Review

The potential use of food therapy to modulate cognitive decline

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Abstract

The incidence of cognitive diseases such as Alzheimer's Dementia is expected to grow and the impacts of these diseases on wellbeing is drastic, therefore requires exploration of contributing factors for their development as well as investigation of potential therapies. Some of these are available in food sources and already available for clinical use. This literature review discusses some of the mechanisms of specific chemicals modulators that prevent neurogenerative decline (mainly polyphenols such as resveratrol, curcumin, flavonoids and EGCG) as well as oral health and food texture which may influence cognitive function.

The main findings are that polyphonic compounds are effective at reducing oxidative stress and, subsequently, Aβ plaque formation, a hallmark of Alzheimer's Dementia. Greater chewing force was related to reduction in stress hormones, depression and central nervous system changes.

Abbreviations

AD – Alzheimer's disease
APP – Amyloid precursor protein
EGCG – Epigallocatechin gallate
MDA – Malondialdehyde
NAD – Nicotinamide adenine dinucleotide
NAPP – N-terminal amyloid precursor protein
NMDA – N-methyl-D-aspartate
ROS – Reactive oxygen species
SGZ – Subgranular zone
SIRT – Sirtuins
SVZ – Subventricular zone

Introduction

Neurogenesis is the process of new neurons being formed in the brain. Previously, neurogenesis had been thought to have stopped in the adult brain but is now widely accepted to continue in adults.[1] Adult neurogenesis mainly occurs in the subventricular zone, subgranular zone and dentate gyrus of the hippocampus,[2] an area that functions to form and consolidate memories and makes up part of the limbic system which functions to influence mood. This area of the brain is majorly affected in Alzheimer's disease causing the symptoms of memory loss and depression, so protection of this area is vital to prevent instances and progression of the disease.[3] This article explores how altering diet may protect the hippocampus and the interactions between the food we eat and neurogenesis.

Methods

To investigate the potential use of food as a diagnostic and protective measure against cognitive decline, literature searches were carried out on PubMed and Google Scholar to specify dietary components that have been implicated in neurology, mainly their oxidative stress mitigation. Less researched areas, such as the effects of EGCG and chewing, were explored via citation chaining and Google Scholar. Articles included were chosen to cover a range of dietary factors, components and composition, to emphasise different elements of diet as well as research that already has clinical implications to further validate usage.

Results

The search initially found 14 articles, however, eight were removed as they were not specific to dietary content or hippocampal neurogenesis in adults.

Discussion

The role of oxidative stress in cognitive decline

One contributor to cognitive decline is oxidative stress which exerts its effects via a plethora of mechanisms.[4] One such mechanism is Aβ metal ion redox potential whereby metal ions such as zinc^{2+} and iron^{3+} bind to the ends of Aβ peptides producing high numbers of reactive oxygen species (ROS) and promoting pathological

plaque development. These ROS then produce a positive feedback loop of oxidation and ROS production, creating a self-sustaining environment in which neuronal cell death is imminent. This is partly because increases of ROS in the brain negatively affect the enzymes glutamine synthetase and creatine kinase[5] leading to damage to the brain. Glutamate synthetase reduces levels of glutamate in the brain however, when oxidised, the enzyme is unable to carry out its function causing a build-up of glutamate.[6] The higher level of glutamate activates NMDA receptors in the surrounding extra-synaptic region of the postsynaptic neuron which then overcome the protective measures of NMDA receptors in the synaptic region leading to excitotoxicity and eventual neuronal cell death.[7] Creatine kinase plays a key role in regulating ATP levels in neural cells therefore its oxidation, and subsequent damage, leads to reduced energy metabolism contributing to cell death. Therefore, oxidative stress and ROS production play major roles in the development of Alzheimer's disease and cognitive decline: aiming to reduce the effects of oxidative stress by modulating the number of ROS may be beneficial to those afflicted.

