Adrià Agut León and Veruska De Castro Pinheiro

ROLE OF RESVERATROL AND OMEGA-3 ON ALZHEIMER'S DISEASE

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Role of Resveratrol and Omega-3 on Alzheimer's Disease

Review

A. Agut[1], V. De Castro[1].

[1]Unit of Biochemistry and Biotechnology, Faculty of Medicine and Health Sciences, University Rovira i Virgili, Reus, Tarragona, Spain.

Abstract. Alzheimer disease is a neurodegenerative disease and the leading cause of dementia above the age of 65 years. Unfortunately, a cure for the condition is not known but is a growing interest in dietary patterns and nutrients as potential modifiable risk factors. In fact, the Mediterranean Diet has been shown to exert positive effects on risk for Alzheimer Disease and cognitive functions during aging. The aim of this paper is to evaluate the recent findings about Resveratrol and Omega-3 fatty acids —two of the main components of Mediterranean Diet— and their impact on Alzheimer Disease, focusing on the possible mechanisms involved.

Keywords: *Alzheimer disease (AD), Mediterranean diet (MD), Docosahexanoic acid (DHA), Resveratrol, Sirtuin-1 (SIRT1), Amyloid-β (A*β*), c-Jun N-terminal Kinase (JNK); Type 2 diabetes mellitus (T2DM).*

INTRODUCTION

Alzheimer disease (AD) is a progressive and debilitating disorder typified by irreversibly loss of memory, cognition and function, until the patient succumbs to the illness within 5-9 years after the diagnosis[1,2,3]. By 2014, more than 26 million people worldwide had Alzheimer[4] (the highest prevalence was showed in North America and Western Europe, followed by Latin America and China)[3] and the number of the disease is projected to reach 106.8 million worldwide by the year 2050[5]. Unfortunately, despite the allocation of enormous amounts of funding and resources to studying this brain disorder, a cure for the condition is not known and there are no effective pharmacological treatments for reducing the severity of pathology and restoring cognitive function in affected people[6,7].

The majority (99%) of the AD dementia cases belong to sporadic variety of the disease[8,9]. It's the leading cause of dementia above the age of 65 years and it is becoming a major challenge to the global health care system due to the progressive increase in the lifespan of the population in most countries[2]. The exact causes of sporadic AD are not yet established[9] although older age is the most obvious risk factor for the disease[10]. Other several factors can contribute to the risk of developing AD including genetic factors, midlife hypertension, history of head trauma, depression, smoking, obesity, diabetes, hypercholesterolemia, life style and low level of education[11,12,13]. Nevertheless, in 1% of the cases, AD is caused by specific point mutations in amyloid β precursor protein (AβPP), presenilin-1 (PS1), or presenilin-2 (PS2)[9] and usually appears in somewhat younger age-group than the sporadic form and follows a more aggressive downhill course[8].

The neurophatological features associated with the disease include the presence of extracellular senile plaques containing amyloid-β (Aβ) protein[13], which are derived from the AβPP through amyloidogenic processing by β- and γ-secretases[11]. AD also include the presence of neurofibrillary tangles (NFTs) that consist mainly of intracellular and abnormally phosphorylated tau protein, and a dramatic loss of neurons and synapses, especially in the hippocampus and cortex. Considering these pathological changes, the "Amyloid Cascade Hypothesis" is certainly the most popular current view[13].

The amyloid hypothesis postulates that Aβ, in a variety of forms, triggers a cascade harming synapses and ultimately neurons, producing the pathological presentations of Aβ plaques, tau tangles, synapse loss and neurodegeneration, leading to dementia. Aβ accumulation is thought to initiate AD pathology by destroying synapses, causing formation of NFTs, and subsequently inducing neuron loss[14].

Despite the evidence for the multifactorial nature of AD and the involvement of several different mechanisms, because of the immense popularity of the "Amyloid Cascade Hypothesis", to date most of the therapeutic efforts have been focused on inhibition and removal of Aβ plaques[9]. However, none of the anti-Aβ treatment have produced a discernible functional recovery, or altered the course of disease. In fact alarmingly some, specifically inhibitors of γ-secretase, lead to an increased decline in cognition. With each successive failure the validity and foundation of

the amyloid hypothesis is called increasingly into question and it is worthwhile to consider alternative possibilities[14].

For example, oxidative stress has been suggested to play a major role in the pathology of AD[15]. It occurs due to an imbalance between pro-oxidant and antioxidant activities in the body leading to the excessive production of reactive oxygen species (ROS) free radicals and peroxides. Brain tissue is more susceptible to oxidative stress due to its greater rate of oxygen consumption, high content of peroxidizable fatty acids, less regenerative capability, and low amounts of antioxidants[16]. Other evidences suggest that neuroinflammation is an important contributor to pathogenesis of AD too[17] because at all stages of the disease have been observed increased levels of pro-inflammatory mediators such as tumor necrosis factor-∝ (TNF-∝), interleukins, prostaglandins, reactive oxygen and nitrogen species[18]. Mitochondrial dysfunction is also believed to play a key role in neurodegenerative diseases especially AD. Mitochondria are known to produce the majority of Adenosine triphosphate (ATP) in cells and also function to maintain Ca+2 homeostasis. Since mitochondria are regulators for both cellular metabolism and apoptosis, any oxidation damage to the mitochondria may be relevant to the pathogenesis of AD[19].

However, stream of human and experimental studies have provided convincing evidence that AD is a metabolic disease whereby the brain loses its capacity to efficiently utilize glucose for energy production and respond to critical trophic factors signals due to insulin as well as insulin-like growth factor resistance[20]. Numerous articles support the hypothesis that there is a link between AD and type 2 diabetes mellitus (T2DM)[21,22] since people with diabetes have a higher incidence of cognitive decline and an increased risk of developing all types of dementia[22]. It has even suggested that AD may be termed as “type 3 diabetes” or “brain diabetes”, indicating that AD may represent a form of diabetes that selectively involves the brain with molecular and biochemical features that overlap with diabetes mellitus[8,21]. In a longitudinal cohort study, lasting up to 9 years, the risk of developing AD was 65% higher in people with diabetes than in non-diabetic controls. Other study suggest that frank diabetes (35%) or glucose intolerance (46%) might be present in up to 80% of patients with AD[22]. Several studies have also suggested that longer diabetes duration is generally associated with a higher risk for developing dementia[22]. If current studies have correctly

predicted the association between dementia and T2DM, then the future burden of AD might be even greater than that estimated as the prevalence of diabetes mellitus continues to rise[13].

