

Novel Strategies for Healthy Brain Aging

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WAHL, D., A.N. CAVALIER, and T.J. LARocca. Novel strategies for healthy brain aging. *Exerc. Sport Sci. Rev.*, Vol. 49, No. 2, pp. 115–125, 2021. *One of the best strategies for healthy brain aging is regular aerobic exercise. Commonly studied “anti-aging” compounds may mimic some effects of exercise on the brain, but novel approaches that target energy-sensing pathways similar to exercise probably will be more effective in this context. We review evidence in support of this hypothesis by focusing on biological hallmarks of brain aging.* **Key Words:** brain aging, exercise, anti-aging compounds, neurodegenerative disease, energy-sensing pathways

Key points

- Brain aging is the greatest risk factor for neurodegenerative disease.
- Exercise reduces all major hallmarks of brain aging.
- Anti-aging compounds may recapitulate some but not all of the effects of exercise on the hallmarks of brain aging.
- Emerging compounds and interventions that target energy-sensing pathways similar to exercise may be more effective in this context.

INTRODUCTION

As the world's population ages, the incidence of dementia and neurodegenerative diseases is expected to markedly increase. One key precursor to dementia and neurodegeneration is brain aging itself. Brain aging is characterized by declines in cognitive function (primarily memory and learning, attention/processing speed, and executive function) (1). In some people, these declines may develop into mild cognitive impairment (MCI), which increases the risk for dementia and neurodegenerative diseases like Alzheimer's disease (AD) (2).

Age-related cognitive declines are caused in part by adverse biological events in the brain known as the “hallmarks of brain aging” (Fig. 1). This collection of processes mirrors the hallmarks of aging (3) in peripheral tissues in many ways, but it also includes several brain-specific phenomena. Importantly, the

hallmarks of brain aging also are involved, and often more pronounced, in most neurodegenerative diseases. Thus, brain aging and neurodegeneration may be part of a continuum, and a combination of hallmarks/risk factors may determine whether dementia or disease develops (2). As a result, there is growing interest in strategies for inhibiting the hallmarks of brain aging, which could potentially delay or prevent the onset of neurodegenerative diseases (4).

Regular aerobic exercise is one of the few evidence-based ways to reduce the risk for age-related cognitive decline and neurodegenerative diseases (5). As such, it has been suggested that exercise should be a first-line strategy for healthy brain aging. Still, there is significant interest in exercise alternatives, including pharmacological “anti-aging” compounds that may have similar or complementary effects (especially in Western societies where sedentary lifestyles are common and many find it difficult to maintain an exercise routine). Many compounds have been tested for their effects on health and longevity in model organisms, and several in particular have been shown to suppress hallmarks of aging in peripheral tissues and increase healthy lifespan in the National Institute on Aging's Intervention Testing Program (ITP) (6). These compounds are some of the most studied in the broad field of aging research and may hold some promise for attenuating hallmarks of brain aging specifically.

The literature on how exercise affects the hallmarks of brain aging is relatively new, and the extent to which select/ITP anti-aging compounds influence the hallmarks of brain aging *per se* (and whether these agents can mimic the effects of exercise on the brain) also is an emerging topic. However, we and others have shown that exercise remains among the best approaches to reduce hallmarks of aging and increase health/function in peripheral tissues (4,7). Here, we hypothesize that 1) although most pharmacological agents known to increase lifespan in the ITP may reduce some hallmarks of brain aging, exercise will likely remain a more effective intervention for healthy brain aging because it stimulates key energy-sensing pathways that modulate *multiple* hallmarks, and 2) novel (non-ITP) compounds or

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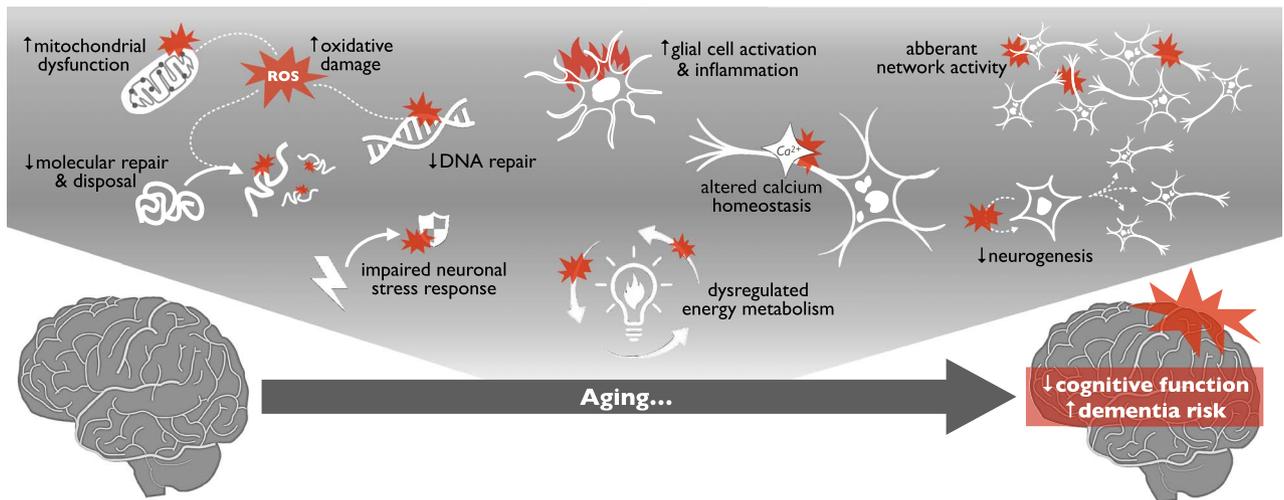


Figure 1. Aging is the primary risk factor for the development of cognitive dysfunction, mild cognitive impairment (MCI), and dementia. Numerous, established biological “hallmarks of brain aging” (shown at top) contribute to age-related reductions in cognitive function and increased neurodegeneration/dementia risk with aging.

interventions that target energy-sensing pathways similar to exercise will prove to be more effective for promoting healthy brain aging in this context. In the following sections, we review the hallmarks of brain aging and the effects of exercise on them, and we compare these to the effects of key ITP compounds on the same hallmarks as a framework for understanding the importance of energy-sensing pathways in healthy brain aging. Afterward, we discuss newer treatments and ideas for targeting bioenergetic signaling pathways similar to exercise that may hold the most promise as exercise alternatives.

