Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

Review

Fatty acids, antioxidants and physical activity in brain aging

Hércules Rezende Freitas [1]*, Gustavo da Costa Ferreira [1], Isis Hara Trevenzoli [2], Karen de Jesus Oliveira [3] and Ricardo Augusto de Melo Reis [1]

[1] Laboratory of Neurochemistry, Institute of Biophysics Carlos Chagas Filho, Universidade Federal do Rio de Janeiro; freitashr@biof.ufrj.br
[2] Laboratory of Molecular Endocrinology, Institute of Biophysics Carlos Chagas Filho, Universidade Federal do Rio de Janeiro; haraisis@biof.ufrj.br
[3] Laboratory of Endocrine Physiology and Metabology, Biomedical Institute, Universidade Federal Fluminense; karenoliveira@id.uff.br
* Correspondence: freitashr@biof.ufrj.br; Tel.: +55 (21)-3938-6594

Abstract: Polyunsaturated fatty acids (PUFAs) and antioxidants are important mediators in the central nervous system (CNS). Lipid derivatives may be used to generate endocannabinoids or prostanoids derived from arachidonic acid, which attenuates excitotoxicity in quadripartite synapses with a focus in astrocytes and microglia; on the other hand, antioxidants, such as glutathione (GSH) and ascorbate, have been shown to signal through transmitter receptors and protect against acute and chronic oxidative stress, modulating the activity of different signaling pathways. Several authors have investigated the role of these nutrients in young and senescent brain, as well as in degenerative conditions such as Alzheimer's and Parkinson's diseases. Through literature review, we aimed to highlight recent data on the role of fatty acids, antioxidants and physical activity in physiology and in molecular mechanisms of brain senescence. Data indicate the complexity and essentiality of endogenous/dietary antioxidants for maintenance of the redox status and control of neuroglial signaling under stress. Recent studies also indicate that omega-3 and -6 fatty acids act in a competitive manner to generate mediators for energy metabolism, feeding behavior, plasticity and memory mechanisms throughout aging. Finding pharmacological or dietary resources that mitigate or prevent neurodegenerative affections continues to be a great challenge and require additional efforts from researchers, clinicians and nutritionists in the field.

Keywords: Essential fatty acids; Ascorbic acid; Glutathione; Aging; Parkinson's disease; Alzheimer's disease; Senescence; Nervous system; Growth factors; Neuroprotection; Docosahexaenoic acid; α-linolenic acid.

1. Introduction

Throughout the 20st century, evidence-based medical knowledge has allowed for a significant increase in life expectancy, especially in well-developed countries. Epidemiological data from 1900 (United States and United Kingdom) indicate that 50% of the population lived approximately until 50 years old, while in the 1990's, half of the population lived until 80 years old (1). The ageing process, however, is permissive for the development of several degenerative disorders and infectious diseases, which are strongly influenced by nutritional imbalances, inflammation, metabolic exhaustion and by the natural process of cellular senescence (2).

Insufficient ingestion and/or deficient absorption of essential nutrients deeply affects health condition of elderly individuals. Frangeskou and coworkers explored the impact of dehydration as an extenuating factor for public expenses with health services, increasing mortality, hospital readmission and period of stay under medical/hospital care (3). Digestion and absorption of nutrients

© 2017 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

is normally deficient in the elderly, as compared to younger individuals. In a recent study, it was shown that essential and branched-chain amino acids reach peak blood levels within 1h hour after young individuals (20-25 years old) receive a protein-rich meal, while the same peak concentrations were reached only 3h post-meal for an elderly (60-75 years old) group (4).

Prevalence of malnutrition, weakness and related disabilities are also relevant factors and may comprehend a large portion of the aged population, mainly those institutionalized (hospitalized) and resident of non-developed/developing countries (5). In a cross-sectional Brazilian epidemiological study with elderly individuals (≥ 60 years old), anemia index, hemoglobin concentration and population frailty were intrinsically related, indicating that low levels of hemoglobin are associated with a greater number of frailty indicators (Fried phenotype criteria) (6).

Western diets, characterized by the high lipid content (mainly saturated fatty acids), refined carbohydrates and low ingestion of vegetables have been associated to the development of serious cardiovascular disorders, cancer and diabetes (7). Loss of endothelial homeostasis during ageing, for example, strongly depends on oxidative stress, inflammation and nutritional factors. Dietetic interventions in elderly people are, however, hardened by cognitive impairment and loss of motility, which limits the autonomy for preparing complex meals, chewing and digesting food (8). Regulation of circadian cycle and decrease in dietetic calories content has been shown to be effective in promoting longevity in several in vivo models (9).

In emerging countries, such as Asian and Latin-American nations, it is possible to observe a marked effect of nutritional transition, parallel to the accelerated expansion of urban areas, which incorporates negative dietary habits in the population (10). Such factor introduces a deep epidemiological concern, once modifications in feeding habits and obesity are strong indicators of health risk, such as high blood cholesterol, pre-diabetes, hypertension, asthma, arthritis and bad or regular self-reported health condition (11). Weight variations affect the well-being of elderly patients, a determinant factor for survival within such group (12).

Depression may also be related to the development of obesity (13), and obesity itself is significantly associated to abusive intake of alcohol and depression, mainly in adult female individuals or highly obese subjects (14, 15). Current dietetic approaches rely on providing balanced amounts of energy, macro and micronutrients; other therapies, such as correction of the gut microbiome and global intestine health, await further clinical evidence (16). Here, we explore post-transitional aspects of modern feeding, especially the intake of fatty acids and antioxidants, which greatly relates to the process of brain ageing, one of the pillars in generalized senescence.

2. Senescence of the Nervous System

Many disabling central nervous system symptoms and diseases are highly associated with the aging process, including cerebrovascular disease, Alzheimer's disease (AD) and Parkinson's disease (PD), as well as decline of attention and memory (17, 18). Despite the current medical advances to extend lifespan, untangling the precise metabolic interactions involved in the process of neural aging continues to be a challenge. Both environmental and endogenous factors have been postulated to play a role in cellular senescence, including genetic alterations (DNA damage and shortening of telomeres) and gene expression (19, 20), accumulation of aberrant proteins (21), excitotoxicity (22), oxidative damage and mitochondrial dysfunction (23, 24), and others.

It has been shown that the disturbances in brain synaptic circuitry that occurs especially in hippocampus and pre-frontal cortex during ageing might promote relevant cognitive decline (25). Oxidative damage accumulates with age and is potentially harmful to many mitochondrial functions. Contributing factors include decreased membrane fluidity and the intrinsic rate of proton leakage across the inner mitochondrial membrane (26). Previous reports showed that mitochondria are chronically depolarized in aged neural cells, including an age-dependent decrease in mitochondrial membrane potential in cerebellar neurons from brain slices (27) and in cultured basal forebrain neurons (28). Brain mitochondria from senescent rats present damaged mitochondrial I complex, which may be related to the increase of Bax/Bcl-2 observed in these mitochondria (29). It has also been shown in rats and humans that senescent subjects feature larger mitochondria than young cells,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

but in a smaller amount (30-32). If on the one hand the total volume of the cell occupied by mitochondria is virtually unaltered in young and old subjects, on the other hand these larger mitochondria do not feature the same bioenergetic capability (32, 33). Potential consequences of mitochondrial chronic depolarization include impaired ATP synthesis and redox homeostasis, as well as disruption of calcium gradient across the mitochondrial membrane with subsequent impairment on mitochondrial calcium stores or increase in the threshold necessary to trigger mitochondrial uptake of calcium (34). Thus, changes in the metabolic status would greatly impair the fuel reserves of the neural cells and consequently make them less capable to respond to injury. In the context of the cognitive impairment of the aged cells, the linchpin seems to be the activity of the fast-spiking interneurons (35), which have high metabolic demands and thus are more susceptible to metabolic dysfunction (36).

Accumulated data indicate that the gradual dysfunction of respiratory chain complexes involved in the electron transfer (mainly complexes I and IV), flaws in compensatory mechanisms, inaccurate gene expression, and increased number of mitochondrial DNA (mtDNA) damage are at least capable of influencing the progression of AD (37). Blood glucose and several associated metabolic pathways appear to be altered in the brain of AD patients; however, these manifestations may be consequence of the ageing and disease progression, which undermine synapses and attenuate the demand for glucose, further contributing to the functional and progressive decline of cerebral functions (38).

One of the main regulators of growth and survival in adverse environmental conditions, the mammalian target of rapamycin (mTOR) is a catalytic subunit of two distinct complexes known as mTOR1 and mTOR2 complexes (mTORC1 and mTORC2, respectively) (39). The intrinsic communication of mTOR complexes (mainly mTORC1) with the metabolic control of glycogenesis and lipogenesis is essential to maintain central homeostasis (39, 40), since neural cells are highly dependent on the continued supply of glucose and other energy substrates (e.g. ketone bodies and lipids) to maintain ATP/AMP ratio. This dynamic allows for the correct regulation of autophagy systems, essential for the clearance of malfunctioning organelles and misfolded proteins, which were found to be dysregulated in central diseases such as AD (41).

Nutritional profile of elder individuals seems to be important to the progression of several pathological conditions affecting CNS. It has been reported that the occurrence of disabilities and signals of fatigue are significantly correlated to diet deficiency of folate (i.e. vitamin B9) and magnesium in patients with multiple sclerosis (MS) (42). The onset of preclinical indicators for AD suggest that the availability of micronutrients and fatty acids, especially docosahexaenoic acid (DHA), is gradually restricted and follows the progression of the disease in aged subjects. Protein-energy nutritional status is also aggravated in AD, but it usually parallels the symptoms of cognitive impairment. Nutritional strategies that combine key nutrients for the formation and maintenance of synaptic integrity have been used primarily to prevent loss or impairment of memory in AD patients (43). In vivo restriction in the supply of nutrients during pre- and post-natal periods cause metabolic changes to the blood-brain barrier, inducing cognitive disorders and predisposition to AD (44). These findings underscore an intrinsic relationship between adequate supply of essential nutrients, especially fatty acids and antioxidants, and maintenance of central homeostasis during aging.

3. Adipose tissue–CNS crosstalk in brain aging

Aging and obesity can affect the central regulation of systemic homeostasis, increasing the risk to develop AD, insulin resistance, diabetes mellitus, cardiovascular and cerebrovascular diseases. However, these two metabolic conditions frequently coexist and it is difficult to distinguish the relative contribution of each one to the disease progression. Neuroinflammation seems to be a common mechanism by which these conditions independently and interactively impair neurogenesis, neural stem cells survival and differentiation, promote age-related cognitive decline and neurodegenerative diseases (45, 46).

Blood-brain barrier (BBB) breakdown may precede and trigger both neuroinflammation and neurodegeneration. Because obesity is related to a persistent pro-inflammatory state (47), plasma-

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

derived deleterious factors such as LPS and saturated fatty acids can pass through the damaged BBB to induce neuroinflammation. In fact, serum derived from aged mice or aged high-fat fed mice produces significant microglia activation, with increased reactive oxygen species production and cytokine expression in hippocampus (48). On the other hand, Nlrp3 inflammasome knockout mice show decreased metabolic and inflammatory markers in peripheral and central tissues, improved functional cognitive decline during aging, and expanded lifespan (49). In the hypothalamus, an important brain region regulating energy homeostasis, both aging and over nutrition increase the proinflammatory axis comprising IκB kinase-β (IKKβ) and its downstream nuclear transcription factor NF-κB (IKKβ/NF-κB signaling). Hypothalamic inflammation decreases satiety response to insulin and to the adipose tissue derived hormone leptin, which can contribute to positive energy balance and obesity (50). Several cellular mechanisms contribute to hypothalamic ageing in healthy and overweight individuals, including genomic instability, telomere shortening, epigenetic mechanisms, stem-cell depletion, endoplasmic reticulum stress and autophagy. Not surprisingly, all these mechanisms are also altered in obese subjects and can contribute to systemic and brain inflammation (51).

