Special bioactive compounds and functional foods may exhibit neuroprotective effects in patients with dementia (Review)

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Abstract. Dementia is a failure of cognitive ability characterized by severe neurodegeneration in select neural systems, and Alzheimer's disease (AD) is the most common type of neurodegenerative disease. Although numerous studies have provided insights into the pathogenesis of AD, the underlying signaling and molecular pathways mediating the progressive decline of cognitive function remain poorly understood. Recent progress in molecular biology has provided an improved understanding of the importance of molecular pathogenesis of AD, and has proposed an association between DNA repair mechanisms and AD. In particular, the fundamental roles of phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and breast cancer gene 1 (BRCA1) tumor suppressors have been shown to regulate the pathogenesis of neurodegeneration. Consequently, onset of neurodegenerative diseases may be deferred with the use of dietary neuroprotective agents which alter the signaling mediated by the aforementioned tumor suppressors. In a healthy neuron, homeostasis of key intracellular molecules is of great importance, and preventing neuronal apoptosis is one of the primary goals of treatments designed for dementia-associated diseases. In the present review, progress into the understanding of dietary regulation for preventing or limiting development of dementia is discussed with a focus on the modulatory roles of PTEN and BRCA1 signaling.

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1. Introduction

Dementia is a failure of cognitive abilities characterized by severe neurodegeneration in selective neural systems, and the incidence of dementia is predicted to increase significantly within 20 years (1). Dementia is one of the most significant health burdens, and, at present, there are no suitable disease-modifying agents for treatment of progressive dementia. Alzheimer's disease (AD) is the most common form of dementia, and is the most significant health-concern worldwide (2). Pathologically, AD is a slowly progressing neurodegenerative disorder categorized by severe damage of neurons and synapses (3). Aberrations of amyloid-β peptide may be responsible for the neuro-synaptic malfunctions leading to cognitive deficits in AD (4). Genetic factors account for ~80% of the risk contributing to AD, while modifiable factors associated with lifestyle may also be involved (5). Epidemiological studies have suggested that nutrition is one of the most important yet modifiable risk factors of AD (6). Risk factors for vascular dementia, the second most common cause of dementia, include hypertension and metabolic syndrome, which are also modifiable lifestyle factors. Managing these non-genetic risk factors may provide effective opportunities to prevent the progressive cognitive decline.

Studies have shown that oxidative stress represents a major risk factor associated with the pathology of dementia (7,8). Substantial evidence has established that oxidative stress as an aspect in AD is associated with neuronal apoptosis and brain...
Interactions of ROS with amyloid-damage in the brain may inhibit or reduce the damage to neurons. Therefore, decreasing oxidative long-term potentiation in neurons which is prevented by treatment with antioxidants (19). Thus, increased oxidative stress may result in increased DNA damage, and subsequently apoptosis, which contributes to the degeneration of neuronal tissue. Detoxification of ROS and/or reduction of ROS levels may protect neurons from DNA damage and apoptosis. Since metabolic processes physiologically produce ROS, any means used to reduce ROS levels may assist in decreasing the prevalence and incidence of dementia. Cells possess machinery to retain genomic integrity in response to genotoxic damage. There is increasing evidence which supports the use of different antioxidants as a treatment for AD (11), including vitamins (12). In addition, dietary and nutritional approaches are of significant importance in the management of AD. Improving and altering nutrient intake may reduce the progression of chronic neurodegenerative diseases, an area which has recently been gaining increased interest (13), and nutritional plans are progressively being integrated into public health strategies (14). In the present review, the functions of key intra-cellular signaling molecules involved in oxidative genotoxic stress and DNA repair in neurons are summarized, offering a clarification on the molecular mechanisms for the treatment of dementia.

Specific attention is placed on the mechanisms underlying the neuroprotective effects of specific nutrients against dementia in reducing brain damage, which may be used as an efficient therapeutic intervention.