Dysregulated Energy Metabolism: A Central Mechanism

Dysregulated energy metabolism is an underlying contributor to all hallmarks of brain aging. During aging, fasting glucose levels increase as cells become less effective at importing glucose in response to insulin (insulin resistance). Peripheral insulin resistance and elevated fasting glucose are linked with accelerated brain aging, poorer cognitive function, and dementia. Brain function is particularly sensitive to the adverse effects of insulin resistance as glucose is a key energy source for neurons, and this can be compounded by metabolic and cardiovascular changes with aging (e.g., dyslipidemia, increased triglycerides and low-density lipoprotein cholesterol). Consequently, sedentary lifestyles and unhealthy diets that impair peripheral function and metabolic health also are linked with accelerated brain aging (4,8).

Importantly, exercise is an energetic stress (reduced cellular energy levels) that peripheral tissues and the brain react to with many metabolic, mitochondrial, and cellular responses (known as hormesis). These adaptive responses involve the activation of energy-sensitive pathways that restore bioenergetic homeostasis in both peripheral tissues and in the brain. Key examples include upregulation of glucose transporters (GLUT) and increased signaling through the low-energy sensors AMP protein kinase (AMPK), sirtuin 1 (SIRT1; an NAD⁺ sensor), and the amino acid-sensing mammalian target of rapamycin (mTOR) pathway (Fig. 2) (8,9). The activation of these systems results in enhanced glucose utilization (GLUT), supports neuronal energy levels by regulating glycolysis and respiration (AMPK), controls the activity of transcription factors and

energy-metabolizing enzymes (SIRT1), and modulates the turnover of proteins/macromolecules that can be used for energy (mTOR). These signaling proteins also may directly impact neural gene expression, synaptic plasticity, and memory formation. Moreover, prolonged exercise leads to glycogen depletion, fatty acid oxidation, and the production of ketone bodies, which are another important energy source for the brain and can independently activate these same sensors (8). In addition to all of this, exercise increases the expression of brain-derived neurotrophic factor (BDNF), which powerfully regulates neuron function and development as well as energy intake/behavior and can interact directly with or be activated by energy sensors like AMPK, mTOR, and SIRT1 (10,11). Importantly, all of these signaling pathways 1) contribute to stress resistance by enhancing cellular function and quality control, 2) have been reported to decline with aging, and 3) *modulate other hallmarks of aging/brain aging*, as emphasized in Figure 2 and described in the following sections (3,8,9). Thus, the activation of these energy-regulating pathways is central and perhaps the most important mechanism underlying the beneficial influence of exercise on the aging brain.

Mitochondrial Dysfunction

Aging is associated with a decline in efficiency of the electron transport chain, resulting in reduced ATP generation and electron leakage that propagates reactive oxygen species (ROS). These ROS can damage cellular structures, including mitochondria and even mitochondrial DNA (mtDNA). This mitochondrial dysfunction is a universal hallmark of aging that impairs overall tissue function, and it is exacerbated by age-related declines in mitochondrial biogenesis and disposal of damaged mitochondria (mitophagy) (3).

Mitochondria are centrally important in the brain, where they play key roles in calcium homeostasis and neuronal metabolism. Numerous studies have shown that mitochondrial dysfunction, especially in neurons, increases with brain aging (8). Dysfunctional mitochondria also are centrally implicated in neurodegenerative diseases, including Parkinson disease (PD) and AD. However, evidence shows that exercise reduces mitochondrial dysfunction in peripheral tissues and the brain. For example, in

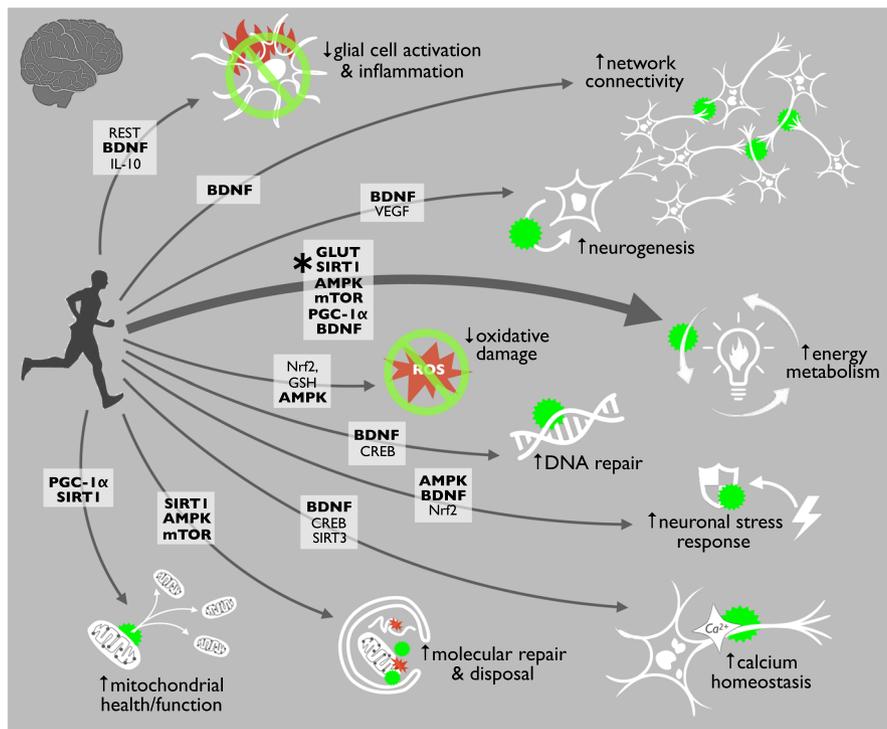


Figure 2. Exercise is perhaps the best strategy for inhibiting all major hallmarks of brain aging, largely because it activates key cellular energy-sensing pathways. This enhanced energy metabolism/regulation with exercise is important because the proteins and cellular pathways involved (in bold) can also directly influence other hallmarks. GSH, glutathione; VEGF, vascular endothelial growth factor.