In diet-induced obesity, white adipose tissue dysfunction is the primarily source of altered levels of circulating free fatty acids, several hormones called adipokines, and proinflammatory cytokines. White adipose tissue depots are in the subcutaneous and visceral compartments. In addition to controlling fuel accumulation, the adipose tissue is an important endocrine organ releasing adipokines allowing its effective interaction with several other tissues including central nervous system, liver, muscle and pancreas to regulate energy metabolism in an efficient and integrated manner in health individuals (52).

White adipose tissue depots present a complex cell composition, including the main cell type, adipocytes, but also pre-adipocytes, fibroblasts, mesenchymal cells, immune cells (macrophages, T cells and others), endothelial cells, and smooth muscle cells (52, 53). Adipose tissue cellularity can present alterations depending on the metabolic status, lean or obese. In lean adipose tissue, resident or recruited macrophages are mostly M2-anti-inflammatory that produce TGF-β, IL-10, CCL17, 18, 22 and 24. In adipose tissue from obese subjects the main macrophage population is the M1-proinflammatory cells that produce mainly IL-6, TNF-α, IL-1β, IFN-γ (54).

There are marked differences between visceral and subcutaneous white adipose depots. Despite of different anatomic distribution, visceral depots are more vascular and innervated, present larger adipocytes, higher lipolytic activity, and increased production of proinflammatory molecules and free fatty acids, as compared with subcutaneous adipose tissue. Regarding endocrine function, visceral adipocytes produce more of the anti-inflammatory adipokine adiponectin while subcutaneous adipocytes produce more leptin, an important regulator of body energy homeostasis that decreases food intake and stimulates energy expenditure. These structural and functional differences characterize the visceral adipose tissue as more insulin-resistant and detrimental in the context of cardiometabolic diseases (55).

Leptin is an important hormone involved in the white adipose tissue and brain crosstalk. Leptin production positively correlates with the fat mass. Therefore, obese individuals present hyperleptinemia (56). Leptin acts mainly on the arcuate hypothalamic nucleus (Arc) activating anorexigenic neurons that express proopiomelanocortin and cocaine/amphetamine-related transcript (POMC/CART neurons), thus inhibiting orexigenic neurons that express the neurotransmitters neuropeptide Y and agouti-related protein (NPY/AgRP neurons) (57, 58). In lean individuals, leptin action results in decreased food intake and increased energy expenditure to control fat mass expansion by a negative feedback loop. However, in obese individuals, hyperleptinemia is commonly associated with hypothalamic leptin resistance and a progressive increase of adiposity (59).

In experimental models of aging, hypothalamic regulation of lifespan has been suggested since it was demonstrated increased hypothalamic expression of NFkB pathway in experimental models of advanced age, and that inhibition of this pathway delays ageing and extends lifespan in rodents (60, 61). In old rats, brain inflammation induced by LPS has been associated with increased peripheral inflammatory markers and hyperleptinemia, while treatment with anti-leptin serum partially

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

reverses brain inflammation, highlighting the crucial role of leptin as a mediator of brain inflammation in aging (62).

In humans, the relationship between leptin and cognition in elderly population is controversial and deserves careful interpretation. While mid-life obesity and systemic metabolic changes, such as high leptin circulating levels, are risk factors to the development of dementia, low plasma leptin levels later in life are associated with worsening cognitive decline and increased risk of developing AD (63, 64). This controversial pattern seems to be time-dependent. Possibly, higher levels of leptin in mid-life could trigger initial deleterious mechanisms in the brain predisposing for age-related diseases, and after the actual development of cognitive impairment in elderly individuals, changes in whole body energy metabolism can result in weight loss and consequently lower leptin levels.

In healthy elderly subjects, plasma leptin levels are positively correlated with grey matter volume of several brain regions, including the hippocampus (65), and inversely correlated with age-related cognitive decline (66). In a prospective study of the Framingham original cohort, circulating leptin levels were associated with reduced incidence of dementia and AD in asymptomatic older adults (67). Therefore, these studies suggest a protective effect of leptin on brain function. Contrarily, mild cognitive impairment was positively correlated with serum leptin and IL-1β levels, and inversely correlated with the adiponectin in elderly population (68). Additionally, in elderly individuals included in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, higher leptin levels were associated with deficits in frontal, parietal, temporal and occipital lobes, brainstem, and the cerebellum (69).

In contrast to obesity and hyperleptinemia, caloric restriction is another energetic challenge that can modulate adiposity, brain function and lifespan. From the evolutionary perspective, the brain is a unique organ that presents optimal cognitive function performance under hunger/food scarcity conditions (70). Caloric restriction can optimize brain function throughout several molecular and cellular mechanisms that include modulation of synaptic activity, BDNF signaling, mitochondrial biogenesis, DNA repair, protein homeostasis, and reduced inflammation (71). Sirtuins are important mediators of the brain metabolic adaptation during caloric restriction. Sirtuins (SIRT1–SIRT7) are enzymes commonly known as NAD+-dependent histone deacetylases (HDAC). However, in addition to controlling gene expression by chromatin remodeling, sirtuins can regulate a variety of cellular functions by modulating the activity of kinases, transcription factors and other molecular targets (72). Brain content of SIRT1 increases in response to caloric restriction and is involved in several brain and behavioral adaptation in mice (73, 74).

4. Fatty Acids

Polyunsaturated fatty acids PUFAs, especially DHA, play an essential role in the maintenance of central and peripheral metabolism. DHA is produced by desaturation and elongation of α-linolenic acid (ALA), which is considered essential in the diet, since mammals are unable to biosynthesize DHA and eicosapentaenoic acid (EPA) from precursors with shorter hydrocarbon chains (75). Humans are required to intake dietary ALA present in leafy vegetables and oil, together with EPA and DHA from fish oil (76). ALA, DHA and EPA (i.e. omega-3) should be maintained at appropriate levels in the diet, since the quantitative ratio between linoleic acid (LA, i.e. omega-6) and ALA is critical to control the production of arachidonic acid (ARA) and pro-inflammatory mediators (e.g. eicosanoids), which play an important role in the progression of cardiovascular diseases, diabetes and brain disorders (77).

Cerebrovascular diseases and neurodegenerative processes are highly dependent on the stability of central blood. The proper functioning of reperfusion systems attenuates cell death and prevents stroke episodes, resulting in less cognitive impairment over time (78, 79). Maintenance of the connective brain structure in patients with AD is one of the major challenges in preserving memory and associated functions, changes such as severe hippocampal atrophy and increased lesions in white matter are, at least, prevented by interventions in which polyunsaturated fatty acids-enriched diets are provided, especially DHA and EPA. In addition, patients undergoing diets rich in

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

these fatty acids are less likely to develop neurodegenerative processes or functional and cognitive loss toward the progression of the disease (80).

In a recent study, senescent rodents depleted of omega-3 had greater dysfunction in glutamatergic synapses and 30% lower uptake of glutamate in astroglia from CA1 hippocampal area (81). Studies using imaging methods have shown that, even in individuals with normal cognition, fish oil supplementation is positively associated with a greater average volume of the hippocampus, cingulate cortex and orbitofrontal areas. Fish oil supplementation was also related to higher scores on standardized cognitive tests. Presence of the ApoE4 allele seems to be a determining factor in the outcome of clinical trials with DHA, since patients without this allele present better results from dietary and pharmacological interventions using omega-3 (82, 83).

Omega-3 fatty acids decrease the synthesis of proinflammatory lipid mediators produced by the omega-6 and ARA metabolism in a competitive manner. Omega-3 act as endogenous ligand of the transcriptional factors peroxisome proliferator-activated receptors (PPAR-γ and α) that attenuate the activity of NF-κB mediated inflammatory pathways (e.g. COX-2, TNF, IL-1) and modulate the mechanism of fatty acid oxidation, peroxisome proliferation, sensitization to insulin and adipocyte differentiation, a potential therapeutic target in the treatment of dyslipidemia (84, 85). In the brain, PPAR-γ participates in many aspects of microglial activation, myelination, heat shock protein (HSP) response, cell death, production of TNFα, inhibition of Activator Protein 1 (AP-1) and NF-κB, besides reducing the synthesis of nitric oxide (NO) and prostaglandin E2 (PGE2). Therefore, PPAR-γ plays a critical anti-inflammatory role in diseases such as Parkinson's disease, multiple sclerosis and AD (86, 87). PPAR-γ have also been demonstrated to be effective in preventing intracerebral ischemic damage, especially in patients with associated morbidities, such as type II diabetes (88).

Afshordel and colleagues (2015) have recently explored another central mechanism of DHA, which can be converted to neuroprotectin D-1 (NPD-1), an unesterified derivative with neuroprotective properties. Authors showed that fish oil supplementation in aged rodents can raise levels of unesterified DHA and NPD-1-like metabolites in parallel to increased Bcl-2 levels in the brain, suggesting that EPA and/or DHA contribute to the control of apoptotic mechanisms and mitochondrial function (89).

Omega 3 fatty acids play an important role in preventing chronic injuries in the peripheral and central metabolism, especially for patients undergoing Western diets. In fact, recent data on in vivo models suggest that supplementation of these fatty acids can prevent cognitive decline, promote hippocampal protection and neuroplasticity (90). The balance between saturated and unsaturated fatty acids may control features of the peripheral metabolism. Kaplan and Greenwood discuss the importance of saturated fatty acids (SFA) consumption on the control of feeding behavior in animal models, highlighting its negative influence on the hepatic metabolism of glucose, which in turn regulates its availability to the brain, where it can control the production of neurotransmitters, trophic factors, feeding behavior and general cognitive performance (91).

The benefits of consuming low-calorie meals, fibers and omega-3 rich foods are well supported by the literature. Eating patterns, however, depend on the individual's ability to control dietary intake. Subjects undergoing nutritional counseling, the adherence to prescribed nutritional programs greatly varies (13-76%) according to how complex and deep is the involvement of the patient with inadequate eating habits (92). A recent study investigated the role of SFA on feeding behavior, and epidemiological and experimental data suggest that the indiscriminate consumption of SFA and simple sugars promotes damage in hippocampal regions involved in negative control of appetite and cognitive processing of reward (93).

Finally, glucolipotoxicity describes the synergistic effect of glucose and SFA on the induction of apoptosis in human β pancreatic cells, and the presence of an omega-6 polyunsaturated (LA) or monounsaturated (i.e. oleic acid) fatty acid reduces this toxicity (94). Several authors have demonstrated the deleterious effect of glucolipotoxicity on pancreatic β cells, highlighting its role in the progression of type II diabetes, mitochondrial dysfunction, production of reactive oxygen species (ROS) and deposition of cholesterol and ceramide in β cells (95-97). Novel therapeutic targets for the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

treatment of type II diabetes now consider the strong synergistic effect of SFA and glucose in progression of the disease (98, 99).