2. Role of ROS in the pathogenesis of dementia

In AD, significant molecular and biochemical changes result in an increase in amyloid-β substance, which is modified by ROS into a toxic product that promotes apoptosis of neurons (15), suggesting a link between progression of AD and oxidative stress. In cells, metabolic processes physiologically produce ROS that cause oxidative damage to DNA (16), and this physiological production of ROS is associated with aging of the brain and neurodegeneration. Under physiological conditions, ROS may act as a second messenger in cells (17). ROS controls several physiological processes, such as the hypoxic response and inflammation, as well as the regulation of growth factor signaling (18). Abnormal accumulation of amyloid-β inhibits long-term potentiation in neurons which is prevented by treatment with antioxidants (19). Therefore, decreasing oxidative damage in the brain may inhibit or reduce the damage to neurons. ROS may exert its effects on cells through the regulation of several target molecules, including PI3K/AKT/PTEN (20). Interactions of ROS with amyloid-β have been shown to prevent mitochondrial respiration (21). In addition, increased levels of ROS within the mitochondria of neurons may disturb synaptic plasticity, and thus memory formation/retention (22). Therefore, ensuring that ROS levels are maintained within physiological ranges may improve outcomes in patients with AD by preventing/reducing damage to neurons. Neurons exhibit considerably high levels of metabolic activity and use distinct oxidative damage-repair mechanisms to reverse DNA damage (23). Therefore, malfunctions of the DNA repair system in the brain may result in neurological dysfunction. Damaged DNA can be repaired by the DNA repair machinery, which consists of ataxia telangiectasia-mutated (ATM) and ATR, BRCA1, PTEN and others (24). Abnormalities in these molecules are often observed in patients with neurodegenerative diseases (25).

ROS are free radicals under physiological conditions. Hyperglycemia exacerbates the accumulation of ROS in neurons leading to increased apoptosis (26). Several environmental and lifestyle associated factors, including tobacco smoking, alcohol consumption, exposure to ionizing radiation, infections, inflammation and even the aging process may result in increased oxidative stress (27). In addition, in population studies, obese patients have been shown to possess significantly higher serum levels of ROS, suggesting that obesity may increase oxidative stress (28). High-intensity exercise increases oxidative damage and induces disruption of the blood-brain barrier (28). Exercising may upregulate the expression of endogenous antioxidants and thus reduce oxidative damage; however, vigorous exercise may result in the accumulation of ROS (29). Consistent exposure to oxidative stress is an initiator of various chronic diseases including degenerative disorders, diabetes, cardiovascular diseases and cancer. In general however, cells are able to correct damage to DNA as a result of oxidative stress to a certain extent.

3. PTEN and BRCA1 tumor suppressors participate in DNA repair initiated by oxidative DNA damage

PTEN is a tumor suppressor with dual-specificity phosphatase activity; protein phosphatase activity and lipid phosphatase activity, and antagonizes the activity of PI3K (30). Cells lacking PTEN have higher levels of PIP3 which activates downstream targets of PI3K/AKT. The PI3K/AKT signal regulates a variety of cellular events including proliferation, survival and apoptosis of cells (Fig. 1). PTEN is associated with the apoptotic cascade, which may be a result of its effect on decreasing PI3K/AKT signaling (31). In part, neuronal cell death may be attributed to the differences in PTEN expression (32). Inhibition of PTEN protects synaptic function and thus cognition in animal models of AD (33). Suppressing PTEN and/or increasing the activity of AKT reduces the levels of oxidative stress, and thus decreases cell death, suggesting that AKT activation may be required for neuroprotection. Thus, PTEN contributes to the defense mechanisms against severe oxidative damage in the brain. It has been shown that PTEN insufficiency results in an increase in mitochondrial activity, consistent with the activation of the AKT signaling pathway (34), and thus may increase the levels of ROS.

In addition to PTEN, BRCA1 serves an important role in the response to DNA damage (35). The PI3K/AKT signaling pathway has been shown to be constitutively activated in BRCA1-defective cells (35). BRCA1, is one of the best studied and prominent suppressors of breast cancer, mutations of which are associated with breast and/or ovarian cancer risk in addition to genetic susceptibility (36). BRCA1 exerts several effects on the DNA repair system (37). BRCA1-related hereditary cancer is a type of cancer with functional defects...
in the DNA repair mechanisms (38). Mutations of the BRCA1 gene are associated with increased genomic instability (30,31), which may increase the rate of accumulation of genetic mutations. The primary recognition molecule for DNA damage is ATM, which is the checkpoint kinase that phosphorylates a number of proteins including BRCA1 in response to DNA damage (39). Reduced levels of BRCA1 expression have been observed in the brains of patients with AD (40). Knocking down neuronal expression of BRCA1 results in an increased rate of DNA double-stranded breaks, synaptic plasticity impairments and memory deficits (40). Therefore, BRCA1 may support neuronal integrity and cognitive function by protecting the neuronal genome, and depletion of neuronal BRCA1 may result in cognitive deficits. Activation of the DNA repair system to protect neurons may occur during the early stages of neurodegeneration, as the impairment of BRCA1 accelerates disease progression (41). Oxidative damage to the DNA of neurons has been demonstrated to be a significant contributing factor in the development of dementia. BRCA1 reduces the production of ROS (42), which in-turn, results in decreased oxidative damage to the DNA (35). BRCA1 also supports the telomere, alterations of which may result in neurodegeneration (43). BRCA1 serves an important role in telomere maintenance, although the exact mechanisms remain unknown (43). Telomere length insufficiency is a typical feature of degenerating neurons in the brains of patients with dementia (44). Additionally, there may be an indirect association between PTEN and BRCA1 gene function (45). PTEN inhibition represses nuclear translocation of BRCA1, which impairs DNA repair resulting in an accumulation of DNA damage (46).