old mice, chronic high-intensity running increases mtDNA copy number and enhances mitochondrial biogenesis by activating proliferator-activated receptor gamma coactivator-1 α (PGC-1 α) (12), which is downstream of the key energy sensors AMPK and SIRT1. Long-term wheel running also activates autophagy (the cellular process of recycling damaged internal components, including mitochondria) (13), and similar experiments in rats show that running enhances mitochondrial network formation and mitochondrial respiration (14).

As with many of the hallmarks of brain aging, there is limited *direct* evidence for the effects of exercise on brain mitochondrial function with aging in humans (because access to brain tissue/cells is limited). However, at least one study has shown that hippocampal gene expression patterns in older adults who are more physically active reflect enhanced mitochondrial energy production (15). As methods for monitoring mitochondrial function *in vivo* become more advanced, there may be opportunities to demonstrate such cellular effects of exercise more directly.

Accumulation of Oxidatively Damaged Molecules

Oxidatively damaged biomolecules accumulate with aging as a result of oxidative stress, an imbalance between antioxidant defenses and ROS production (3). These ROS can damage biomolecules like proteins, lipids, and DNA, as well as organelles—all of which can impair cellular function directly (because damaged components do not function properly) or indirectly (because damaged biomolecules may interfere with function in other cellular compartments). Neurons are especially sensitive to ROS because of their high, oxidizable lipid content and rate of oxidative metabolism (8).

Interestingly, exercise is associated with oxidative stress, as increased metabolism with exercise increases ROS generation.

However, this effect is likely hormetic because exercise-associated oxidative stress leads to greater long-term antioxidant capacity (9). In fact, habitual aerobic exercise is associated with reduced levels of biomolecule damage in the brain. In old rodents, for example, both long-term running and swimming improve cognitive function and reduce ROS, oxidized proteins (carbonyls), and peroxidized lipids in the brain, in part by increasing antioxidants like glutathione and various neurotrophic factors (16)—many of which are modulated by AMPK, mTOR, and SIRT1. Long-term wheel running even reduces peroxidized lipids, improves memory, and protects against AD pathology in transgenic mouse models (17). Some evidence suggests that these beneficial effects require longer exercise interventions in older mice, which is consistent with the idea that exercise is a hormetic stress on the brain (18). Although there is little direct evidence for the effects of exercise on oxidative damage in the human brain, clinical studies have shown that exercise increases antioxidant defenses and reduces pro-oxidant processes systemically (9), and, similar effects likely occur in the brain.

Reduced Molecular Repair and Disposal

One main reason for both mitochondrial dysfunction and oxidative damage accumulation with aging is reduced activity of cellular repair and disposal systems. Many reports have documented systemic, age-related reductions in 1) autophagolysosomal degradation of proteins and organelles, and 2) activity of the proteasome (degrading old/damaged proteins). These systems are critical in neurons, which are postmitotic and must maintain their functional capacity throughout the lifespan. Moreover, the accumulation of undegraded, damaged, or aggregated proteins due to reduced autophagy and proteasome activity is central to the pathology of many neurodegenerative

diseases (e.g., amyloid beta plaques in AD, alpha synuclein deposits in PD) (2).

Exercise increases autophagy and proteasome activity in both preclinical models and clinical settings (9), and although there is limited direct evidence for these effects in the brain, rodent studies indicate that swimming enhances autophagy and mitochondrial function in the hippocampus of older animals (19) and may protect against pharmacologically induced “premature” brain aging by activating the same systems (20). Running also increases proteasome activity in the brain (21), which may explain reductions in smaller, damaged biomolecules (e.g., protein carbonyls). These effects of exercise on molecular quality control likely involve multiple signaling networks for which autophagy and the proteasome are common downstream effector mechanisms. For example, studies in mice show that exercise activates autophagy in the brain by increasing the activity of AMPK and SIRT1 (13). Exercise also increases mitophagy and enhances mitochondrial network dynamics, in part by activating PGC-1 α (14). In transgenic mice, the activation of these protective quality control systems by exercise may even reduce neurodegenerative protein aggregation (22).

Dysregulated Calcium Homeostasis

Cellular control of important ions and minerals becomes dysregulated in most aged tissues, but impaired calcium (Ca²⁺) homeostasis with aging is a particular problem in neurons. Ca²⁺ plays a role in numerous brain functions, including neurotransmission, neuronal excitability, synaptic plasticity, and long-term memory consolidation. Ca²⁺ levels also modulate gene expression, as Ca²⁺ influx through *N*-methyl-D-aspartate (NMDA) receptors can activate transcription factors like cyclic AMP response element-binding protein (CREB) and PGC-1 α . With aging, neuronal Ca²⁺ homeostasis becomes impaired due to increased Ca²⁺ influx and dysregulation of intracellular Ca²⁺ modulators like mitochondria. This leads to altered gene expression and neuronal function that are linked with cognitive decline and can also contribute directly to neuronal death via Ca²⁺-driven excitotoxicity (8).

There is limited direct evidence for the effects of exercise on calcium homeostasis in the context of brain aging *per se*. However, many studies show that exercise increases BDNF, which has been reported to reduce neurotoxic extrasynaptic Ca²⁺ influx mediated by the NMDA receptor (23). Some of the beneficial effects of exercise on neuronal mitochondria likely improve Ca²⁺ homeostasis as well, as exercise enhances mitochondrial Ca²⁺ handling. In fact, studies in transgenic mice show that exercise increases the expression of the protective mitochondrial sirtuin, SIRT3, and that this is required for protection against Ca²⁺-related excitotoxicity (24). Studies of neuronal Ca²⁺ homeostasis in humans are lacking, but there is strong interest in related systemic biomarkers like S100 calcium-binding protein β (S100 β), which is linked with brain aging, injury, and neurodegeneration, and is reduced by exercise (25).