Together, recent data demonstrate the important neuroprotective role of omega-3 fatty acids, attenuating the deleterious effects of excessive omega-6 consumption, and demonstrating the negative impacts of glucolipotoxicity. Intake of the correct amount of fatty acids and carbohydrates play an essential role in the aging process, neuroinflammation, AD and other neurodegenerative diseases (100).

5. Antioxidants

Central degenerative processes are importantly linked to the excessive production of ROS, which promote oxidative damage to proteins, lipids, and nucleotides, causing connective and vascular disorders, loss of neuronal content, activation of microglia/macrophages and induction of mechanisms preceding the onset of AD. The use of antioxidants, such as ascorbic acid (AAC) and vitamin E (VE) has shown to be effective in combating the symptoms of cognitive loss and oxidative stress (101).

Humans and primates have lost the ability to synthesize ascorbic acid due to absence of the gene coding for L-gulono-γ-lactone oxidase enzyme (i.e. Gulo), that converts gulonolactone into L-ascorbic acid. In animals expressing this enzyme, inactivation of the Gulo gene implies the need for antioxidant supplementation even prenatally, becoming required for survival. If supplementation of AAC is removed, the subjects become anemic, lose weight and die, presenting damage to vascular integrity, proliferation of smooth muscle cells and increased oxidative stress, which recruits compensatory antioxidant mechanisms (102, 103). In humans, consumption of approximately 10mg/day of AAC is enough to prevent the onset of deficiency symptoms (104).

AAC transport into the brain is mediated by the sodium-vitamin C co-transporters 2 (SVCT2), ensuring a sharp concentration gradient through the choroid plexus (105). Although not responsible for the central concentrations of AAC, SVCT1 transporters are essential for the maintenance of plasma levels of the antioxidant, which in turn modulates the availability of AAC into the cerebrospinal fluid (CSF) and ultimately to the brain.

After cerebrovascular disorders, such as transient ischemia and stroke, AAC absorption and SVCT2 expression rises significantly, especially in capillary endothelial cells located in the ischemic region, indicating that AAC is involved in neutralization of ROS produced by the oxidative stress or specifically due to macrophage activity in the damaged region (106). Lin et al. (2010) showed that intraperitoneal injections of AAC (500mg/kg in PBS), following compression of the somatosensory cortex of rats, prevented disruption of the BBB and maintained the integrity of the sensory system (107). This preservation phenomenon may be extended to other types of BBB damage or cerebrovascular disorders that occur in the aging process (108).

Recently, it has been proposed that AAC is involved in the prevention of cognitive decay and depression in in vivo models, primarily in situations where damage is promoted by the oxidative stress or pro-oxidant agents (109, 110). In a cohort study with 117 elderly individuals, the supplementation of AAC was associated with a lower incidence of severe cognitive impairment, with no effect on verbal ability (111). Guidi and colleagues (2006) evaluated plasma levels of homocysteine (tHcy), a marker of ROS and total antioxidant capacity, in AD elderly patients with either mild cognitive impairment or vascular dementia. Data obtained showed high levels of tHcy and reduced total antioxidant capacity in AD and mild cognitive impairment patients. tHcy levels were also high in vascular dementia patients, while low total antioxidant capacity was exclusively related to AD individuals. ROS levels were homogenous between groups, indicating that the loss of total antioxidant capacity may be related to progression of cognitive complications (112).

Besides the isolated supplementation of AAC, population studies seek to highlight the participation of other dietary components in preventing cognitive/motor impairment and AD progression. In a study from Morris and colleagues, consumption of antioxidant nutrients, VE, AAC and β-carotene was investigated according to the incidence of AD in a population of individuals aged over 65 years. In this study, only dietary intake of VE was associated with reduced risk of AD,

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

surprisingly, this relationship was observed only in subjects without the allele ApoE4 (113). Determining the contribution of a specific antioxidant is, however, a difficult task, as these and other phytochemicals apparently act synergistically when present in foods and complex phytoextracts (114).

Another antioxidant intrinsically involved in the metabolic signs of aging and in pathological dynamics of neurodegenerative diseases is glutathione (GSH), a tripeptide composed of glutamic acid, cysteine and glycine residues. GSH is the most prevalent thiol compound in cells from virtually all body tissues. GSH is essential for cell proliferation, participates in apoptotic processes, ROS neutralization and also maintains the reduced form of intracellular protein's sulfhydryl groups (115). In the brain, GSH is found in higher concentrations in the glial cells, while in neurons this concentration is slightly lower (116).

GSH is involved in the prevention of mitochondrial damage, cell death and in the pathogenesis of CNS, providing evidence for the relationship between GSH and diseases such as PD and AD (117-118). Elucidating the complexity of the neuroprotective mechanisms performed by GSH, in a recent study, it was shown that even non-toxic decreases in GSH concentrations are able to cause an imbalance in NO activity, allowing the nitration of proteins, a predictive marker for neurodegenerative diseases (119).

Attenuation of central levels of GSH, especially in the mitochondria, appears to be a strong indicator of oxidative damage during ageing (120). In a recent work with proton magnetic resonance spectroscopy, authors showed depletion of GSH, increase in lactate and unchanged levels of AAC in the occipital cortex of elderly compared to young individuals (121). In another study, Mandal and colleagues showed a linear reduction of GSH concentrations in the frontal cortex during ageing, mild cognitive impairment and diagnosed AD, with gender-specific components (122). Lower GSH levels were also observed (post-mortem samples) in patients with autism, bipolar disorder, major depression and schizophrenia (123, 124). Finally, recent investigations from our group suggest that GSH may also act as a signaling molecule in CNS (Figure 1), regulating purinergic activity, ion channel opening and GABA release. Incubation with milimolar concentrations of GSH induces an acute increase in intracellular calcium levels ([Ca2+]i), and may act in consonance with reducing properties of GSH during disease and tissue injury (125, 126).

6. Physical Activity

Regular physical activity has several beneficial effects on health and the exercise capacity is a strong and independent predictor of morbidity and mortality for patients of all ages (127, 128). Over the last decades, life expectancy has been increasing and the continuous reduction in the mortality rates among the elderly population is associated with dietary factors and exercise (129). In fact, exercise can not only improve life expectancy but slow down, delay or prevent many age-associated chronic pathologies, extending health span for an optimal longevity (130, 131) Physical activity can also reverse or attenuate the progression of brain aging, being associated to positive vascular, structural, and neuromolecular changes, including insulin resistance, inflammation and oxidative stress, which contribute to cognitive decline and brain-related diseases (132, 133).

The cerebral blood flow is tightly coupled to the cerebral metabolic rate and neuronal metabolism, thus systemic vascular dysfunction associated with brain hypoperfusion can compromise cognitive performance (134, 135). Injuries in endothelium and central/peripheral vascular structure involve increased inflammation and oxidative stress (132). In addition, cerebral blood flow declines with age (136, 137), which strongly contributes to the decrease in cognitive function in the elderly (138). Exercise, in contrast, increases cerebral blood flow in an intensity-dependent manner and has been shown to improve cognitive function and brain aging (136, 139). Aged mice presented lower cerebral blood flow, accompanied by a lower content of endothelial nitric oxide synthase (e-NOS) and vascular endothelial growth factor (VEGF) in the brain microvasculature, when compared to young mice; training in aged mice improve all parameters (140). Mice submitted to running exercise exhibit reduced cerebral lesion sizes after a cerebral ischemia episode, and this effect was blunted in the e-NOS deficient mice. Running also improved functional outcome

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

associated with higher cerebral blood flow and angiogenesis in the ischemic striatum, which was completely abrogated in animals treated with L-NAME, a NOS inhibitor. These data indicate that exercise improves short-term stroke outcome via NO-dependent mechanisms (141).

In an animal model of vascular dementia induced by bilateral carotid artery occlusion, treadmill exercise reduced the memory impairment caused by the chronic cerebral hypoperfusion and induced hippocampal neurogenesis via the BDNF-pCREB pathway (142). Imaging analyses conducted both in mice and in young/middle-aged humans showed that exercise-induced neurogenesis associated with increased cerebral blood volume occurs selectively at the hippocampal dentate gyrus (143, 144). Similarly, a study conducted in healthy older humans (60–77 years) also observed that aerobic fitness improvement was associated with positive changes in hippocampal perfusion, early recall and recognition memory, however, these benefits decrease with progressing age, indicating that the capacity for vascular hippocampal plasticity may be age-dependent (145).

Age-related brain atrophy is commonly associated with cognitive impairment and memory loss. In fact, the rate, extent, and brain regions showing atrophy can vary among the individuals (144). A recent study by Hanning and colleagues (146) found that brain atrophy in the elderly is associated with higher IL-6 and IL-8 circulating levels, suggesting a role for systemic inflammation in the brain atrophy pathogenesis. Greater brain volumes are associated with greater cognitive reserve and a higher capacity to deal with AD pathology without the clinical manifestation of cognitive impairment (139). In individuals at the age of 75 years, a higher level of physical activity was associated with better memory performance and with greater volumes of both total brain and white matter (147, 148). In addition, higher aerobic fitness level was related to higher hippocampal volume and better memory performance in older non-demented individuals (148), older individuals in the earliest stages of AD (149), and in preadolescent children (150), highlighting the impact of physical activity in increasing brain volume of individuals from all ages. Interestingly, a 42-year follow-up identified that men with high cardiovascular fitness at age 18 had a lower risk of early-onset dementia and mild cognitive impairment later in life (151).

Sexual dimorphism is observed on brain anatomical structures, neurochemicals and functions, and not surprisingly men and women also differ in the incidence and nature of CNS-related diseases, such as cognitive impairment, AD, autism, schizophrenia and eating disorders (152). In addition, females exhibit stronger immune response, improved antioxidant capacity, better redox and functional state of their immune cells and, accordingly, the “inflammaging” process in the elderly show gender differences, including higher serum levels of IL-6 in men than in women (153, 154). Elderly individuals with mild cognitive impairment have higher mortality rates, compared with cognitively normal age-matched individuals, and the mortality rate was highest in men (155). Although cerebral blood flow decreases with age, women have higher levels than men in all ages (156). The human male brain exhibit more global gene expression changes than the female brain throughout ageing, with gene expression mostly down-regulated until the 60 years old in men. On the other hand, in older ages, women showed progressively more gene expression changes than men. Interestingly, the major category of down-regulated genes in men was related to protein processing and energy generation (157).

Not surprisingly, exercise impact between genders is also different, and is explored in mixed gender studies. Overall, studies comparing male and female indicate that the positive effect of physical activity or exercise on brain volume, cognition, and AD risk is more pronounced in females (158, 159). However, this subject remains controversial. It was observed that cardiorespiratory fitness was positively associated with total and cortical gray matter volumes in elderly men at increased risk for AD (160). This profile was not observed in women, and authors suggested that cardiorespiratory fitness might be beneficial to the brain health, only in men, at the age of 60 years and older.