4. Certain dietary compounds exhibit neuroprotective effects by modulating PTEN and/or BRCA1 activity

Due to a lack of reliable treatment options, brain dysfunction and/or dementia is an increasing public health concern. A number of disease-protective factors, such as physical activity, sleep and dietary patterns, have been proposed by epidemiological research (47). Among these factors, dietary choices may exhibit certain neuroprotective effects. In particular, dietary choices may result in alterations to AKT/PTEN as well as BRCA1 signaling, and may prevent neurodegenerative diseases or reduce progression. Several plants and fruits are promising candidates for reducing the progression or risk of dementia diseases. An ingredient derived from the root of Curcuma longa, curcumin, present in culinary turmeric, may reverse the effects of dementia on memory (48). The neuroprotective effects of curcumin may be mediated through modification of the PI3K/AKT signaling pathway (49). Kaempferol is a flavanol present in several plants, including grapefruit and edible berries, which has been shown to demonstrate neuroprotective effects in a rat animal model (50), and Kaempferol protects neurons through activation of AKT signaling (51). A neuroprotective ingredient of a Chinese medicinal herb, Herba epimedii, Icariin, reduces PTEN expression following activation of PI3K/AKT signaling (52). Furthermore, certain components of rosemary herb prevent the expression of PTEN in K562 myeloid cells (53). In contrast to this, the expression levels of PTEN are increased following treatment with Ginsenoside (54).
Fat soluble lycopene is a carotenoid with a red pigment found in several fruits and vegetables such as tomatoes. Treatment with the lycopene increased the mRNA expression levels of BRCA1 (55). In addition, lycopene increases phosphorylation of BRCA1 in breast cancer cells (56). Treatment with phytoestrogens result in higher expression levels of BRCA1 by reversing DNA hypermethylation (57), and individuals with phytoestrogen-rich diets possessed increased expression levels of BRCA1 mRNA (58). Rats exposed to genistein showed higher expression levels of BRCA1 in the mammary glands (59). Genistein and indole-3-carbinol are biochemicals derived from soy and green vegetables, respectively. These phytoestrogens have been shown to reduce the risk of AD progression (60). Furthermore, gallic acid, a phenolic compound present in natural plants, increases the phosphorylation of BRCA1 (61).

The aforementioned potential compounds found in foodstuffs which may exhibit neuroprotective effects, predominantly do so by exerting some sort of influence on tumor suppressor molecules, such as PTEN and BRCA1. Thus, PTEN and BRCA1 functions may be important for individual brain health (Fig. 2). As mentioned above, imbalances in the activity between PTEN and AKT may contribute to the pathogenesis of dementia. Therefore, appropriate activation and/or inhibition for maintaining the balance of kinases may be important (31). Certain food and/or dietary components may aid in maintaining the balance of these signaling molecules by modulating their functional activities (Fig. 3). Thus, future studies should focus on determining the most appropriate method of using these neuroprotective compounds identified in in vitro studies and animal models, and translating them to bedside therapeutics.

5. Dietary nutrients may reduce oxidative stress

Superoxide dismutases (SODs) exhibit robust antioxidant activity characterized by their ability to scavenge ROS (61). SODs catalyze the reaction of superoxide to hydrogen peroxide (62). As aberrantly increased ROS levels results in extensive oxidative DNA damage, SODs have been suggested to serve as a principal defense system against oxidative stress. There are three types of SODs that have been identified in humans, SOD1-3. Cytosolic SOD1 may serve a role in conjunction with Cu²⁺/Zn²⁺ ions in the prevention of central nervous system damage (63). Several mutations in the SOD1 gene are responsible for mitochondrial impairments, leading to progressive neurodegenerative diseases including familial amyotrophic lateral sclerosis (64). SOD1-null animals also develop other seemingly unrelated diseases, such as muscle atrophy (65). SOD2 is a functional tumor suppressor, and SOD2 expression has been reported to be significantly reduced in several tumors (65). SOD2 and Mn²⁺ ions are present in the matrix of the mitochondria, the primary site of free radical formation from the electron transport chain. ATP production in mitochondria is impaired in patients with AD (66). Therefore, the primary function of SOD2 may be to protect the mitochondria against oxidative damage. SOD3 and Cu²⁺/Zn²⁺ ions are secreted into the extracellular matrix and contribute to metabolic regulation of neurons by altering the rate of blood flow (67), and may be induced by chemical antioxidants such as vitamin C (68). Dietary intake of Cu²⁺ stabilizes SOD activity, indicating a potential therapeutic benefit (69). It has been suggested that inhibition of ROS by SODs decreases neuronal cell apoptosis, microglial cell activation, and disruption of the blood brain barrier, thus maintaining brain health (70). Active
aglycone-genistein inhibits ROS production by activating SODs (71). Lycopene also inhibits neuronal apoptosis by reducing ROS levels, and by improving mitochondrial function (72). Expression of SODs is dependent on the activity of peroxisome proliferator-activated receptors (73). Therefore, resveratrol analogs, which activates peroxisome proliferator-activated receptors, may increase the mRNA and protein expression levels of SODs (74). Furthermore, increased expression of SOD2 has been observed following administration of grape juice (75). The polyphenolic antioxidant, resveratrol, and calorie restriction may promote human longevity. Stevioside, a natural sweetener, may also increase the expression of SOD1-3 (76). In addition, butyrate, a short-chain fatty acid, increases the expression of SODs (77).