Impaired Adaptive Cellular Stress Response

All cells activate stress resistance networks (e.g., antioxidant and anti-inflammatory pathways) in response to stressors. In the brain, these adaptive responses are important in settings of electrochemical, ionic, and even psychological stress. With aging, however, most cells become markedly less effective at mounting

adaptive stress responses (3). In neurons, this is partly due to age-related decreases in the expression/activity of stress sensors like AMPK and SIRT1, and protective neurotrophic factors, such as BDNF and nerve growth factor (NGF). These proteins stimulate gene expression that promotes antioxidant defenses, healthy mitochondrial function, and Ca²⁺ handling (8).

As a hormetic stress itself, exercise activates adaptive cellular stress responses, and it increases the ability of these same systems to respond to other stressors. The metabolic stress associated with exercise activates antioxidant systems in mouse neurons, such as those controlled by nuclear factor erythroid 2-related factor 2 (Nrf2), and these protect against aging-relevant neurotoxic stressors (8,26). This exercise-induced Nrf2 activation increases endogenous antioxidants like catalase and superoxide dismutases that directly reduce ROS, and it activates other protective processes (e.g., autophagy) that further protect against oxidative stress. Studies in aged rodents also show that exercise potentiates stress response systems that protect neurons against inflammatory insults, in part by activating BDNF and anti-inflammatory cytokines like interleukin 10 (IL-10) (27).

In humans, there is some evidence that routine exercise increases tolerance for psychological stressors with aging, but direct data on cellular stress responses are limited. Still, many clinical studies have shown that aerobic exercise increases the activity of systemic antioxidant and anti-inflammatory defense systems, and some have even demonstrated that these effects are associated with increases in BDNF and reductions in S100 β (28).

Aberrant Neuronal Network Activity

The brain relies on communication among billions of neurons. Optimal function of neuronal networks requires balanced activity of glutamatergic (excitatory) neurons and GABAergic (inhibitory) interneurons. However, during aging, activity within these circuits (largely white matter communication via myelinated axons) is dysregulated, which can result in hyperexcitability and excitotoxic damage. This may lead to degeneration of fiber systems involved in decision making and learning/memory (8,26).

Some studies have investigated the influence of exercise on neuronal network activity. One showed that pharmacologically induced brain aging is mitigated by swimming, which reduces neurotoxicity and improves synaptic transmission by influencing the expression of glutamate-receptor 1 and synaptophysin (a marker of synaptic integrity) in rats (29). Exercise may also confer neuroprotection by modulating GABA disinhibition (26) and by enhancing dendritic outgrowth, maintaining structural integrity, and improving long-term potentiation in aged animals via BDNF and other proteins also involved in energy sensing. These changes coincide with increased hippocampal glutamate synthesis and an increase in NGFs (30).

In humans, there is evidence that exercise may positively influence neuronal transmission and connectivity. For example, greater cardiovascular fitness in older adults is associated with improved prefrontal cortex (important for decision making) processing speed and heightened synaptic plasticity (31), and meta-analyses find that exercise is associated with greater hippocampus volume and may influence network functional connectivity in this region (32).

Inflammation

Neuroinflammation is characterized by increased numbers of immune-activated, proinflammatory astrocytes and microglia

that secrete neurotoxic cytokines (26). This glial cell activation is linked with brain aging, MCI, and most neurodegenerative diseases. In fact, markers of neuroinflammation and related neurodegeneration [e.g., glial fibrillary acidic protein (GFAP) and neurofilament light chain (NFL)] even have been shown to increase with aging in cognitively unimpaired people (2). Evidence shows that exercise decreases brain inflammation, marked by lower levels of the proinflammatory transcription factor nuclear factor κ B and tumor necrosis factor α (TNF- α), and that these changes are associated with improved spatial memory (26). Exercise even prevents obesity-induced cognitive decline in rodents by influencing inflammatory genes, reducing the number of reactive astroglia and microglia, and reducing major markers of hippocampal inflammation (33). Finally, in old mice, running reduces brain proinflammatory cytokine levels, in part by activating BDNF and RE1-silencing transcription factor (REST), which is linked with numerous neurological disorders (34).

In humans, peripheral inflammation has been linked with brain structural abnormalities, reduced cognitive function, and greater dementia risk. As an example, recent studies demonstrate that high levels of C-reactive protein (CRP; a common clinical marker of inflammation) are associated with reduced brain white matter integrity in older adults (35), and epidemiological data show that systemic inflammation may precede neurodegenerative diseases by decades. However, meta-analyses show that habitual exercise is associated with reduced proinflammatory cytokines including CRP and TNF- α (36).

Impaired DNA Repair

The accumulation of DNA damage is an important hallmark of aging, and it plays a causal role in several premature aging syndromes. DNA damage also is closely linked with brain aging, cognitive decline, and neurodegenerative diseases (8). The genomic damage that accumulates with aging can contribute to cellular senescence (in which cells cease dividing and begin to produce proinflammatory molecules) and apoptosis (programmed cell death), leading to functional decline of organs/systems (including the brain) and reduced longevity (3).

The mechanisms by which exercise reduces DNA damage during aging are not well understood, but evidence points toward several DNA repair pathways, many of which are modulated by SIRT1 and other energy sensors (37). Rodent studies have shown that running stimulates DNA repair in brain tissue by upregulating the expression of CREB and apurinic/apyrimidinic endonuclease 1, which is a key enzyme for DNA base excision repair (38). Treadmill exercise has also been shown to reduce hippocampal DNA fragmentation and neuronal apoptosis in rat models of traumatic brain injury (39). Moreover, in animal models of AD, treadmill exercise is associated with reduced DNA damage and fewer double-stranded breaks in the hippocampus (40).