Polyphonic protection of neurons and cognitive decline

Multiple studies[8] show polyphenols, found naturally in plants, have the ability to directly stimulate neuronal cell proliferation, reduce effects of oxidative stress and attenuate inflammation. For example, resveratrol (RSV), found in grapes and red wine, is a highly studied polyphenol that is able to induce beneficial effects to the brain by activating sirtuins (SIRTs).[9] These are regulatory enzymes involved in a variety of functions including metabolism and brain function, which primarily work by editing histones to prevent DNA damage. SIRTs increase the content of NAD in cells, which increases energy production, thereby enabling greater cell survival, synaptic plasticity and neuronal stress resistance.[10] One study[11] found SIRT1 activation reduced tau protein phosphorylation, premature cell death and synaptic loss in the brains of pathological mice models. This had the downstream effect of reducing behavioural deficits, hence supporting the use SIRT1 activation as a therapeutic method for AD and other neurological conditions. Furthermore, resveratrol is able to reduce ROS, scavenge free radicals and upregulate enzymes such as glutathione peroxidase, which protects cells from oxidative damage, therefore the properties of resveratrol allow it to produce powerful antioxidant effects. Additional actions include inhibiting pro-inflammatory mechanisms such as tumour necrotic factor-α production and cytokine release, indicating that resveratrol could produce positive clinical effects in patients suffering from neurological conditions.[12] However, resveratrol has low bioavailability in humans and little work has been done to tackle this problem for clinical use.[13] Additionally, the bioavailability measurements may be inaccurate as the distribution to other tissues is not considered. Hence, future research needs to fully explore targeted therapy in order to fully utilise the benefits of resveratrol and make use of it in a clinical setting.

Like resveratrol, curcumin can reduce oxidative stress and inflammatory responses in the brain to prevent damage. It is also useful to diagnose Alzheimer's disease at an earlier stage through its ability to bind to Aβ plaques and produce a strong fluorescent signal, making it useful for positron emission tomography (PET), magnetic resonance imaging (MRI)[14] as well as other modalities. Its use has already been approved by the US Food and Drug Administration for clinical use and earlier diagnosis allows for patients to plan ahead. It gives people greater autonomy when making decisions about their healthcare while they have capacity and increases the opportunity to live independently.[15] Additionally, curcumin significantly reduced BACE-1 levels (an enzyme involved in Aβ plaque production) so its inhibition prevents amyloid precursor protein maturation thus may be used to provide therapeutic benefit in AD.[16] However, when administered orally, curcumin showed no difference in cognitive impairment amongst AD patients when trialled clinically which may be due to low bioavailability. This mirrored the same problem as resveratrol hence these findings, again, emphasise the need to find modalities to make polyphenols more available in the brain in order to achieve therapeutic effects and for clinical use.

Flavonoids are also implicated to be protective against dementia and reverse some deficit in cognitive function. They have an ability to interact with multiple pathways to produce resistance to oxidants and inflammatory mediators and influence neuronal differentiation, long-term potentiation and memory.[17] Already there is evidence that flavonoid intake is associated with improved cognitive function in people aged 65 or over. For example, a study found intake of flavonoids produced better Mini-Mental State Examination scores in a dose-dependent relationship over a 10-year period.[18] One mode flavonoids are able to exhibit neuroprotective effects is through the inhibition of β-secretase and activation of α-secretase.[19] β-secretase is essential for the generation of β-amyloid plaques due its function of cleaving APP into Aβ peptides and N-APP bringing about apoptotic destruction of neuronal cells[20] which are hallmarks of AD. Hence, inhibition of β-secretase would prevent cleavage of APP from occurring and reduce risk of plaque and disease development.

EGCG, the main flavonoid in green tea, was investigated for its potential therapeutic effect on cognition. A study[21] conducted in Wuhan, China explored the relationship between green tea consumption and cognitive function in Chinese middle-aged and elderly people. The results showed individuals consuming green tea had significantly lower levels of tau proteins and Aβ peptide levels in comparison to those who did not as well as lower levels of oxidative stress markers in serum, such as MDA, indicating green tea consumption may reduce AD pathology through antioxidant mechanisms. ECGC is able to produce neuroprotective effects through many mechanisms, one of which is the increased expression of antioxidant enzymes such as glutamate-cysteine ligase.[22] This enzyme produces glutathione, a major antioxidant, which is significantly lower in AD patients[23] so increasing glutathione levels may be protective against oxidative stress. Additionally, ECGC is able to prevent hyperphosphorylation of tau proteins and accumulation of neurofibrillary tangles in the brain via activation of the Akt signalling pathway. This functions to reduce tau hyperphosphorylation[24], a key feature in AD therefore, supplementation with ECGC may increase antioxidant abilities in patients and reduce abnormal build-up of these tangles.

