Nutritional and Botanical Approaches to Antiaging

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As the human population ages and increases in longevity, study of biological aging is emerging. According to the Centers for Disease Control and Prevention, for 2003, an estimated 35.9 million Americans were over the age of 65 and more than 25 percent of this population was in fair-to-poor health.[1] The mechanism of cellular aging is elusive and many theories have been proposed to explain the decrease in physiologic function that occurs with aging. As a result of increased risks of disease and mortality, decreases in quality of life, and rising health care costs, aging and longevity research is necessary to address problems related to aging. A wide range of nutrients and interventions have been shown to decrease cellular aging and age-related disease.

Theories of Aging

There are several theories of cellular aging. These theories are not mutually exclusive, and many complement each other. Aging was initially believed to be a result of genetically programmed cell death. Subsequently, it was proposed that aging might be a result of accumulation of cellular damage and mutation. Given that evidence has surfaced suggesting that aging may be a result of cellular damage, this implies that interventions to influence aging are possible.

Oxidative Stress and Free Radicals

Damage caused by free radicals is the most popular and universal theory of cellular aging. These highly reactive molecules are formed in many biochemical reactions as well as being introduced via exogenous exposures. Free radicals react with molecules causing damage and mutations, and have been implicated in many disease processes.[2]

Studies indicate that an increase in the accumulation of oxidative damage increases functional deficits during aging, and treatments that decrease oxidative damage have been shown to delay age-related loss of function.[3] Other evidence suggests that increases in oxidative stress cause increases in inflammatory mediators, leading to age-related inflammatory diseases, such as arthritis, atherosclerosis, osteoporosis, and dementia.[4]

Mitochondrial Damage

Mitochondria produce most of the energy used by the body in the form of adenosine triphosphate (ATP). Oxidative phosphorylation provides the majority of ATP production via the electron transport chain. Aging has been shown to decrease the efficiency of mitochondrial oxidative phosphorylation. Specifically, aging decreases cellular energy production, impairs substrate oxidation, and increases the production of free radicals.[5] Loss of muscle mass and function seen with aging is associated with mitochondrial damage in muscle cells.[6]

Studies indicate that aging is associated with a decrease in number and increase in size of mitochondria, making them less efficient with age.[7] Small amounts of reactive oxygen species (ROS) are formed via energy production that regulates some cellular functions, and that can act as a second messenger for transcription factors.[8]

Cells have several antioxidant enzymes to prevent excess ROS from causing damage. Enzymes required for oxidative phosphorylation and antioxidant enzymes decrease with age as the number of cells completely lacking the enzyme cytochrome oxidase increases.[9] In addition, mitochondrial DNA is more susceptible to free-radical damage and mutation than nuclear DNA.[10]

Research indicates that mitochondrial DNA mutation in postmitotic cells begins accumulating in individuals after the mid-30s.[11] These mutations may lead to impaired protein transcription and translation causing the decrease in cellular respiration. Studies have shown that human cells with increased levels of mutant mitochondrial DNA produce less ATP and release increased levels of ROS.[12]

Studies also show a decrease in mitochondrial membrane potential with aging. This causes an increase in proton leakage and a decrease in ATP production, thus affecting the efficiency of cellular respiration.[13] Mitochondrial defects and the resultant decline in mitochondrial function are implicated in the induction of apoptosis. Increased oxidant levels have been shown to cause an increase of events such as increased activation of the mitochondrial permeability transition pore leading to an increase in the release of proapoptotic proteins from the mitochondria.[14]

Telomeres

Telomeres are repeat sequences at the ends of eukaryotic chromosomes that provide protection and stabilization. Telomeres generally shorten with each replication because of the inability of

DNA polymerase to copy the lagging DNA strand. Telomerase is a reverse transcriptase that synthesizes the telomere. Most human cells are deficient in telomerase, allowing the attrition of the telomere. Short telomeres activate irreversible cell-cycle arrest (cellular senescence and apoptosis).[15]

Cancer cells have been shown to upregulate telomerase, prolonging the lifespan of the tumor cells.[16] Approximately 90 percent of cancer cells have high levels of telomerase activity.[17] Oxidative damage has been shown to accelerate telomere shortening, and antioxidants have been shown to slow telomere attrition.[18] Research suggests that telomere length is a highly heritable trait and that telomeres are longer in women than in men.[19] Obesity and smoking have also been shown to decrease telomere length.[20]