The pathogenic mechanisms by which T2DM causes cognitive impairment have not been clearly established. A number of explanations for the link between diabetes and dementia have been proposed, including vascular lesions, chronic hypoperfusion in the brain, inflammation, oxidative stress and elevated levels of end products of glycolysis[21,23]. Recently, there is a rapid growth in the literature pointing toward insulin deficiency and insulin resistance as possible links between diabetes and AD[21,22]. In fact, in some studies, Alzheimer patients were found to be more insulin-resistant than control subjects without dementia and to have higher levels of hyperglycaemia[21].

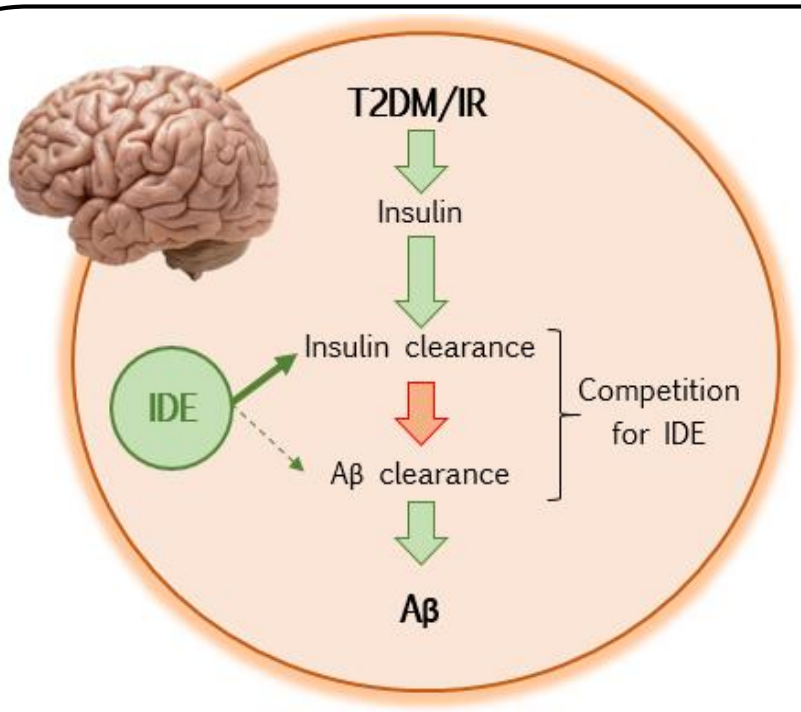

Figure 1. Possible mechanism by which T2DM and AD are linked. IDE is an enzyme that degrades both insulin and Aβ peptides, although IDE is much more selective by insulin (this difference is represented in the figure through arrow's thickness). Because of that, increased insulin in the brain as it occurs in T2DM or IR, reduce Aβ clearance and favors its accumulation. Green arrows represent positive effects while red arrows indicate inhibition.

The importance of the role of insulin as a neurothrophic factor in moderate concentrations has long been known. Nevertheless, a state of chronic hyperinsulinemia, as it occurs in insulin-resistance conditions and in T2DM, may be a risk factor for AD. In fact, elevated concentrations of insulin in the brain are associated with reduced Aβ clearance due to competition for their common and main degrading mechanism-the "Insulin-Degrading Enzyme" (IDE). Insulin modulates metabolism of AβPP decreasing intracellular accumulation. Insulin is degraded by the IDE, which is also involved in the metabolism and degradation of Aβ. This multifunctional enzyme degrades insulin and amylin, peptides related to the pathology of T2DM, together with Aβ peptide in the AD brain. Since IDE is much more selective for insulin than for Aβ, hyperinsulinemia may elevate Aβ through insulin's competition with Aβ for IDE. Consequently, brain hyperinsulinemia may deprive Aβ of its main clearance mechanism, favoring its accumulation in the brain, and its consequent neurotoxic effects (figure 1)[22].

Since evidence is increasing that changes in the quality of ingested foods of the diet may be used for prevention and treatment of insulin resistance[24], improve the metabolic risk factor profile and potentially reduce T2DM risk[,25,26,], it's reasonable to think that diet modification can be also useful on prevention of AD. In recent years has been increasing evidence supporting the role of nutrition in AD[6] and there is a growing interest in dietary patterns and nutrients as potential modifiable risk factors, among others[4]. A number of dietary factors such as antioxidants, vitamins, polyphenols and fish have been reported to decrease the risk of AD, while saturated fatty acids, high-calorie intake and excess alcohol consumption were identified as risk factors[5]. This data suggests that nutritional intake may influence the development and progression of AD[6] and that following healthful diet steps may reduce the risk of developing AD[11]. Because of that, while the search for a cure remains elusive, there is much hope that preventative strategies, such as dietary modification and nutritional supplementation, may reduce the global burden of AD[6]. Nutritional measures that could be useful in this context include a Mediterranean-like dietary pattern[24].

The Mediterranean diet (MD) is a collection of eating habits traditionally followed by people in the different countries bordering the Mediterranean Sea[27]. It is characterized by a high consumption of fruit, vegetables, legumes, whole grains, nuts, dairy products (principally cheese and yogurt), moderate

consumption of fish and poultry, olive oil as the main source of fats and a regular but moderate amount of ethanol, primarily in the form of red wine during meals[27,28,29,30]. There is enough evidence that a diet rich in plant fiber, phytosterols, fatty acids derived from fish and plant oil, is beneficial[28]. In fact, MD has long been reported to be the optimal diet for preserving good health[27]. The low intake percentage of total energy from saturated fatty acids correlated with lower serum cholesterol and a decrease of cardiovascular risk in Mediterranean countries in comparison to countries adhering to a Western-type diet[31]. Moreover, consistent evidence suggests that it is an effective and feasible tool enhancing quality of life, protecting against mortality and reducing the occurrence of T2DM[27,28,31].

