MEDICINE UPDATE™

ISSN:0971-7684

REPRINT

Volume 23, Number 10 Passi HealthCom

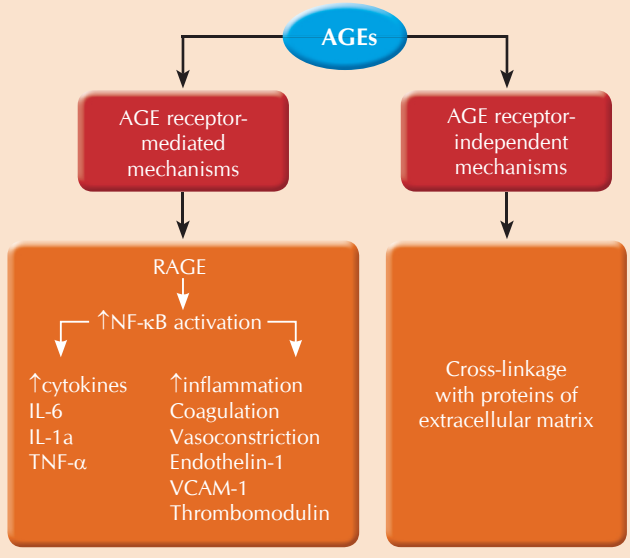
Accumulation of AGEs and Disorders of the Brain: Targets to Dietary Restriction and Resveratrol

AGEs accumulation in the body

Advanced glycation end products (AGEs) are highly reactive irreversible adducts, formed by non-enzymatic reactions of reducing sugars with amino groups of proteins, nucleic acids, and lipids.[1-3] The family consists of more than 20 members of complex and heterogeneous group of compounds, such as N-carboxymethyl-lysine (CML), pentosidine and reactive intermediates like methyl-glyoxal (MG). These reactive species are not only produced in the body through endogenous rearrangement and condensation reactions mainly within the so-called "Maillard reaction," but are also present preformed in a variety of food products, where substantial increase in their concentration can occur because of thermal processing and modifications of the food.[4,5]

People are thus more prone to contain high levels of AGEs as they age and increasingly diverge towards modern heat processed foods;[6] particularly, dry-heat processed foods contain very high level of AGEs per gram of food.[7] This continued supply of AGEs through both endogenous and exogenous routes results in high systemic pool of AGEs in the body, contributing to their potential negative metabolic consequences.[8] In this event, gross derangements can be seen in metabolic profile of subjects, while elevation in AGEs concentrations in specific tissues can contribute to increased risk of various disorders dependent on the organ system primarily involved. At tissue level, AGEs can act through both direct and indirect mechanisms to cause variety of microvascular and macrovascular damage. While direct action involves its cross linkage with extracellular membrane (receptor independent), thereby deteriorating physiological function and structural integrity in organ systems;[9] the indirect mechanism is mediated via interaction with their receptors – RAGE – that are present on the cell surfaces of many tissues (Figure 1).[1,7] This latter indirect mechanism, involving the AGE-RAGE interaction leads to activation of pro-inflammatory and oxidative stress cascades, such as Nuclear Factor-Kappa B (NF-κB), by inducing expression of

Figure 1. AGEs' mechanisms of action contributing to tissue damage



Source: Palimeri S, Palioura E, Diamanti-Kandarakis E. Current perspectives on the health risks associated with the consumption of advanced glycation end products: recommendations for dietary management. *Diabetes Metab Syndr Obes.* 2015;8:415-26.

> Accumulation of AGEs in the brain has been related to pathogenesis of several neurological degenerative diseases

several pro-inflammatory genes; thereby leading to tissue damage and contributing to development and progression of various disorders.

Risk of neural disorders in consequences to AGEs accumulation

There is growing evidence that AGEs play pathological role in numerous disorders, and this encompasses disorders of the brain, since brain is uniquely vulnerable to oxidative stress injuries. As well, seeing that AGEs formation and accumulation progresses more rapidly in diabetes, it is prudent to consider that individuals with deranged metabolic homeostasis would be at a higher risk of diseases wherein AGEs seem to have a contributory etiological role.[10] This has been corroborated in epidemiological studies, which have reported moderately increased risk of neurodegenerative disorder in diabetic patients, compared with general population.