Insulin is also an important player in the control of degenerative scenarios. In addition to the modulation of energy metabolism, it regulates several features that are essential for healthy aging: cerebral blood flow, inflammatory responses, oxidative stress, Aβ clearance, tau phosphorylation, apoptosis, synaptic plasticity and memory formation (161). In humans, insulin resistance and type 2 diabetes have been shown to predict the development of age-related diseases and a preserved insulin

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

action is strongly associated with longevity (162, 163). AD development and symptoms are closely related to an insulin-resistant brain state, and type 2 diabetes mellitus is a risk factor for dementia and AD (164). Intranasal insulin therapy in patients with AD or mild cognitive impairment has been associated with improvement in cognitive function (165-167), increased brain volume, including hippocampus, and reduction in the tau-P181/Aβ42 ratio (166).

Exercise can stimulate cellular insulin signaling and sensitivity in peripheral organs (168) and in the brain with a beneficial impact on brain structure (169) and function (170, 171). A major factor for the development of insulin resistance is obesity (172), and the impact of obesity on unhealth brain aging has been discussed previously in this review. Exercise is an effective intervention to prevent or treat obesity and obesity-related insulin resistance (173) and improve adipokine profile in obese individuals increasing adiponectin and reducing hyperleptinemia (174-176). In addition, the exercise-induced hippocampal neurogenesis was remarkably attenuated in an adiponectin-deficient mice, highlighting that adiponectin may be an essential factor mediating this effect via its receptor 1 (ADNR1) and AMPK activation (177).

Exercise induces insulin sensitivity and glucose disposal through several pathways, including improvement in inflammation and oxidative stress that are high-risk factors for cognitive impairment and accelerated aging (161, 163). In elderly individuals of both sexes, exercise improves inflammatory profile by reducing serum inflammatory markers, such as C-reactive protein, IL-6, TNF-α (176, 178-180). In peripheral blood mononuclear cells obtained from aged individuals, exercise training induced lower protein expression of toll-like receptors (TLR2 and TLR4) associated with an anti-inflammatory status linked to myeloid differentiation primary response gene 88 (MyD88)-dependent and MyD88-independent pathways (181). Additionally, the exercise-induced improvement in inflammatory profile in the elderly was associated with positive changes in cognition (182) and greater total brain volume (183). In young healthy mice, exercise did not promote changes in serum inflammatory markers, however, induced lower content of IL-6 and TNF-α in the hippocampus, indicating that it can promote an anti-inflammatory effect in the brain without affecting the peripheral cytokines production (184). Although the exercise promotes several long-term benefits, including improvement in the proinflammatory state, the acute exercise responses are associated with increased serum levels and tissue expression of IL-6 and TNFα (185, 186). In a mice model of traumatic brain injury associated with neurodegeneration and chronic neuroinflammation, it was observed that delayed exercise onset (5 weeks after trauma) caused improvements in working and retention memory, decreased lesion volume, increased neurogenesis in the hippocampus and reduced IL-1b gene expression. However, these improvements were not observed when exercise was initiated 1 week after the brain injury. In fact, it exacerbated chronic classical inflammatory responses, highlighting the importance of timing of exercise onset and its relation to cognitive outcomes and neuroinflammation (187).

Autophagy is a physiological and catabolic process, vital for the maintenance of cell homeostasis, by effectively getting rid of dysfunctional organelles such as damaged mitochondria and malformed proteins, and disrupted autophagy contributes to unhealth aging and decreased longevity (188, 189). Elderly individuals submitted to exercise training exhibit increased expression of autophagy related-genes, including beclin-1, Atg12, Atg16, and the LC3II/I in peripheral blood mononuclear cells compared with sedentary individuals (190, 191). In addition, the expression of NLRP3, Bcl-2 and Bcl-xL was reduced in peripheral blood mononuclear cells of trained elderly individuals, indicating improvement in autophagy, prevention of NLRP3 inflammasome activation, and reduction of apoptosis (190).

Several studies have revealed that physical activity or exercise elicits a combined effect improving the redox state and enhancing inflammatory defenses, combating the “oxi-inflamm-aging” process (131, 154). Healthy aged female rats submitted to long-term exercise training showed lower ROS content, lower protein carbonyl content and increased SOD 1 and SOD 2 protein expression in the hippocampus compared with sedentary age-matched rats, indicating a beneficial effect on the oxidative status (192). In an aged mice model of AD (3xTg-AD), voluntary exercise reversed lipoperoxidation and oxidized glutathione levels, while improving the antioxidant enzyme

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

CuZn-SOD content in the cerebral cortex. These changes were associated with optimized behavior and cognition, and reduced amyloid/tau pathology, highlighting the neuroprotective effect of exercise through regulation of redox homeostasis (193). Neuronal mitochondria are especially susceptible to oxidative stress, therefore, the beneficial impact of exercise on redox balance has many positive effects on mitochondrial function (194). In young and aged rats, exercise induced a reduction in oxidative stress accompanied by increased mitochondrial biogenesis, dynamic and mitophagy in the brain (192, 195).

Physical activity and exercise affect directly the skeletal muscle physiology, which is a metabolically active tissue that releases myokines, which might be involved in the beneficial effects of exercise (196, 197). Important neural factors associated with neurogenesis, angiogenesis, and cognition, such as BDNF and VEGF are also produced by skeletal muscle and modulated by exercise (198). Indeed, the significance of these factors released by the skeletal muscle during exercise to the brain physiology is still unclear. In both young and elderly individuals, the skeletal muscle BDNF expression and the serum concentration of BDNF increase after exercise, and it was associated with structural and functional benefits to the brain (197-199). However, it has been proposed that the brain contributes to 70–80% of circulating BDNF at rest and during exercise, therefore, the systemic impact of the BDNF released from the muscle needs further investigation (200).

Finally, irisin is an exercise-induced myokine that is highly expressed in the brain (196, 201). Interestingly, the knockdown of the precursor of irisin, FNDC5, in neuronal precursors impaired their development into mature neurons (202). Since the FNDC5 expression in the brain is upregulated with exercise, the specific tissue contribution to the beneficial effect of exercise on the brain is still to be defined (201).

7. Conclusions

Aging is a sensitive period for the maintenance of metabolic and functional balance of the brain. When compiled, data indicate the complexity of action and essentiality of various dietary/endogenous antioxidants, in addition to the proper balance in the consumption of essential fatty acids (omega-3 and -6), whose synergistic actions allow for the maintenance of physiological conditions, even throughout severe metabolic stress (Figure 2). Recent investigations aim to elucidate mechanisms for preventing the intrinsic effects of the aging process in affections such as ischemic disorders (203) and functional decay of mitochondria (204). However, finding pharmacological or dietary resources capable of significantly intervening with the neurodegenerative affections remains a great challenge (205, 206). Future research should rely on novel integrative methods present in systems biology, which allows for a broad analysis of the metabolic interactions in ageing and disease processes.

Supplementary Materials: There are no supplementary materials provided

Acknowledgments: Grants from Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Instituto Nacional de Ciência e Tecnologia de Neurociênca Translacional (INCT-INNT) supported this work. HRF is recipient of a Ph.D. research fellowship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). RAMR, IHT, KJO and GCF receive a research fellowship from CNPq.

Author Contributions: All authors contributed equally to the writing and reviewing of this paper.

Conflicts of Interest: The authors declare no conflict of interest.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

Figure 1. Mechanisms of functional compartmentalization mediated by glutathione in the retinal environment.

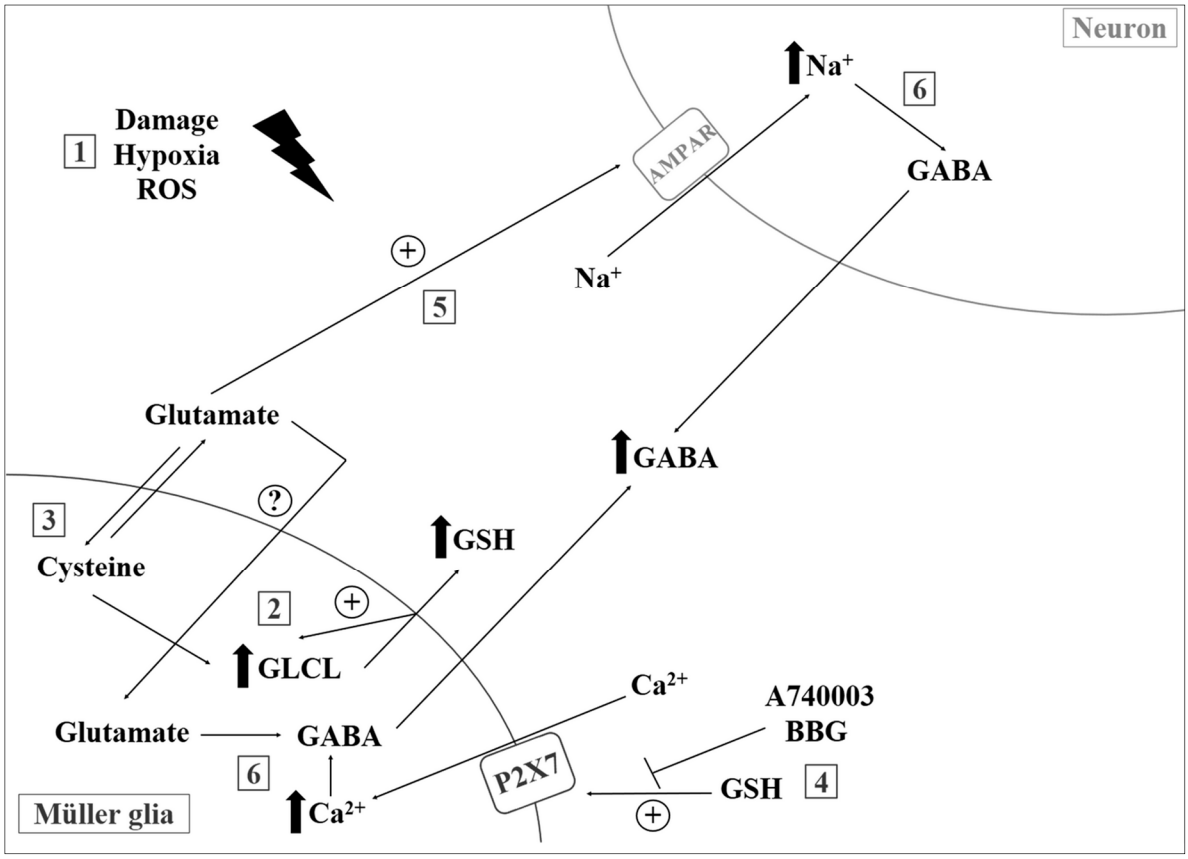

Figure 1 legend: Tissue damage, hypoxia and ROS (1) promote increased activity of antioxidant system intermediates in Müller glial cells, such as γ-glutamylcysteine ligase (GLCL), which stimulates the synthesis/release of GSH (2) and the uptake of cysteine through a glutamate-cysteine antiporter system (3). When released, GSH is capable of activating P2X7 receptors, allowing for intense Ca2+ increase in the Müller cells (4), while extracellular glutamate promotes activation of AMPA receptors in retinal neurons, leading to higher Na+ levels in these cells (5). Finally, intracellular Ca2+ (glia) and Na+ (neurons) stimulate GABA release to the extracellular environment.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

Figure 2. Brain dynamics in healthy and unhealthy aging.

