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Cognitive decline, dietary factors and gut–brain interactions

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ABSTRACT

Cognitive decline in elderly people often derives from the interaction between aging-related changes and age-related diseases and covers a large spectrum of clinical manifestations, from intact cognition through mild cognitive impairment and dementia. Epidemiological evidence supports the hypothesis that modifiable lifestyle-related factors are associated with cognitive decline, opening new avenues for prevention. Diet in particular has become the object of intense research in relation to cognitive aging and neurodegenerative disease. We reviewed the most recent findings in this rapidly expanding field. Some nutrients, such as vitamins and fatty acids, have been studied longer than others, but strong scientific evidence of an association is lacking even for these compounds. Specific dietary patterns, like the Mediterranean diet, may be more beneficial than a high consumption of single nutrients or specific food items. A strong link between vascular risk factors and dementia has been shown, and the association of diet with several vascular and metabolic diseases is well known. Other plausible mechanisms underlying the relationship between diet and cognitive decline, such as inflammation and oxidative stress, have been established. In addition to the traditional etiological pathways, new hypotheses, such as the role of the intestinal microbiome in cognitive function, have been suggested and warrant further investigation.

1. Introduction

Aging affects the brain in several ways, from the cellular to the functional level. Changes associated with age manifest themselves as decline in several abilities, including sensory, motor, and higher cognitive functions (Salthouse, 2009; Schaffer et al., 2012). Specific diseases strongly related to age cause lesions in the brain that exacerbate the physiological changes that occur during normal aging. Cognitive decline is a classic example of this interaction between aging-related changes and age-related diseases in older people. Cognitive decline covers a large spectrum of clinical manifestations, a continuum that ranges from intact cognition through mild cognitive impairment (MCI), and finally, dementia.

Dementia is characterized by progressive deterioration in multiple cognitive domains that is severe enough to interfere with daily functioning (APA, 2013). Alzheimer's disease is the most common cause of dementia in elderly people, accounting for 60–70% of all dementia cases when traditional diagnostic criteria for dementia subtypes are used (Blennow et al., 2006; Fratiglioni et al., 1999). AD is strictly related to a neuropathological diagnosis determined by the presence of neurofibrillary tangles and senile plaques in the brain (Blennow et al., 2006). Vascular dementia (VaD) is the second most common cause of dementia in elderly people. VaD is defined as loss of cognitive function resulting from ischemic, hypoperfusive, or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology (Roman, 2003). The combination of AD and VaD pathological changes in the brain of older people is extremely common, making mixed dementia probably the most common type of dementia (Langa et al., 2004).

The age-specific prevalence of dementia nearly doubles every five years, from approximately 1.5% in persons aged 60–69 years to 40% in nonagenarians. The global prevalence of dementia in people over 60 years is 3.9%. The regional prevalence varies from 1.6% in Africa to 3.9% in Eastern Europe, 4.0% in China, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America. There is a similar pattern in the distribution of dementia subtypes across the world (Qiu et al., 2007). In Europe, the age-adjusted prevalence of dementia of any kind among people 65 years and older is 6.4%; of AD, 4.4%; and of VaD, 1.6% (Lobo et al., 2000; McVeigh and Passmore, 2006). It has been estimated that 36 million people have

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dementia worldwide (Wimo and Prince, 2010) and that there are 4.6 million new cases of dementia every year (Ferri et al., 2005). A study from UK reported that later-born populations have a lower risk of prevalent dementia than those born earlier in the past century (Matthews et al., 2013). Dementia incidence does not show great geographical variation in the world. The global annual incidence of dementia is around 7.5 per 1000 person-years. The incidence rate of dementia increases exponentially with age, from approximately one per 1000 person-years in people aged 60–64 years to more than 70 per 1000 person-years in 90+ years (Qiu et al., 2007). A recent study showed that prevalence of dementia was stable from the late 1980s to the early 2000s in central Stockholm, Sweden, whereas survival of patients with dementia increased. These results suggest that incidence of dementia may have decreased during this period (Qiu et al., 2013).

Dementia represents an advanced stage of cognitive deterioration and can be regarded as the tip of an iceberg, as milder cognitive syndromes are even more common than dementia among older adults (Caracciolo et al., 2012; Wimo and Prince, 2010). The term mild cognitive impairment (MCI) indicates an intermediate stage of cognitive deterioration in which functional independence is preserved but there is impairment in one or more cognitive areas, as confirmed by neuropsychological investigation (Petersen, 2004). Prevalence estimates of MCI are highly variable, spanning a range between 3% and 42% (Ward et al., 2012), but most studies converge toward a prevalence of around 16.5% among people 60 years or older (Petersen et al., 2009). Incidence rates of MCI also exhibit variation, ranging between 21.5 and 71.3 per 1000 person-years (Caracciolo et al., 2008; Luck et al., 2010; Ward et al., 2012).