A study done with long-term estrogen and progesterone hormone therapy in postmenopausal women showed that longer telomeres appeared in women on hormone replacement than in women without hormone therapy.[21]

In addition, individuals with mood disorders have been shown to have significantly shorter telomeres, possibly providing the link between mood disorders and increased morbidity and mortality.[22]

Another study revealed that women with the most chronic and highest levels of perceived stress had lower telomerase activity and shorter telomeres.[23] Research has also shown that telomere shortening in vascular cells is associated with endothelial dysfunction and atherosclerosis formation.[24]

Neurologic and Endocrine Dysfunction

This theory suggests that aging is caused by endocrine dysfunction, which is common in elderly people. Changes in hormonal secretion, loss of receptor sensitivity to stimulatory or inhibitory stimuli, anatomic changes of endocrine glands, and altered transport of hormones occur in aging.[25]

Many hormones decrease with aging. Studies have shown that melatonin secreted from the pineal gland (responsible for regulation of circadian rhythms) decreases with age. Specifically, increasing age is directly proportional to decreasing levels of plasma melatonin and delayed melatonin elevation.[26]

Growth hormone decreases at approximately 14 percent per decade. After age 60, growth hormone is decreased by approximately 50–70 percent compared with levels in the third and fourth decade of life.[27]

Steroid hormones, such as estrogen and testosterone, also decrease with age.[28] Interestingly, estrogen has been shown to upregulate telomerase activity.[29] Animal studies have also demonstrated that testosterone may decrease telomerase activity.[30]

Crosslinkages

Proteins and other macromolecules can undergo crosslinking reactions. Proteins that undergo these reactions become less elastic, less soluble, and less digestible by enzymes. This theory suggests that large molecules undergo crosslinkage when exposed to a crosslinking agent causing cellular damage and cell death. Advanced glycosylation endproducts (AGEs) are formed by a reaction between reducing sugars and biologic proteins. Glycated proteins are stable and accumulate over time. AGEs react with molecules creating crosslinkages.

Potential Antiaging Supplements

- Dimethylaminoethanol (DMAE)
- Dehydroepiandrosterone (DHEA)
- Growth hormone
- Melatonin
- Carnosine
- Niacinamide
- Coenzyme Q10
- Resveratrol
- Glutathione
- Vitamin E
- Vitamin C
- β-carotene
- α-lipoic acid.
- *Astragalus membranaceus* (astragalus)
- *Ginkgo biloba* (ginkgo)

Evidence suggests that, although antioxidants may not be able to prolong life, they may improve quality of life as they provide benefit for patients who have cancer and age-related diseases, such as atherosclerosis, neurodegenerative, and ocular diseases.[a]

[a]From ref. 96.

These reactions have been implicated in the pathology of several diseases. Hyperglycemic conditions such as diabetes have an increase in glycosylation of proteins, which may explain the increase in chronic diseases that occur with these conditions.[31] Collagen crosslinkage has been shown to cause increased stiffness in cartilage possibly leading to decreased resistance to damage and osteoarthritis.[32]

Decreases in vascular and myocardial elasticity, and hypertension, endothelial dysfunction, and atherosclerosis formation are associated with increased AGE accumulation.[33] Protein crosslinking is also found in the brains of individuals with Alzheimer's disease.[34] Research also suggests that cataracts may be associated with crosslinkage in eye lenses.[35]

Nutritional and Supplement-Based Antiaging Interventions

Calorie Restriction

Calorie restriction is one of the most supported interventions in aging and longevity research. Studies with numerous animal types have demonstrated that calorie restriction increases longevity and decreases age-related diseases. Calorie restriction is widely studied in attempts to define which biochemical pathways are affected by fasting and the induced stress response.