More recently, research also focused on neurodegenerative diseases and the impact of MD[31]. A number of observational studies have examined whether adherence to a MD is associated with a reduced risk of cognitive decline, development of mild cognitive impairment or AD, and these studies have been subjected to systematic review and meta-analysis[32]. These reviews have presented evidence for an association between a MD and decreased risk of dementia[33], showing that greater adherence to MD may be associated with slower cognitive decline and reduced risk of AD[33,34], and suggesting that MD may be neuroprotective[34]. Interestingly, a prospective cohort of 192 community-based individuals diagnosed of dementia, observed that adherence to the MD may affect not only risk for AD but also subsequent disease course, reducing mortality and suggesting a possible dose-response effect[35]. In sum, the MD has been shown to exert positive effects on risk for AD and cognitive functions during aging[36]. Much research has been conducted in regards to the potentially beneficial nutrients abundant in the MD, namely mono- and polyunsaturated fatty acids (PUFAs), fiber, antioxidants such as vitamins E and C, resveratrol, polyphenols…[36]. Next, we are going to evaluate the recent findings concerning the effects of some of these single components of the MD and their impact on cognition and AD.

RESVERATROL

About twenty years ago, the consumption of red wine was linked to the low mortality of the French population due to cardiovascular disease (CVD), in comparison with other Western countries despite sharing CVD risk factors[37], i.e. a diet rich in saturated fats[27]. This apparent contraindication gave rise to the term “French Paradox”. A possible explanation of this phenomenon has been linked to the national consumption of wine (20-30 g/day)[38]. It is believed that the cardioprotective effects is partially due to the anti-platelet aggregation properties of the polyphenols in red wine and their ability to prevent the development of atherosclerotic plaques[39.] The beneficial effects of red wine were also further associated with the reduction of oxidative stress and improvement of endothelial function both in healthy people and in patients with acute coronary syndrome[37]. Several epidemiological studies have shown that moderate wine consumption can be also effective in slowing down age-related cognitive decline[38] and might provide preventive and/or therapeutic value in AD[40] decreasing plaque formation and protecting against Aβ-induced neurotoxicity[36].

Resveratrol (3, 5, 4'-trihydroxy- trans-stilbene), one of the primary components in red wine[27], has been identified as a key compound responsible for the effects[4] mentioned above. Resveratrol is a naturally occurring polyphenolic compound that belongs to the stilbene family and that exists in two geometric isomers with trans and cis configuaration[15,40]. Resveratrol is present in skin and seeds of more than 70 different plant species, including grapes, berries, grains, tea and peanuts[42].

Recent data provide interesting insights into the effect of resveratrol[43] miming caloric restriction (CR). CR is a dietary regimen involving strictly reduced caloric intake (approximately 30-40% compared to normal intake)[44] which extends the lifespan of a wide range of animals and protects against many aging-related diseases as T2DM, CVDs, cancer and neurodegeneration diseases including AD[45]. These benefits have been demonstrated to be partly mediated by sirtuins[44], deacylase proteins that act on histones in the presence of nicotinamide adenine dinucleotide (NAD+)[46]. Sirtuins, particularly Sirtuin-1 (SIRT1)[47], have been shown to regulate diverse cellular processes including aging, inflammation and stress resistance[46]by regulating the activity of key cellular proteins[48] and genes involved in antioxidant response, anti-inflammatory response, anti-apoptotic response,

insulin response and gene transcription[44]. Despite these demonstrated benefits, CR is difficult to maintain for long periods in humans from western countries[45]. Because of that, therapeutic potential of resveratrol as a CR mimetic and SIRT1-activating compound has attracted the interest of researchers [17,48].

Resveratrol is also reported to possess anti-amyloidogenic activity in several studies[44]. It ha ve been show to promote proteolytic clearance, destabilization and metabolism of Aβ[16,43,49] through sirtuin-dependent regulation of α-secretase, a disintegrin that can inhibit the generation of amyloidogenic peptides [44,48]. Resveratrol can also induce autophagic and lysosomal Aβ degradation[38], as well as protect both nerves and blood vessels against Aβ insults[47]. The ability to counteract Aβ toxicity can occur through its antioxidant properties but also through SIRT1 activation[44]. In fact, overexpression of SIRT1 is reported to prevent Aβ toxicity through an inhibition of Nuclear Factor kappa β (NFkβ) signaling[44].

Other studied mechanism is deacetylation of acetylated tau mediated by resveratrol activation of SIRT1. Acetylated tau is a major aspect of AD pathology that correlates with cognitive impairment. Thus, deacetylation promotes its proteosomal degradation and consequently reduces its level, improves cognitive function and reduces neuronal cell death[38,49,50].

Beneficial effects of resveratrol in neurological diseases may be due to its antioxidative properties[15]. It suppresses oxygen free radical formation by inhibiting pro-oxidative genes and inducing various antioxidant enzymes like catalase, while lowering the activity of enzymes involved in the development of oxidative stress[16,51].

Recently, resveratrol has been also shown to prevent pro-inflammatory effect of Aβ[16]. Mechanisms by which resveratrol attenuate inflammation are still not completely clear. A major pathway seems to involve the suppression of NFkβ pathway through the activation of SIRT1[52]. NFkβ is the most important transcription factor in inflammatory responses that regulates the production of various pro-inflammatory factors [52]. This step results in downstream blockade of microglia activation[38]. Microglia, the resident immune cells in brain, serve as the first line of defense when injury or disease occurs and plays a homeostatic role in the central nervous system[41]. Aβ peptides, can trigger microglial activation[16],

which may contribute to neuronal death during brain damage by releasing neurotoxic pro-inflammatory molecules[51] including cytokines, chemokines, nitric oxide synthase, Interleukin-1β, TNFα, ROS, reactive nitrogen specie, and prostaglandins[16,41,52]. The accumulation of these factors contributes to neuronal damage, and subsequently, the damaged neurons release debris and soluble factors, which in turn induce microglial activation[41] (figure 2). Inhibiting microglia activation and neurotoxic molecules production through resveratrol action should be beneficial for combating inflammation-mediated neurological disorders[52].