2. Diet: a key modifiable risk factor for dementia and predementia syndromes

Epidemiological evidence supports the hypothesis that modifiable lifestyle-related factors are associated with cognitive decline, which opens new avenues for prevention (Solfrizzi et al., 2008). Diet in particular has become the object of intense research in relation to cognitive aging and neurodegenerative diseases. In this critical review, we summarize and update the state of the art of this rapidly expanding research field by focusing both on key individual studies and on previous reviews.

2.1. Brain, nutrients, and neuroprotection

Nutrients are bioactive molecules that are essential for human health and functioning (Morris, 2012). Most cannot be synthesized internally by human body (not at all, or not in sufficient amount) and need to be obtained from food. The brain is a complex organ with high metabolism and high turnover of nutrients, and this makes it a high-maintenance device in terms of optimal nutrient intake. Indeed, a myriad of nutrient-specific transport systems and physiological mechanisms constantly work to replace the nutrients used by the brain (Morris, 2012).

The possible biological effects of dietary nutrients on underlying mechanisms of neuronal and cell aging is discussed below.

2.1.1. Oxidative stress and vitamins

Since the brain is an organ with high metabolism rate, oxidative stress is a common phenomenon in its neural tissue (Bishop et al., 2010). Two main types of antioxidant compounds are involved in oxidative stress regulation in the body: antioxidant enzymes, that catalyze neutralizing reactions against free radicals and reactive oxygen species, and antioxidant nutrients, which help as co-factors in catalytic activities (Morris, 2012; Sardesai, 1995). Antioxidant enzymes are endogenous; however, they need exogenous nutrients for proper functioning (Sardesai, 1995). These exogenous antioxidants include—but are not limited to—vitamin E (tocopherols), vitamin C, carotenoids such as β-carotene (vitamin A), and trace-minerals such as manganese, copper, selenium and zinc.

2.1.1.1. ACE vitamins. Epidemiological studies evaluating the association between dietary intake of antioxidants and cognitive decline have reported inconsistent results. The majority of longitudinal studies that focused on vitamin E found an association between higher levels of vitamin E dietary intake and a decrease in the risk of AD (Devore et al., 2010; Engelhart et al., 2002b) and cognitive decline (Morris et al., 2002, 2005b; Wengreen et al., 2007). However, discordant findings have also been reported, and some studies found no effect of vitamin E on dementia/AD and cognitive decline (Corrada et al., 2005; Laurin et al., 2004; Luchsinger et al., 2003). Evidence of a protective effect of vitamins C and A on the development of dementia and cognitive decline has been sparse (Engelhart et al., 2002b; Wengreen et al., 2007), as the majority of the prospective longitudinal studies found no association between vitamin C (Corrada et al., 2005; Devore et al., 2010; Laurin et al., 2004; Luchsinger et al., 2003; Morris et al., 2002) or β-carotene (Corrada et al., 2005; Devore et al., 2010; Engelhart et al., 2002b; Laurin et al., 2004; Luchsinger et al., 2003; Morris et al., 2002) and cognitive change over time.

Most randomized controlled trials (RCTs) of antioxidant vitamin supplementation have shown either no association between supplementation and dementia/cognitive decline (Gillette-Guyonnet et al., 2013), or even an harmful effect of high supplement intake (Gillette-Guyonnet et al., 2013). A possible explanation for the failure of RCTs of vitamin E supplementation could be the fact that in such studies high doses of a specific type of vitamin E, i.e. alpha-tocopherol, were administered; while what is generally consumed as food is a mix of different forms of vitamin E (alpha-, beta-, delta- and gamma-tocopherols). In particular, plasma levels of total tocopherols rather than the concentration of specific single tocopherols have been found to predict AD development (Mangialasche et al., 2010). Therefore, studies modeling vitamin E as a single tocopherol may not be as valid as studies considering total tocopherols. What has been shown for vitamin E can also easily translate to vitamins in general, as it has been shown that a combined intake of different dietary antioxidants has higher neuroprotective effects than single antioxidants intake. Indeed some of the few RCT studies that did find an association between cognition and antioxidants supplementation used a complex (up to 34 different elements) antioxidant blend (Kawsar et al., 2010; Stevenson and Hurst, 2007).

2.1.2. Inflammation, polyphenols and unsaturated fats

Inflammation plays an important role in the pathogenesis of atherosclerosis, and neuroinflammation is believed to be part of the neurodegenerative cascade that leads to Alzheimer's pathologies and clinical dementia (Gorelick, 2010). Elevated serum C-reactive protein (CRP) in midlife is associated with an increased risk of both AD and VaD, which supports the hypothesis that inflammatory markers are involved in dementia and act through both peripheral and cerebral vascular mechanisms (Gorelick, 2010).

Several nutrients have been found to exert an anti-inflammatory action on the brain; among these, polyphenols and unsaturated fatty acids have been widely investigated.

2.1.2.1. Polyphenols. Phenolic compounds are secondary metabolites of plants and include flavonoids, lignans, stilbenes, coumarins, and tannins (Ghosh and Scheepens, 2009). Flavonoids are the most-studied group of polyphenols in relation to brain health.

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