Antioxidant supplements may reduce cognitive decline. Vitamin C, vitamin E and the vitamin-like substance coenzyme Q10 have been used to treat patients with dementia with some efficacy (78), and the plasma levels of vitamin C have been found to be considerably lower in patients with AD (79). Decreased levels of plasma vitamin E are associated with an increased risk of neurodegenerative disorders (80). Vitamin E acts as a scavenger of free radicals (81), and thus, may exhibit a neuroprotective effect by scavenging ROS. In addition, ingestion of vitamin E is associated with an increase in the levels of SODs (80). Dietary omega-3 polyunsaturated fatty acid (PUFA) has been demonstrated to improve memory and learning processes (82). Long-term diets rich in omega-3 PUFA may lead to lower levels of DNA damage caused by oxidative stress (83). *Perilla frutescens* is a good source of the omega-3 PUFA. The perilla-diet promotes neuronal signaling and alters synaptic plasticity, improving learning and memory (84), possibly by enhancing intracellular SOD activity (85). Together, these studies support the hypothesis that SODs, as well as antioxidant vitamins, offer a certain degree of neural protection against dementia progression. However, the association between neuroprotection and nutrient consumption is a complex matter of study. Difficulties in the variabilities of human-diets makes this a challenging subject to research.

6. Conclusion

To maintain physiological cellular function, cells prevent against oxidative damage through the use of antioxidants. In neurons, excess oxidative stress may result in neuronal cell death and potentially dementia. In dementia, genomic DNA damage is a feature of the pathogenesis of neurodegeneration; however, DNA damage may be additionally explained by a lack of or improper DNA repair mechanisms. Therefore, increased production of ROS and/or alterations in BRCA1 and PTEN function concurrently suggest a neurodegenerative stimulus present in dementia. Several compounds in naturally occurring foodstuffs may exhibit neuroprotective effects, which may facilitate DNA repair or reduce ROS-production, and some of these neuroprotective compounds may form the basis of future potential therapeutic options for preventing or limiting the progression of dementia. Future therapeutic strategies should utilize the observation that defects in the key processes required for neuronal homeostasis, which results in unfavorable neuronal conditions, and this should represent a basis for the
development of dietary treatments for dementia. One aspect to consider is the difference between psychiatric illnesses and dementia. For treatment of psychiatric illnesses, it is important to maintain the levels of key intracellular molecules balanced (31). For dementia, it is also imperative to limit or prevent neuronal apoptosis (Fig. 3). However, both these aspects are important for keeping the brain functioning healthily.

Numerous neuroprotective factors have been suggested as potential targets for preventing or limiting neuronal apoptosis. For example, phytoestrogens may rescue neurons and glial cells from cell apoptosis by preventing oxidative stress. However, despite experimental interpretations based on in vitro and in vivo studies, the translational value of the neuroprotective compounds in the clinical setting remains to be determined. The potential therapeutic effects for preventing dementia should be more cautiously considered in clinical research (86). It may also be possible to use these compounds found in natural foodstuffs as an adjuvant alongside established treatment modalities. Further mechanistic studies are required to understand the detailed molecular mechanisms underlying the neuroprotective effects of the compounds highlighted in the present review. Additionally, clinical studies are required to determine their efficacy in humans.

In conclusion, ROS as well as PTEN and BRCA1 tumor suppressors may be involved in the pathogenesis of dementia and neuroprotective compounds found in certain diets may reduce or prevent dementia by reducing oxidative DNA damage.

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Authors' contributions

MM and SM conceived the subject of the review. MM, YI, YN, AT, YK and SM participated in writing and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
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