Nutritional approaches to modulate oxidative stress that induce Alzheimer’s disease. Nutritional approaches to prevent Alzheimer’s disease

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Abstract

Alzheimer’s disease is the most common cause of dementia in the world; symptoms first appear after age 65 and have a progressive evolution. Expecting an increase on its incidence and knowing there is currently no cure for Alzheimer’s disease, it is a necessity to prevent progression. The change in diet due to globalization may explain the growth of the incidence in places such as Japan and Mediterranean countries, which used to have fewer incidences. There is a direct correlation between disease progression and the increased intake of alcohol, saturated fats, and red meat. Therefore, we find obesity and higher serum levels in cholesterol due to saturated fat as a result. A way to decrease the progression of Alzheimer’s is through a diet rich in polyphenols (potent antioxidants), unsaturated fats (monounsaturated and polyunsaturated), fish, vegetable fat, fruits with low glycemic index, and a moderate consumption of red wine. Through this potent antioxidant diet we accomplish the prevention of dementia and the progression of Alzheimer’s disease. This article emphasizes the food and other components that have been demonstrated to decrease the oxidative stress related to these progressive diseases.

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Introduction

Alzheimer’s disease (AD) is the main cause of dementia in the world. It is a neurological progressive disease and the most important degenerative disease, more common than Parkinson. It has generated a series of problems for society, since, currently, 35 million people have it and this number of patients is expected to be doubled by the year 2030, and tripled by 2050. It is more common for American-Africans to suffer from this disease than for Hispanics and Caucasians. There is no cure as yet, since physiologically the brain starts deteriorating in old age; different approaches have been tried searching for some alternatives for its prevention.

AD was described by Alois Alzheimer in 1906, and its main symptoms are loss of memory and anterograde amnesia. These symptoms usually start after the age of 65 years. Clinically, AD is characterized by a progressive loss of memory, deterioration of all mental functions, loss of speech, disorientation and walking problems; hallucinations, hypokinesia, rigor and tremors can also be observed.
The disease can be genetic or produced by inappropriate folding of a β-amyloid (βA) peptide, due to cleavage of the amyloid precursor protein (APP) by three enzymes, α, β, and γ-secretase, which create βA peptide extracellular senile plaques and hyperphosphorylation of the tau protein, which in turn produces intracellular neurofibrillary tangles; especially, these accumulations create toxic substances against neurons gathering in the hippocampal region. This protein tau hyperphosphorylation is caused by overexpression of the enzyme glycogen synthase kinase-3 (GSK-3). Recent studies show that the hippocampus is one of the parts of the brain where recent memory develops and the one suffering more damage due to neuronal apoptosis, which results in the onset of the AD symptoms.

βA peptides are the principal molecules related to AD pathogenesis and, in general, to neurodegenerative diseases and to the production of neurotoxicity. Although the precise molecular mechanisms are not yet fully elucidated, a body of evidence points at actions by reactive oxygen species, which are produced by the effect of βA soluble oligomers at nanomolar concentrations. Oxidative stress resulting from this reaction is considered to be the mediator and trigger of a cascade of degenerative and inflammatory events in this and other neurodegenerative diseases.

Recent epidemiological studies indicate that dietary habits associated with a diet based on antioxidants hinder oxidative stress, which can prevent the incidence of neurodegenerative diseases such as Alzheimer or Parkinson. Recently, different research articles have demonstrated the neuroprotective effects of phenols due to their action as potent antioxidants.

Therefore, different phytochemicals are being studied, such as carnosic acid (CA), curcumin, catechin and resveratrol, which, according to recent publications, have antioxidant neuroprotective effects and inhibit βA buildup. Different hormones, such as melatonin, corticosteroids and estradiol have also been reported to act as neuroprotective antioxidants. The onset of this disease results from βA buildups, which subsequently create neurofibrillary tangles made up by hyperphosphorylated tau protein; therefore, all the compounds that will be later mentioned inhibit both these abnormal buildups.

### Nutrition and risk for developing AD

A healthy diet, cognition-stimulating activities and constant physical activities reduce the risk for suffering from AD. Conversely, diabetes, apolipoprotein E (APO-4), smoking and depression are associated with increased progression of AD.