Research with humans indicates that calorie restriction modulates energy metabolism, reduces free-radical production, and alters endocrine function.[36] A study with monkeys demonstrated that a 30 percent reduction in calories lowered core body temperature and decreased energy expenditure.[37] Calorie restriction also increases the levels of nicotinamide adenine dinucleotide (NAD)–dependent protein deacetylases (known as sirtuins), which are involved in energy metabolism and gene silencing, and are associated with increased longevity.[38] Specifically, these

proteins deacetylate and inactivate p53, allowing cells to bypass apoptosis and survive DNA damage, giving cells time to repair damage.[39]

Another study showed that calorie restriction decreased mitochondrial proton leakage, cellular oxygen consumption, and ROS production in rat muscle.[40] In addition, insulin and tri-iodothyronine are decreased with calorie restriction.[41] Insulin replacement reverses the beneficial effects of calorie restriction in the mitochondria by increasing ROS formation.[42]

A study with rats also revealed that calorie restriction decreases the age-related decline of the glutathione and thioredoxin systems, supporting the antioxidant function of calorie restriction.[43] This intervention also reduces DNA damage and mutations and increases DNA repair by increasing the activity and reliability of DNA polymerases, which decline with aging.[44]

Cancer and age-related immunologic defects, which are associated with DNA damage, also decrease with calorie restriction.[45] Calorie reduction decreases the release of leptin, a peptide hormone secreted from adipocytes. This alteration in leptin levels has been shown to activate the adrenal axis while suppressing the thyroid, gonadal, and somatotropic axes.[46]

Studies have also shown that calorie restriction alters levels of heat-shock proteins, which are protective for cells and which are induced by stressful stimuli. Heat-shock proteins decrease with age, and dietary restriction has reversed this process in the cardiac tissue of animals.[47]

Dimethylaminoethanol

Dimethylaminoethanol (DMAE), also known as deanol, is a naturally occurring substance that has been studied as a possible antiaging therapy that can also improve cognitive function. DMAE is the precursor to choline and may increase acetylcholine levels.[48]

DMAE inhibits production of the age-related pigment lipofuscin, which accumulates in all aging tissues. This is significant because cells with increased lipofuscin cause lysosomes to perform poorly, which leads to increased accumulation of poorly functioning mitochondria and increased ROS production.[49] Evidence also suggests that DMAE decreases the extent of crosslinking of proteins possibly by acting as a free-radical scavenger.[50]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone produced primarily in the adrenal cortex as well as in the liver, brain, and testes. DHEA is the precursor to androstenedione, which is then converted to androgens and estrogen. DHEA peaks at approximately age 20 and declines steadily with age.[51]

DHEA levels have been studied relative to numerous age-related diseases. Research has suggested that low DHEA levels may be correlated with cardiovascular disease (CVD), cancer, obesity, immune deficiency, insulin resistance, and depression.[52]

Evidence has shown that DHEA supplementation of 50 mg per day for 1 year improved bone mineral density in both men and women over age 60.[53] DHEA supplementation has been shown to decrease visceral and subcutaneous fat and insulin levels in elderly men and women.[54] Studies have also revealed the antiatherogenic effects of short-term supplementation when 50 mg of DHEA per day was given to elderly individuals.

In addition, this research has shown increased platelet cGMP production, signifying nitric oxide (NO) production, decreased levels of plasminogen activator inhibitor, decreased levels of low-density lipoprotein (LDL) cholesterol, and increased levels of testosterone and estradiol.[55]

Data obtained in a study indicate that DHEA sulfate (DHEAS) is decreased in elderly patients with congestive heart failure (CHF) compared with age-matched controls. This study also showed that the decline in DHEAS is proportionate to the severity of CHF and is associated with oxidative stress.[56]

Recent evidence also indicates that DHEA improves muscle mass and strength in elderly individuals when combined with weight-lifting exercise compared with weight lifting alone.[57]

A study of DHEA supplementation with individuals ages 45–65 with midlife-onset minor or major depression showed a significant improvement in the participants' Hamilton Depression Rating Scale scores compared with baseline after 6 weeks of treatment.[58]

Growth Hormone

Growth hormone (GH) is secreted by the pituitary gland and exerts its effects either directly or indirectly via insulin-like growth factor–1 (IGF-1). GH and IGF-1 decrease significantly with age. Low IGF-1 levels have been associated with numerous age-related diseases, such as atherosclerosis, CVD, dementia, and sarcopenia.[59]

IGF-1 can stimulate NO production from endothelial and vascular smooth-muscle cells, indicating a vascular protective function.[60] IGF-1 also has antiapoptotic and neuroprotective effects.[61] In addition, serum IGF-1 levels are correlated significantly with muscle strength and physical performance.[62]

Melatonin

Melatonin* is a hormone secreted from the pineal gland primarily at night and regulates circadian rhythms. Both total output and rhythmicity of melatonin decrease with age.[63] Melatonin provides protection from oxidative damage by functioning as a free-radical scavenger and regulates the expression of antioxidant enzymes.[64] This hormone also exhibits immune-stimulating benefits.