Impaired Neurogenesis/Stem Cell Exhaustion

Most neurons do not proliferate, but the dentate gyrus of the hippocampus, subventricular zone of the lateral ventricle, and the olfactory bulbs all contain stem cells (41). As is the case with most stem cells, the ability of these stem cells to self-renew and generate new progenitors (neurogenesis) declines with aging, which may account for some of the structural declines observed in the aging brain (8). However, exercise enhances neurogenesis

within these areas, and there is strong interest in determining underlying mechanisms in the hippocampus, which is crucial for learning and memory.

To date, most studies on exercise and hippocampal neurogenesis have been in rodents. Some studies have demonstrated that running induces neurogenesis in the hippocampal dentate gyrus and is associated with increased neurogenesis and improved memory (42). Others have investigated the influence of long-term exercise on hippocampal neurogenesis in old mice and found that exercise increases neurogenesis and improves neuronal structure (43), and these results likely linked with increased activity of BDNF. In humans, neurogenesis may correlate with cerebral blood flow, which has been shown to increase with exercise.

Other: Telomere Attrition and Cellular Senescence

Telomeres are repetitive DNA sequences that cap the ends of chromosomes and protect DNA from degradation. They also protect overall cellular function, as critically short telomeres can lead to cell death or senescence. Telomere shortening and cellular senescence are established hallmarks of aging in peripheral tissues. Their role in brain aging is less clear, but telomere maintenance, which contributes to the production of neuronal stem cells, may protect against neurodegenerative diseases — and there is evidence that habitual exercise is associated with longer telomeres and reduced cellular senescence in both mice and humans (3,8,9).

ITP ALTERNATIVES TO AEROBIC EXERCISE FOR HEALTHY BRAIN AGING

Aerobic exercise is perhaps the best way to protect brain health during aging, but it may not be feasible for some people. In addition, in Western societies where sedentary lifestyles have become common, many may find it difficult to exercise regularly. It is therefore an opportune time to consider whether anti-aging compounds may recapitulate some benefits of exercise on the brain. The National Institute on Aging's ITP has tested the effects of many compounds on healthspan and lifespan in genetically heterogeneous mice. To date, a number of compounds tested by the ITP have been shown to improve health, increase lifespan, and reduce many hallmarks of aging *in vitro* and *in vivo*. The six ITP compounds that are the most heavily studied include aspirin, rapamycin, 17- α -estradiol (17 α E), acarbose, nordihydroguaiaretic acid (NDGA), and Protandim. All of these compounds elicit beneficial health responses in peripheral tissues. Thus, these pharmacological interventions may also improve brain health (44) and reduce some hallmarks of brain aging (Fig. 3). As these are among the most-studied pharmacological anti-aging interventions, comparing the evidence for the effects of these ITP compounds with those of exercise on the brain may provide insight on key mechanisms/targets for healthy brain aging.

Aspirin

Aspirin may enhance health/lifespan both by suppressing inflammation and through its antioxidant properties (44). Evidence suggests that aspirin supplementation improves brain health during aging by reducing oxidative stress and inflammation and by protecting against neurotoxic stressors in dopaminergic neurons (which are important for learning and memory) via enhanced mitochondrial function and reduced ROS production (45). In addition, aspirin improves lysosomal biogenesis and autophagy and

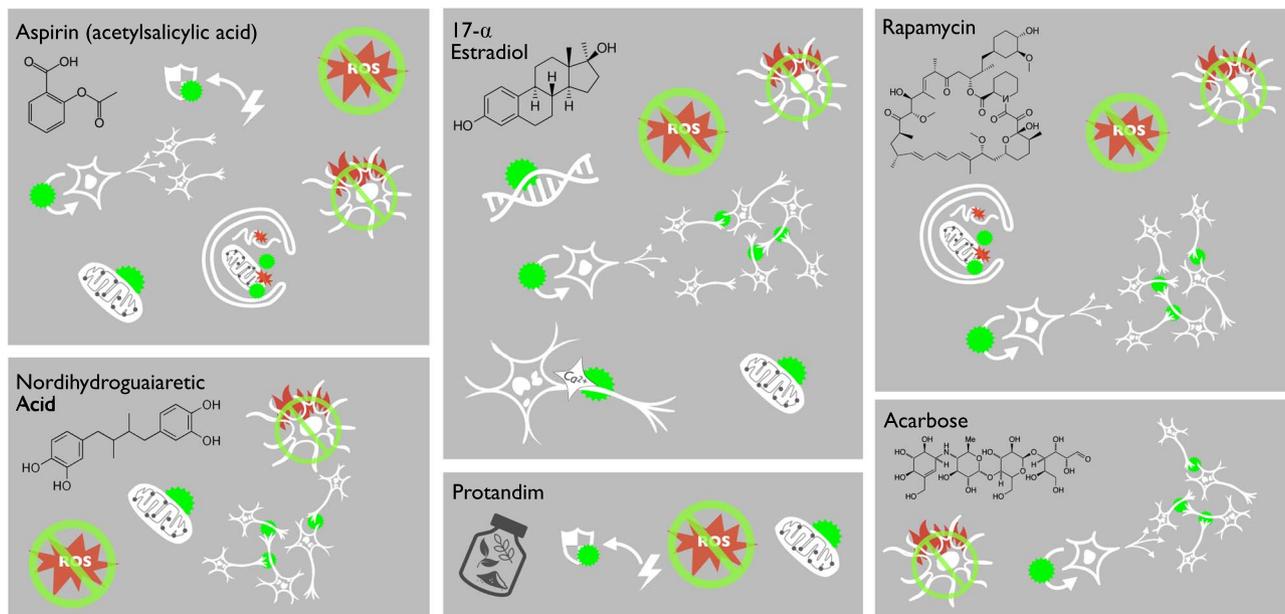


Figure 3. Select pharmacological “anti-aging” treatments that have been shown to increase lifespan/healthspan in the National Institute on Aging’s Intervention Testing Program (ITP) may inhibit certain hallmarks of brain aging, but some are supported by more evidence than others. To date, rapamycin and 17aE seem to be the most effective in this context. However, more research is needed to determine how these and other compounds affect additional hallmarks of brain aging and to fully characterize bioavailability and safety in humans.

reduces plaque pathology in transgenic AD mice (46). Aspirin treatment also reduces stress sensitivity in mice by lowering the activity of the hypothalamic-pituitary-adrenal stress axis and decreasing the expression of GFAP (a marker of proinflammatory astrocytes) (47). Finally, both low-dose and high-dose aspirin supplementation improve neurogenesis by increasing oligodendrocyte proliferation and white matter integrity in rats (48).

