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Review Article

Modulation of cholesterol in midlife affords cognitive advantage during ageing – a role for altered redox balance

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Abstract: General practitioners, geriatricians, neurologists and health care professionals all over the world will be facing by 2040 the diagnostic, therapeutic and socioeconomic challenges of over 80 million people with dementia. Dementia is one of the most common diseases in the elderly which drastically affects daily life and everyday personal activities, is often associated with behavioural symptoms, personality change and numerous clinical complications and increases the risk for urinary incontinence, hip fracture, and – most markedly – the dependence on nursing care. The costs of care for patients with dementia are therefore immense. Serum cholesterol levels above 6.5 mmol/L are known to be associated with an increased RR of 1.5 and 2.1 to develop Alzheimer's disease, the most common form of dementia, and a reduction of serum cholesterol in midlife is associated with a lowered dementia risk. The aim of this work is to critically discuss some of the main results reported recently in the literature in this respect and to provide the pathophysiological rationale for the control of dyslipidemia in the prevention of dementia onset and progression.

Keywords: Cholesterol, LDL, oxidation, ageing, cognition

Introduction

General practitioners, geriatricians, neurologists and health care professionals all over the world will be facing by 2040 the diagnostic, therapeutic and socioeconomic challenges of over 80 million people with dementia, 70% of which will be residing in the least developed world countries. There are currently 18 million people with dementia in Europe, Africa, Asia and Latin America, and nearly 29 million demented subject are predicted by 2020 [1-3]. There is, however, a striking possibility of underestimation, not only in developing countries, due to inadequate diagnosis, lack of awareness and low education [4].

Dementia is one of the most common diseases in the elderly, with crude prevalence rates between 5.9-9.4% for subjects aged over 65 in the European Union [5]. The lowest age- and gender-specific prevalence of all-causes de-

mentia reported in the literature is 61.1% among women aged 100 or greater [6-8]. Dementia drastically affects daily life and everyday personal activities. It is often associated with behavioural symptoms, personality change and numerous clinical complications, it increases the risk for urinary incontinence, hip fracture, and – most markedly – increases the dependence on nursing care. The costs of care for patients with dementia are therefore immense [9].

This review will focus on specific aspects of dementia prevention. Prevention appears to be particularly prominent among anti-dementia strategies because of the lack of cure for dementia [10] and because it can be carried out within a multidimensional scheme with the highest chances of success if adopted in the early adulthood.

Primary prevention is directed against dementia

prior to its biological onset or against dementia's risk factors, while secondary prevention refers to the early detection of asymptomatic disease with associated opportunities for intervention before symptoms are evident. However, the US Preventive Services Task Force suggests there is insufficient evidence to support instituting a universal dementia screening programme [11]. Syndromes of cognitive impairment in non-demented older adults have been the focus of studies aiming to identify subjects at high risk to develop dementia. Mild cognitive impairment (MCI) is characterized by isolated memory deficits in non-demented persons with subjective memory problems, normal general cognitive functioning, and intact activities of daily living [12]. In the attempt of avoiding dementia development, there are several risk factors to be taken into account, some of which are non-modifiable and include age with age-influencing early-life deleterious conditions [13], gender, and genetic influence [14]. In addition, there are several inborn physical attributes, factors such as illiteracy and lack of early education, environmental stress, as well as accidents and traumas that have been associated with increased risk for dementia [13,15].

A great deal of attention is being dedicated to the identification and modulation of those factors which have a large potential to be managed before the onset or during the early asymptomatic course of the disease. These include vascular and lifestyle factors. Among vascular risk factors, considerable evidence from randomized controlled trials and longitudinal cohort studies has established the relationship between hypertension and dementia as well as between hyperlipidemia and dementia. Both systolic hypertension above 160 mmHg and serum cholesterol above 6.5 mmol/L are known to be associated with an increased RR of 1.5 and 2.1 to develop AD [reviewed in 15]. Based on the recommendations of the Third Canadian Consensus Conference on Diagnosis and Treatment of Dementia held in March 2006 [15], statin therapy, acetylsalicylic acid and carotid artery stenosis re-opening on a first level of evidence and control of type 2 diabetes mellitus, hyperlipidemia and hyperhomocysteinemia on a second level of evidence should not be recommended with the single specific purpose of reducing the risk of dementia. Similarly, a recent Cochrane review concluded that there was insufficient evidence to suggest the use of statins for the prevention

of AD based on two prospective randomised, placebo-controlled studies (RCTs); the Heart Protection Study and the PROSPER study. Both studies examined the effects of statins in subjects aged over 70 years of age. However, these RCTs do not address the primary epidemiological observations and nested case-control studies, that reduction of serum cholesterol in mid-life offers benefit [16, 17].

The aim of this work is to critically discuss some of the main results reported recently in the literature in this respect and to provide the pathophysiological rationale for the control of dyslipidemia in the prevention of dementia onset and progression.

