Chapter

Primary Prevention of Alzheimer's Disease (AD)

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Abstract

Alzheimer dementia (AD) is a complex, aging-associated disease whose effects on the brain (an organ made up by nonreplaceable cells) are devastating. Disease is not curable, but progress in pathobiology shows that intervention on aging can make primary prevention of AD feasible. According to the amyloid-cascade hypothesis, mechanisms of AD include: an age-related alteration of free radical metabolism in membranes, leading to a higher yield in the toxic Aβ1-42 peptide and an overwhelming impact on the weaker repair mechanisms of the aging cells. The proposed intervention on aging with anti-AD effects includes a daily assumption of antioxidants (red wine polyphenols enriched with resveratrol), a reinforcement of membrane antioxidant defenses by the assumption of polyunsaturated fatty acids at the first meal after fasting, and an enhancement of cell repair function (at the proteasome and autophagy level by an intermittent feeding regimen and physical exercise plus the assumption of antilipolytic agents during time of fasting). The beneficial effects of diet and physical activity on the endogenous production of protective nerve growth factors are magnified by an enriched environment. Treatment has already been started on healthy individuals at a higher risk of AD in the city of Volterra.

Keywords: Alzheimer's disease, proteasome, autophagy, antioxidants, PUFAs, APP, cholesterol, antilipolytic drugs, calorie restriction, physical exercise, brain plasticity, nerve growth factors

1. Introduction

Like many other degenerative diseases, AD is an irreversible and progressive cerebropathy, the cause of one of the most common types of dementia affecting the elderly. It is a brain disorder characterized by the accumulation of two main protein aggregates, senile plaques and neurofibrillary tangles, leading to a progressive neuronal degeneration. It causes death after years of disability, progressive loss of memory, inability to perform normal daily activities, and, finally, dementia. The senile plaques are generated by the deposition in human brain of fibrils of the β-amyloid peptide (Aβ), a fragment derived from the proteolytic processing of the amyloid precursor protein (APP). There is evidence that oxidative stress might be the main factor that turns APP into a proteolytically processable substrate. The neurofibrillary tangles (NFTs) are seen as a compact filamentous network formed by paired helical filaments (PHFs), whose major component is a hyperphosphorylated Tau protein. Two main protein kinases appear to be involved in the anomalous tau phosphorylation: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3. Dysfunction of the ubiquitin-proteasome system may be the cause [1]

possibly together with a secondary failure of the engulfed lysosomal degradation resulting in apoptosis. Pathology is a consequence of the extensive neuronal death, and when it manifests clinically, it is already incurable. Human, social, and health costs of this incurable disease are immense. It is highly desirable indeed an effective primary prevention to postpone the appearance of the debilitating manifestations, hopefully to the time of death.

