Aging: calm before the storm of cognitive impairment: protective effect of beneficial antiaging strategies

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Abstract

A multitude of factors can affect the brain in aging, including age-related comorbid risk factors that sustain the impact of oxidative stress on several neurochemical systems. Aging perturbs volumetric changes in both the white and gray matter of the brain promoting axonopathy and atrophy in various cortical regions including the hippocampus. The pathophysiological pathways of oxidative and nitrosative stress are emphasized here based on a large body of evidence that links these stresses to aging-related pathologic processes, including neuropathology. For example, vasculature in aging has the propensity to generate an excess of reactive superoxide and hydrogen peroxide species that inhibit nitric oxide and its vasodilatory activity. Both oxidative stress and inflammation are increased in aging, and each can enhance the generation of the other in a cyclical manner. Neurodegenerative changes in cognitively intact elderly persons may be associated with deposition of neurofibrillary tangles and senile plaques of amyloid. These pathologies, however, are promoted by oxidative stress and inflammation. Moreover, the hippocampal CA1 area exhibits increasing densities of neurofibrillary tangles with age. There are significant data that link neurofibrillary tangles to neurodegeneration as a function of age and age-related comorbid conditions. However, opinion is divided on senile plaques being causative for cognitive decline. Several key interventions/approaches are described here for mitigating dysfunctional aging and neuropathology. These protective strategies should be important window(s) of opportunity for prolonging healthy longevity with attenuated age-induced cognitive impairment.

Keywords: Aging, Oxidative stress, Nitrosative stress, Alzheimer’s disease, Neuropathology, Circadian rhythm, Mitochondrial dysfunction, Endothelial dysfunction, Neurofibrillary tangles, Amyloid plaques

Introduction

The molecular, cellular, and functional alterations that occur during normal healthy aging are regarded as a consequence of adaptation and plasticity. They may also undergo an obligatory decline in dysfunctional aging. The latter is considered to arise from a combination of environmental, epigenetic, and metabolic effects. Although there is no overt loss of neurons during normal aging, however, there are subtle pathologic changes in individual neurons. These include shrinkage in soma size, loss or regression of dendrites and dendritic spines, alterations in neurotransmitter receptors, and changes in electrophysiological properties.

Ever since Harman presented the free radical theory of aging, significant corroborative evidence has documented that increased production of reactive oxygen species (ROS) correlates with cellular dysfunction in aged humans and animals. Therefore, in accordance with the oxidative stress theory of aging, ROS induce several macromolecular oxidative alterations that result in cumulative oxidative damage in aging. At the center of this theory of aging are the mitochondria specifically, the diffusion of mitochondria-derived H₂O₂, which upregulates macromolecular oxidative damage. Further, when produced in excess, mitochondrial ROS cause oxidative damage to tissues. ROS also damage mitochondrial DNA (mtDNA), thus altering mitochondrial function and causing a decrease in ATP production.

The main sources of ROS generation are the mitochondrial respiratory chain, NADPH oxidases, and nitric oxide synthase (NOS). In addition, the reduced antioxidant response mediated by enhanced erythroid-2-related factor-2 (Nrf2) and downregulation of superoxide dismutase (SOD) contribute to chronic oxidative stress in aging. The redox-sensitive transcription factor nuclear factor-κB (NF-κB), is upregulated in vascular cells from old subjects and drives a proinflammatory shift that further enhances oxidative stress. This chronic NF-κB activation is upregulated not only by downregulation of sirtuins but by increased angiotensin II signaling as well.