Recently, evidence indicating that nutrition plays an important role in preventing the progression of this disease has increased. Epidemiological studies compellingly suggest that diet can be a modifiable factor among the risk factors for AD. A diet rich in antioxidants, vitamin B, polyphenols, polyunsaturated and monounsaturated fatty acids is beneficial against AD, and their consumption is achieved by ingesting fish, fruits, vegetables, coffee and red wine. Therefore, adhering to a healthy diet such as the Japanese and the Mediterranean is associated with lower risk for suffering from AD. On the other hand, the Western diet, which is based on higher consumption of saturated fatty acids, high caloric intake and excess of alcoholic beverages, increases the risk of suffering from this incurable and progressive disease (Table 1).

### Fish

According to recent epidemiological studies, consumption of fish reduces the risk of suffering from AD, especially among patients lacking APOE-4, due to the eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids it contains; when subjects consumed fish more than once a week, the risk decreased by 60%, as compared with subjects who never ate fish.

### Fruits and vegetables

People who consume fruit and vegetables regularly have been compared with others who don’t, and benefit and a decrease in the risk of AD have been found in consumers; this may be due to the fact that fruit and vegetables are a source of antioxidants and bioactive compounds, as well as to their low contents of saturated fat.

Strong protection against AD has been demonstrated for the consumption of vegetables, especially those with green leaves, which contain vitamin E. The consumption of certain grains related to the Mediterranean diet has also been proven useful.

### Green tea

Observational studies suggest that green tea decreases the risk for cognitive problems. Polyphenols in green tea inhibit cognitive problems by modulating oxidative stress. Additionally, it has been shown to possess a potent antioxidant, epigallocatechin-3-gallate (EGCG), which reduces the generation
Table 1. Antioxidants

<table>
<thead>
<tr>
<th>Antioxidant diet</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>Contains omega-3 fatty acids, EPA and DHA</td>
</tr>
<tr>
<td></td>
<td>Consumption &gt; 2 times per week reduces the risk for AD by 60%</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>Low saturated fat contents</td>
</tr>
<tr>
<td></td>
<td>Green leaf vegetables contain vitamin E</td>
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</tbody>
</table>

Phytochemicals

<table>
<thead>
<tr>
<th>Polyphenols</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranberries</td>
<td>Increase cAMP</td>
</tr>
<tr>
<td></td>
<td>Improve synaptic transmission</td>
</tr>
<tr>
<td></td>
<td>Reduce βA toxicity</td>
</tr>
<tr>
<td>Turmeric curcumin</td>
<td>Inhibits βA formation</td>
</tr>
<tr>
<td></td>
<td>Promotes fibrillary and neurofibrillary tangles degradation</td>
</tr>
<tr>
<td></td>
<td>Inhibits APP</td>
</tr>
<tr>
<td>Tea catechines</td>
<td>Modulate oxidative stress</td>
</tr>
<tr>
<td></td>
<td>Increase SOD enzyme activity</td>
</tr>
<tr>
<td></td>
<td>Modulate the α-secretase, β-secretase and γ-secretase enzymes</td>
</tr>
<tr>
<td></td>
<td>EGCG reduces the generation of βA and tau isoforms</td>
</tr>
<tr>
<td>• Resveratol from grapes</td>
<td>Promotes βA intracellular buildup elimination</td>
</tr>
<tr>
<td></td>
<td>Activates proteasomal neurotoxic degradation</td>
</tr>
<tr>
<td></td>
<td>Decreases plaque formation</td>
</tr>
<tr>
<td></td>
<td>Protects from βA-induced neurotoxicity</td>
</tr>
<tr>
<td>• Peanuts</td>
<td>Elevate cAMP</td>
</tr>
<tr>
<td></td>
<td>Improve synaptic transmission</td>
</tr>
<tr>
<td></td>
<td>Reduce βA toxicity</td>
</tr>
<tr>
<td>CA</td>
<td>Increases α-secretase enzyme ADAM17 and ADAM10</td>
</tr>
<tr>
<td></td>
<td>Prevents neuronal apoptosis and degradation</td>
</tr>
<tr>
<td></td>
<td>Suppresses βA production</td>
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Hormones