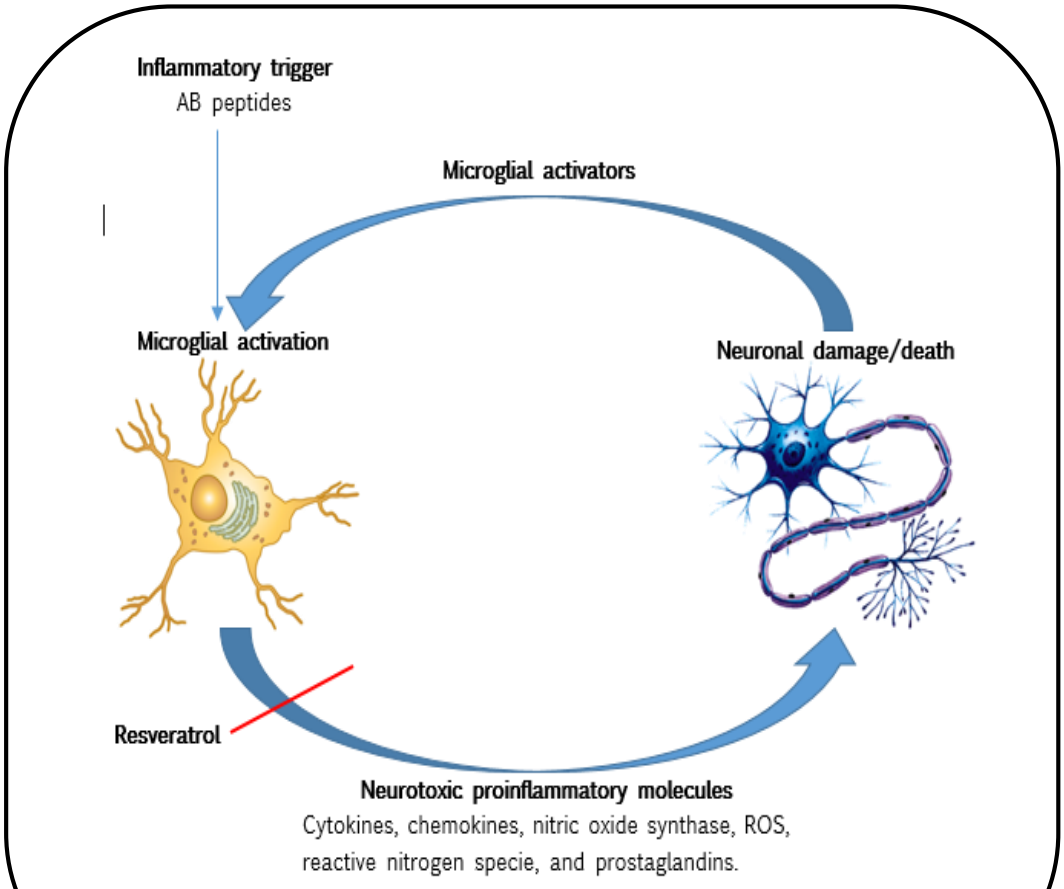

Figure 2. Summary of the neuroprotective action of resveratrol.

In sum, plenty of trials have been exerted to find the concrete details of the neuroprotective mechanisms of resveratrol and some official systematic clinical trials about resveratrol treatment in AD have also been underway. Nevertheless, the mechanism for the favorable effects of resveratrol in the brain remains unclear and scientists are still trying to seek out the detailed mechanism. More studies and further controlled clinical trials should be conducted in different AD models in

order to clarify the role of resveratrol and explore its mechanisms of action in humans[17,41,53,54].

Interestingly, a large number of studies have focused also on the effects of resveratrol on Diabetes Mellitus because of the tight association between AD and T2DM[54]. The results obtained in animal models show that resveratrol is capable of inducing beneficial effects in diabetic animals and thereby ameliorates diabetes[56]. Numerous studies on diabetic rats revealed the anti-hyperglicemic action of resveratrol and its capacity to diminish levels of glycosylated hemoglobin (HbA1c), which reflects the prolonged reduction of glycemia. Other studies provide evidence that resveratrol may be useful as a compound improving insulin action in T2DM. The improvement in insulin action in animals with genetic obesity-induced T2DM indicates that resveratrol is effective not only when insulin resistance is induced by a high-calorie diet[57]. Human studies have also been performed, providing interesting and promising data. Preliminary clinical trials confirm the effectiveness of resveratrol and indicate that this compound may decrease insulin resistance and hyperglycemia in T2DM patients[56,57]. In a clinical trial evaluating the effect of resveratrol administration on metabolic syndrome, conclude that administration of resveratrol significantly decreases weight, body mass index and fat mass, among others, all of which are linked to insulin resistance and T2DM development[55,58]. Moreover, a meta-analysis of eleven randommized controlled clinical trials showed that the consumption of resveratrol had a favorable effect on glucose control and insulin sensitivity in participants with diabetes[59]. Although human studies provide promising results, are not fully consistent[56], and well-designed clinical trials with resveratrol supplementation in a larger T2DM population and over a longer duration are required[60]. However, the current state of knowledge encourages the further research which would result in common use of resveratrol in diabetic humans[56]. For this reason, resveratrol has been proposed to play a role in the prevention of dementia through the improvement of diabetes and associated pathologies[55]. The mechanisms underlying the beneficial effect of resveratrol on glucose control may involve aspects as activation of SIRT1, increase the expression of Glucose Transporter Type 4 (GLUT4) or activation of glucose uptake in the absence of insulin, among others[59].

OMEGA-3 FATTY ACIDS

Lipids are the major source of brain dry weight because they are the basic structural component of neuronal cell membranes[61]. So it is reasonable to assume that the composition of fatty acids in the brain has relevance for brain functions, including cognition and neuropsychiatric development[62]. A number of prospective epidemiological studies have investigated the relationship of dietary fatty acid composition to the risk of developing dementia[61]. The fatty acid that has attracted major interest in the prevention of cognitive decline is omega-3 fatty acids[62].

Omega-3 PUFAs are dietary fats with an array of health benefits[63] defined by having their first double bond three carbons from the methyl terminals[64]. They are incorporated in many parts of the body including cell membranes[60] playing a major role in cell membrane[63] stability, fluidity and synaptic connectivity. They are also vital components in human metabolic function[65].