There are significant data that show an age-related increase in oxidative stress in the arterial system, both in humans and...
animals\textsuperscript{[14,32,33]}. Indeed, increased oxidative stress in aging causes inactivation of NO by higher $\text{O}_2^-$, and promotes increased ONOO$^-$ formation\textsuperscript{[14,27,32,33]}. Thus, a decrease in NO availability will decrease vasodilation and tissue perfusion\textsuperscript{[54,35]}. Furthermore, ROS not only cause oxidative damage and scavenging of NO, but may also have widespread signalling roles during aging, including upregulation of arterial inflammation\textsuperscript{[56-41]}. In an arterial occlusion experiment, aged mice exhibited significantly worsened infarct volume (on postoperative day 7) compared with juvenile and young mice. The effects of aging involved oxidative damage and mitochondrial dysfunction following ischemia\textsuperscript{[42]}. Thus, mitochondrial protection and reduction of ROS generation are important targets for protective therapy in the aged. Antioxidants such as vitamins C and E, or the Ginkgo biloba extract EGB 761, may protect against the age-related oxidative damage to mtDNA and oxidation of mitochondrial glutathione\textsuperscript{[17,18,43]}. Obstructive sleep apnea (OSA) is a common condition in obese elderly\textsuperscript{[44-46]}. Aging diminishes the quality of sleep with decreased sleep duration and increased time awake at night. This is exacerbated by chronic OSA-related recurrent awakenings after sleep. Dysfunctional sleep architecture is progressive in aging\textsuperscript{[47]}, from middle age onwards, it leads to a decrease in non-REM-slow wave sleep (the deepest stage). Compared with young adults, older adults awaken more, particularly from non-REM sleep\textsuperscript{[48]}. Additional non-REM changes include a reduction in sleep spindles and K-complex numbers\textsuperscript{[49,50]}, however, the amount of REM alters much less. Aging has a distinct impact on both circadian and homeostatic sleep-regulatory processes. Circadian rhythms (of temperature, melatonin, and cortisol secretion) are phase-advanced with a decrease in their amplitude. An increased number of nocturnal awakenings and increased daytime sleepiness characterizes sleep dyshomeostasis in OSA\textsuperscript{[50]}. This article considers the processes of age-related pathology from an oxidative-nitrosative stress perspective, and as such emphasizes therapeutic strategies regarding utilization of antioxidants and other relevant approaches to ameliorate age-induced metabolic dyshomeostasis. It is not intended to be all-encompassing, but highlights several salient features of aging and their impact in promoting age-related neurodegeneration. Owing to space constraint, several important references could not be included.

**Aging: pivotal factors reinforce pathophysiology—multiple hits**

**Aging and hypertension**

Nondemented older adults with long-term fluctuating blood pressure (BP) and hypertension may undergo insidious cerebrovascular disease. These hypertensive persons show enhanced volume of white matter (WM) hyperintensity compared with normotensives. Hypertensives (compared with normotensives) also exhibit an increased rate of thinning in several brain regions including the frontomarginal gyrus in the left hemisphere, and the superior temporal, fusiform, and lateral orbitofrontal cortex in the right hemisphere\textsuperscript{[51]}. Interestingly, higher midlife BP was associated with a higher rate of cortical thinning in the right superior temporal gyrus. Importantly, long-term fluctuating systolic BP (but not diastolic BP) predicted a higher rate of thinning in the 3 brain regions\textsuperscript{[51]}. **Aging and diabetes**

Type 2 diabetes mellitus (T2DM), exemplified by metabolic dysregulation (ie, hyperglycemia and insulin resistance), can have a profound influence on the brain’s vasculature, its structure, and function. The combined deleterious impact of T2DM plus hypertension exceeds their individual effects. Decreased gray matter cortical thickness (CThk) (in comparison with age-matched controls) in brain regions including posterior cingulate, precuneus, superior and middle frontal, and middle and inferior temporal were significantly associated with executive dysfunction\textsuperscript{[52]}. This demonstrates that the combined effects of comorbid T2DM and hypertension have a significant impact on the brain regions mentioned above, as well as measures of cognitive function. **Aging and sleep disordered breathing (SDB)**

Although elderly individuals tend to have decreased sleep quality and quantity, comorbid SDB may add to their sleep disruption. About 50% of elderly persons suffer from various sleep disorders including OSA, overt daytime sleepiness, insomnia, and Restless Legs Syndrome\textsuperscript{[53]}. The incidence of OSA is much higher in men\textsuperscript{[54,55]} and its prevalence increases with aging\textsuperscript{[56]}. Importantly, the number of hypoglossal motoneuron dendrites has been shown to decrease significantly with age; indeed, loss of dendrites may correlate with decreased synaptic inputs and physiological dysfunction\textsuperscript{[57]}. In cerebrovascular disease patients, SDB correlates with poorer functional prognosis and higher mortality after an acute pathophysiological event\textsuperscript{[58]}. SDB occurs more frequently in the elderly and its severity may impact cognitive impairment\textsuperscript{[48,46,58]}. **Aging impacts circadian rhythm, sleep duration, and metabolism**

