Chapter 9

Beneficial effects of nutraceuticals in healthy brain aging

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Chapter outline

Introduction

Aging is a highly complex biological process whose progression is generally associated with time-dependent accumulation of cellular damages [46,111] and characterized by inflammatory mechanisms leading to an organism becoming more susceptible to infections and diseases. Various phenomena contribute to the aging process, one of which is the oxidative stress during normal metabolism. The highly reactive byproducts generated during metabolism, such as ROS and to a lesser extent reactive nitrogen species, have the capacity to rapidly oxidize, and thus damage, many classes of molecules such as proteins, lipids, carbohydrates, and DNA [67]. The accumulated damage to the biological macromolecules by the ROS greatly contributes to the age-related changes at the cellular level.

The brain is particularly vulnerable to oxidative stress due to its high aerobic metabolic rate, abundance of redox modifiable substrates like iron and polyunsaturated fatty acids, relatively low antioxidant capacity, and limited cell turnover and neuroplasticity. Oxidative stress is an underlying risk factor for the pathogenesis of many neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke. The age-related decline in the neurophysiological functions of the brain includes motor coordination and activity, memory, cognitive flexibility, and problem-solving ability [107]. Oxidative damage in the aging brain varies in different regions of the brain and the redox state of glutathione (GSH:GSSG; reduced glutathione:oxidized glutathione) acts as a sensitive indicator of cellular oxidative stress [119]. Protein oxidative damage in the cerebral cortex and in the cerebellum of old mice vary directly with the severity of their cognitive (water maze acquisition) and motor (bridge walking) impairments, respectively [33]. At high concentrations, ROS are detrimental and challenge the integrity of DNA which may cause cellular dysfunction and cell death.

Innovative treatment strategies in combating age-related neurodegenerative diseases involve the usage of antioxidative and antiinflammatory effects of natural compounds, which can prevent the deleterious effects triggered by oxidative stress. Studies have shown that synthetic drugs used for the treatment of neurodegenerative diseases ameliorate symptoms but do not alter the course of disease progression and have even shown some undesired effects [83]. Hence, the use of natural dietary compounds with therapeutic potential (nutraceuticals), which are generally safe and well-tolerated, has gained prominence in the treatment of such diseases.

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the CR regimen can ameliorate the increased content of protein carbonyl species in the brain of aging mice as compared to the younger ones [26].

CR is documented to increase the expression of genes involved with DNA repair, which will increase the efficiency at which cells cope with oxidative damage. CR has shown to activate transcription factors controlling gene expression leading to increased levels of proteins mediating cellular stress responses. SIRT1 activation via CR results in decreased levels of inflammation by downregulation of genes encoding cytokines [82]. In macrophages, SIRT1 activation results in deacetylation of the RelA/p65 component of nuclear factor-kB (NF-kB) complex [121]. The forkhead family transcription factor, FOXO3a is a key regulator of the insulin receptor (IR)/insulinlike growth factor-I signaling pathway mediating extension of lifespan. CR stimulates the hyperphosphorylation of FOXO3a leading to its exclusion from the nucleus, which corresponds to an attenuation of AD in AD model, Tg2576 mice indicating a link between CR, FOXO3a, and age-related neurological pathologies [95]. PPAR and SIRT1 levels are decreased in aged individuals leading to increased inflammation. CR has been shown to restore SIRT1 and PPARg expression, decreasing inflammatory responses. HIF-1α, hypoxia-inducible factor 1-alpha, is associated with inflammation and oxidative stress. Its activity is increased in aged rats, leading to upregulation of genes such as vascular endothelial growth factor, hemeoxygenase-1(HO-1), inducible nitric oxide synthase (iNOS), and erythropoietin (EPO). CR has been shown to decrease the expression of HIF-1α-mediated genes thereby decreasing inflammation [156].

Conclusion

Many people may not follow the regular CR regimens; keeping this in mind, nutraceuticals are prescribed to rescue such individuals by providing health benefits. These nutraceuticals act as CR mimetic, as if individuals have followed the CR, in giving rise to the biochemical and molecular modulations of CR for healthy brain aging (Fig. 9.2). Nutraceuticals such as resveratrol, curcumin, EGCG, quercetin, and many others mentioned in the text mimic a similar action as that of the CR. In future, such nutraceuticals could be of great benefit as replacement of pharmaceuticals in providing health benefits to elderly population.

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