The omega-3 PUFAs that are essential in human physiology are ∝-linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexanoic acid (DHA). These PUFAs are termed essential because the human body is incapable of synthesizing omega-3 PUFAs that are longer than 14 carbons[65]. ALA is a prominent component of our diet as it is found in many land plants that are commonly eaten (ALA is the predominant omega-3 PUFA found in plant food and commonly found in some vegetable oils such as flaxseed, perilla, canola, soybean and walnut oils)[66], but it does not provide the health benefits seen with EPA and DHA[63]. EPA and DHA are mainly obtained by eating oily fish such as tuna, salmon, mackerel, herring and sardines[65].

There has been increasing concern over safety from contaminants in some fishes such as heavy metal mercury, lead, chromium and cadmium, especially cultured freshwater species since it was directly affected by the heavy pollution of water resources, especially in some offshore areas. The public is facing conflicting reports on the benefits and risks of fish intake, resulting in confusion over the role of fish consumption in a healthy diet. However, there are no data to show that certain clinical condition is caused by the fish consumption[66]. This has led to the American Heart Association's recommendation that oily fish should be consumed at least twice per week[65].

Research has since been undertaken on omega-3 PUFAs to investigate their health benefits in a vast array of medical conditions and also their role in primary prevention in many of these[65]. Most of the evidence suggests that omega-3 PUFAs consumption have beneficial effects in decreasing stroke and coronary heart disease[64]. But the benefits of omega-3 PUFAs transcend CVD management: omega-3 PUFAs may reduce systemic inflammatory diseases, prevent prostate cancer and improve prognosis in those with prostate cancer, treat depression and bipolar disorder and, interestingly, prevent the development of dementia[65]. In the last 15 years, omega-3 PUFAs have emerged as a possible modifiable environmental AD risk factor and, consequently, as a potential nutraceutical tool against AD. A wealth of epidemiological data has been generated from case-control and longitudinal observational studies based on reported food consumption or blood fatty acids measurements[67].

Overall, a majority of studies indicate that the consumption of fish is associated with better overall cognitive function, reduced speed of cognitive decline in patients between the ages of 45 and 70 years and, finally, with a lower risk of developing AD compared with those patients who rarely or never eat fish[65,67]. Interestingly, a dose-response meta-analysis showed that each 100 g per week higher intake of fish was associated with an 11% lower risk of AD[68]. Although the protective effect of fish intake is mainly attributed to its high content in omega-3 PUFAs, this protective effect may have several alternative explanations: fish is also a good source of other nutrients; a higher fish intake may simply be an indicator of a healthier dietary pattern or higher socioeconomic status; higher fish intake may associate with a lower intake of other type of fat such as saturated fat. Because of that, well-designed randomized controlled trials that address a specific mechanism ofi fish intake and reduced risk of AD are urgently needed[68]. Another study has found that a diet characterized by higher intakes of foods high in omega-3 PUFAs (salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, dark and green leafy vegetables), and a lower intake of foods low in omega-3 PUFAs (high-fat dairy products, red meat, organ meat, butter) is strongly associated with a lower AD risk[63]

Sadly, the current diet has changed over time to be high in saturated fatty acids and low in omega-3 PUFAs. This change in eating habits is centered on fast food

containing small amounts of essential omega-3 PUFAs and high amounts of saturated fat and cholesterol[63].

Several, although not all, prospective studies indicate that saturated and trans fatty acids are associated with an increased risk of AD. Many possible mechanisms link saturated or trans fat intake to dementia risk. Both types of fat tend to elevate total plasma and low-density protein cholesterol concentrations which, in turn, may be associated with AD risk[61,69]

Cholesterol may play an important role in AD. Specifically, cholesterol may have a key role in Aβ production and deposition. Interestingly, a number of cohort studies that measured total blood cholesterol in mid-life found that participants with higher levels of total cholesterol or hypercholesterolemia had an increased risk of developing dementia in late-life compared with the participants who had normal or low cholesterol levels[61].

Moreover, it can be challenging to get the appropriate intake of EPA and DHA through diet alone, even though EPA and DHA are produced by water plants and are prevalent in marine animals. This low intake of dietary EPA and DHA is thought to be associated with increased inflammatory processes as well as increased risk of dementia and development of AD[63].

The omega-3 PUFAs supplements may become an alternative source for the dietary omega-3 PUFAs balance and health promotion[70]. Thus, the role of omega-3 supplementation in improving cognitive function has recently become a clinical focus[70] and there have been many studies conducted regarding the use of omega-3 PUFAs supplementation and AD[63]. Although the results from studies seem to be promising, there are conflicting data[64]. Several of these studies have found confounders such as apolipoprotein E allele status and omega-6 intake that have limited the reliability of studies across cohorts. Several studies have demonstrated a lack of association of omega-3 supplementation on a background of a diet high in omega-6 fatty acids, which act similarly to saturated fatty acids decreasing membrane fluidity in opposition to the effects of omega-3 PUFAs. These data suggest that nutritional benefit may be overcome or canceled in the presence of negative dietary contributions. It is intriguing that the dramatic increase in the prevalence of AD over the last century not only parallels the increase in average lifespan, but also an increase from 2 to more than 20 of the ratio of omega-6 to omega-3 PUFAs in the average Western diet.

Furthermore, most of the data obtained with DHA are on dementia prevention. The evidence for the use of DHA in the treatment of patients with already clinically diagnosed dementia is less promising[65]. Supplementation may improve cognitive functioning in patients with very mild AD[63] but, generally, several clinical trials have failed to demonstrate that DHA supplementation is effective in the treatment of AD[65,71,72].

The beneficial effect of omega-3 PUFAs on noncommunicable diseases may be attributed to direct actions on plasma membranes, inflammatory responses, antioxidant system and gene expression. The membrane effects appear to be related to alterations in the biophysical properties of the cell membranes and modulation of phosphatidylserine (PS), a kind of phospholipid that accounts for 13-15% of the phospholipids in the human cerebral cortex. Further, EPA and DHA are the precursors of anti-inflammatory resolvins such as the neuroprotectin D1 (NPD1), which appears to be a major bioactive effector in neuronal tissues. DHA and NPD1 inhibit pro-apoptotic proteins and enhance apoptotic ones by up-regulating anti-apoptotic genes. DHA also influences ion channels and enhances endogenous antioxidant systems (figure 3)[62,66,73,74].

