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Interventions for Healthy Aging

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Introduction

Given the complexities of the molecular, cellular and organismic mechanisms involved in the aging process, attempts are being made to achieve healthy aging. Studies in humans and other experimental animals indicate that proper nutrition and regular physical exercise not only contribute significantly to health and well being, but also prolong mean and maximum lifespan. A major goal of biomedical gerontologists is to 'add life into years' and 'not the years into life.' Preventive and rehabilitative strategies may help the elderly maintain an active lifestyle as well as preserve intellectual and functional competence in old age. In experimental animals, one of the simplest and most effective methods for expanding healthy lifespan is dietary restriction. Various interventions to achieve healthy aging are depicted in (Fig.158.1).

Macronutrients

In the elderly, protein deficiency may be due to impaired utilization, lower metabolic demand, low calorie intake and possibly lower protein requirements. Protein deficiency is associated with lack of energy, weakness, decreased muscular strength, cognitive function and depression. Evidence showed that when the elderly participate in regular physical exercise, their protein synthesis rates are restored to a level similar to that found in younger individuals. Carbohydrates should represent 55–60 % of the total caloric intake in a well balanced diet. Soluble fibers (fruits, legumes, vegetables) and insoluble fibers (wheat bran, breads and cereals) should be included in the diet. The intake of dietary fats should be 30% or less of the total energy requirements. The omega 3 polyunsaturated fatty acids found in fishes can prevent cardiovascular diseases by lowering LDL and increasing HDL levels.[1]

Micronutrients

A healthy diet including fruits and vegetables containing vitamins and minerals, as well as useful phytochemicals, is needed to meet the nutritional requirements of the elderly. Supplementation is needed in cases of less healthly diets, especially to maintain a normal immune system.

Vitamins

Ascorbic acid (vitamin C) is essential for collagen and lipid metabolism. It acts as a one electron or two electron reductant for a wide variety of biological reactions. The antioxidant properties of ascorbate have been used to treat various conditions such as type 2 diabetes, macular degeneration and atherosclerosis where oxidative stress is involved. It suppresses the activation of NF-κB, inhibits the activation of hypoxia inducible factor-1α (HIF-1α) and p38 MAPK pathways leading to the down regulation of antiapoptotic, cell proliferative, invasive and angiogenic gene products.[2] It helps in the regeneration of vitamin E. It has also been observed to decrease protein carbonyl levels and lipid peroxidation, which are markers of oxidative stress.

Vitamin E (α tocopherol) acts as a chain breaking free radical scavenger. It is a potent antioxidant with anti-inflammatory properties. Its supplementation in human subjects and animal models decreases lipid peroxidation, superoxide ($O_2^{\cdot -}$) production by impairing the assembly of nicotinamide adenine dinucleotide phosphate (reduced form) oxidase as well as by decreasing the expression of scavenger receptors (SR-A and CD36). At high doses, it decreases the release of proinflammatory cytokines, the chemokine IL-8 (interleukin-8) and plasminogen activator inhibitor-1 (PAI-1) levels as well as decrease adhesion of monocytes to endothelium and cytochrome proteins (CRP) levels, in patients with cardiovascular diseases.[3] High dose of α tocopherol, in association with ascorbic acid, may delay the progression of Parkinson's disease.

Phytochemicals

Curcumin, a phytochemical, derived from the rhizome of *Curcuma longa*, has free radical scavenging capability. Curcumin possesses antioxidant and anti-lipidperoxidative capability against a variety of oxidative stresses. Curcumin can significantly reduce the age related increase in ROS and the protein carbonyl levels in the cerebral hemispheres

of mice.[4] It has both neuroprotective and anti-aging effects. It ameliorates a series of pathogenic conditions that share an inflammatory or oxidative basis, such as cardiovascular diseases, neurodegenerative diseases (Parkinson's disease, Alzheimer's disease (AD) and amyotrophic lateral sclerosis), sarcopenia, type II diabetes and arthritis among others.