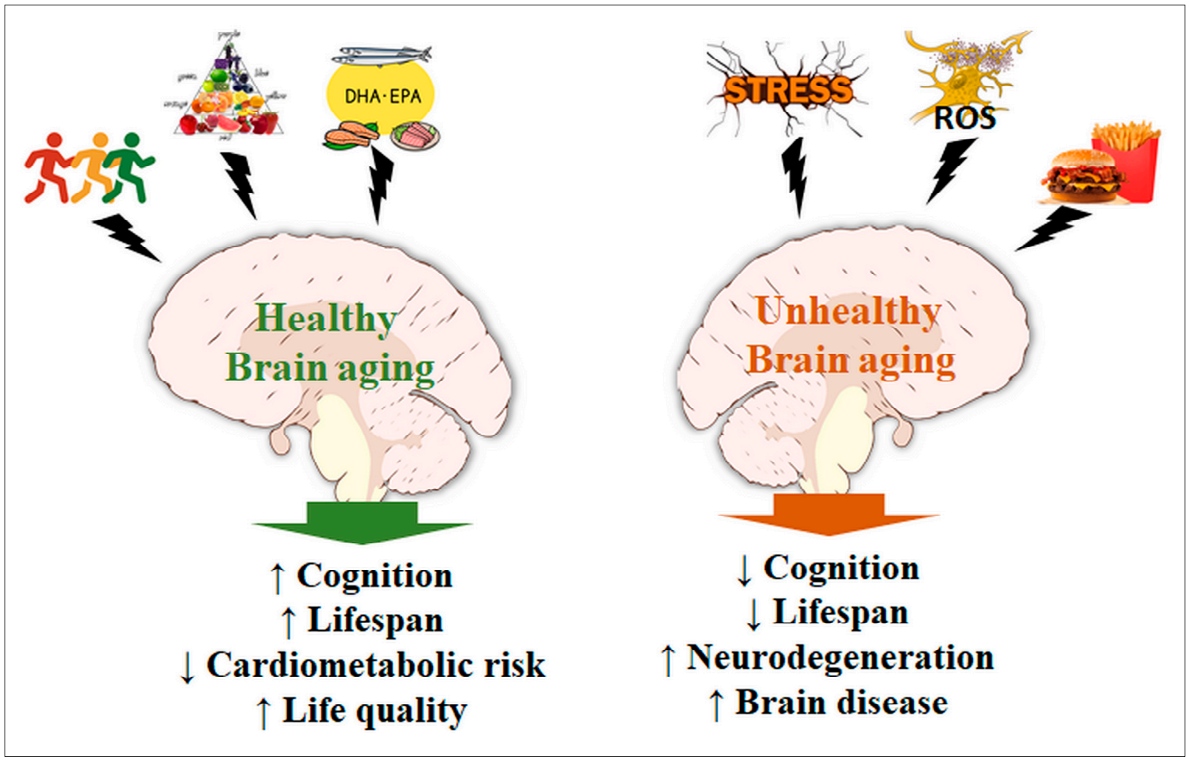

Figure 2 legend: Moderate physical activity, low-calorie diets and essential fatty acids are amongst the main elements of a healthy brain, where we observe less or no cognitive decline, greater lifespan, reduced cardiovascular (and metabolic) risks and thus overall better quality of life. Conversely, a continuously stressed brain, either by an unstable environment or by chemical mediators (e.g. ROS, RNS and other radicals). Also, high caloric meals and/or typical cafeteria diets are risk factors for the development of several such affections.

References

1. Khaw KT. Epidemiological aspects of ageing. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 1997;352(1363):1829-35.
2. Finch CE. Evolution in health and medicine Sackler colloquium: Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. Proc Natl Acad Sci U S A. 2010;107 Suppl 1:1718-24.
3. Frangeskou M, Lopez-Valcarcel B, Serra-Majem L. Dehydration in the Elderly: A Review Focused on Economic Burden. The journal of nutrition, health & aging. 2015;19(6):619-27.
4. Milan AM, D'Souza RF, Pundir S, Pileggi CA, Thorstensen EB, Barnett MP, et al. Older Adults Have Delayed Amino Acid Absorption after a High Protein Mixed Breakfast Meal. The journal of nutrition, health & aging. 2015;19(8):839-45.
5. Nguyen TN, Cumming RG, Hilmer SN. A Review of Frailty in Developing Countries. The journal of nutrition, health & aging. 2015;19(9):941-6.
6. Pires Corona L, Drumond Andrade FC, de Oliveira Duarte YA, Lebrao ML. The Relationship between Anemia, Hemoglobin Concentration and Frailty in Brazilian Older Adults. The journal of nutrition, health & aging. 2015;19(9):935-40.
7. Kearney J. Food consumption trends and drivers. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 2010;365(1554):2793-807.
8. Miller MS, Callahan DM, Toth MJ. Skeletal muscle myofilament adaptations to aging, disease, and disuse and their effects on whole muscle performance in older adult humans. Frontiers in physiology. 2014;5:369.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

609 9. Newgard CB, Pessin JE. Recent progress in metabolic signaling pathways regulating aging and life span.
610 The journals of gerontology Series A, Biological sciences and medical sciences. 2014;69 Suppl 1:S21-7.
611 10. Popkin BM. The nutrition transition and obesity in the developing world. J Nutr. 2001;131(3):871s-3s.
612 11. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. N
613 Engl J Med. 2007;356(3):213-5.
614 12. Steptoe A, Deaton A, Stone AA. Subjective wellbeing, health, and ageing. Lancet. 2015;385(9968):640-8.
615 13. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and
616 persistence of adolescent obesity. Pediatrics. 2002;110(3):497-504.
617 14. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is obesity associated with major depression?
618 Results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2003;158(12):1139-
619 47.
620 15. McCarty CA, Kosterman R, Mason WA, McCauley E, Hawkins JD, Herrenkohl TI, et al. Longitudinal
621 associations among depression, obesity and alcohol use disorders in young adulthood. Gen Hosp Psychiatry.
622 2009;31(5):442-50.
623 16. Saunier K, Dore J. Gastrointestinal tract and the elderly: functional foods, gut microflora and healthy
624 ageing. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian
625 Association for the Study of the Liver. 2002;34 Suppl 2:S19-24.
626 17. Lopez-Leon M, Outeiro TF, Goya RG. CELL REPROGRAMMING: THERAPEUTIC POTENTIAL AND
627 THE PROMISE OF REJUVENATION FOR THE AGING BRAIN. Ageing research reviews. 2017.
628 18. Cararo JH, Streck EL, Schuck PF, Ferreira Gda C. Carnosine and Related Peptides: Therapeutic Potential in
629 Age-Related Disorders. Aging and disease. 2015;6(5):369-79.
630 19. Jager K, Walter M. Therapeutic Targeting of Telomerase. Genes. 2016;7(7).
631 20. Wang Y, Xu Q, Sack L, Kang C, Elledge SJ. A gain-of-function senescence bypass screen identifies the
632 homeobox transcription factor DLX2 as a regulator of ATM-p53 signaling. Genes & development. 2016;30(3):293-
633 306.
634 21. Reeg S, Grune T. Protein Oxidation in Aging: Does It Play a Role in Aging Progression? Antioxidants &
635 redox signaling. 2015;23(3):239-55.
636 22. Poon HF, Calabrese V, Calvani M, Butterfield DA. Proteomics analyses of specific protein oxidation and
637 protein expression in aged rat brain and its modulation by L-acetylcarnitine: insights into the mechanisms of
638 action of this proposed therapeutic agent for CNS disorders associated with oxidative stress. Antioxidants &
639 redox signaling. 2006;8(3-4):381-94.
640 23. Lionaki E, Tavernarakis N. Oxidative stress and mitochondrial protein quality control in aging. Journal of
641 proteomics. 2013;92:181-94.
642 24. Kudryavtseva AV, Krasnov GS, Dmitriev AA, Alekseev BY, Kardymon OL, Sadritdinova AF, et al.
643 Mitochondrial dysfunction and oxidative stress in aging and cancer. Oncotarget. 2016;7(29):44879-905.
644 25. Samson RD, Barnes CA. Impact of aging brain circuits on cognition. Eur J Neurosci. 2013;37(12):1903-15.
645 26. Shigenaga MK, Hagen TM, Ames BN. Oxidative damage and mitochondrial decay in aging. Proc Natl Acad
646 Sci U S A. 1994;91(23):10771-8.
647 27. Xiong J, Camello PJ, Verkhratsky A, Toescu EC. Mitochondrial polarisation status and [Ca2+]i signalling in
648 rat cerebellar granule neurones aged in vitro. Neurobiol Aging. 2004;25(3):349-59.
649 28. Murchison D, Zawieja DC, Griffith WH. Reduced mitochondrial buffering of voltage-gated calcium influx
650 in aged rat basal forebrain neurons. Cell Calcium. 2004;36(1):61-75.
651 29. Tatarkova Z, Kovalska M, Timkova V, Racay P, Lehotsky J, Kaplan P. The Effect of Aging on Mitochondrial
652 Complex I and the Extent of Oxidative Stress in the Rat Brain Cortex. Neurochem Res. 2016;41(8):2160-72.
653 30. Miquel J. An update on the mitochondrial-DNA mutation hypothesis of cell aging. Mutation 25research.
654 1992;275(3-6):209-16.
655 31. Bertoni-Freddari C, Fattoretti P, Casoli T, Spagna C, Meier-Ruge W. Morphological alterations of synaptic
656 mitochondria during aging. The effect of Hydergine treatment. Annals of the New York Academy of Sciences.
657 1994;717:137-49.
658 32. Sastre J, Millan A, Garcia de la Asuncion J, Pla R, Juan G, Pallardo, et al. A Ginkgo biloba extract (EGb 761)
659 prevents mitochondrial aging by protecting against oxidative stress. Free radical biology & medicine.
660 1998;24(2):298-304.
661 33. Wakabayashi T. Megamitochondria formation - physiology and pathology. Journal of cellular and
662 molecular medicine. 2002;6(4):497-538.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