Cholesterol metabolism in the brain

In the central nervous system, cholesterol is unesterified and resides in the myelin sheaths (oligodendroglia) and in the plasma membranes of astrocytes and neurons. Up to 70% of brain cholesterol is myelin-associated. As half of the brain's white matter is composed of myelin, the brain is the most cholesterol-rich organ in the body. Cholesterol plays an essential role in membrane organization and function as it induces large changes in membrane fluidity. The bulk of brain cholesterol in the adult human brain has a half-life of at least five years, showing the efficiency of cholesterol reutilization which is achieved via the cholesterol 24-hydroxylase enzyme that is expressed in neurons particularly in the hippocampus and cortex where it is considered important for memory and learning [18]. The current consensus is that cholesterol in the brain is insulated from changes in circulating cholesterol. The blood-brain barrier prevents diffusion of large molecules at the level of tight junctional attachments between adjacent capillary endothelial cells; however, brain endothelial cells have the potential to take-up low-density lipoprotein cholesterol through luminal LDL receptors that recognize apolipoprotein E (apoE) and translocate LDL across the cell (reviewed in [15]).

ApoE, cholesterol and dementias

ApoE is one of the major apolipoproteins in plasma and quantitatively the most important transport protein for cholesterol in the brain. It is mainly synthesized by the astrocytes [19], although microglia and neurons are also able to

synthesize some apoE under specific conditions [20]. One of the 3 human isoforms of apoE, apoE4, is a well-documented risk factor for Alzheimer's disease (AD) (reviewed in [21]). The discovery that apoE4 alleles and certain genetic variants of IL-1 are linked to dementia support the involvement of both inflammation and dysregulation of lipid metabolism in the development of dementia [22,23].

ApoE plays a crucial role in lipid transport in the blood, brain, and cerebrospinal fluid in health and disease. There are important associations between dietary factors and apoE polymorphisms, which give us a clue to consider dietary fat patterns in the population. Recently, a number of dietary elements and foods have been reported to be either risk or protective factors for the development of dementia and AD. These include fat, fatty acids, antioxidants, fish, homocysteine/methionine, vitamins and alcohol [24].

The relationship between β -amyloid (A β) and cholesterol was first investigated in cultured cells [25] and later work in a transgenic mouse model of AD amyloidosis which demonstrated that diet-induced hypercholesterolemia resulted in a dramatic acceleration of the neuropathological and biochemical changes in the transgenic mice [26]. These initial studies also showed the correlation between levels of total A β and both plasma and CNS total cholesterol as well as the relationship between cholesterol levels and A β cleavage [27] and were confirmed by in vitro observations of a decreased rate of A β secretion in cells depleted of cholesterol [28].

Several clinical studies have identified the association, in humans, between total plasma cholesterol and AD risk. After controlling for age and apoE isoforms, previous and midlife high plasma cholesterol levels are a consistent predictor of AD and MCI. In some reports, increased levels of midlife total cholesterol are associated with two- and threefold increase in the risk to develop dementia and AD in later life [29-32]. In addition, low HDL-cholesterol are associated with elevated risk for dementia and high levels of HDL cholesterol are associated with larger hippocampal volume and protection against dementia and AD [33]. Hypercholesterolemia in midlife may lead to enhanced cholesterol membrane content, and a corresponding increase in the surface area of lipid rafts

that can potentiate the activity of b-secretase and therefore A β production. Statins, the most prescribed lipid-altering drugs, are used to successfully decrease vascular death, myocardial infarction, stroke and in general to prevent cardiovascular diseases that are correlated with AD. In light of the hypothesis that the competitive inhibitors of HMG-CoA reductase could have beneficial effects on AD, the efficacy of statin treatment has been studied in AD. This treatment has been in fact found to be associated with reduced prevalence for probable AD by up to 73%, reduce A β production by 50%, reduce plaque formation [34-36] and cholesterol CSF levels [37]. In this respect, modulation of cholesterol in midlife appears to afford cognitive advantage during ageing, despite the fact that some of the statins studied do not cross the blood brain barrier. One potential mechanism by which a reduction in peripheral serum cholesterol may be effective in reducing AD incidence is through a reduction in oxidative stress, as the longer LDL circulation time observed in patients with hypercholesterolaemia gives rise to elevated levels of oxidized lipids that are in themselves lipophilic and cytotoxic oxidative stressors.

Oxidative stress and the AD brain

Evidence that AD brain is subject to a critical oxidative stress load and that an initial source of oxidative stress such as high cholesterol may initiate amyloid formation is increasing. Lipid peroxidation is the mechanism by which lipids are attacked by free radicals. The latter must have sufficient reactivity to abstract a hydrogen atom from a methylene carbon in their side chain. The greater the number of double bonds in the molecule, the higher the chance that the hydrogen atom is removed. Polyunsaturated fatty acids, in fact, are particularly susceptible to lipid peroxidation. Brain membrane phospholipids are composed by PUFAs, primarily arachidonic and docosahexaenoic acid. Oxidation of these acids produced aldehydes, such as malondialdehyde and 4-hydroxy-nonanal. In addition, F2-isoprostanes are prostaglandin-like compounds formed non-enzymatically by free radical-induced oxidation of fatty acids. Peroxidation of cellular membranes can, in turn, propagate free radical chain reactions. Several neurotoxic substances of altered lipid metabolism have been found in AD which may involve free radical damage and include 24s-

hydroxycholesterol (the main cholesterol elimination byproduct of the brain) [38], malondialdehyde [39], lipofuscin and several aldehydes and F2-isoprostanes (reviewed in [40]).

