et al., 2005). In the last years, the study approach was to associate single micro- or macronutrients to ARCD, MCI, AD, or VaD. In this picture, several hallmarks of the Mediterranean diet were linked to increased risk or with a protective effect against cognitive impairment (Panza et al., 2004b). The typical dietary pattern of Mediterranean diet (MeDi) is characterized by high intakes of vegetables, fruits and nuts, legumes, cereals, fish, and MUFA; relatively low intakes of meat, and dairy products, and moderate consumption of alcohol. In fact, higher levels of consumption of olive oil are considered the hallmark of the traditional MeDi.

In a cross-sectional French study, a positive relationship was found in elderly women between lipid intake and the Mini Mental State Examination (MMSE) score (global cognitive functions). A positive relationship was also found between PUFA intake and mobility in elderly men, and between functional variables and alcohol intake in the whole sample. These findings, contradictory to the results of the subsequent studies, were explained by the authors with the fact that high intakes of these dietary factors can be considered as an indicator of a better health status (Pradignac et al., 1995) (Table 1). Another cross-sectional study from Spain, showed that the older subjects with a lower intake of MUFA, SFA, and cholesterol, and higher intakes of total calories, fresh fruit, carbohydrate, thiamine, foliate, vitamin C, and minerals (iron and zinc) had the best performance in global cognitive tests, with a statistical significance after adjustment for age and sex (Ortega et al., 1997) (Table 1).

As seen above, MUFA, consequently to the high consumption of extra-virgin olive oil, represent the most important fat in MeDi. In North American diets, a major source of MUFA is canola oil, while olive oil consumption is much less frequent. Cumulative evidence suggests that extra-virgin olive oil may have a role in the protection against cognitive decline, other than against coronary disease and several types of cancer because of its high levels MUFA and polyphenolic compounds. The cross-sectional association between dietary macronutrients and cognitive impairment was examined in elderly subjects aged 65–84 years from the Italian Longitudinal Study on Aging (ILSA). After adjustment for educational level, the odds ratios of cognitive decline (MMSE score < 24) decreased exponentially with the increase of MUFA energy intakes. Furthermore, selective attention performances were independently associated with MUFA intake (Solfrizzi et al., 1999) (Table 1). In another Northern Italian cross-sectional study on older subjects, the Progetto Veneto Anziani (Pro.V.A. study), in a multiple regression analysis, age and educational level accounted for 29.6% of the MMSE variance, while the contribution of the other variables considered [low-density lipoproteins (LDL) cholesterol, diastolic blood pressure, MUFA, and PUFA] was almost negligible. The authors acknowledged that these results were limited by the fact that total energy intake, which is known to be reduced in patients with cognitive impairment, was not considered, and by the fact that the study was a cross-sectional survey (Manzato et al., 2003) (Table 1). More recently, in the Doetinchem Cohort Study, higher dietary cholesterol was associated with an increased risk of