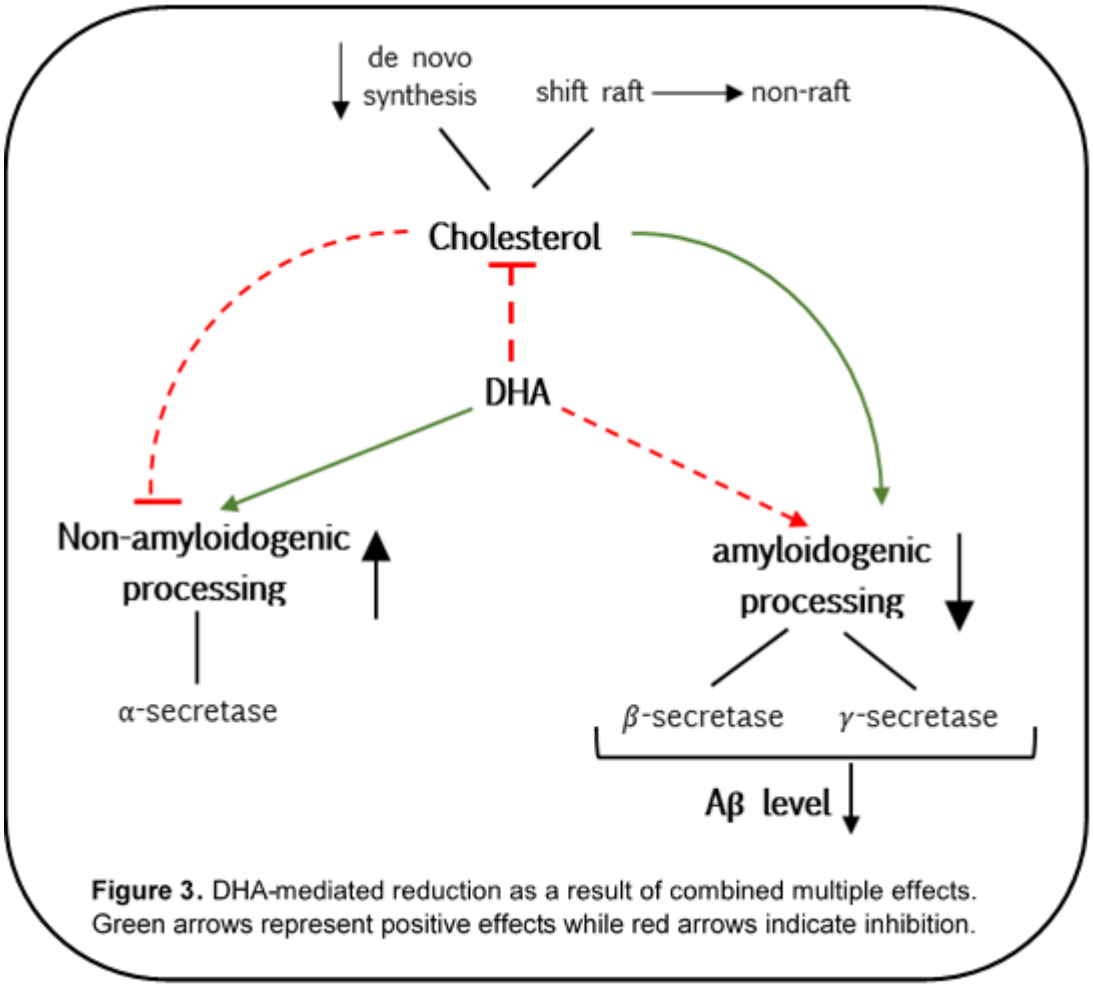

Figure 3. DHA-mediated reduction as a result of combined multiple effects. Green arrows represent positive effects while red arrows indicate inhibition.

Moreover, it suppresses amyloidogenesis by inhibiting the generation of Aβ peptides. This DHA-mediated Aβ reduction is not the consequence of a single major mechanism but is the result of combined multiple effects: DHA decreases β- and γ-secretase activity and increases α-secretase activity, resulting an increased non-amyloidogenic processing in parallel to reduced amyloidogenic processing (figure 4). DHA also decreases cholesterol production and exclude cholesterol from the lipid raft micro-domains of cellular membranes. This is of particular interest because, as mentioned above, cholesterol affect Aβ generation, and because in the brains of AD patients, highly ordered membrane lipids rafts have been found with increased levels of cholesterol[72,75].