2. Biological aging: Is it a major risk or the basic causative factor for neurodegeneration?

Age is the main factor in major debilitating and life-threatening conditions, including cancer, cardiovascular disease, diabetes, and neurodegeneration, all of which are therefore increasing in prevalence [2]. Nowadays almost all can make it to the old and nobody can say anymore that reaching old age is a fortune, and between those who should solve social and health problems of older people prevails the old slogan "old age is not a disease." For many scholars, however, modern scientific discoveries confirm the deductions of ancient philosophers: all living beings, without exception, would be affected by an innate chronic degenerative disease, we call it aging, characterized by having an incubation period as long as be compatible with the reproductive success of the species. If aging is a disease and not a simple disability and disease risk factor, it is not surprising that the diseases associated with it (cancer, neurodegeneration, atherosclerosis, diabetes, etc.) can be regarded as signs or easily preventable complications, all together, by fighting the underlying disease. The prescription is simple but hard to follow a sober physically active lifestyle; to eat fruits, vegetables, fish, and little red meat; to take food after having been hungry for a few hours; to take supplements rich in polyunsaturated fatty acids (PUFAs) after dinner regularly; and to make good use of all functions of all organs of our body, including brain. This is exactly what cardiologists, diabetologists, oncologists, and neurologists all recommend for primary prevention. Understanding exactly the causes of aging and of all age-associated diseases may help to tackle the growing problem of neurodegeneration. Free radicals are the root of all evil. They may be generated either by endogenous (metabolic) causes or by environmental factors, including pollution (living less than 50 m from a major traffic road may increase hazards ratio of incident dementia by a 10% [3] and even oral hygiene and chronic inflammation [4]). Perhaps, we should remind here the oxygen paradox: without oxygen we die in minutes; with oxygen we grow old and die [5]. Oxygen is actually slowly poisonous, and it just takes 75–100 years to kill us, difference depending on how much we use and how we deal with it and repair the endogenous oxidative damage to protein, lipids, and (most important) DNA responsible for intrinsic aging, as well as the additional free radical-mediated damage from the inflammatory responses and environmental factors (e.g., ionizing radiation) [6]. It was computed that the oxygen consumption of human brain may be higher than 3 mL (i.e., about 1020 oxygen molecules)/g/min. In humans, over 99% of these molecules do generate water safely, but 10^{18} per min will produce free radicals, approximately 10^{6} free radicals per cell per min. It was estimated that the number of oxidative hits to DNA in the human cell per day is about 10,000 and that DNA-repair enzymes efficiently remove 99.9% of the lesions formed so that only one oxidative lesion accumulate in the DNA of any cell every day. This is not nothing: it makes over 30,000 lesions in a long life [7]. Since there are about 20,000 genes in human cells, by the age of 100 years, all neurons may carry about two mutations a gene on the average. Why be surprised if over time cell functions are reduced?

3. Pathology of AD

With AD patients, the brain is smaller than normal and of reduced weight. A reduction of the thickness of the convolutions is evident. Atrophy is more evident in the temporal lobe, particularly in the parahippocampus, but also in the frontal and parietal regions. The occipital lobe and the motor cortex may be spared. Histologically, several major changes are recognized in AD. Amyloid, consisting of accumulations of Aβ peptide, is deposed in the cerebral cortex in the form of spherical deposits called senile plaques. Intraneuronal inclusions are formed in the cortical neurons, constituted by abnormal, often flame-shaped, bundles of filaments called neurofibrillary tangles, which occupy a large part of the neuronal cytoplasm, and are made up of a protein that binds to the microtubules, called tau protein. The processes of the cortical nerve cells diverge, twist, and dilate due to the accumulation of filaments in the form of tangles [8]. Changes are due to oxidative stress damage and to the relative failure of repair mechanisms at the molecular and subcellular (autophagy) level and result in the disruption of the neural network (**Table 1**). It is customary to distinguish two forms of AD. There is indeed a precocious rare form that occurs between 30 and 60 years, with a peak in the fifties, with a formation of the amyloidogenic peptide Aβ (1-42) from APP genetically favored by particular isoforms of presenilin 1 and 2 or of APP. The other form, sporadic, more frequent, late-onset (observed after age 65 with a frequency that increases with age) is due to the progressive increase in oxidative stress and decline with increasing age in mitochondrial and peroxisomal maintenance and in the efficiency of the mechanisms that neutralize free radicals and repair damage. This latter form might be postponed successfully to time of death by anti-aging interventions (nutrition, physical activity, damage repair, nerve growth factors).

4. The primary cause of AD and the roles of cholesterol and unsaturated fatty acids

It is obvious that native APP cannot be the ultimate substrate for γ-secretase trimming. Hence, both with the earlier and the later form of AD, the rate of Aβ

Mechanism of repair	**Effects of the age-related decline**
Molecular level	
DNA repair Proteasome Phospholipid repair	Accumulation of DNA lesion Accumulation of altered proteins Changes in polyunsaturated fatty acids
Subcellular Level	
Autophagy and lysosomal function	Accumulation of altered mitochondria Accumulation of protein aggregates Changes in membrane proteins and lipids
Cellular and tissue level	
Apoptosis	Accumulation of damaged, misfunctional cells in all tissues

There is evidence that the above-mentioned repair mechanisms are responsible for cleaning cells from any produced waste and for getting tissues rid of irreversibly altered cells. In younger persons, functions are redundant but progressively decline with increasing age, and may gradually fail in older persons resulting in the accumulation of "waste" in cells and tissues. On a healthy life, "waste" is the limiting factor for cell and tissue "cleaning" activities, but waste recognition-acuity co-varies with cell and body request for nutrients and repair. Function of all repair mechanisms are inducible (or suppressible) depending on life style. Benefits from healthy life style, diet restriction, and physical activity depend at least in part from the induction of repair mechanisms.