Humans, like other mammals, possess a circadian clock regarding the light-dark cycle; the latter is controlled by the supra-chiasmatic nuclei located in the hypothalamus. The circadian clock synchronizes behavioral and physiological mechanisms\textsuperscript{[59]}. Elderly persons sleep earlier and wake up earlier owing to their altered normal circadian sleep cycle—viz., the phase advance. A significant shortening of the circadian period may occur in aging\textsuperscript{[60]}. **Circadian rhythm impacts mitochondria**

A complex association has been shown between aging, metabolic dysfunctions, and the circadian clock. Copious evidence suggests that age and decline in circadian rhythms are correlated. This relationship is intertwined with age-related diseases and metabolic dysfunctions\textsuperscript{[59,61]}. Normal mitochondrial function is imperative for metabolic homeostasis. During aging, ROS generation is enhanced; mitochondrial oxidative stress is upregulated in conjunction with the expression rhythms of some mitochondrial genes\textsuperscript{[17-19,62]}. Dysfunctional circadian rhythms may involve several important mechanisms including inflammation, redox dyshomeostasis, and epigenetic perturbations. The circadian clock controls nicotinamide adenine dinucleotide (NAD$^+$) synthesis and sirtuin deacetylase activity (an NAD$^+$-dependent enzyme) and regulates mitochondrial function. Dysfunction of circadian rhythms,
therefore, would have a negative impact on mitochondrial function\textsuperscript{[63,64]}.

**Discussion**

**Aging enhances oxidative stress**

A 2015 meta-analysis showed that there is a consistent relationship between shorter sleep duration in aging and higher total energy intake/higher total fat intake\textsuperscript{[65]}. A chronic association between short sleep duration and changes in dietary intake, therefore, may be linked to the development of obesity, T2DM, hypertension, cerebrovascular diseases,\textsuperscript{[65]} and ROS generation\textsuperscript{[54,55]}. Hence, it is no coincidence that pathologic risk factors in aging, such as OSA and obesity\textsuperscript{[61,62]} should be associated with oxidative stress\textsuperscript{[44–46,66,67]}. Such associations, therefore, underscore the promotion of oxidative stress in age-related comorbid conditions. Thus, health promotion strategies in aging should encompass reducing oxidative stress via improved sleep and healthy diet, as well as decreased energy intake and obesity control.

An integral aspect of aging is the impairment of cerebral blood flow and oxidative metabolism (among many other factors), which lead to neuronal loss. Older persons with severe OSA have cerebral hypoperfusion mainly in the sensorimotor and parietal areas\textsuperscript{[68]}. Indeed, cerebral ischemia is attributed, in part, to mitochondrial susceptibility to hypoxia promoting mitochondrial injury\textsuperscript{[69]}. Owing to nutritional deficiency, the elderly may be deficient in micronutrients including thiamine. Accelerated senescence-prone 8 (SAMP8) mice undergo age-related alterations in the brain showing deficits in learning and memory. The submedial thalamic nucleus (SmTN) in SAMP8 mice shows severe neuronal loss. Importantly, 8 days after thiamine deficiency (TD), loss of neurons in the SmTN of SAMP8 mice was as high as 65%. Accumulation of amyloid precursor protein in the thalamus of SAMP8 mice also occurred after TD. The above data correlate with impairment of oxidative metabolism induced by TD in senescence\textsuperscript{[70]}.

Aging upregulates oxidative stress per se, in vascular endothelial and smooth muscle cells. This may promote cerebrovascular disease. An essential aspect of healthy aging is the maintenance of endothelial function, while vascular dysfunction in aging compromises endothelial vasodilation. The latter, therefore, is an early hallmark pathology and a modifiable risk factor that precedes the clinical manifestations of cerebrovascular disease. Aging-related vascular dysfunction is promoted by higher generation of ROS and H$_2$O$_2$; these attenuate NO and its vasodilatory function and enhance the deleterious radical peroxynitrite\textsuperscript{[23]}. In the vasculature of younger animals, Nrf2 is activated by ROS, which in turn promotes expression of ROS antioxidant and detoxifying genes (NQO1, GCLC, and HMOX1). This is exemplified in cultured vascular smooth muscle cells derived from young rhesus macaques (Macaca mulatta, age: 10 y), and subjected to H$_2$O$_2$ and high glucose. This resulted in Nrf2 upregulation and increased expression of Nrf2-targeted NQO1, GCLC, and HMOX1 genes. However, the above-mentioned result was blunted in aged rhesus macaques (≥ 20 y)\textsuperscript{[71]}. Further, H$_2$O$_2$ production was higher in aged vascular smooth muscle cells than those derived from young macaques\textsuperscript{[71,72]}. Hence, aging-related Nrf2 dysfunction may exacerbate age-related oxidative stress, activate cellular NF-κB activation, and promote vascular inflammation/dysfunction.