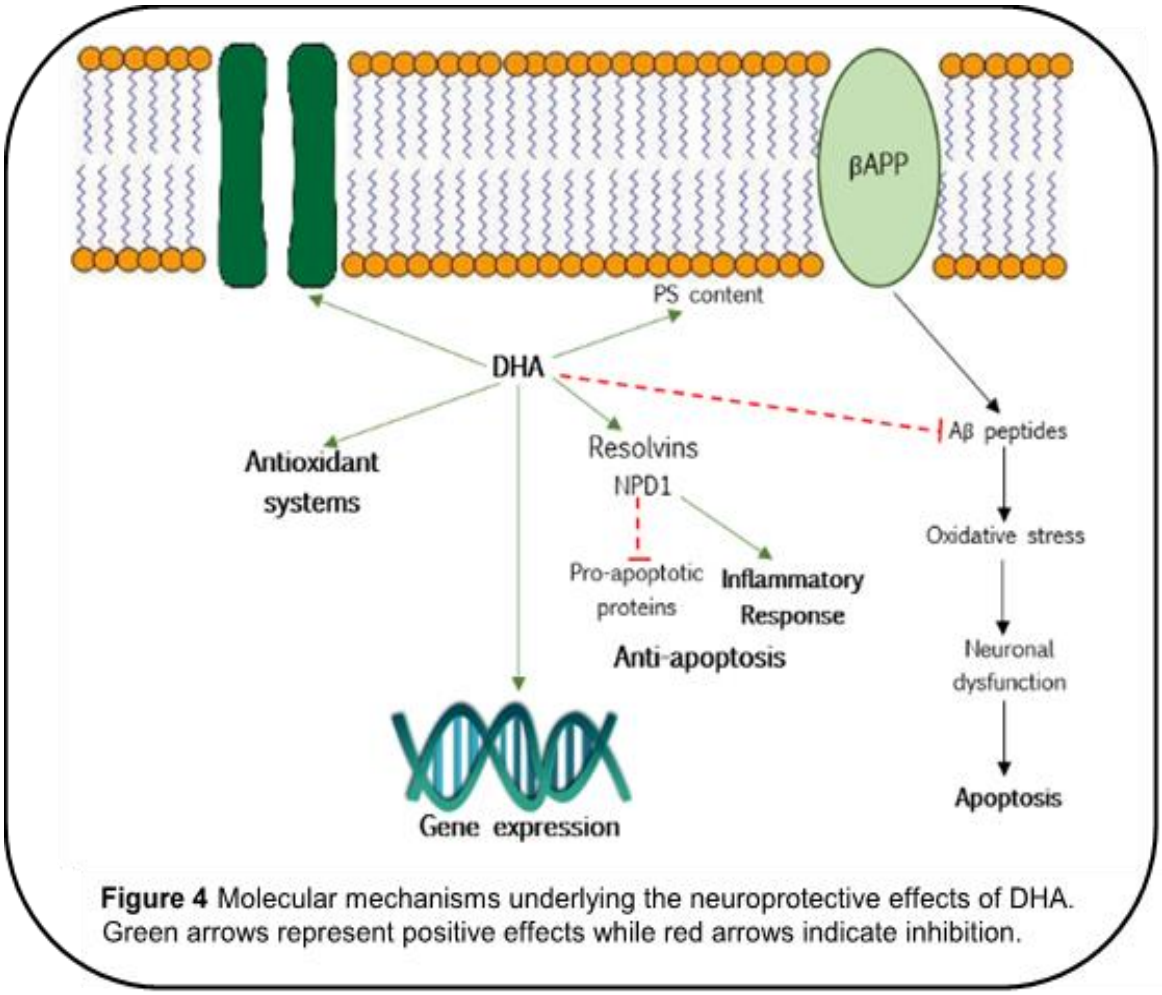

Figure 4 Molecular mechanisms underlying the neuroprotective effects of DHA. Green arrows represent positive effects while red arrows indicate inhibition.

Despite this findings, the possible mechanism relevant to them clinical cognitive benefits of omega-3 PUFAs remains unclear[70]. We hypothesized that omega-3 PUFAs may exert his protective effect on AD through the improvement of T2DM. As we did with resveratrol, in order to know the feasibility of this theory we want to summarize the existent evidences linking omega-3 PUFAs and T2DM.

There is increasing evidence suggesting that dietary omega-3 PUFAs, may improve insulin sensitivity or reduce the incidence of T2DM[76]. Rodent studies have shown that supplementation with fish oil, reverse insulin resistance, impair glucose homeostasis and produce lower blood sugar levels[76,77,78]. It has also been demonstrated that the replacement of only 6 % ALA in the high fat diet for EPA and DHA protect the animals against the development of insulin resistance and lower plasma concentrations of insulin. A review conducted on 2014 about the effect of omega-3 on glucose homeostasis and insulin sensivity concludes that omega-3 has beneficial effects on insulin sensitivity and glucose tolerance, metabolic flexibility to carbohydrates, lipid metabolism and obesity[78].

Despite the beneficial effects of omega-3 PUFAs documented on animal experiments, human intervention trials have yielded inconclusive results[76,78], suggesting that the situation in humans is more complicated and that omega-3 PUFAs effects may depend on disease progression, age of subjects and other variables[78]. In a meta-analisis of 16 prospective studies, neither EPA+DHA nor fish/seafood intake have significant associations with risk of T2DM overall[79]. In accordance with this, a systematic review that included 11 randomized controlled trials and 618 participants showed that omega-3 PUFAs supplementation did not influence insulin sensitivity[76]. However, the individual trials were highly heterogeneous, including participants with and without T2DM, utilizing a wide range of omega-3 PUFAs doses, as well as adopting a range of treatment and control oils[76]. Other meta-analysis showed that in people with types 1 and 2 diabetes supplied with omega-3 PUFAs, fasting plasma glucose and HbA1c were not modified[80] and a review conducted on Rovira y Virgili University says that fatty acids have not been shown to help restore insulin activity in humans[81].

Notwithstanding, recently there is growing and promising evidence supporting the beneficial role of omega-3 PUFAs on T2DM and related conditions in humans. A majority of association studies analyzing dietary intake or plasma levels of omega-3 PUFAs, and metabolic parameters in various populations confirm that, in the long term, omega-3 PUFAs have a beneficial effect[78]. These results are in agreement with the findings of another large prospective cohort study concluded in 2013, which showed a long term lower risk of T2DM in older men with high plasma EPA+DHA levels[78]. Population studies have also suggested that a diet high in omega-3 PUFAs may improve glucose tolerance and insulin sensivity in

nondiabetics, especially in elderly persons. In addition, levels of adiponectin, a factor associated with reduced inflammation and improved insulin sensitivity, trended higher[77]. Most of the cross-sectional studies in healthy populations, as well as intervention studies in people with metabolic syndrome, document that omega-3 PUFAs could prevent development of T2DM and ameliorate disorders of glucose homeostasis[78]. Emerging evidence indicates that omega-3 PUFAs may improve insulin secretion from pancreatic β-cells under the conditions of diabetes, but the mechanism is largely unknown[80].

In summary, in spite of the negative results observed in many clinical studies, namely EPA and DHA have been shown to exert numerous beneficial effects on health and should be increasingly used in the prevention of T2DM. Because of that, since T2DM significantly and independently increase the risk of neurodegeneration and are therefore risk factors in the development of AD, omega-3 PUFAs may protect against AD by reducing the development of T2DM. Studies with larger number of subjects and of longer duration will be required to further investigate the effects of omega-3 PUFAs intake on T2DM and its related conditions[76,78,82].

POTENTIAL MECHANISM LINKING T2DM AND ITS RELATED CONDITIONS TO AD

AD and T2DM are both more prevalent with ageing, but it has generally been assumed that this is coincidental, not a reflection of co-morbidity. However, as we have been discussing throughout this review, numerous epidemiological studies and some pharmacological clinical trials show the close connection between AD and T2DM and thereby, shed more light into the existence of possible similar pathogenic mechanisms between these two diseases These events may have a causal role in the pathogenesis of the two diseases[83,84].