Age-related decline of humoral, innate, and cellular immunity is implicated in the increase in disease, physical degeneration, and cancer in elderly patients. Studies indicate that melatonin enhances cellular and innate immunity. The hormone stimulates progenitor cells of granulocytes, natural-killer cells, macrophages, and several cytokines.[65] Melatonin also increases the production of T-helper cells.[66]

In addition, melatonin affects mitochondrial function directly. The free-radical activity of melatonin limits decline in intramitochondrial glutathione and decreases mitochondrial protein and DNA damage, allowing for more efficient electron transport chain function and increased ATP production. This activity

EDITOR'S NOTE: For more information on melatonin, see the article on pages 282–291 by Amy Fitzpatrick, M.S., R.D.

blocks the decline in mitochondrial-membrane potential, which would cause opening of the mitochondrial transition pore and possibly induce the apoptotic cascade.[67]

Studies indicate that melatonin has neuroprotective qualities and can slow the progression of Alzheimer's disease.[68] Melatonin also produces anticancer activity and has been shown to inhibit tumor-cell proliferation, stimulate tumor-cell differentiation and apoptosis, and inhibit tumor-cell uptake of linoleic acid at both physiologic and pharmacologic doses.[69] Decreased melatonin synthesis caused by increased light during the night has been shown to increase cancer-cell proliferation.[70]

Carnosine

Carnosine is a dipeptide composed of β-alanine and L-histadine. It is found in high concentrations in skeletal muscle, cardiac muscle, and the brain.[71] Human studies indicate that muscle carnosine levels decrease significantly with age, demonstrating a 63 percent decrease from age 10 to age 70.[72]

Studies have shown several biochemical functions of carnosine suggesting antiaging properties. Carnosine acts as an antioxidant decreasing lipid oxidation and protecting membranes from free-radical damage as well as chelating reactive metals.[73] Carnosine has been shown to extend the lifespan of human fibroblasts, possibly because of the dipeptide's ability to slow telomere attrition and decrease damage to telomere DNA.[74]

Studies indicate that carnosine can prevent crosslinking, glycation, protein carbonyl group formation, and the formation of AGEs, which play a role in aging and age-related disease.[75] Carnosine has also been shown to inhibit toxic effects of amyloid peptide, malondialdehyde, and hypochlorite to cells.[76]

Niacinamide

Niacinamide (vitamin B_3), also known as nicotinamide, is the amide form of niacin and is necessary for numerous biochemical reactions. Niacin is the precursor to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP are essential for oxidation-reduction reactions and ATP synthesis. Niacinamide is necessary for modulating cell metabolism, cell longevity, and mitochondrial-membrane potential.[77]

Research shows that nicotinamide can reverse aging phenotypes in aging human fibroblasts. This study revealed that aging cells exposed to nicotinamide showed increased replicative potential and histone acetyltransferase activity, suggesting restoration of altered gene expression.[78]

There is supportive evidence that niacin may be protective against age-related cognitive decline and Alzheimer's disease, and that higher niacin intake from the diet produces a slower annual rate of cognitive decline.[79] Niacin supplementation has also been shown to provide benefit for patients with age-related CVDs, such as atherosclerosis, hyperlipidemia, and coronary artery disease.[80,81]

Coenzyme Q10

Coenzyme Q10 (CoQ10), or ubiquinone, is a compound made by the body and primarily functions as an antioxidant, membrane stabilizer, and a cofactor in cellular respiration. CoQ10 supplementation has been shown to ameliorate cardiovascular diseases, neurologic disorders, and possibly cancer. Studies indicate that CoQ10 supplementation in individuals with CHF improved ejection fraction, stroke volume, and cardiac output.[82] CoQ10 has also been shown to decrease systolic hypertension, with 12 weeks of supplementation producing a mean decrease in systolic blood pressure of 17.8 mm Hg.[83] Additional research showed that 120 mg of CoQ10, given for 28 days after acute myocardial infarction, decreased angina, arrhythmias, poor left ventricular function, total cardiac events, and oxidative free radicals.[84]