Resveratrol, a polyphenol, is found in grapes, berries and peanuts. It exhibits anti-aging, antidiabetogenic, cardioprotective and anti-cancer properties. Resveratrol exerts health benefits by activating intracellular pathways, some of which are the same as those activated by dietary restriction (DR), an intervention known to enhance health and prolong lifespan.[5] Resveratrol activates SIRT-1–mediated pathways whose actions result in prevention of common age related diseases. Health benefits include reduced mortality associated with the high fat diet, improved motor performance and improved insulin sensitivity.[6]

Epigallocatechin gallate (EGCG) is the major catechin antioxidant and chemopreventive polyphenol that is found in green tea. It has anti-inflammatory, anti-aging and anti-cancer properties. EGCG can reduce age-associated inflammation and oxidative stress through the inhibition of NF-κB signaling leading to the activation of the longevity factors, FoxO3a and SIRT1.[7] Its supplementation can decrease the expression of hydroxynonenal in aged brain, upregulates the antioxidant system and augments the activities of Krebs cycle enzymes and electron transport chain complexes in aged brain mitochondria thus proving its antioxidant potential at the mitochondrial level.[8] It prevents tumorigenesis in multiple organ sites including skin, lung, esophagus, stomach, small intestine, breast, prostate, liver, pancreas, colon and bladder.

Cinnamaldehyde is an active component of cinnamon. It inhibits the age-related NF-κB activation, via the redox-related NIK/IKK, ERK and p38 MAPK pathways showing that it plays an important role in the regulation of age-related alterations in signal transduction pathways.[9] Cinnamon has a potential role in the treatment of obesity and diabetic conditions.

Endogenous Antioxidants

Melatonin, a hormone of the pineal gland, is a high efficacy free radical scavenger and indirect antioxidant. Melatonin prevents membrane lipid peroxidation, mitochondrial and nuclear DNA oxidation induced by enhanced oxidative stress and possesses anti-apoptotic activity in several experimental model systems.[10] It reduces β amyloid protein toxicity in Alzheimer's disease animal models, oxidative damage in several models of Parkinson's disease, protects against glutamate excitotoxicity, lowers neural damage due to δ-aminolevulinic acid (porphyria), hyperbaric hyperoxia, brain trauma, γ radiation, focal ischemia and a variety of neural toxins. It ameliorates age-dependent increase in protein carbonyls in cerebral hemispheres and liver of mice.[11]

Coenzyme Q_{10} (CoQ), an essential component of the mitochondrial respiratory chain, shuttles electrons from complexes I and II and from electron transferring flavoprotein dehydrogenase (ETF-DH) to complex III. CoQ supplementation can protect the aging heart from oxidative stress. It can improve energy production in mitochondria by passing defective components in the respiratory chain as well as by reducing the effects of oxidative stress. It reverses age related impairments in spatial learning and lowers protein oxidation in the mitochondria from the heart, liver, and skeletal muscle.[12]

Alpha lipoic acid is a necessary cofactor for mitochondrial α-ketoacid dehydrogenases and thus serves a critical role in mitochondrial energy metabolism. The orally supplied lipoic acid has been reported to elicit biochemical activities with potential pharmacotherapeutic value against a host of pathophysiologic insults. It has been used to improve age-associated cardiovascular, cognitive and neuromuscular deficits and has been implicated as a modulator of various inflammatory signaling pathways.[13]

Dietary Restriction (DR)

Dietary restriction, i.e., calorie restriction without malnutrition has been found to retard the aging processes in many organisms. DR feeding regimes have been shown to reduce the concentration of tissue oxidative damage biomarkers, such as peroxidation of membrane lipids, protein carbonyl formation and oxidative damage to DNA bases and strand breaks in nuclear and mtDNA.[14] Three and a half months of DR feeding in 26.5 month old rats upregulates the activity of the proteasome in rat liver. Seventy five persent of tissue gene expression changes induced by long-term DR were seen within 8 weeks of beginning DR feeding and conversely, were lost within the same timeframe when DR fed animals were returned to control feeding indicating that DR lacks memory effect. DR feeding regimes upregulate enzymatic and non enzymatic antioxidants as well as decrease the rate of free radical generation.[15] It reduces the secretion of hormones from the pituitary gland and affects the rate of aging and the development of many age-related diseases.

DR has been proposed to have a hormetic effect. *Hormesis in aging refers to beneficial effects resulting from the cellular responses to mild, repeated stress.*[16] As an aging retardant, hormesis is based on the principle that repeated exposure to mild stress stimulates maintenance and repair

processes. DR results in a decrease in body weight of animals leading to multiple metabolic and physiological beneficial effects and thus suggesting that DR acts as a hormetic agent. An increase in the levels of corticosteroids and a loss of body weight has been observed during short-term and long term dietary restriction. DR appears to elicit better stress management by elevating the level of glucocorticoid receptor (GR), its activation and binding to nuclear DNA, which is significantly reduced in aged animals.[17]