The memory function of the old rats has been shown to decline; this was associated with apoptosis in the hippocampus. Further, following 10 days of oxidative stress, Aβ appeared in the CA1 region\textsuperscript{[73]}. In Tg2576 mouse brains, levels of soluble Aβ (both 1–40 and 1–42 oligomers) steadily increased in the cortex with age. The latter also showed peak levels of ROS and nitric oxide around 9 months of age\textsuperscript{[74]}. Indeed, healthy older adults show significant Aβ deposition (with PIB radiotracers–positron emission tomography imaging\textsuperscript{[75–78]}). Normal elderly controls (NC) from the Berkeley Aging Cohort (BAC NC) and the Alzheimer’s disease neuroimaging initiative (ADNI NC) showed Aβ deposition (with PIB–positron emission tomography), hippocampal atrophy, and episodic memory decline (sequentially) in elderly subjects\textsuperscript{[79]}. Thus, ROS, Aβ, and apoptosis in the hippocampus may synergize to cause cognitive deficit in aging in animals\textsuperscript{[73,74]} and humans\textsuperscript{[79]}.

**Oxidative stress—mitochondrial dysfunction**

In excess, ROS production may induce irreversible cellular damage and promote apoptotic pathways and cell death. A decrease in the expression of antioxidant enzymes is another reason for an overproduction of ROS. Since ROS generation occurs through mitochondrial dysfunction via impairment of oxidative phosphorylation, mitochondria are at the epicenter of cell death\textsuperscript{[80]}. A higher expression of Cu/Zn SOD in human aortic endothelial cells has been shown to suppress c-JUN N-terminal kinase and p38 phosphorylation, and attenuate intracellular NADPH oxidase activity and ROS production\textsuperscript{[80]}. Further, SOD has anti-inflammatory properties; it attenuates tumor necrosis factor (TNF)-α-induced ROS generation and adhesion molecule expression, mediated by NF-κB inactivation\textsuperscript{[80]}.

Age-related oxidative stress may promote vascular inflammation in the presence of risk factors including hypertension and/or metabolic diseases. The proinflammatory pathways, for example, via TNF-α and other cytokines, may converge on NF-κB in the aged arterial wall; the NF-κB transcriptional activity is then upregulated by the nuclear enzymes poly(ADP-ribose) polymerase (PARP) and SIRT-1\textsuperscript{[81]}.

NO functions as a messenger molecule; it is found in its highest levels in neurons. It is generated from arginine by 3 distinct NOS enzymes—viz., εNOS (from endothelial cells), nNOS (neuronal), and iNOS (inducible NOS)\textsuperscript{[82]}. Similar to ROS, an excessive accumulation of NO upregulates nitrosative (NO-related) stress, and mediates neuronal cell injury/death. S-nitrosylation—a redox reaction requiring cysteine thiol molecules—impacts neuronal function via thiol modification of proteins\textsuperscript{[83]}. The S-nitrosylation mechanism modulates several cellular physiological processes, including transcriptional activity, synaptic plasticity, and neuronal survival\textsuperscript{[84]}. Notably, N-methyl-D-aspartate receptor activation with Ca$^{2+}$ influx in neurons can induce NO to increase via neuronal NO synthase\textsuperscript{[85]}. Further, an excess of NO production via aging and disease-linked risk factors also exacerbate nitrosative stress. S-nitrosylation mediated by the formation of peroxynitrite enhances pathology, viz., mitochondrial dysfunction\textsuperscript{[86]}. Consequently, both NO excess and aberrantly enhanced S-nitrosylation encompass important pathologic features that may promote the onset and progression of neurodegenerative disorders including Alzheimer’s disease\textsuperscript{[84,85]}. 
Aging promotes endothelial dysfunction

There is endothelial dysfunction during aging\(^{[13,87]}\). In addition, there may be resting endothelial dysfunction in asymptomatic aged obese men and women (compared with ideal bodyweight or overweight adults) having predisease conditions (prediabetes and prehypertension, that is, with normoglycemia and normal blood pressure, respectively) as cardiometabolic risk factor\(^{[88,89]}\).