Importance of oral health

Not only does the contents influence dementia occurrence, the mode of ingestion contributes to its progression. As people age, oral health reduces and they experience more oral problems that impair mastication such as dental caries, tooth loss and periodontal disease.[25] This makes people more likely to opt for a softer diet[26] causing them to miss out on preventative measures such as nutrients sourced in hard foods putting them at greater risk of malnutrition. Those experiencing dental problems opt to avoid harder foods such as fruits and vegetables which exposes them to low grade inflammation and oxidative stress[27], a major factor during pathological conditions such as Parkinson's disease and AD.[28]

Impact of food texture on neuroprotection

The action of chewing itself may also prevent dementia. Some studies show chewing increases blood oxygen level dependent signals in MRI scans in the primary sensorimotor cortex, cerebellum, thalamus and prefrontal cortex.[29] The prefrontal cortex is important for the consolidation of memories in the hippocampus as information from the prefrontal cortex streams into areas of the hippocampus where objects and places are encoded within a context.[30] This information can then be retrieved and relayed back to the prefrontal cortex when stimulated. This hippocampal-prefrontal relay system is impaired in AD and other cognitive impairments[31], which partly explains why affected patients struggle to form new memories and retrieve old memories. Increased blood flow to this region serves as a protective force to its degradation. Another investigation[32] explored the effects of hard-diet feeding and soft-diet feeding on neurogenesis in the

subventricular zone of mice. It revealed that mice on a soft-diet had reduced neurogenesis and reduced odour avoidance suggesting a soft-diet can induce adverse effects on adult neurogenesis such as long-term memory loss and hyposmia, key features in Alzheimer's disease.

Chewing hard foods has additional effects which may contribute to a person's risk of developing dementia. It attenuates corticosterone and catecholamine levels in stressful situations and reduces changes in the central nervous system, particularly the hippocampus and hypothalamus which are especially sensitive to stress.[33] In rats, it was observed to prevent impairment of NMDA receptors suggesting chewing is a useful mechanism to cope with stress by suppressing endocrine responses. These NMDA receptors increase glutamate uptake in the hippocampus and contribute to neuronal cell death which is a key feature in dementia. Furthermore, a study explored the effects of chewing on nutritional status and rates of depression in elderly people. It found those with chewing problems consumed less energy than those with no chewing problems and there was a significant difference between the two groups; the prevalence of depression in those with chewing problems was twice as high as those without chewing problems.[34] The study considered socio-economic factors which may have contributed to depression prevalence and adjusted depression scores to account for this. Other studies[35] have similar findings that show chewing ability is significantly associated with health-related quality of life, as well as other aspects of the EQ-5D which includes aspects of pain, anxiety and depression. This indicates some causal relationship between chewing and depression.

Depression in later life is also suggested to increase the risk of developing dementia.[36] A study investigating the association between depression and cognitive decline found that those with late onset depression performed worse in verbal skills, delayed memory and global cognitive function in comparison to those who were never depressed.[37] Therefore, factors such as nutrition and oral health which influence depression development need to be modulated to reduce risks of depression associated with dementia.

Conclusion

Overall, diet has the potential to influence neurogenesis through multiple pathways, such as polyphonic activation of sirtuins which downregulate inflammatory markers and combat oxidative stress as well as directly influencing enzymes involved in Aβ plaque development and tau hyperphosphorylation. The importance of oral health is emphasised as it affects food choice, nutrition and improves blood oxygen flow to the brain reducing incidence of depression and subsequent cognitive decline. Therefore, there is much potential to modulate diet to prevent AD incidence and utilise polyphenols for clinical use. Advances in medical knowledge[38] enable better survival and allows people to live longer however this gives rise to greater incidence of dementia and the number of people affected is expected to grow.[39] Hence it is vitally important to explore the domains which influence these conditions such as dietary factors, to compose new treatment, earlier diagnosis and provide individuals with better knowledge of preventative measures to influence health outcomes.

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