Table 1.
Effects of failure of repair mechanisms at the molecular, subcellular, and cellular level.

production from APP should depend on a higher production of the ultimate substrate, possibly by a posttranslational modification of the APP molecules, likely to be secondary to oxidative stress. Age-related changes in the machinery that protects membrane proteins from free radical-mediated injury might help to account for age dependency [9]. With regard to the higher production of Aβ (1-42) in AD patients, a displacement of the free radical-mediated attack from the wanted site in the APP molecule might account for the higher involvement of the β and γ secretase pathways and the higher yield in Aβ 1-42. The effect may be favored either by genetic factors and/or aging.

4.1 Role of cholesterol

Elevated cholesterol levels may be associated with a higher risk of AD [10]. Evidence was found suggesting an intimate connection between APP processing and lipid rafts [11]. An age-related increase in cholesterol and oxidized cholesterol products (namely 24-hydroxycholesterol and 27-hydroxycholesterol) was shown indeed to be increasingly associated with AD progression (brain levels are higher in AD patients, and levels of 24-hydroxycholesterol, 27-hydroxycholesterol and cholesterol in the cerebrospinal fluid appear to be useful biomarkers for the evaluation of mild cognitive impairment (MCI) and AD, together with Aβ42, total tau, and phospho-tau) [12]. It has been shown recently that higher total cholesterol levels in the blood are observed long before the clinical manifestation of MCI and AD in patients without psychiatric or somatic comorbidities and are independent of APOE genotype [13]. However, evidence was produced that changes in cholesterol metabolism in AD may not be the primary cause of the disease (see below): they may simply be a tightly associated sign with Aβ production by sharing a common cause (a higher intramembrane oxidative stress) (see below).

4.2 Role of polyunsaturated fatty acids (PUFAs)

PUFAs and their oxylipins may affect the onset of AD [14]. The administration of omega-3 fatty acids may cause a dose-dependent reduction of triglyceridemia and cholesterolemia and exert an antiatherogenic effect [15]. With regard to mechanisms, in view of the proposed protective role of unsaturated fatty acids in phospholipids against the free radical-mediated injury of membrane proteins [9], it should be mentioned that the distribution of unsaturation (the trap for unpaired electrons) across the membrane leaflets is not uniform, and minima (the least protected areas from oxidative stress) were observed close to the C-6 site (i.e., very close to the membrane exterior, to the phosphorylable site of HMGCoAR, and to the vulnerable site of APP) and at the C-15 and C-17 levels (closer to the free radical conductor dolichol) [16]. Quite interestingly, signal might help focus free radical-mediated injury on the right target; more interestingly, in ad-libitum-fed (shorter-lived) rats, is its recognizability that may fade on aging: the abundancy of double bonds near the C-6 site (but not at the C-15 and C-17) indeed appears to increase up to a doubling by age 24 months. Furthermore, this age-related change is prevented in part by nutritional anti-aging intervention [17]. Perhaps age-related changes in the production of Aβ1-42, in the activity of HMGCoA reductase, and in the PUFA content of membrane phospholipids are all somehow bound together and involved all in the risk of AD. As an additional comment, beneficial intervention on Aβ1-42 production may require the administration of antioxidants (e.g., polyphenols and resveratrol) to curb oxidative stress and of omega-3 fatty acids at a high dosage at the first good meal after fast (on the anabolic phase of metabolism) to counteract age-related changes in phospholipid unsaturated fatty acids and increase membrane

resistance to oxidative stress. An enhancement of the membrane turnover rate may be useful (e.g., by dietary restriction and/or pharmacological stimulation of autophagy) [18].