34. Nicholls DG. Mitochondrial membrane potential and aging. Aging cell. 2004;3(1):35-40.
35. Sik A, Penttonen M, Buzsaki G. Interneurons in the hippocampal dentate gyrus: an in vivo intracellular study. Eur J Neurosci. 1997;9(3):573-88.
36. Kann O, Papageorgiou IE, Draguhn A. Highly energized inhibitory interneurons are a central element for information processing in cortical networks. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2014;34(8):1270-82.
37. Swerdlow RH. Brain aging, Alzheimer's disease, and mitochondria. Biochim Biophys Acta. 2011;1812(12):1630-9.
38. Cunnane S, Nugent S, Roy M, Courchesne-Loyer A, Croteau E, Tremblay S, et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition. 2011;27(1):3-20.
39. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nature reviews Molecular cell biology. 2011;12(1):21-35.
40. Cornu M, Albert V, Hall MN. mTOR in aging, metabolism, and cancer. Current opinion in genetics & development. 2013;23(1):53-62.
41. Perluigi M, Di Domenico F, Butterfield DA. mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy. Neurobiology of disease. 2015;84:39-49.
42. Bitarafan S, Harirchian MH, Nafissi S, Sahraian MA, Togha M, Siassi F, et al. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iranian journal of neurology. 2014;13(1):28-32.
43. Mi W, van Wijk N, Cansev M, Sijben JW, Kamphuis PJ. Nutritional approaches in the risk reduction and management of Alzheimer's disease. Nutrition. 2013;29(9):1080-9.
44. Tomi M, Zhao Y, Thamotharan S, Shin BC, Devaskar SU. Early life nutrient restriction impairs blood-brain metabolic profile and neurobehavior predisposing to Alzheimer's disease with aging. Brain Res. 2013;1495:61-75.
45. Banks WA, Abrass CK, Hansen KM. Differentiating the Influences of Aging and Adiposity on Brain Weights, Levels of Serum and Brain Cytokines, Gastrointestinal Hormones, and Amyloid Precursor Protein. J Gerontol A Biol Sci Med Sci. 2016;71(1):21-9.
46. Purkayastha S, Cai D. Disruption of neurogenesis by hypothalamic inflammation in obesity or aging. Rev Endocr Metab Disord. 2013;14(4):351-6.
47. Ahima RS. Digging deeper into obesity. The Journal of clinical investigation. 2011;121(6):2076-9.
48. Tucsek Z, Toth P, Sosnowska D, Gautam T, Mitschelen M, Koller A, et al. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. J Gerontol A Biol Sci Med Sci. 2014;69(10):1212-26.
49. Youm YH, Grant RW, McCabe LR, Albarado DC, Nguyen KY, Ravussin A, et al. Canonical Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging. Cell Metab. 2013;18(4):519-32.
50. De Souza CT, Araujo EP, Bordin S, Ashimine R, Zollner RL, Boschero AC, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology. 2005;146(10):4192-9.
51. Cavadas C, Aveleira CA, Souza GF, Velloso LA. The pathophysiology of defective proteostasis in the hypothalamus - from obesity to ageing. Nat Rev Endocrinol. 2016;12(12):723-33.
52. Rodriguez A, Ezquerro S, Mendez-Gimenez L, Becerril S, Fruhbeck G. Revisiting the adipocyte: a model for integration of cytokine signaling in the regulation of energy metabolism. Am J Physiol Endocrinol Metab. 2015;309(8):E691-714.
53. Strissel KJ, DeFuria J, Shaul ME, Bennett G, Greenberg AS, Obin MS. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. Obesity (Silver Spring). 2010;18(10):1918-25.
54. Castoldi A, Naffah de Souza C, Camara NO, Moraes-Vieira PM. The Macrophage Switch in Obesity Development. Front Immunol. 2015;6:637.
55. Badimon L, Cubedo J. Adipose tissue depots and inflammation: effects on plasticity and resident mesenchymal stem cell function. Cardiovasc Res. 2017.
56. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763-70.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

717 57. Sahu A. Leptin decreases food intake induced by melanin-concentrating hormone (MCH), galanin (GAL)
718 and neuropeptide Y (NPY) in the rat. Endocrinology. 1998;139(11):4739-42.
719 58. Ahima RS, Osei SY. Leptin signaling. Physiol Behav. 2004;81(2):223-41.
720 59. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator
721 of central leptin resistance. Mol Cell. 1998;1(4):619-25.
722 60. Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, et al. Hypothalamic programming of systemic ageing
723 involving IKK-beta, NF-kappaB and GnRH. Nature. 2013;497(7448):211-6.
724 61. Horrillo D, Sierra J, Arribas C, Garcia-San Frutos M, Carrascosa JM, Lauzurica N, et al. Age-associated
725 development of inflammation in Wistar rats: Effects of caloric restriction. Arch Physiol Biochem. 2011;117(3):140-
726 50.
727 62. Koenig S, Luheshi GN, Wenz T, Gerstberger R, Roth J, Rummel C. Leptin is involved in age-dependent
728 changes in response to systemic inflammation in the rat. Brain, behavior, and immunity. 2014;36:128-38.
729 63. McGuire MJ, Ishii M. Leptin Dysfunction and Alzheimer's Disease: Evidence from Cellular, Animal, and
730 Human Studies. Cell Mol Neurobiol. 2016;36(2):203-17.
731 64. Ronan L, Alexander-Bloch AF, Wagstyl K, Farooqi S, Brayne C, Tyler LK, et al. Obesity associated with
732 increased brain age from midlife. Neurobiol Aging. 2016;47:63-70.
733 65. Narita K, Kosaka H, Okazawa H, Murata T, Wada Y. Relationship between plasma leptin level and brain
734 structure in elderly: a voxel-based morphometric study. Biol Psychiatry. 2009;65(11):992-4.
735 66. Holden KF, Lindquist K, Tylavsky FA, Rosano C, Harris TB, Yaffe K, et al. Serum leptin level and cognition
736 in the elderly: Findings from the Health ABC Study. Neurobiol Aging. 2009;30(9):1483-9.
737 67. Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, et al. Association of plasma leptin levels with
738 incident Alzheimer disease and MRI measures of brain aging. JAMA. 2009;302(23):2565-72.
739 68. Gorska-Ciebiada M, Saryusz-Wolska M, Borkowska A, Ciebiada M, Loba J. Adiponectin, leptin and IL-1
740 beta in elderly diabetic patients with mild cognitive impairment. Metab Brain Dis. 2016;31(2):257-66.
741 69. Rajagopalan P, Toga AW, Jack CR, Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging I. Fat-
742 mass-related hormone, plasma leptin, predicts brain volumes in the elderly. Neuroreport. 2013;24(2):58-62.
743 70. Mattson MP. Lifelong brain health is a lifelong challenge: from evolutionary principles to empirical
744 evidence. Ageing Res Rev. 2015;20:37-45.
745 71. Phillips C. Lifestyle Modulators of Neuroplasticity: How Physical Activity, Mental Engagement, and Diet
746 Promote Cognitive Health during Aging. Neural Plast. 2017;2017:3589271.
747 72. Jesko H, Wencel P, Strosznajder RP, Strosznajder JB. Sirtuins and Their Roles in Brain Aging and
748 Neurodegenerative Disorders. Neurochem Res. 2017;42(3):876-90.
749 73. Cohen DE, Supinski AM, Bonkowski MS, Donmez G, Guarente LP. Neuronal SIRT1 regulates endocrine
750 and behavioral responses to calorie restriction. Genes Dev. 2009;23(24):2812-7.
751 74. Fusco S, Ripoli C, Podda MV, Ranieri SC, Leone L, Toietta G, et al. A role for neuronal cAMP responsive-
752 element binding (CREB)-1 in brain responses to calorie restriction. Proc Natl Acad Sci U S A. 2012;109(2):621-6.
753 75. Freitas HR, Isaac AR, Malcher-Lopes R, Diaz BL, Trevenzoli IH, De Melo Reis RA. Polyunsaturated fatty
754 acids and endocannabinoids in health and disease. Nutr Neurosci. 2017:1-20.
755 76. Simopoulos AP. Essential fatty acids in health and chronic disease. The American journal of clinical
756 nutrition. 1999;70(3 Suppl):560s-9s.
757 77. Simopoulos AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. Biomedicine &
758 pharmacotherapy = Biomedecine & pharmacotherapie. 2002;56(8):365-79.
759 78. Denis I, Potier B, Vancassel S, Heberden C, Lavialle M. Omega-3 fatty acids and brain resistance to ageing
760 and stress: body of evidence and possible mechanisms. Ageing research reviews. 2013;12(2):579-94.
761 79. Denis I, Potier B, Heberden C, Vancassel S. Omega-3 polyunsaturated fatty acids and brain aging. Curr
762 Opin Clin Nutr Metab Care. 2015;18(2):139-46.
763 80. Haast RA, Kiliaan AJ. Impact of fatty acids on brain circulation, structure and function. Prostaglandins,
764 leukotrienes, and essential fatty acids. 2015;92:3-14.
765 81. Latour A, Grintal B, Champeil-Potokar G, Hennebelle M, Lavialle M, Dutar P, et al. Omega-3 fatty acids
766 deficiency aggravates glutamatergic synapse and astroglial aging in the rat hippocampal CA1. Aging Cell.
767 2013;12(1):76-84.
768 82. Chouinard-Watkins R, Plourde M. Fatty acid metabolism in carriers of apolipoprotein E epsilon 4 allele: is
769 it contributing to higher risk of cognitive decline and coronary heart disease? Nutrients. 2014;6(10):4452-71.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

83. Salem N, Jr., Vandal M, Calon F. The benefit of docosahexaenoic acid for the adult brain in aging and dementia. Prostaglandins, leukotrienes, and essential fatty acids. 2015;92:15-22.
84. Nagasawa M, Hara T, Kashino A, Akasaka Y, Ide T, Murakami K. Identification of a functional peroxisome proliferator-activated receptor (PPAR) response element (PPRE) in the human apolipoprotein A-IV gene. Biochemical pharmacology. 2009;78(5):523-30.
85. Xue B, Yang Z, Wang X, Shi H. Omega-3 polyunsaturated fatty acids antagonize macrophage inflammation via activation of AMPK/SIRT1 pathway. PLoS One. 2012;7(10):e45990.
86. Bernardo A, Minghetti L. PPAR-gamma agonists as regulators of microglial activation and brain inflammation. Current pharmaceutical design. 2006;12(1):93-109.
87. Heneka MT, Landreth GE. PPARs in the brain. Biochim Biophys Acta. 2007;1771(8):1031-45.
88. Culman J, Zhao Y, Gohlke P, Herdegen T. PPAR-gamma: therapeutic target for ischemic stroke. Trends in pharmacological sciences. 2007;28(5):244-9.
89. Afshordel S, Hagl S, Werner D, Rohner N, Kogel D, Bazan NG, et al. Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging--impact of Bcl-2 and NPD-1 like metabolites. Prostaglandins, leukotrienes, and essential fatty acids. 2015;92:23-31.
90. Cutuli D, De Bartolo P, Caporali P, Laricchiuta D, Foti F, Ronci M, et al. n-3 polyunsaturated fatty acids supplementation enhances hippocampal functionality in aged mice. Frontiers in aging neuroscience. 2014;6:220.
91. Kaplan RJ, Greenwood CE. Dietary saturated fatty acids and brain function. Neurochem Res. 1998;23(5):615-26.
92. Burke LE, Dunbar-Jacob J. Adherence to medication, diet, and activity recommendations: from assessment to maintenance. The Journal of cardiovascular nursing. 1995;9(2):62-79.
93. Kanoski SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiology & behavior. 2011;103(1):59-68.
94. El-Assaad W, Buteau J, Peyot ML, Nolan C, Roduit R, Hardy S, et al. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. Endocrinology. 2003;144(9):4154-63.
95. El-Assaad W, Joly E, Barbeau A, Sladek R, Buteau J, Maestre I, et al. Glucolipotoxicity alters lipid partitioning and causes mitochondrial dysfunction, cholesterol, and ceramide deposition and reactive oxygen species production in INS832/13 ss-cells. Endocrinology. 2010;151(7):3061-73.
96. Fontes G, Zarrouki B, Hagman DK, Latour MG, Semache M, Roskens V, et al. Glucolipotoxicity age-dependently impairs beta cell function in rats despite a marked increase in beta cell mass. Diabetologia. 2010;53(11):2369-79.
97. Poitout V, Amyot J, Semache M, Zarrouki B, Hagman D, Fontes G. Glucolipotoxicity of the pancreatic beta cell. Biochim Biophys Acta. 2010;1801(3):289-98.
98. van Raalte DH, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? Diabetes research and clinical practice. 2011;93 Suppl 1:S37-46.
99. Liu Z, Stanojevic V, Brindamour LJ, Habener JF. GLP1-derived nonapeptide GLP1(28-36)amide protects pancreatic beta-cells from glucolipotoxicity. The Journal of endocrinology. 2012;213(2):143-54.
100. Bazan NG, Molina MF, Gordon WC. Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegenerative diseases. Annual review of nutrition. 2011;31:321-51.
101. Head E, Rofina J, Zicker S. Oxidative stress, aging, and central nervous system disease in the canine model of human brain aging. The Veterinary clinics of North America Small animal practice. 2008;38(1):167-78, vi.
102. Maeda N, Hagihara H, Nakata Y, Hiller S, Wilder J, Reddick R. Aortic wall damage in mice unable to synthesize ascorbic acid. Proc Natl Acad Sci U S A. 2000;97(2):841-6.
103. Harrison FE, Meredith ME, Dawes SM, Saskowski JL, May JM. Low ascorbic acid and increased oxidative stress in gulo(-/-) mice during development. Brain Res. 2010;1349:143-52.
104. Hodges RE, Hood J, Canham JE, Sauberlich HE, Baker EM. Clinical manifestations of ascorbic acid deficiency in man. The American journal of clinical nutrition. 1971;24(4):432-43.
105. Harrison FE, May JM. Vitamin C function in the brain: vital role of the ascorbate transporter SVCT2. Free radical biology & medicine. 2009;46(6):719-30.
106. Gess B, Sevimli S, Strecker JK, Young P, Schabitz WR. Sodium-dependent vitamin C transporter 2 (SVCT2) expression and activity in brain capillary endothelial cells after transient ischemia in mice. PLoS One. 2011;6(2):e17139.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