<table>
<thead>
<tr>
<th>Melatonin</th>
<th>Effect</th>
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<tbody>
<tr>
<td></td>
<td>Protects the cholinergic system</td>
</tr>
<tr>
<td></td>
<td>Has an anti-inflammatory effect</td>
</tr>
<tr>
<td></td>
<td>Inhibits βA fibrillary generation and formation</td>
</tr>
<tr>
<td></td>
<td>Inhibits protein tau hyperphosphorylation</td>
</tr>
<tr>
<td></td>
<td>Has great capacity to capture free radicals</td>
</tr>
<tr>
<td></td>
<td>Inhibits βA precursor protein</td>
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<tr>
<td></td>
<td>Activates protein kinase C</td>
</tr>
<tr>
<td></td>
<td>Inhibits the GSK-3 enzyme</td>
</tr>
<tr>
<td>Estradiol, estrogen and progesterone</td>
<td>Inhibit APP proteolysis</td>
</tr>
<tr>
<td></td>
<td>Prevent the formation of βA</td>
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<tr>
<td></td>
<td>Improve neuronal functioning and elasticity</td>
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<tr>
<td></td>
<td>Protect neurons from cell apoptosis</td>
</tr>
<tr>
<td></td>
<td>Prevent senile plaques and neurofibrillary tangles accumulation</td>
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</tbody>
</table>

of βA and tau isoforms in animal models. Therefore, consumption of green tea can be considered for the prevention of AD43.

Alcoholic beverages

Epidemiological studies have suggested that moderate consumption of alcoholic beverages reduces the risk for developing AD, but high consumption is associated with increased risk. Different beverages yield different results: red wine, for example, contains high levels of resveratrol and other polyphenols that, since they are potent antioxidants, decrease plaque formation and protect against βA-induced neurotoxicity44.

Phytochemicals

Food polyphenols

Polyphenols, which include green and white tea, are neuroprotective against AD; their anti-βA action has been demonstrated, especially in grape polyphenols.
The antioxidant potential of polyphenols obtained from the diet (anthocyanins from cranberries, catechins from tea, curcumin from turmeric, resveratrol from grapes and peanuts) has neuroprotective effects that have been demonstrated in preclinical models. The capability of polyphenols to improve synaptic transmission by elevating cyclic adenosine monophosphate (cAMP), by targeting several signaling pathways and reducing βA toxicity, suggests their therapeutic utility against diseases related to age, such as AD and dementia. 

CA

A member of the phenolic compounds family, CA is a diterpene with the formula C_{20}H_{28}O_{4} that is found in Salvia officinalis and Rosmarinus officinalis. It is known to act as an antioxidant against Staphylococcus aureus and has been found to have anti-cancer effects that mainly prevent the proliferation of some malignant cells.

CA is a potent antioxidant with neuroprotective effect, which prevents neuronal apoptosis and degradation. The treatment with CA suppresses the production of βA and, therefore, increases the expression of messenger RNA (mRNA) of the α-secretase tumor necrosis factor-alpha-converting enzyme (TACE), better known as ADAM17, and α-secretase ADAM10, with no changes in β-secretase (BACE1), and, therefore, it doesn’t promote it, thus avoiding βA generation. CA was tested in the University of Teheran of Medical Sciences in an experiment with ill transgenic rats, which were divided into two groups: surgery with CA and no surgery with CA, each one with a corresponding control group. The CA was dissolved in dimethyl sulfoxide and stored at −20 ºC; then, 10 mg/kg were intraperitoneally injected. CA was a potent antioxidant that can be administered orally, but due to its low bioavailability, it is inadequate in aqueous solutions; therefore, it has been modified and formulated in high concentrations of cyclodextrin, in order to improve it and to enable its availability in aqueous solutions.

In order to observe the prevalence of amyloid plaque, experiments were conducted with mice, which were injected in the tail with a 0.1 ml solution of curcumin and cyclodextrin solubilized in 4 mM until they were 4 months of age. Injections were resumed at 10 months with 6 mM, and during the last six weeks the animals were injected twice-weekly with 24 nM. Twice-weekly-injected mice developed 70% less amyloid plaques than the control group.

Catechin (EGCG)

It is a phenolic compound, originating from green tea, with potent capacity to capture free radicals, which is attributed to the presence of a trihydroxy group in the B-ring. EGCG increases the activity of the superoxide dismutase (SOD) enzyme that protects neurons, thus decreasing their oxidative stress and a glutathione (GSH) cluster owing to the γ-glutamylcysteine ligase mRNA, therefore providing protection to the neurone against βA cytotoxic substances. On the other hand, it is able to modulate the α-secretase, β-secretase and γ-secretase enzymes involved in the APP processing, since βA is synthesized from it. In particular, catechin inhibits βA fibrinogenesis and prevents the formation of substances that are toxic to neurons. Furthermore, the compound improves spatial memory and prevents the development of AD.