Endothelial dysfunction is an early insidious perturbation that precedes fatty streaks/atherosclerosis. Several pathologic factors upregulate endothelial dysfunction; these include inflammation\(^{[90–92]}\), oxidative stress/ROS\(^{[93,94]}\), nitrosative stress\(^{[95,96]}\), enhanced procoagulants\(^{[97]}\), and/or hyperglycemia\(^{[98–100]}\). Aging-associated mitochondrial oxidative stress in the cerebrovascular system upregulates lipid peroxidation. However, ROS may also induce NF-κB activation (and vice versa)\(^{[72,84,88]}\), a procoagulant state in endothelial cells\(^{[97]}\), and nitrosative stress\(^{[93]}\). Further, ROS-induced NF-κB activation may enhance the expression of proinflammatory cytokines such as TNF-α and IL-6, and inflammation; the latter may further enhance oxidative stress (via NADPH oxidase activation) cyclically during aging. This scenario is abundantly capable of enhancing arterial inflammation in aging\(^{[67]}\). The above observations, therefore, imply that mitochondrial dysfunction and higher ROS are responsible for aging-related arterial inflammation/pathology\(^{[106,72,92,101,102]}\).

Aging and WM loss

Aging is characterized by brain degeneration and a decline in cognitive function. Diffusion tensor imaging exhibits WM changes in the aging brain. The cingulum is the earliest structure that undergoes age-related WM changes\(^{[103]}\). Using diffusion tensor imaging, prefrontal fractional anisotropy was found to be decreased in older subjects compared with younger adults. Such fractional anisotropy–related microstructural index of decline was also found in the posterior limb of the internal capsule, and the genu of the corpus callosum\(^{[104]}\). During normal aging, evidence has shown deterioration of the structural integrity of myelin sheaths, for example, in the frontal lobes. In fact, the frontal lobe WM volume is taken as an indirect measure of the structural integrity of WM. Frontal lobe WM has defined WM maturation continuing into middle age; this is followed by progressive loss of myelin integrity\(^{[105]}\). The above evidence highlights that age-related breakdown of myelin and WM structural integrity may impact cortical connectivity and promote age-related neurodegenerative diseases including AD\(^{[106]}\). The ensuing network “disconnections” may conceivably impact normal functions in neural networks, and cause neuronal dysfunction and neurodegeneration\(^{[106]}\).

Further, measures of WM structural integrity have indicated that the rate and severity of myelin pathology in healthy older persons are associated with APO status; APOE4 + individuals showed the highest decline compared with individuals carrying APOE2 + and APOE3/3 alleles\(^{[107]}\). The above data on myelin degradation, as well as the association of amyloid-β protein precursor (AβPP), Ap1–42, and amyloid plaques with myelin protein, are implicated in the pathogenesis of cognitive decline and AD\(^{[108]}\).

Microglia increase the expression of iNOS and ROS production, and this activation has been shown to promote demyelination and axonal damage\(^{[109]}\). However, blocking microglial activation significantly reduced both axonal damage and demyelination\(^{[109]}\). Indeed, oxidative stress-related mitochondrial dysfunction, ROS production, and energy depletion, as well as myelin and axonal damage may contribute to age-related neurodegenerative conditions including AD\(^{[109,110]}\).

Aging and gray matter (GM) loss

There is significant evidence that the brain is plastic and its volume changes throughout life. Indeed, the phenomenon of GM decrease during aging has been documented in humans\(^{[111]}\) and animals\(^{[112]}\). In a meta-analysis, data on brain volume from healthy individuals were analyzed from 56 longitudinal studies utilizing magnetic resonance imaging (MRI) methodologies. A steady GM volume loss of 0.2% per year occurs after the age of 35 years; the loss gradually continues to increase to 0.5% at age 60, and further exceeds in individuals over the age of 60 years\(^{[113]}\). During healthy aging, widespread age-related volume differences exist in GM of the cerebral cortex—in pallidum, putamen, and nucleus accumbens, but not the brainstem. In addition, the caudate and hippocampus showed nonlinear age-related GM changes\(^{[114]}\). In 169 cognitively normal subjects, 1 interesting data set revealed older age–associated GM volume atrophy in the sensorimotor and heteromodal association areas in frontal, temporal, occipital, and parietal lobes, as well as in the cerebellum\(^{[115]}\). Additional atrophy was observed in the posterior hippocampus, thalamus, and the middle cingulate gyrus. In normal elderly persons, cerebrospinal fluid tau markers have been shown to be associated with lower GM volume in the precuneus (utilizing voxel-based morphometry)\(^{[116]}\). Individuals with hypertension had higher GM atrophy in the cerebellum, occipital, and frontal regions.