107. Lin JL, Huang YH, Shen YC, Huang HC, Liu PH. Ascorbic acid prevents blood-brain barrier disruption and sensory deficit caused by sustained compression of primary somatosensory cortex. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2010;30(6):1121-36.
108. Hall ED, Vaishnav RA, Mustafa AG. Antioxidant therapies for traumatic brain injury. Neurotherapeutics. 2010;7(1):51-61.
109. Narayanan SN, Kumar RS, Paval J, Nayak S. Effect of ascorbic acid on the monosodium glutamate-induced neurobehavioral changes in periadolescent rats. Bratislavske lekarske listy. 2010;111(5):247-52.
110. Moretti M, Colla A, de Oliveira Balen G, dos Santos DB, Budni J, de Freitas AE, et al. Ascorbic acid treatment, similarly to fluoxetine, reverses depressive-like behavior and brain oxidative damage induced by chronic unpredictable stress. Journal of psychiatric research. 2012;46(3):331-40.
111. Paleologos M, Cumming RG, Lazarus R. Cohort study of vitamin C intake and cognitive impairment. Am J Epidemiol. 1998;148(1):45-50.
112. Guidi I, Galimberti D, Lonati S, Novembrino C, Bamonti F, Tiriticco M, et al. Oxidative imbalance in patients with mild cognitive impairment and Alzheimer's disease. Neurobiol Aging. 2006;27(2):262-9.
113. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. Jama. 2002;287(24):3230-7.
114. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, et al. Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. J Neurosci. 1999;19(18):8114-21.
115. Dringen R. Metabolism and functions of glutathione in brain. Progress in neurobiology. 2000;62(6):649-71.
116. Rice ME, Russo-Menna I. Differential compartmentalization of brain ascorbate and glutathione between neurons and glia. Neuroscience. 1998;82(4):1213-23.
117. Kish SJ, Morito C, Hornykiewicz O. Glutathione peroxidase activity in Parkinson's disease brain. Neuroscience letters. 1985;58(3):343-6.
118. Volicer L, Crino PB. Involvement of free radicals in dementia of the Alzheimer type: a hypothesis. Neurobiol Aging. 1990;11(5):567-71.
119. Aquilano K, Baldelli S, Ciriolo MR. Glutathione is a crucial guardian of protein integrity in the brain upon nitric oxide imbalance. Commun Integr Biol. 2011;4(4):477-9.
120. Perluigi M, Di Domenico F, Giorgi A, Schinina ME, Coccia R, Cini C, et al. Redox proteomics in aging rat brain: involvement of mitochondrial reduced glutathione status and mitochondrial protein oxidation in the aging process. J Neurosci Res. 2010;88(16):3498-507.
121. Emir UE, Raatz S, McPherson S, Hodges JS, Torkelson C, Tawfik P, et al. Noninvasive quantification of ascorbate and glutathione concentration in the elderly human brain. NMR in biomedicine. 2011;24(7):888-94.
122. Mandal PK, Tripathi M, Sugunan S. Brain oxidative stress: detection and mapping of anti-oxidant marker 'Glutathione' in different brain regions of healthy male/female, MCI and Alzheimer patients using non-invasive magnetic resonance spectroscopy. Biochem Biophys Res Commun. 2012;417(1):43-8.
123. Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int J Neuropsychopharmacol. 2011;14(1):123-30.
124. Chauhan A, Audhya T, Chauhan V. Brain region-specific glutathione redox imbalance in autism. Neurochem Res. 2012;37(8):1681-9.
125. Freitas HR, Reis RA. Glutathione induces GABA release through P2X7R activation on Muller glia. Neurogenesis (Austin, Tex). 2017;4(1):e1283188.
126. Faria RX, Freitas HR, Reis RAM. P2X7 receptor large pore signaling in avian Muller glial cells. J Bioenerg Biomembr. 2017.
127. Blaha MJ, Hung RK, Dardari Z, Feldman DI, Whelton SP, Nasir K, et al. Age-dependent prognostic value of exercise capacity and derivation of fitness-associated biologic age. Heart. 2016;102(6):431-7.
128. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. J Appl Physiol (1985). 2011;111(5):1505-13.
129. Vijg J, de Grey AD. Innovating aging: promises and pitfalls on the road to life extension. Gerontology. 2014;60(4):373-80.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

130. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. The Journal of physiology. 2016;594(8):2001-24.
131. Di Benedetto S, Muller L, Wenger E, Duzel S, Pawelec G. Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. Neuroscience and biobehavioral reviews. 2017;75:114-28.
132. Jackson PA, Pialoux V, Corbett D, Drogos L, Erickson KI, Eskes GA, et al. Promoting brain health through exercise and diet in older adults: a physiological perspective. The Journal of physiology. 2016;594(16):4485-98.
133. Guure CB, Ibrahim NA, Adam MB, Said SM. Impact of Physical Activity on Cognitive Decline, Dementia, and Its Subtypes: Meta-Analysis of Prospective Studies. BioMed research international. 2017;2017:9016924.
134. Bolduc V, Thorin-Trescases N, Thorin E. Endothelium-dependent control of cerebrovascular functions through age: exercise for healthy cerebrovascular aging. American journal of physiology Heart and circulatory physiology. 2013;305(5):H620-33.
135. De la Torre R, Corella D, Castaner O, Martinez-Gonzalez MA, Salas-Salvador J, Vila J, et al. Protective effect of homovanillyl alcohol on cardiovascular disease and total mortality: virgin olive oil, wine, and catechol-methylathion. The American journal of clinical nutrition. 2017;105(6):1297-304.
136. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. The Journal of physiology. 2008;586(16):4005-10.
137. Xing CY, Tarumi T, Meijers RL, Turner M, Repshas J, Xiong L, et al. Arterial Pressure, Heart Rate, and Cerebral Hemodynamics Across the Adult Life Span. Hypertension. 2017;69(4):712-20.
138. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovascular psychiatry and neurology. 2012;2012:367516.
139. Barnes JN. Exercise, cognitive function, and aging. Advances in physiology education. 2015;39(2):55-62.
140. Viboolvorakul S, Patumraj S. Exercise training could improve age-related changes in cerebral blood flow and capillary vascularity through the upregulation of VEGF and eNOS. BioMed research international. 2014;2014:230791.
141. Gertz K, Priller J, Kronenberg G, Fink KB, Winter B, Schrock H, et al. Physical activity improves long-term stroke outcome via endothelial nitric oxide synthase-dependent augmentation of neovascularization and cerebral blood flow. Circulation research. 2006;99(10):1132-40.
142. Choi DH, Lee KH, Lee J. Effect of exercise-induced neurogenesis on cognitive function deficit in a rat model of vascular dementia. Molecular medicine reports. 2016;13(4):2981-90.
143. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A. 2007;104(13):5638-43.
144. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging. 2014;35 Suppl 2:S20-8.
145. Maass A, Duzel S, Goerke M, Becke A, Sobieray U, Neumann K, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. Molecular psychiatry. 2015;20(5):585-93.
146. Hanning U, Roesler A, Peters A, Berger K, Baune BT. Structural brain changes and all-cause mortality in the elderly population-the mediating role of inflammation. Age (Dordrecht, Netherlands). 2016;38(5-6):455-64.
147. Benedict C, Brooks SJ, Kullberg J, Nordenskjold R, Burgos J, Le Greves M, et al. Association between physical activity and brain health in older adults. Neurobiol Aging. 2013;34(1):83-90.
148. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus. 2009;19(10):1030-9.
149. Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, et al. Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial. PLoS One. 2017;12(2):e0170547.
150. Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, Vanpatter M, et al. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain Res. 2010;1358:172-83.
151. Nyberg J, Aberg MA, Schioler L, Nilsson M, Wallin A, Toren K, et al. Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia. Brain. 2014;137(Pt 5):1514-23.
152. Cahill L. Why sex matters for neuroscience. Nature reviews Neuroscience. 2006;7(6):477-84.
153. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with physical performance in elderly persons: MacArthur studies of