Accumulation of these highly reactive pro-oxidants – AGEs – in the brain has been related to pathogenesis of several neurological degenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, and peripheral diabetic polyneuropathies as well. At brain level, the pathophysiological mechanism is possibly related to the pathological amyloid glycation and the induction of oxidative stress causing potential neurotoxic effects. The mechanism suggests that glycation induces formation of the β-sheet structure in β-amyloid protein, α-synuclein, transthyretin (TTR), copper-zinc superoxide dismutase 1, and prion protein. In sequence, aggregation of the β-sheet structure in each case creates fibrillar structures, respectively causing Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, familial amyloid polyneuropathy, and prion disease.[11] Additionally, AGEs accumulation in brain may have a pathogenic role in development and progression of psychiatric illness, such as schizophrenia, as well.[12]

Reduced AGEs as possible prevention strategy for neurodegenerative disorders

It now seems evident that AGEs accumulation and activation of its receptor (RAGE) can lead to signaling through several inflammatory signaling pathways and further damaging effects in the brain. Particularly, methyl-glyoxal derivatives are considered to be neurotoxic and a modifiable risk factor for neurodegeneration, possibly acting via suppression of survival factor sirtuin 1 (SIRT1) and other host defenses, to promote chronic oxidant stress and inflammation. As follows, a significant therapeutic premise is that since SIRT1 deficiency in humans is both preventable and reversible by AGE reduction, a strategy that includes AGE reduction and modulation of the AGE-RAGE axis may offer a novel approach to combat development of neurodegenerative diseases, especially in the more prone ageing population in whom high serum AGEs may be related to a decline in cognitive function.[13] RAGE is the main factor mediating Aβ cytotoxicity, and hence, attenuation of RAGE activity may inhibit Aβ from accumulation in the cerebral blood vessels and prevent neurotoxicity.[14] Emerging evidence renders hope that dietary restriction of calories and AGEs could help to reduce total systemic load of AGEs in all individuals.[15]

Resveratrol: A potential neuroprotector

Resveratrol is a natural compound that is believed to nicely mimic the beneficial effects those related to calorie restriction.[16] Several studies have demonstrated the ability of resveratrol to suppress neuroinflammatory responses.[17] It may induce its neuroprotective properties by reducing mitochondrial dysfunction and oxidative damage, by improving vascular function, and by activating longevity genes including sirtuins.[18] As such, resveratrol with its intrinsic

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Resveratrol improves memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults

Dietary habits including calorie restriction or intake of nutrients that mimic these effects may exert beneficial effects on the ageing brain. Resveratrol – a plant-derived polyphenol – has been shown to increase memory performance in primates, but interventional studies in older humans are lacking. In the current study, Witte et al investigated whether resveratrol supplementation would enhance memory performance in older adults, alongside addressing potential mechanisms underlying this effect. Per protocol, 23 healthy overweight older individuals (50–75 years) who successfully completed 26 weeks of resveratrol intake (200 mg/d) were pairwise matched to equal number of subjects in same age group that received placebo. Before and after the intervention/control period, subjects underwent memory tasks and neuroimaging to assess the volume, microstructure, and functional connectivity of the hippocampus, an important region implicated in memory functions. Additionally, methodology included assays for anthropometry, glucose and lipid metabolism, inflammation, neurotrophic factors, and vascular parameters. The investigators observed a significant effect of resveratrol on retention of words over 30 minutes compared with the placebo. Moreover, resveratrol led to significant increases in hippocampal functional connectivity, decreases in glycated hemoglobin (HbA1c) and body fat, and increases in leptin compared with placebo. Increases in functional connectivity between the left posterior hippocampus and the medial prefrontal cortex were observed to exhibit correlation with increases in retention scores and with decreases in HbA1c. The study thus provides initial evidence that resveratrol supplementation improves memory performance in association with improved glucose metabolism and increased hippocampal functional connectivity in older adults.

Source: Witte AV, Kerti L, Margulies DS, Floel A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. *The Journal of Neuroscience.* 2014;34(23):7862–7870.

antioxidant capabilities and influence on blood flow, cell death, and inflammatory cascades could be used to protect the brain against a wide variety of stress and injury,[19] and enhance the prognosis of neurological disorders, including neurodegenerative disease models.[20]

Resveratrol is proposed to modulate neuronal energy homeostasis and provide cellular resistance against the insults that AGEs induce in the brain to cause neurodegenerative conditions, such as Parkinson's, Alzheimer's, and amyotrophic lateral sclerosis.[21] It has been noted to directly increase the activity of SIRT1, which is related to increased lifespan in various species similar to calorie restriction. Acting via this SIRT1 activation mechanism, resveratrol could confer a neuroprotective effect that is similar to ischemic preconditioning-induced neuroprotection, which protects against lethal ischemic insults in the brain.[22]

> Resveratrol supplementation improves memory performance in older adults

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