In humans, there is mixed evidence that aspirin supplementation in older age may protect against cognitive decline. For example, low-dose aspirin intake is associated with higher scores on cognitive tests in older adults in some studies; however, some meta-analyses have found no association between low-dose aspirin supplementation and improved cognitive health or protection against dementia in older adults (49). Other promising anti-inflammatories currently under investigation for healthy aging/brain aging in humans include salsalate and naproxen (50).

Rapamycin

Rapamycin inhibits intracellular growth cascades (largely by inhibiting mTOR), and it increases median and maximal lifespan in male and female mice (6). There is evidence that rapamycin influences most hallmarks of aging in peripheral tissues and growing support for similar effects in the brain. For example, rapamycin reduces oxidative stress in the brains of old rats by activating autophagy, decreasing neuroinflammation, and improving neuronal integrity (51). Acute injection of rapamycin also reduces proinflammatory cytokines and chemokines and inhibits the activity of macrophages and microglia (4).

Research on rapamycin and the brain is evolving, and the compound may reduce some markers of brain aging via recently discovered mechanisms. For example, rapamycin supplementation is reported to influence the expression of brain telomerase reverse transcriptase (TERT), which maintains telomere integrity and reduces ROS (52). Chronic rapamycin supplementation

also improves NMDA (a glutamate and ion channel receptor that plays a role in synaptic plasticity) signaling. In addition, rapamycin suppresses senescence in rat models of accelerated aging and improves myelination and neuronal structure (53). Long-term rapamycin supplementation even enhances vasculature and brain/neuronal metabolism in mouse models of AD (54). To date, there have been no clinical trials investigating the influence of rapamycin on the hallmarks of brain aging. However, some argue that such trials should soon occur because of the large number of positive results in animal models. There also is a current phase 1b/2a trial underway to determine whether mTOR inhibition with the novel compound RTB101 may benefit patients with PD (ACTRN12619000372189).

17- α -Estradiol

17aE is an endogenous steroid with an affinity for estrogen receptors. Long-term treatment with 17aE increases median lifespan in male mice but not females (6). Interestingly, the brain has many estrogen receptors (which decline in number during aging), and it has therefore been suggested that 17aE might reduce hallmarks of brain aging. Estrogen also modulates neuron-to-neuron communication, helps in the production of brain growth factors, and has a supportive role for glial cells. In fact, 17aE has been shown to reduce age-associated hypothalamic inflammation, in part by diminishing the activity of reactive/proinflammatory microglia and suppressing TNF- α and GFAP (*i.e.*, astrocyte activation) (55). Other reports show that 17aE protects against intraneuronal ROS production and reduces markers of oxidative stress in the brain (56).

There also is evidence that estrogen may improve neuronal calcium homeostasis by suppressing intracellular calcium accumulation, reduce DNA damage in the brain, and stimulate neurogenesis in the hippocampus. Moreover, it has been shown that estradiol can have a direct impact on neuronal network activity by stimulating synaptic excitatory activity, enhancing calcium

dynamics, and improving neuronal structure (57). 17 α E may even reduce amyloid beta-induced neuronal cell death (a feature of AD), in part by enhancing mitochondrial function (56).

Although preclinical evidence in favor of 17 α E is promising, existing data in humans are less clear. Studies on postmenopausal women given hormone replacement therapy have documented a mild association with self-reported estrogen supplementation and reduced risk of dementia (58). However, others have reported that long-term 17- β -estradiol (an isomer of 17 α E) does not influence verbal memory, executive function, or global cognitive ability (59). Thus, more studies are needed to determine whether estrogen or related hormones may influence cognitive function or dementia in larger cohorts and whether these compounds may do so by modulating hallmarks of brain aging.

Acarbose

Acarbose is an inhibitor of small intestinal α -glucosidase that prevents the breakdown of complex carbohydrates into glucose, resulting in decreased glucose absorption and lower blood glucose levels. Acarbose increased median lifespan in the ITP, but the effect was greater in male mice (6). One recent study has shown that chronic acarbose treatment improves synaptic integrity and increases the expression of NGFs, which coincides with improved memory in a mouse model of accelerated aging (60). Acarbose also decreases age-associated hypothalamic inflammation in male mice but not females (55). One population-based retrospective cohort study showed that acarbose use is associated with a reduced risk of dementia in persons with type 2; however, this effect was seen only in women (61).

Nordihydroguaiaretic Acid

NDGA, an antioxidant compound found in the creosote bush, has reported anti-inflammatory and antioxidant capabilities. NDGA improved median lifespan in the ITP, but only in male mice (6). There is limited evidence that NDGA may protect against several hallmarks of brain aging in rodents. For example, NDGA supplementation is associated with reduced age-related hypothalamic inflammation and glial cell reactivity in old mice (55). In addition, NDGA improves mitochondrial function, membrane potential, ATP generation and morphology, and synaptic structure in the striatum of mice. These positive changes are associated with reduced lipid peroxidation and attenuated oxidative stress (62). Finally, NDGA protects cerebellar neurons against H₂O₂-induced oxidative stress by activating Nrf2 antioxidant pathways (63). Despite these few studies suggesting that NDGA may be protective against brain aging and neurodegenerative diseases in animal models, there have been no studies investigating the influence of this compound on brain aging in humans.