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

929 successful aging. The journals of gerontology Series A, Biological sciences and medical sciences.
930 2000;55(12):M709-15.
931 154. De la Fuente M, Cruces J, Hernandez O, Ortega E. Strategies to improve the functions and redox state of
932 the immune system in aged subjects. Current pharmaceutical design. 2011;17(36):3966-93.
933 155. Vassilaki M, Cha RH, Aakre JA, Therneau TM, Geda YE, Mielke MM, et al. Mortality in mild cognitive
934 impairment varies by subtype, sex, and lifestyle factors: the Mayo Clinic Study of Aging. Journal of Alzheimer's
935 disease : JAD. 2015;45(4):1237-45.
936 156. Xing CY, Tarumi T, Liu J, Zhang Y, Turner M, Riley J, et al. Distribution of cardiac output to the brain across
937 the adult lifespan. Journal of cerebral blood flow and metabolism : official journal of the International Society of
938 Cerebral Blood Flow and Metabolism. 2017;37(8):2848-56.
939 157. Berchtold NC, Cribbs DH, Coleman PD, Rogers J, Head E, Kim R, et al. Gene expression changes in the
940 course of normal brain aging are sexually dimorphic. Proc Natl Acad Sci U S A. 2008;105(40):15605-10.
941 158. Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of
942 brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? Molecular psychiatry.
943 2013;18(8):864-74.
944 159. Varma VR, Chuang YF, Harris GC, Tan EJ, Carlson MC. Low-intensity daily walking activity is associated
945 with hippocampal volume in older adults. Hippocampus. 2015;25(5):605-15.
946 160. Pentikainen H, Ngandu T, Liu Y, Savonen K, Komulainen P, Hallikainen M, et al. Cardiorespiratory fitness
947 and brain volumes in men and women in the FINGER study. Age and ageing. 2017;46(2):310-3.
948 161. Talbot K. Brain insulin resistance in Alzheimer's disease and its potential treatment with GLP-1 analogs.
949 Neurodegenerative disease management. 2014;4(1):31-40.
950 162. Akintola AA, van Heemst D. Insulin, aging, and the brain: mechanisms and implications. Frontiers in
951 endocrinology. 2015;6:13.
952 163. Paolisso G, Gambardella A, Ammendola S, D'Amore A, Balbi V, Varricchio M, et al. Glucose tolerance and
953 insulin action in healty centenarians. The American journal of physiology. 1996;270(5 Pt 1):E890-4.
954 164. Bertram S, Brixius K, Brinkmann C. Exercise for the diabetic brain: how physical training may help prevent
955 dementia and Alzheimer's disease in T2DM patients. Endocrine. 2016;53(2):350-63.
956 165. Claxton A, Baker LD, Hanson A, Trittschuh EH, Cholerton B, Morgan A, et al. Long Acting Intranasal
957 Insulin Detemir Improves Cognition for Adults with Mild Cognitive Impairment or Early-Stage Alzheimer's
958 Disease Dementia. Journal of Alzheimer's disease : JAD. 2015;45(4):1269-70.
959 166. Craft S, Claxton A, Baker LD, Hanson AJ, Cholerton B, Trittschuh EH, et al. Effects of Regular and Long-
960 Acting Insulin on Cognition and Alzheimer's Disease Biomarkers: A Pilot Clinical Trial. Journal of Alzheimer's
961 disease : JAD. 2017;57(4):1325-34.
962 167. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton B, et al. Intranasal insulin improves
963 cognition and modulates beta-amyloid in early AD. Neurology. 2008;70(6):440-8.
964 168. Hoene M, Lehmann R, Hennige AM, Pohl AK, Haring HU, Schleicher ED, et al. Acute regulation of
965 metabolic genes and insulin receptor substrates in the liver of mice by one single bout of treadmill exercise. The
966 Journal of physiology. 2009;587(1):241-52.
967 169. Castro MG, Venutolo C, Yau PL, Convit A. Fitness, insulin sensitivity, and frontal lobe integrity in adults
968 with overweight and obesity. Obesity (Silver Spring, Md). 2016;24(6):1283-9.
969 170. Kang EB, Cho JY. Effects of treadmill exercise on brain insulin signaling and beta-amyloid in
970 intracerebroventricular streptozotocin induced-memory impairment in rats. Journal of exercise nutrition &
971 biochemistry. 2014;18(1):89-96.
972 171. Muller AP, Gnoatto J, Moreira JD, Zimmer ER, Haas CB, Lulhier F, et al. Exercise increases insulin signaling
973 in the hippocampus: physiological effects and pharmacological impact of intracerebroventricular insulin
974 administration in mice. Hippocampus. 2011;21(10):1082-92.
975 172. Zhang H, Zhang C. Adipose "talks" to distant organs to regulate insulin sensitivity and vascular function.
976 Obesity (Silver Spring, Md). 2010;18(11):2071-6.
977 173. Ringseis R, Eder K, Mooren FC, Kruger K. Metabolic signals and innate immune activation in obesity and
978 exercise. Exercise immunology review. 2015;21:58-68.
979 174. Khoo J, Dhamodaran S, Chen DD, Yap SY, Chen RY, Tian RH. Exercise-Induced Weight Loss is More
980 Effective than Dieting for Improving Adipokine Profile, Insulin Resistance, and Inflammation in Obese Men.
981 International journal of sport nutrition and exercise metabolism. 2015;25(6):566-75.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

982 175. Lowndes J, Zoeller RF, Kyriazis GE, Miles MP, Seip RL, Moyna NM, et al. Hyperleptinemia is associated
983 with CRP, but not apolipoprotein E, and is reduced by exercise training. International journal of sport nutrition
984 and exercise metabolism. 2014;24(5):524-31.
985 176. Markofski MM, Carrillo AE, Timmerman KL, Jennings K, Coen PM, Pence BD, et al. Exercise training
986 modifies ghrelin and adiponectin concentrations and is related to inflammation in older adults. The journals of
987 gerontology Series A, Biological sciences and medical sciences. 2014;69(6):675-81.
988 177. Vella CA, Allison MA, Cushman M, Jenny NS, Miles MP, Larsen B, et al. Physical Activity and Adiposity-
989 related Inflammation: The MESA. Medicine and science in sports and exercise. 2017;49(5):915-21.
990 178. Yau SY, Li A, Hoo RL, Ching YP, Christie BR, Lee TM, et al. Physical exercise-induced hippocampal
991 neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc Natl Acad
992 Sci U S A. 2014;111(44):15810-5.
993 179. Ogawa K, Sanada K, Machida S, Okutsu M, Suzuki K. Resistance exercise training-induced muscle
994 hypertrophy was associated with reduction of inflammatory markers in elderly women. Mediators of
995 inflammation. 2010;2010:171023.
996 180. Santos RV, Viana VA, Boscolo RA, Marques VG, Santana MG, Lira FS, et al. Moderate exercise training
997 modulates cytokine profile and sleep in elderly people. Cytokine. 2012;60(3):731-5.
998 181. Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, Mejias Y, Rivas A, de Paz JA, et al. Role of Toll-
999 like receptor 2 and 4 signaling pathways on the inflammatory response to resistance training in elderly subjects.
1000 Age (Dordrecht, Netherlands). 2014;36(6):9734.
1001 182. Chupel MU, Direito F, Furtado GE, Minuzzi LG, Pedrosa FM, Colado JC, et al. Strength Training Decreases
1002 Inflammation and Increases Cognition and Physical Fitness in Older Women with Cognitive Impairment.
1003 Frontiers in physiology. 2017;8:377.
1004 183. Braskie MN, Boyle CP, Rajagopalan P, Gutman BA, Toga AW, Raji CA, et al. Physical activity,
1005 inflammation, and volume of the aging brain. Neuroscience. 2014;273:199-209.
1006 184. Chennaoui M, Gomez-Merino D, Drogou C, Geoffroy H, Dispersyn G, Langrume C, et al. Effects of exercise
1007 on brain and peripheral inflammatory biomarkers induced by total sleep deprivation in rats. Journal of
1008 inflammation (London, England). 2015;12:56.
1009 185. Nieman DC, Davis JM, Brown VA, Henson DA, Dumke CL, Utter AC, et al. Influence of carbohydrate
1010 ingestion on immune changes after 2 h of intensive resistance training. Journal of applied physiology.
1011 2004;96(4):1292-8.
1012 186. Della Gatta PA, Garnham AP, Peake JM, Cameron-Smith D. Effect of exercise training on skeletal muscle
1013 cytokine expression in the elderly. Brain, behavior, and immunity. 2014;39:80-6.
1014 187. Piao CS, Stoica BA, Wu J, Sabirzhanov B, Zhao Z, Cabatbat R, et al. Late exercise reduces
1015 neuroinflammation and cognitive dysfunction after traumatic brain injury. Neurobiology of disease.
1016 2013;54:252-63.
1017 188. de la Torre JC. Are Major Dementias Triggered by Poor Blood Flow to the Brain? Theoretical
1018 Considerations. Journal of Alzheimer's disease : JAD. 2017;57(2):353-71.
1019 189. Pyo JO, Yoo SM, Ahn HH, Nah J, Hong SH, Kam TI, et al. Overexpression of Atg5 in mice activates
1020 autophagy and extends lifespan. Nature communications. 2013;4:2300.
1021 190. Mejias-Pena Y, Estebanez B, Rodriguez-Miguelez P, Fernandez-Gonzalo R, Almar M, de Paz JA, et al.
1022 Impact of resistance training on the autophagy-inflammation-apoptosis crosstalk in elderly subjects. Aging.
1023 2017;9(2):408-18.
1024 191. Mejias-Pena Y, Rodriguez-Miguelez P, Fernandez-Gonzalo R, Martinez-Florez S, Almar M, de Paz JA, et
1025 al. Effects of aerobic training on markers of autophagy in the elderly. Age (Dordr). 2016;38(2):33.
1026 192. Marosi K, Bori Z, Hart N, Sarga L, Koltai E, Radak Z, et al. Long-term exercise treatment reduces oxidative
1027 stress in the hippocampus of aging rats. Neuroscience. 2012;226:21-8.
1028 193. Garcia-Mesa Y, Colie S, Corpas R, Cristofol R, Comellas F, Nebreda AR, et al. Oxidative Stress Is a Central
1029 Target for Physical Exercise Neuroprotection Against Pathological Brain Aging. The journals of gerontology
1030 Series A, Biological sciences and medical sciences. 2016;71(1):40-9.
1031 194. Raefsky SM, Mattson MP. Adaptive responses of neuronal mitochondria to bioenergetic challenges: Roles
1032 in neuroplasticity and disease resistance. Free radical biology & medicine. 2017;102:203-16.
1033 195. Marques-Aleixo I, Santos-Alves E, Balca MM, Rizo-Roca D, Moreira PI, Oliveira PJ, et al. Physical exercise
1034 improves brain cortex and cerebellum mitochondrial bioenergetics and alters apoptotic, dynamic and
1035 auto(mito)phagy markers. Neuroscience. 2015;301:480-95.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 2 October 2017 doi:10.20944/preprints201710.0006.v1

Peer-reviewed version available at Nutrients 2017, 9, 1263; doi:10.3390/nu9111263

196. Panati K, Suneetha Y, Narala VR. Irisin/FNDC5--An updated review. European review for medical and pharmacological sciences. 2016;20(4):689-97.
197. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin--mediators of inflammation and mediators of exercise. Mediators of inflammation. 2013;2013:320724.
198. Dinoff A, Herrmann N, Swardfager W, Liu CS, Sherman C, Chan S, et al. The Effect of Exercise Training on Resting Concentrations of Peripheral Brain-Derived Neurotrophic Factor (BDNF): A Meta-Analysis. PLoS One. 2016;11(9):e0163037.
199. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry. 2012;18(1):82-97.
200. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Experimental physiology. 2009;94(10):1062-9.
201. Wrann CD. FNDC5/irisin - their role in the nervous system and as a mediator for beneficial effects of exercise on the brain. Brain plasticity. 2015;1(1):55-61.
202. Hashemi MS, Ghaedi K, Salamian A, Karbalaie K, Emadi-Baygi M, Tanhaei S, et al. Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells. Neuroscience. 2013;231:296-304.
203. Warner DS, Sheng H, Batinic-Haberle I. Oxidants, antioxidants and the ischemic brain. The Journal of experimental biology. 2004;207(Pt 18):3221-31.
204. Liu J, Atamna H, Kuratsune H, Ames BN. Delaying brain mitochondrial decay and aging with mitochondrial antioxidants and metabolites. Annals of the New York Academy of Sciences. 2002;959:133-66.
205. Gilgun-Sherki Y, Melamed E, Offen D. Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier. Neuropharmacology. 2001;40(8):959-75.
206. Slemmer JE, Shacka JJ, Sweeney MI, Weber JT. Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging. Current medicinal chemistry. 2008;15(4):404-14.