5. The pathogenesis of AD

The hypothesis of the amyloid cascade attributes to beta-amyloid, the responsibility of all cases of AD, and considers the tau pathology and other degenerative changes secondary to the Aβ pathology. Indeed, the extracellular accumulation of Aβ, a hallmark of AD, produces ROS, including hydrogen peroxide (H_2O_2) in the presence of Fe^{3+}or Cu^{2+} [19, 20]. The amyloid β-peptide responsible for AD is generated within the transmembrane domain (TMD) of a C-terminal fragment of the amyloid β protein-precursor (APP CTFβ) by the proteolytic action of the γ-secretase complex [21]. Very interestingly, it was shown that some mutation(s) that promote destabilization of TMD helix might affect the length of the accumulated Aβ species and the ratio of the toxic Aβ42 to the safer Aβ40 peptide and may result in a young-onset AD [22]. Hence, the speculation may be invited that a free radical-induced modification in (some) amino acids of APP close to the C-6 carbon of phospholipid fatty acids might have a similar effect and enhance amyloid deposition. With regard to disease progression, many different active factors in sequence would determine timing of neuronal damage and symptom development, such as: (1) an overproduction of the toxic Aβ peptide (1-42) for genetic reasons and/or decrease in the quality of the antioxidant device of the membranes, (2) an ensuing increase in Aβ excretion in the oligomeric form may concentrate the redox-active copper at neuronal membranes before stacking in amyloid fibrils to form an ROS generating complex, (3) oxidative stress may be enhanced with an ensuing increase in lipid peroxidation and di-tyrosine formation, and (4) inflammation and activation of the microglia, which may further increase free radical generation, spread lytic enzymes, and cause cytotoxicity and anticipation of apoptotic neuronal death [23].

6. AD-associated changes in cholesterol metabolism

Abnormal cholesterol metabolism is an established feature of AD: levels of cholesterol are increased in MCI subjects and levels of 24-hydroxycholesterol and 27-hydroxycholesterol are elevated compared to controls both in AD and MCI subjects [24]. It appears that the rate of cholesterol production may be boosted by a free radical attack via a constitutive activation of HMGCoA-reductase, the rate-limiting step in sterol biosynthesis. Mechanism was clarified by Bergamini group in Pisa in cooperation with Trentalance group in Rome: in the rat, a free radical attack may prevent AMP-dependent protein kinase from phosphorylating a serine residue close to the C-terminus of HMGCoA reductase, Ser 872 with human enzyme [25, 26]. It has been proposed by several authors that higher cholesterol may disturb the lipid raft domains in various membrane organelles and affect the functioning of α, β, and γ secretases as well as APP itself and the production of Aβ 42; and that by converse, the toxicity of Aβ may be produced, in part, by disturbing the composition of the lipid raft domains in which they reside [27, 28]. Both with in vitro experiments and with animal models, statins strongly lowered blood cholesterol and reduced the levels of Aβ peptides, Aβ 42 and A β40 [29, 30]. However, a statistically significant correlation between two events does not necessarily imply the existence of a causal link: an alternative explanation is that the events share a common cause. This might

be the case here: aging is known to lower antioxidant defenses, and any increase in oxidative stress either in vitro (e.g., by UV radiation of isolated rat liver cells) or in vivo (by chronic deprivation either of vitamin E or PUFA) may cause the constitutive increase in HMGCoA reductase and deregulate cholesterol synthesis [26, 31].

7. Alzheimer's disease: treatment or prevention strategies?

The pharmacological treatments for AD can be divided into two categories: symptomatic treatments such as acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists and etiology-based treatments such as secretase inhibitors, amyloid binders, and tau therapies [32].

Despite significant investments in therapeutic drug discovery programs, no drugs to alter the course of disease have been found so far. Only four drugs with cholinergic (donepezil, galantamine, rivastigmine) or glutamatergic activity (Memantine) are currently approved and marketed for the treatment of AD-associated dementia, and their utility is very limited; several trials on inhibitors of γ-secretase and β-secretase have been discontinued; the available drug treatments of AD are merely symptomatic and unsatisfactory, and only minor benefits are obtained even if therapy is started at a very early time [33]. By the way, the physiological function of the amyloidogenic peptide has not been clarified yet, though it may be synchronized with life history [34].