Physical Exercise

Physical exercise promotes substantial gains in muscle strength, even among the very old. Skeletal muscles undergo significant structural and metabolic responses such as: (a) an increase in the number and size of mitochondria resulting in an increase in oxidative enzymatic activity, (b) an increase in muscle fibre myoglobin, (c) an increase in muscle capillary network and blood circulation, (d) an increase in glycogen storage capacity of the skeletal muscle, (e) an increased mobilization of free fatty acids from fat deposits, leading to increased activity of muscle enzymes responsible for fat oxidation.[18] Physical exercise can modulate various responses of the endocrine system. The most significant hormonal responses are those that regulate blood glucose. In older individuals, an imbalance of the insulin and glucagon may induce the onset of diabetes mellitus and vice versa. Exercise has been found to restore normal glucose metabolism. Exercise performed regularly normalizes the age related shift in redox balance, as evident from significantly lower levels of protein carbonylation and expression of HIF-1 and vascular endothelial growth factor(VEGF).[19]

Conclusion

Taking account of the above interventions for healthy aging, it seems reasonable to realize the immense benefit of right nutrition, dietary restriction and regular physical exercise in achieving healthy aging. The practice of such interventions might give rise to a healthy aging with much lesser morbidity during later part of lifespan. It may ultimately lead to a good quality life with increased health span of aging population.

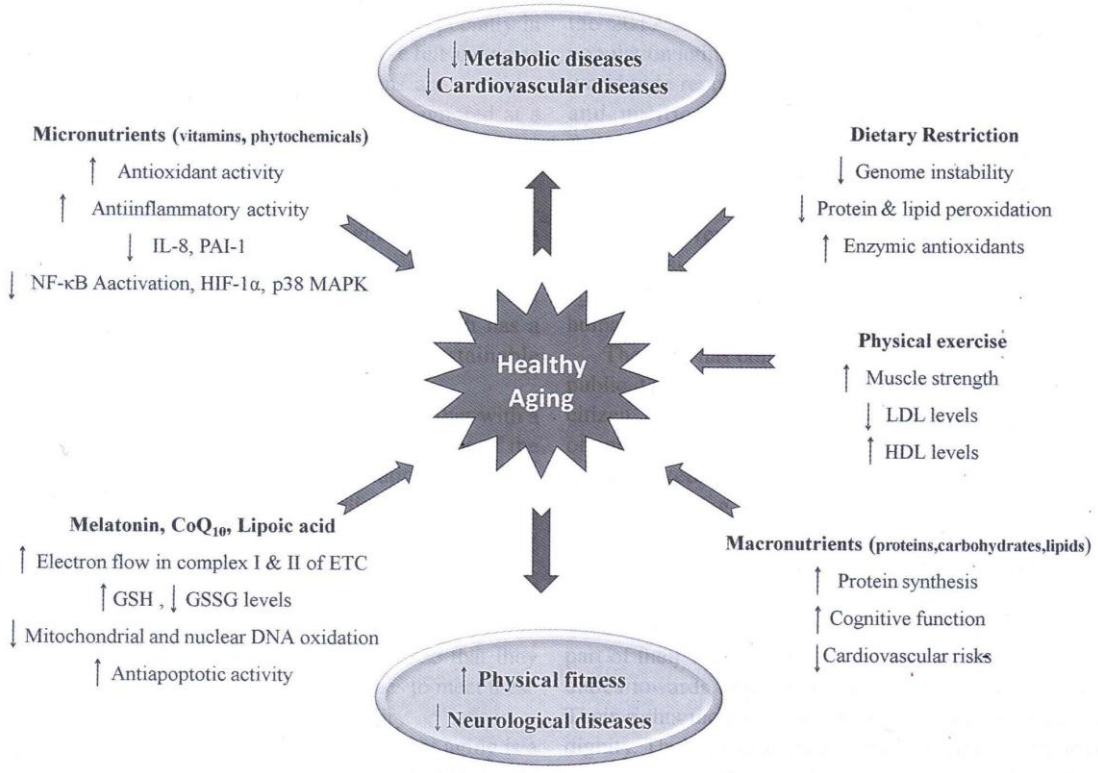

Fig. 158.1 The various interventions involved in achieving healthy aging: IL-8: Interleukin-8; PAI-1: Plasminogen activator inhibitor-1; NF-κB: Nuclear factor-kappa B; HIF-1α: Hypoxia-inducible factor 1-alpha; p38 MAPK: p38 mitogen-activated protein kinase; GSH: Reduced glutathione; GSSG: Oxidized glutathione; LDL: Low density lipoproteins; HDL: High density lipoproteins.

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