CoQ10 appears to be promising for slowing functional decline in individuals with neurodegenerative diseases caused by mitochondrial dysfunction or oxidative damage such as Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and Friedreich's ataxia.[85] CoQ10 supplementation is also effective as a migraine prophylactic therapy.[86] In addition, some evidence supports CoQ10 as having immunomodulating and anticancer actions.[87]

Resveratrol

Resveratrol is a natural polyphenol found in high concentrations in red-grape skins and berries. It is widely studied because of its antioxidant, anti-inflammatory, anticancer, and possibly antiaging properties. Evidence suggests that resveratrol increases lifespan in simple organisms and mimics calorie restriction by activating sirtuin.[88]

Additional studies indicate that resveratrol may provide chemoprotective action by inhibiting tumor initiation, promotion, and progression by possibly downregulating proinflammatory mediators.[89] Resveratrol has also been shown to be cardioprotective, suppressing platelet aggregation, inhibiting LDL oxidation, and reducing myocardial damage during ischemia-reperfusion.[90] Research suggests that age-related neurologic diseases, such as stroke, ischemia, Huntington's disease, and possibly Alzheimer's disease may be ameliorated with resveratrol.[91]

Glutathione

Glutathione is a tripeptide made primarily in the liver. This tripeptide acts as a free-radical scavenger, modulates DNA synthesis and immune function, and detoxifies xenobiotics and their metabolites.[92] Plasma glutathione levels are significantly decreased in elderly people and the glutathione in this population is in a more oxidized state, implying increased oxidative stress.[93]

Evidence suggests that oxidative stress and glutathione deficiency play a role in neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.[94] Increased oxidation of glutathione is found with cigarette smoking, chemotherapy, and age-related diseases, such as cardiovascular disease and type 2 diabetes.[95]

Other Antioxidants

Numerous additional antioxidants have shown antiaging benefits such as vitamin E, vitamin C, β-carotene, and α-lipoic acid. Almost all age-related diseases are caused or exacerbated by oxidation and free-radical damage.

Evidence suggests that, although antioxidants may not be able to prolong life, they may improve quality of life as they provide benefit for patients who have age-related diseases, such as cancer, atherosclerosis, neurodegenerative, and ocular diseases.[96]

Studies have also shown that supplementation, using antioxidants, such as vitamins C and E, zinc, selenium, and β-carotene, improves leukocyte function and restores redox balance in prematurely aging animals.[97] In addition, antioxidants such as vitamins C and E and carotenoids decrease DNA damage and malignant transformation in cells, and are associated with lower risks of cancer, ischemic heart disease, and cataracts.[98]

Botanical Antiaging Interventions

Astragalus

Astragalus membranaceus (astragalus) is a botanical frequently used because of its antioxidant activity. Research suggests that this herb inhibits free radicals, decreases lipid peroxidation, and increases antioxidant enzymes.[99] Studies also suggest that astragalus provides cardioprotective and immune-stimulatory effects.[100,101] Evidence indicates that astragalosides exert antiaging effects on mice by delaying senility, improving brain function, and improving cellular immunity.[102]

Ginkgo

Ginkgo biloba (ginkgo) leaf has antioxidant, anticancer, and free-radical scavenging actions as well as improving microcirculation and protecting neurons from oxidative damage. The herb also decreases platelet aggregation and induces NO.[103] Evidence suggests that ginkgo has cardioprotective activity and may provide benefit for patients who have arterial and venous insufficiency as well as preventing thrombosis.[104] In addition, ginkgo is well-known for its ability to slow age-related cognitive functional decline and Alzheimer's disease.[105]

Conclusions

Much research is underway to understand the aging process and study potential antiaging interventions. As the population ages it is important to investigate potential therapeutics to slow aging and improve quality of life. According to research, interventions that produce antioxidant activity seem to be a common denominator in antiaging treatment. □

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