In conclusion, no effective therapy is available to cure AD so far, and attention had to be shifted to the primary prevention of the disease. It was realized indeed that there is an extremely long, symptom-free prodromal phase in the path toward dementia in which deficits in synaptic density and plasticity are the principal alteration [35]. As an additional comment, better diagnostic tools and earlier diagnosis are needed (earlier timing is an important factor for the success rate of intervention), and novel strategies toward primary intervention may be wanted [36].

Problems in primary prevention were tackled recently. Qiu et al. [37] stressed the potential risk roles of vascular risk factors and disorders (e.g., cigarette smoking, midlife high blood pressure and obesity, diabetes, and cerebrovascular lesions) and the possible beneficial roles of psychosocial factors (e.g., high education, active social engagement, physical exercise, and mentally stimulating activity) in the pathogenetic process and clinical manifestation of the dementing disorders. Paillard-Borg et al. [38] showed that the participation in activities (mental, physical, or social activity) can retard the onset of dementia significantly (a 17 months' delay was seen in mean age at dementia onset between an inactive group and the most active group).

It may be worthwhile to remind here that the primary risk factor for AD is old age and that the prevalence of AD and other age-related dementias increases with increasing age [2]. It is very surprising, indeed, that little attention has been given so far to benefits from the most effective antiaging interventions (dietary restriction and physical activity) on the age of onset of neurodegeneration [39].

Antiaging diet restriction is known to be the most effective intervention that retards aging and extends lifespan and health span. Effects are known to involve the activation of macroautophagy, a cell repair mechanism [40] that can be intensified by the administration of antilipolytic agents during fasting to safely improve cell housekeeping and boost the benefits of caloric restriction [41]. Physical exercise, which is available at low cost and largely free of adverse effects, is another powerful antiaging strategy that can influence, at least partly, most of the hallmarks of biological aging [42]. It is known that greater levels of physical activity are associated with decreased risk of a future diagnosis of MCI or AD [43], extend longevity, and

reduce the risk of physical disability and may be an important adjunct to pharmacological treatment of AD [44].

Looking at mechanisms, it appears that dietary restriction and physical exercise share common neuroprotective mechanisms and should be included both in primary prevention of AD to increase the quality of nerve cells and oppose neurodegeneration and apoptosis (the third item in the **Table 1**, a repair mechanism harmful to brain) and give synergic support in a "train body and brain" program aimed to enhance neurotrophic antiapoptotic signals and defer or suppress neuron misfunctioning and death [45].

Antiaging diet restriction improves metabolism and promotes rejuvenation (by stimulating autophagy) of visceral organs that talk to brain via the vagus nerve and spinal afferent nerves [46]. Physical exercise improves metabolism and promotes rejuvenation of the lean body mass by the process of autophagy, which is very active in skeletal muscle and more intense when strenuous exercise is performed in the fasted state [47] and helps communication of the exercising muscle with the brain via increase in the discharge frequency of thinly myelinated (Group III) and unmyelinated (Group IV) nerve fibers [48]. Under these conditions, physical exercise is good both for physical health and mental health and abilities, and constitutes a practical neuroprotective strategy that provides a remarkable protection against brain insults of different etiology and anatomy [49].

Quite interesting, it has been clarified that dietary restriction and physical exercise share also common neuroprotective metabolic mechanism: the increased availability to brain of 3-hydroxybutyrate and an ensuing endogenous production of the brain-derived-neurotrophic-factor BDNF [50], and thus, both shelter the aging brain from memory loss and neurodegeneration, ameliorate mitochondrial function, and reduce the expression of apoptotic and inflammatory mediators [51]. As an additional evidence: both treatments safely modulate the endogenous production of BDNF, a neurotrophin that is vital to the survival, growth, and maintenance of neurons in key brain circuits involved in emotional and cognitive function [52, 53]. As an additional benefit, sustained levels of physical exercise together with dietary intervention may increase brain uptake of physiologically relevant neuroprotective trophic factors, such as IGF-I [49].