Significant increases in levels of membrane-associated oxidative stress, and free cholesterol in brain cells during normal aging have been detected in mice, in AD patients and in neurons exposed to A β . This associates with a reduction in intracellular glutathione and an altered redox balance within the cells that signals activation of several transcription factors (e.g. NF- κ B) and enzymes (acid sphingomyelinase). The latter catalyses the release of long chain ceramides from membrane sphingolipids and alters the structure of the lipid rafts in membranes. As the membrane microdomains rich in cholesterol and sphingolipids play important roles in various signaling pathways, cell proliferation, differentiation and death, the observed reversion of ceramide changes in vitro by α -tocopherol (probably by conserving the intracellular redox state) is not a minor finding [41].

24s-hydroxycholesterol is an oxysterol generated in the brain by the cytochrome P-450 (CYP46A1) and can escape the recycling mechanism by traversing the blood-brain barrier. The ability for cholesterol transport or recycling in the brain seems to be of importance for the development of AD as 24s-hydroxycholesterol is an effective inhibitor of beta amyloid formation [42]. In contrast, the systemically oxidized cholesterol product, 27-hydroxycholesterol, can be transported from the periphery across the blood-brain barrier and is observed at increased levels in the AD brain [43]. Indeed, the increased ratio of 27:24s-hydroxycholesterol has been proposed to favour the formation of beta amyloid [44].

Epidemiological evidence for a protective role of diet against AD development

The foregoing evidence implicates a role for dyslipidemia and lipid peroxidation in increasing AD risk, possibly through the uptake of systemically oxidized cholesterol such as 27-hydroxycholesterol, that can result in neuronal toxicity either directly or indirectly via increased amyloid beta secretion, GSH oxidation, ceramide formation and enhanced cytotoxic signaling. This has prompted the evaluation of protective dietary patterns against dementia develop-

ment. Among various composite dietary patterns, a large amount of attention has been lately dedicated to the Mediterranean Diet (MeDi). This is characterized by high intake of vegetables, legumes, fruits, cereals, unsaturated fatty acids (mostly in the form of olive oil), low intake of saturated fatty acids, moderately high intake of fish, and a tendency for low intake of dairy products and meat. In the typical MeDi, alcohol intake is low to moderate but regular, generally during meals. High MeDi adherence is associated with lower AD risk [45, 46] and furthermore may impact on AD course and prognosis, as shown by the observation that AD patients in the middle and higher tertile of MeDi adherence have lower and lowest mortality risk, respectively compared to AD patients in the lowest tertile [47]. After adjusting for age, gender, education, marital status, depressive symptomatology, taking 5 drugs or more, apoE genotype, stroke and cardiovascular risk factors, a higher MeDi score was recently found to be associated with fewer errors at MMSE in a prospective cohort study of 1410 elderly subjects [40]. In this study, the performance on three further neuropsychological tests was not consistently associated with MeDi adherence [48]. The authors suggested that the main reason for the discrepancy between the previous US studies [45-47] and the latter French one [48] might be related to the different population studied and the country-specific characteristics of the dietary patterns. The association between cognitive performance and MeDi, however, appears to be a strong one and has been recently confirmed by the relationship between high adherence to the MeDi and reduced risk for developing MCI and for converting from MCI to AD [49]. Both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD in a prospective cohort study of two cohorts comprising 1880 community dwellers without dementia living in New York [50]. It might be possible that the synergistic lipid-lowering and antioxidant activity of specific MeDi food categories is able to influence the onset and course of dementia.

A large amount of attention has been dedicated in the past decades to the role of oxidative stress and altered redox balance in the progression of aging brain to mild cognitive impairment and dementia [51] as well to the protective role of antioxidant micronutrients against AD devel-

opment [52]. Recently, the simultaneous association between antioxidant micronutrient, fruit and vegetable intake and cognitive performance has been observed in healthy individuals across a broad age range, suggesting that at least some of the cognitive-enhancing effects of a fruit and vegetable-rich diet are mediated by oxidative stress-lowering substances [53]. These results need to be confirmed in larger population studies, as health-conscious subjects further increasing their fruit and vegetable intake for a longitudinal period of three months do not appear to benefit from a simultaneous decrease in systemic oxidative stress biomarkers [54]. As oxidative LDL modification appears to be inversely correlated to cognitive performance [55], the impact of dietary modifications with increased fruit and vegetable intake on levels of oxidized molecules that can cross the blood-brain barrier e.g. 27-hydroxycholesterol may prove more informative for assessing a reduction in risk for AD.

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Cholesterol and cognition

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