Importantly, subjects with higher p-tau(231) and p-tau(231)/Aβ42 had lower GM in the temporal lobes. Further, low Aβ42/Aβ40 was also associated with less GM in many brain regions including the thalamus, caudate, and midbrain\(^{[116]}\). These results are significant in that they are present when there is no cognitive impairment.

It is possible that in the above-mentioned studies on so-called healthy individuals, some may be asymptomatic elderly in a prodromal state, who might later show clinical neurodegenerative disease\(^{[117]}\). As they are asymptomatic, they may be categorized as “healthy,” while their underlying subclinical pathology smoulders undetected. Consequently, it is not surprising that the age-related loss of brain parenchyma varies considerably across brain regions among different individuals. It is from the stable elderly cohort with normal levels of cognitive performance that the declining elderly cohort who convert to cognitive impairment arise. It is beyond the scope of the current article to further discuss for and against the proposition that GM shrinkage is inherent in healthy aging. Nevertheless, brain volume decrease may arise not only from neuronal loss, but also from heterogenous members of the neuropil, including axons, dendrites, synapses, and glia. However, detailed longitudinal studies are required on the differential impacts of aging on the above structures of the GM.

Aging and neuropathology

The brains of a substantial percentage of cognitively normal elderly people contain degenerative changes. Compared with this, only a small percentage of older individuals possess brains free from such changes. Elderly subjects devoid of cognitive
impairment may contain senile plaques (SPs) and/or neurofibrillary tangles (NFTs) in their brains\textsuperscript{[118]}. The distribution of NFT and SP varies among the cortical regions with age\textsuperscript{[119]}. The hippocampal CA1 area of the inferior temporal cortex exhibited increasing densities of NFT with age\textsuperscript{[119]}. In studies of a cognitively intact older population, NFT were evident in layer II of the entorhinal cortex. In all subjects, amyloid deposition as SP was not correlated either with age or with the NFT number\textsuperscript{[120]}. Indeed, an age-related increase in phosphorylated tau has been documented in mice\textsuperscript{[121]} and monkeys\textsuperscript{[122]}. However, there was evidence of progression of NFT from the entorhinal cortex to the hippocampus and amygdala as a function of age\textsuperscript{[118]}. It is noteworthy that, in several cases, NFT was present without amyloid deposition, but amyloid deposition never occurred without NFT\textsuperscript{[123]}. Finally, interesting work has shown in normal individuals that elevated phosphorylated tau is related to progressive atrophy of crucial brain regions such as the medial temporal lobe, and a decrease in declarative memory\textsuperscript{[124]}. The neuropathologic changes noted in the hippocampus in normal brain aging are associated with age-related memory impairment\textsuperscript{[125]}. The patterns of lesion distribution in cerebral aging were reviewed in the clinicopathologic analysis of 1144 nondemented subjects. Invariably, layer II of the entorhinal cortex was affected with NFT in all cases. Neocortex area 20 was particularly susceptible to NFT accumulation in intellectually intact seniors, while other neocortical regions were relatively spared. Substantial SP may be present in the neocortex of nondemented cases. The extent of SP deposition, however, was not correlated with the clinical diagnosis of cognitive impairment\textsuperscript{[123]}. In contrast, MCI was correlated with quantitatively higher NFT densities in layer II of the entorhinal cortex\textsuperscript{[125]}. This conclusion has been reached repeatedly in that amyloidosis alone in the brain is insufficient to produce cognitive decline\textsuperscript{[126,127]}. On the basis of the pathologic distribution of NFTs and SP, and the WM and GM pathology, it is conceivable that a global corticocortical disconnection may greatly increase the odds of developing cognitive pathology, and thus lead to memory dysfunction, observed in amnestic MCI and AD. A detailed discussion on the relative roles of SP and NFT in the pathogenesis of dementia (in neurodegenerative disease/AD) is beyond the scope of this paper.

**Beneficial antiaging strategies**

First and foremost, elderly individuals suffering from OSA, hypertension, T2DM, and obesity should have these conditions treated with appropriate and effective treatments. In addition, appropriate strategies must be used to retard aging and to prolong longevity. The following antiaging strategies are not exhaustive; however, they are considered important.