In conclusion, both (dietary and physical) interventions should be included in primary prevention of AD to increase quality of nerve cells and oppose neurodegeneration and apoptosis to implement reported programs aimed to enhance neurotrophic antiapoptotic signals and defer or suppress neuron misfunctioning and death.

8. The "train body and brain" protocol for a primary intervention on AD in the city of Volterra (Tuscany, Italy)

In view of the continuing increase in the prevalence of dementia to a magnitude growing to emergency [54, 55], a free of charge program to train people at higher risk of disease has been started in the Italian city of Volterra. Since AD is an aging-associated multifaceted disease that is hard to treat by single-modal treatment, a corresponding multifaceted preventive approach was included in a teaching program on how to counteract in practice the effects of biological and pathological aging on human body and brain.

Program includes activation of the global antioxidant defense system in order to attenuate the AD-causative oxidative stress, improvement of the function of the free radical conducting mechanism responsible for membrane resistance to oxidative stress, reinforcement of cell repair mechanisms at the molecular and subcellular

level by dietary and physical intervention, and targeted high-intensity training of cognitive brain functions to boost the induction of neurotrophic factors by the physiological mechanism. Here, a few details on protocol are given.

a. Strengthening antioxidant defenses by nutritional intervention. It is said that the efficiency of antioxidant defenses may be boosted by eating the colors in the peel of fruits and vegetables that are known to contain complex mixtures of polyphenols and other phytochemicals. (e.g., polyphenols in blueberries and red grapes and wine [56]; epigallocatechin-3-gallate in green tea [57]; total phenolic, flavonoids, and flavonols in pomegranate [58, 59]). Red wine is particularly rich in specific polyphenolic compounds that appear to affect the biological processes of AD and Parkinson's disease, such as quercetin, myricetin, catechins, tannins, anthocyanidins, resveratrol, and ferulic acid. Indeed, there is now a consistent body of in vitro and in vivo data on the neuroprotective activity of red wine polyphenols [60], and it is known that effects may be boosted by adding more resveratrol [61]. Obviously, to enjoy optimum benefits, participants are taught to assume phytochemicals in a way to ensure protection throughout the day.

b. Increasing the resistance of cell membranes to oxidative stress. In order to get a better resistance to ROS-induced damage to brain and prevent from neurodegeneration and neuronal apoptosis, participants are instructed to a timed assumption of omega-3-rich fish oil. PUFAs are essential to control oxidative damage to neurons [62] when they are incorporated in the phospholipid molecules as a part in the proposed antioxidant machinery that protects membrane proteins from peroxidation (**Figure 1**) (On the contrary, free PUFAs are very sensitive to a free radical attack and ready to peroxidation.) To get full benefit from supplement, participants are requested to take pills at the first good meal after the long time of fasting, when chances to be incorporated in membrane phospholipids are paramount [63].