Protandim

Protandim is a mixture of five botanical compounds (curcumin, bacosides, silymarin, withaferin A, and epigallocatechin-3-gallate). It is an Nrf2 activator and may benefit health by increasing endogenous antioxidant activity. In the ITP, Protandim improved median lifespan, but the effect was only seen in male mice (6). Many studies have investigated the benefits of Nrf2 activation in brain aging and neurodegenerative diseases; however, only a few have specifically looked at the effects of Protandim

supplementation on the brain. A recent study showed that Protandim reduces oxidative stress and mitochondrial oxidizing species in rat brains (64), but further studies are needed to determine the effects of Protandim on other hallmarks of brain aging. There also is some interest in additional/novel Nrf2 activators, such as sulforaphane and dimethyl fumarate, and these may have promise in this context.

Others

Several other promising compounds and phytochemicals (some currently being tested in the ITP) may have the ability to influence the hallmarks of brain aging. Although not described in detail in the current review, these compounds include the polyphenol resveratrol (65), senolytic compounds (which clear senescent cells) (66), curcumin (derived from the Indian spice turmeric) (67), and spermidine (an autophagy activator) (68). Most of these compounds have been shown to influence some hallmarks of brain aging and are well tolerated in humans. These compounds, in addition to those described, may have great potential to positively influence brain health during aging and reduce the risk for neurodegenerative disease. However, more rigorous research is needed to determine effective doses, bioavailability, and mechanisms of action before clinical trials commence.

FUTURE DIRECTIONS: NOVEL ENERGY-TARGETING STRATEGIES FOR HEALTHY BRAIN AGING

Aerobic exercise clearly has a strong, inhibitory influence on *all* hallmarks of brain aging. Several popular pharmacological candidates for improving healthspan may exert similar effects on certain hallmarks, but most are not as broadly effective as exercise. Of the most commonly studied compounds in the ITP, rapamycin, 17 α E, and (to a lesser extent) aspirin seem to be supported by the most encouraging evidence (Fig. 3). Of these compounds, rapamycin may be the most promising candidate, as others already have yielded mixed results in clinical settings. Still, clinical data are limited, and further research is needed to determine whether rapamycin or other ITP compounds may be truly effective for inhibiting the hallmarks of brain aging, improving cognitive function, and preventing neurodegenerative diseases in humans.

One key reason that aerobic exercise outperforms common pharmacological healthspan enhancers in the context of brain aging is that exercise provides a strong physiologic/metabolic stimulus. As described above, exercise causes metabolic stress (low cellular energy) linked with accumulation of important energetic signaling molecules (*e.g.*, AMP, NAD⁺, ketones) (Figs. 1 and 4). These and other exercise-induced metabolites flip a “metabolic switch” that activates numerous protective cellular pathways with pleiotropic effects. Interestingly, although anti-aging compounds are not associated with the same hormetic energy stress, a common denominator among the ITP compounds that most favorably modulate hallmarks of brain aging (rapamycin, 17 α E, and aspirin) is that they have all been linked with activation of exercise-relevant, energy-sensing pathways. Rapamycin specifically modulates mTOR signaling, and both 17 α E and salicylate (the active moiety in aspirin) have been shown to increase signaling/activity of AMPK, SIRT1, and BDNF (69–71). This observation is consistent with the idea that