**Dietary supplements**

Vitamins C and E and the *Ginkgo biloba* extract EGb 761 are antioxidants that may protect against the oxidative damage to mtDNA and oxidation of mitochondrial glutathione\textsuperscript{[17,18,43]}. **Fish oil (FO)**

Metalloprotease (ADAM17 and ADAM10) stimulate inflammatory processes via TNF-α and IL-6 and promote vascular disease. FO supplementation has been shown to be effective against inflammation and atherosclerosis. FO decreased ADAM activity, improved endothelial barrier function, and reduced intimal lipoprotein and macrophage accumulation\textsuperscript{[128]}. FO is rich in n-3 polyunsaturated fatty acids and may modify key risk factors for cerebrovascular disease. In 1 experiment, mice were fed a high-fat diet (HFD), whereas others were fed an HFD with FO. This FO treatment increased NO release and its availability and enhanced endothelial NO synthase activity; these effects protected endothelial cell function and improved mitochondrial function\textsuperscript{[129]}. **Quercetin**

Quercetin is a polyphenol derived from fruit (apples) and vegetables and contributes to cardiovascular health. The effects of dietary quercetin on endothelial function and atherosclerosis were studied in mice fed an HFD. Quercetin protected HFD-fed mice against oxidant-induced endothelial dysfunction and atherosclerosis. Indeed, quercetin activates genes involved in mitochondrial biogenesis and oxidative metabolism in HFD-fed obese mice\textsuperscript{[130]}. The mode of action was found to be via hemeoxygenase-1 (HO-1). HO-1 is an antioxidant enzyme that protects against oxidative stress, inflammation, and metabolic dysregulation. Indeed, quercetin stimulates hepatic mitochondrial oxidative metabolism through HO-1 induction via the Nrf2 pathway\textsuperscript{[130]}. **Mediterranean diet**

Some specific dietary restrictions may have a beneficial impact on the organism and the brain, and may increase resistance to aging and cognitive dysfunction. In a cross-sectional study, MRI data were collected on 674 cognitively intact elderly people. The correlation between a Mediterranean-type diet (MeDi) and brain volume or CThk has been documented\textsuperscript{[131]}. Compared with lower MeDi adherence, higher adherence was associated with larger total brain volume (TBV, ie, the sum of WM and GM)—total GM volume and total WM volume. Larger TBV was associated with lower meat intake, while higher fish consumption was associated with larger mean CThk. Thus, lower meat intake but higher fish consumption seems to be the crucial MeDi food factor that provides the beneficial impact\textsuperscript{[131]}. Indeed, higher fish but lower meat intake, also found that consuming MeDi results in greater TBV and to better cognitive performance. Similarly, a meta-analysis of 5 studies on cognitively normal individuals showed that higher adherence to the MeDi intake was associated with reduced risk of MCI and progression to AD. In 2014, the association between adherence to MeDi and reduced cognitive decline was investigated in cognitively normal individuals using MRI. Subjects with higher adherence to MeDi showed a greater thickness of AD-related vulnerable regions as compared with lower adherence subjects. Results were most pronounced in the orbitofrontal cortex, entorhinal cortex, and posterior cingulate cortex of the left hemisphere\textsuperscript{[132]}. **Probiotics**

Probiotics contain live beneficial bacteria and possess a defined health benefit; moreover, they are accepted as safe. Indeed, studies have reviewed the healthbenefit from probiotics in obesity and excess intake of fat\textsuperscript{[133,134]}. Ingestion of certain probiotics can reduce lactose intolerance and rotavirus-related diarrhea.
Indeed, some studies suggest probiotics to exert an antiaging effect.

**Caloric restriction (CR)**

CR is an important intervention that delays aging in a wide variety of species from yeast to mammals. CR, renin-angiotensin system (RAS) blockade (RAS-bl), and the mammalian target of rapamycin (mTOR) inhibition are beneficial to increase survival and retard aging across species\[135\]. Sirtuins (via deacetylating histone and transcription-related proteins) modulate signalling and survival pathways and mitochondrial functioning. CR regulates several mammalian sirtuins that enhance healthy aging. Readers interested in the details of physiological pathways sub-served by CR, RAS-bl, and mTOR should consult de Cavanagh et al\[135\]. A study in 2014 documented that long-term CR significantly improves age-related survival in rhesus monkeys and reduces age-related and all-cause mortality\[136\]. Mice that exhibit reduced eating (as in alpha-MUPA transgenic mice) live longer and show high amplitude in clock gene expression; they display appropriately reset circadian rhythms and clock-controlled feeding times and body temperature\[137\]. Indeed, the effect of CR involves resetting of the circadian clock, thus leading to synchrony in metabolism and physiology.