C-Jun N-terminal kinases (JNKs), a family of protein kinases, play a crucial role in the regulation of systemic glucose and lipid metabolism by modulating hormones involved in growth and energy homeostasis[85,86]. JNKs has been implicated in the pathogenesis of metabolic syndrome and T2DM, and the inhibition of JNK signaling in the central nervous system could act as a negative regulator of central insulin sensitivity[85].

JNK has also received considerable attention in the context of neurodegenerative diseases. Recent studies have demonstrated the activation of the JNK signaling cascade in neurons in experimental models of neurodegeneration, suggesting its possible role in the processes of neuronal loss. In fact, JNKs is highly expressed and activated in brain tissue and cerebrospinal fluid from patients with AD and statistically correlated with the rate of cognitive decline[86]. Moreover, Aβ may also contribute to JNK activation, which in turn, results in neuroinflammationn and neurodegeneration[85,86]. Genetic depletion of JNK3 in transgenic AD mice resulted in a dramatic reduction in Aβ peptide levels and overall plaque loads as well as in an increased number of neurons and improved cognition[86]. Thus, the apparent relationship between insulin resistance, AD, and diabetes may be partially explained by perturbations in JNK signaling (figure 5)[85].

Interestingly, some studies suggest that both resveratrol and omega-3 PUFAs are able to modulate or inhibit the activity of JNKs [86,87,88].

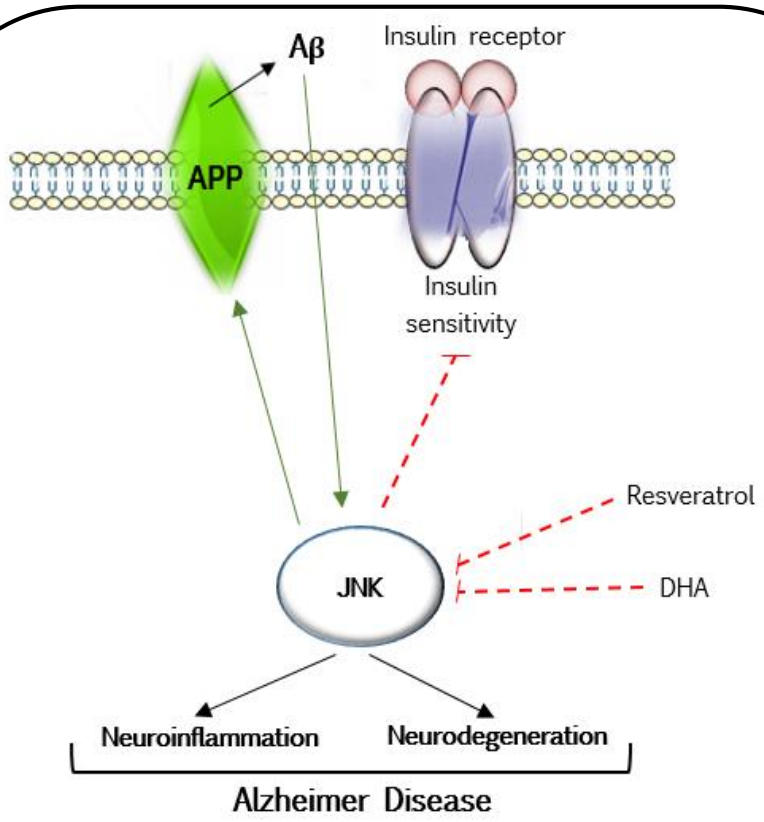

Figure 5 Graphic representation of the possible link between T2DM and AD. Green arrows represent positive effects while red arrows indicate inhibition.

Because of that, while the mechanisms by which resveratrol and omega-3 PUFAs affects positively on AD remains unclear, we postulate that maybe both of them exert its beneficial effects improving T2DM and its related conditions through JNKs inhibition.

CONCLUSION

Sporadic AD is the leading cause of dementia above the age of 65 years and its prevalence is expected to increase exponentially in the coming years. Despite its enormous impact on social and economic level, the pathological mechanism involved in the onset and development of the disease is still not known. Until now, the most widespread hypothesis has been the "Aβ cascade" hypothesis, although in recent years is growing the idea that sporadic AD represents a neuroendocrine disorder that resembles a unique form of T2DM accompanied by neurodegeneration, which is sometimes considered type 3 diabetes.

Currently, neither it has found a drug treatment to cure AD. However, there is increasing interest in certain dietary factors as possible preventive strategies. In this direction, resveratrol and omega-3 PUFAs present in wine and oily fish respectively, have been the subject of much research in both animals and humans to determine their effect on AD. Current evidence supports the preventive effect of these two components and even a beneficial effect on mild disease states. Despite the existence of a large number of hypotheses and proposals, the mechanism through which they exert their neuroprotective action has not yet been clarified.

Because the scientific reports also supports the beneficial effect of resveratrol and omega-3 PUFAs on T2DM, which in turn are linked to AD, it seems logic to hypothesize that both of them prevent AD improving T2DM and its related conditions.

Based on the evidence discussed in this article, it appears possible that in the near future we might consider employing dietary intervention in preventative and possibly therapeutic strategies for AD. It appears to be an innovative and safe approach that may be extremely cost effective, allow ease of administration, and importantly, serve as a socially acceptable intervention or adjunctive approach in the prevention and treatment of AD.

ABBREVIATIONS

Aβ: Amyloid β

AβPP: Amyloid β precursor protein

AD: Alzheimer disease

ALA: ∝-linolenic acid

ATP: Adenosine triphosphate

CR: Caloric restriction

CVD: Cardiovascular disease

DHA: Docosahexanoic acid

EPA: Eicosapentanoic acid

GLUT4: Glucose Transporter Type 4

HbA1c: Hemoglobin glycosilated

IDE: Insulin-Degrading Enzyme

JNKs: C-Jun N-terminal kinases

MD: Mediterranean diet

NAD+: Nicotinamide Adenine Dinucleotide

NFkβ: Nuclear Factor kappa β

NFTs: Neurofibrillary tangles

NPD1: Neuroprotectin D1

PS: Phosphatidylserine

PS1: Presenilin-1

PS2: Presenilin-2

PUFAs: Polyunsaturated fatty acids

ROS: Reactive oxygen species

SIRT1: Sirtuin-1

T2DM: Type 2 diabetes mellitus

TNF-∝: Tumor necrosis factor-∝

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