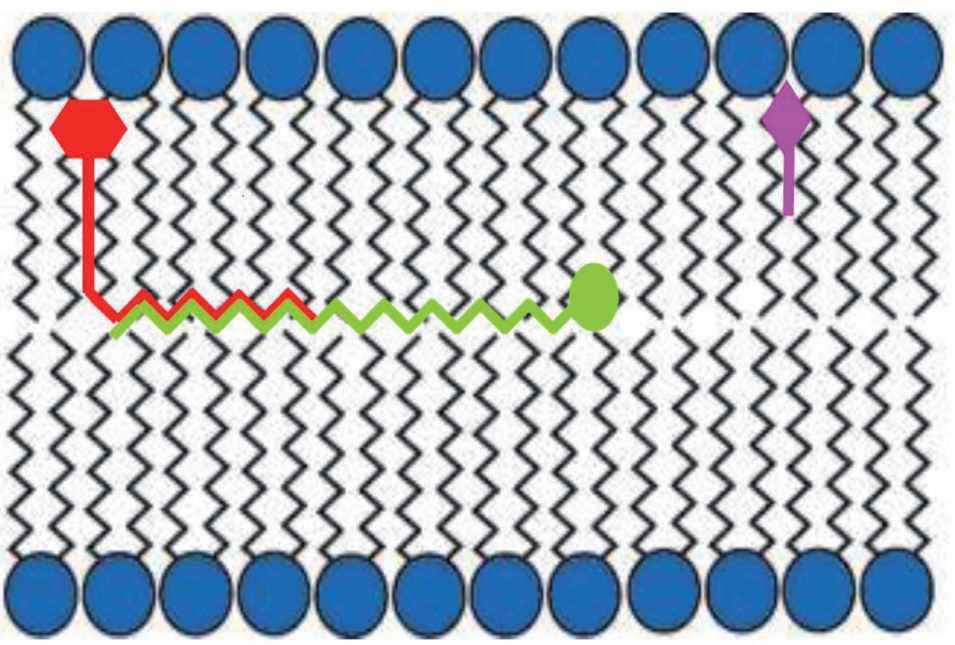

Figure 1.
Model of the membrane antioxidant machinery based on the proposed locations of dolichol (disc, green), ubiquinone (hexagon, red), and vitamin E (rhomb, pink) (see Cathcart et al. [69]; Sharma et al. [70]).

c. Promoting cell cleaning and rejuvenation. It is done by teaching participants in practice how to eat a healthy calorie-restricted diet and to make aerobic physical exercise during fasting. It is known indeed that calorie restriction is the most robust antiaging intervention known so far [64], and that benefit comes from the alternation of a long time of fasting and good meal (twice a week, participants spend a great part of their time in a state of fasting) [65] in order to get cells free of altered ROS-hypergenerating organelles in older cells [66, 67]. Good maintenance will be finalized later, thanks to a good meal. If needed, benefit might be magnified by taking a pill of an antilipolytic drug on the time of fasting [41]. Benefits of protocol might be monitored noninvasively by the assay of the urinary excretion of 8-hydroxy-2′-deoxyguanosine, a recently recommended biomarker for monitoring oxidative status over time [68].

d. A targeted high-intensity training of cognitive brain functions. In addition to the previously described interventions on diet and physical activity, the mental and the social activity protocols tested by Paillard-Borg et al. [38] are being practiced. In view of the results obtained by Dahlgren et al. [51], high intensity interval training (HIIT) and memory training using the PEAK brain training app are included in the protocol.

9. Conclusion

A dynamic antiaging nutritional and physical intervention protocol including enriched living conditions is described useful to prevent the appearance of aging-associated AD. Treatment is already granted for free to the citizens of the city of Volterra known to be at higher risk of AD (relatives of AD patients and persons with mild cognitive impairment, likely to progress to clinically probable AD at a considerably accelerated rate compared with healthy age-matched individuals) to teach them how to counteract and retard the disease. Treatment was designed to delay biological aging and empower adult brain plasticity in order to retard the progress of brain aging and associated diseases. It includes a daily assumption of antioxidants (red wine polyphenols enriched with resveratrol), a reinforcement of membrane antioxidant defenses by the timed assumption of polyunsaturated fatty acids, and an enhancement of cell repair function at the molecular and subcellular level by an intermittent feeding regimen and physical exercise, whose efficiency is empowered by the pharmacological intensification of autophagy by an antilipolytic drug (Acipimox) taken at a very low dosage while fasting. The beneficial effects on neurodegeneration are magnified by living an enriched environment. The effectiveness of the treatment will be detected by comparison with the expected frequencies of disease appearance.

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disease (relatives of patients and patients with MCI) a free service of practical education on how to prevent and slow down the progression of the disease. The first goal is achieved by donating to high school students a pdf entitled "How to keep in shape, preventing diseases and defending good health" (available on the site www.fondazionevolterraricerche.org). The "train body and brain" project was approved by the Istituto Superiore di Sanità and has patronage of the Italian Ministry of Education.

Conflict of interest

The authors disclose no conflicts.

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