**Important antiaging pharmacotherapy**

**Angiotensin II receptor antagonists**

Several studies have targeted the RAS to improve metabolic and cardiovascular function and T2DM. Clinical trials undertaken to improve glucose tolerance and insulin sensitivity through the inhibition of the RAS have reported consistent results regarding reduction in the incidence of T2DM in hypertensive patients treated with angiotensin II receptor antagonists\[138\]. Indeed, angiotensin II blockade has been suggested to be a strategy in slowing down aging through mitochondrial protection\[139\].

**Melatonin**

Disrupted circadian functioning is associated with dysfunctional aging. Desynchronization of circadian rhythms has a negative impact on the health of animals and humans and increases morbidity and mortality. Hence, resynchronization of metabolic and physiological functions through the circadian clock may slow down the aging process. Oxidative stress is associated with impaired circadian rhythm. Melatonin is a pleiotropic regulator molecule that interacts directly with some physiological processes\[140\]. Melatonin is important owing to its action of reducing oxidative stress. Indeed, melatonin has several beneficial effects; it is a well-documented circadian rhythm synchronizer, a free radical scavenger, an anti-inflammatory and immunoregulator, and an antiaging molecule\[140-142\].

Melatonin is a versatile molecule that maintains homeostasis through various pathways. Some of these include: prevention of temperature rhythm disruption and hypothermia\[141\], increasing hippocampal synaptic density, synaptic proteins, and neuroplasticity\[141\]; reversing the toxic effects of H2O2 and protecting against H2O2-induced cell death; and reducing induction of Bax, caspase, calcium overload, and cell death\[138,144\]. The above may enhance Nrf2 (the master regulator of redox homeostasis) induction, antioxidant effects, and neuroprotection\[145\]; and function as an anti-inflammatory, reducing Aβ and tau, and ameliorating cognitive decline\[140\]. Hence, it has been recently recommended that melatonin should be used to attenuate cognitive dysfunction and memory improvement in AD\[140,145\].

**Pioglitazone**

Thiazolidinediones are beneficial in age-related comorbid conditions such as T2DM. Long-term pioglitazone treatment (using a clinically relevant dose) during normal aging was able to blunt several indices of aging\[146\].

**Exercise**

Neurogenesis in hippocampal dentate cells is facilitated by physical exercise\[147\]. Physical activity is associated with cardiorespiratory fitness and beneficial effects on GM volume of the hippocampus and prefrontal cortex in older adults\[148\]. Physical exercise enhances satellite cell activity in skeletal muscles and improves regenerative capacity. Indeed, exercise training has various benefits on lifestyle factors, including activities of daily living, quality of life, and indeed greater survival.

**Conclusions**

Aging is the major risk factor for several common neurological disorders such as Alzheimer’s disease and Parkinson’s disease. Normal brain aging is associated with subtle alterations in specific neuronal circuits. However, aging of the central nervous system induces neuronal atrophy, synaptic atrophy, cytoskeletal abnormalities, and activation of astrocytes and glia. During aging, dendritic spines—the major sites for excitatory functions—decrease in number. Further, aging triggers volumetric changes in both WM and GM of the brain, promoting axonopathy and regional atrophy in the cortex, including the hippocampus. The above mentioned is associated with a decline in cognitive performance.

Oxidative stress increases in aging; it is mediated by several age-related medical conditions, for example, OSA, T2DM, hypertension, and obesity. Mitochondria are implicated as the major source of ROS generation. NADPH oxidase is involved in ROS increase in the vasculature owing to high glucose and advanced glycation end-products, and Aβ deposition. A major factor in aging is vascular aging mediated by endothelial dysfunction. Increased ROS generation leads to oxidative stress, nitrosative stress (loss of NO signaling), and vascular inflammation. The latter, in turn, causes an increase in ROS production. This cascade of events, therefore, may upregulate cognitive impairment. However, some available beneficial antiaging strategies may counter aging-related pathologies.

**Conflicts of interest statement**

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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