In a recent experiment performed with two groups of transgenic mice with the disease, catechin (20 mg/kg) was applied to one group by intraperitoneal injection and orally to the other in a solution with water (50 mg/kg). When the experiment was concluded at six months, both groups were found to have reduced senile plaques by more than 50%, but the intraperitoneal injection attenuated cerebral βA and improved the cognitive function. It should be noted that high concentrations of this antioxidant are associated with neuronal apoptosis and hippocampal degeneration. This evidence suggests that green tea catechin can be used to prevent the development of AD.

Curcumin

Extracted from the turmeric plant, it is a yellow colo- rant with great affinity for βA fibrils and hence it binds in the enol form. Curcumin inhibits βA formation and promotes fibrils and neurofibrillary tangles degradation. Additionally, direct interaction with βA is captured by macrophages, which affects APP maturation and the enzymes for its processing. Curumin is a potent antioxidant that can be administered orally, but due to its low bioavailability, it is inadequate in aqueous solutions; therefore, it has been modified and formulated in high concentrations of cyclodextrin, in order to improve it and to enable its availability in aqueous solutions.

Resveratrol

It is a phenol found in grapes. Resveratrol modulates different systems that protect and favor neuronal cells
neuroprotective functions. There are studies that show that the primary objective of resveratrol is the central nervous system, since it is able to cross the blood-brain barrier. Nevertheless, its bioavailability is low, since it is quickly metabolized. In an experiment with mice that were administered 0.5 µl/min in the right ventricle and then injected βA for 7 days, at the end, resveratrol was shown to have reduced neurodegeneration through the SIRT1 deacetylase enzyme. Therefore, resveratrol activates SIRT1 and is able to protect against oxidative stress exerted by βA buildups on neurons. Consequently, it promotes βA intracellular buildup elimination by activating proteasomal neurotoxic degradation. SIRT1 overexpression reduces AD pathogenesis, since it prevents the synthesis of βA from APP. Finally, resveratrol disrupts βA hydrogens and, by getting adhered, it prevents the formation of fibrils and destabilizes those already existing. The best administration route for this phytochemical is by injection, due to its bioavailability, since resveratrol regulates some enzymes, such as SOD and chloramphenicol acetyltransferase. The above mentioned studies demonstrate that resveratrol modulates AD pathogenesis. Moreover, since it is quickly metabolized. In an experiment with mice that were administered 0.5 µl/min in the right ventricle and then injected βA for 7 days, at the end, resveratrol was shown to have reduced neurodegeneration through the SIRT1 deacetylase enzyme. Therefore, resveratrol activates SIRT1 and is able to prevent the βA buildups on neurons. Consequently, it promotes βA intracellular buildup elimination by activating proteasomal neurotoxic degradation. SIRT1 overexpression reduces AD pathogenesis, since it prevents the synthesis of βA from APP. Finally, resveratrol disrupts βA hydrogens and, by getting adhered, it prevents the formation of fibrils and destabilizes those already existing. 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The best administration route for this phytochemical is by injection, due to its bioavailability, since resveratrol regulates some enzymes, such as SOD and chloramphenicol acetyltransferase. The above mentioned studies demonstrate that resveratrol modulates AD pathogenesis.
testosterone was found to be lower in men with AD than in the control group; this way, a positive correlation between testosterone levels and cognition was demonstrated. This confirms that individuals with hypogonadism are more prone to the development of AD because testosterone levels decrease and, consequently, luteinizing hormone levels rise and this produces a βA increase.33,41-48,52-57.

Conclusions

From the new discoveries on AD, it can be concluded that oxidative stress is the triggering factor of the disease. Therefore, nutrients with large phenolic contents are potent antioxidants and extremely important, since they might prevent the progression of this chronic and degenerative disease. Currently, life expectancy is increasingly longer owing to the advances in medicine and biotechnology and, consequently, this neuro-pathology represents a challenge due to the large numbers of geriatric patients we will be facing in the near future. AD is an incurable disease; the patient progresses from cognitive deficit to dementia until he/she requires sedation with permanent medical care and support. Antioxidant phytochemicals and hormones, owing to their high anti-inflammatory capacity, prevent oxidative stress in the patient. It is vitally important to improve dietary habits in order to prevent this disease, since epidemiologists claim that AD will be the pandemic of 21st century, as it is the 6th cause of death worldwide.

References

H. Herman Lara, et al.: Nutritional approaches to modulate oxidative stress that induce Alzheimer’s disease