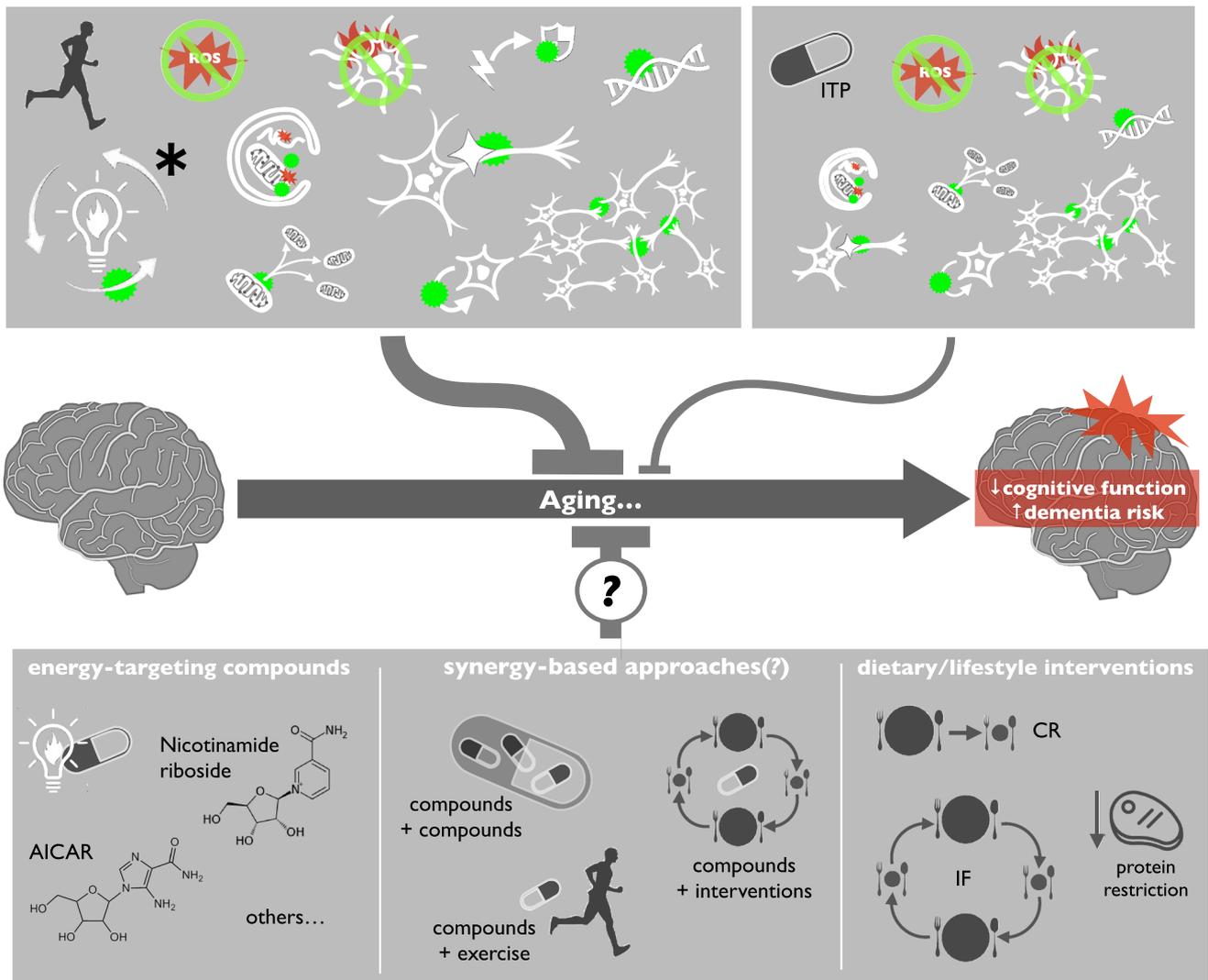


Figure 4. Exercise is more broadly effective than traditional anti-aging compounds for preserving cognitive function and reducing dementia risk because it is associated with a strong bioenergetic stimulus that directly influences all hallmarks of brain aging. However, some energy-targeting pharmacological agents [e.g., and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and nicotinamide riboside (NR)] and lifestyle interventions [e.g., calorie restriction (CR), protein restriction, and intermittent fasting] may better mimic effects of exercise on the hallmarks of brain aging. Potential synergistic effects among these interventions and compounds could hold particular promise for promoting healthy brain aging.

activation of these energy-sensing pathways is likely required to truly mimic the effects of exercise on the brain. Thus, we hypothesize that several less-studied exercise alternatives that focus on activating energy-sensing pathways may be more effective for healthy brain aging than traditional ITP compounds (Fig. 4).

Novel (Non-ITP) Compounds Targeting Energy-Sensing Pathways

Many compounds have not been investigated in the ITP but could have powerful effects on brain aging, and those that directly stimulate energy-sensing systems may hold the most promise. Key examples include NAD⁺-boosting compounds like nicotinamide mononucleotide or nicotinamide riboside (NR; currently under testing in the ITP), 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) or various small molecules that directly activate AMPK (e.g., compound 13, PT-1) (72), as well as metformin (no effect on lifespan in the ITP). There is limited but mostly positive evidence for the effects of these compounds on the brain (73–75). Future studies will need to determine the

bioavailability, ideal dosing, and efficacy of these and other related compounds for healthy brain aging — but given that they directly target exercise-like pathways, this is likely a compelling area for future research.

Novel Dietary/Lifestyle Interventions Targeting Energy-Sensing Pathways

Growing evidence suggests that select nutritional interventions (especially those that target energy-sensing pathways) may be similarly/as effective as exercise for healthy brain aging. For example, calorie restriction (CR; 10%–50% reduction in daily caloric intake) and intermittent fasting (IF; periods of time without food) are considered perhaps the strongest nutritional interventions to reduce hallmarks of brain aging (4). Both CR and IF contribute to hormesis by increasing cellular stress resistance and stress responses (76), and both have been reported to positively influence the brain and reduce essentially all hallmarks of brain aging (77,78). The mechanisms underlying CR and IF include powerful modulation of key energy-sensing

proteins like AMPK, SIRT1, BDNF, and mTOR (79). IF and related approaches (e.g., time-restricted feeding (80)), as well as other strategies for mimicking CR (e.g., protein restriction (81)), may be the most practical dietary strategies, as CR is difficult to implement clinically (82) — but the influence of these interventions on human cognitive function/brain aging warrants significant study in the future, as most current evidence is preclinical or limited to peripheral tissues (83).

Synergistic, Energy-Targeted Compound/Intervention Combinations

An interesting direction for future research on strategies for healthy brain aging may be to study similarities/interactions among compounds or interventions. For example, could combinations of compounds targeting energy-sensing pathways more effectively mimic the effects of exercise on the hallmarks of brain aging (i.e., vs. one compound alone)? Or, could exercise, CR, or IF in combination with select compounds have synergistic, protective effects on the aged brain? These ideas are intriguing and could lead to highly translatable strategies for healthy brain aging by reducing the inherent challenges of individual approaches. For instance, a synergistic cocktail of compounds targeting multiple energy-sensing pathways might stimulate greater hormesis (like exercise), and the compounds potentially could be included in lower doses to avoid side effects. Similarly, exercise, CR, or IF could be combined with complementary compounds (i.e., that stimulate similar signaling pathways).

There is conceptual precedent for novel, combinatorial approaches to promote healthy brain aging in other settings. Indeed, the “polypill” concept (combining multiple drugs) is a current and popular research topic in the effort to prevent cardiovascular diseases (84). End points in any study of an energy pathway–focused polypill for healthy brain aging would be less specific, but focusing on cognitive function and hallmarks of brain aging, as described here, should be a starting point. As for lifestyle intervention/compound synergy, some studies in older adults have pointed to adverse interactions between exercise and otherwise protective compounds like metformin (85) and antioxidants (86), which may blunt the beneficial hormetic influence of exercise. These reports have focused on peripheral effects of the interventions (e.g., exercise tolerance, performance) rather than brain health, but they suggest a cautionary approach to this area of research. One possible strategy for avoiding these problems might be to combine less intense exercise, or partial CR or IF, with compounds that target complementary energy-sensing pathways. Such interventions could be more manageable for the average adult who might otherwise not adhere, and they would be associated with fewer risks (e.g., injury, malnourishment), which are especially significant concerns among older adults (82).

CONCLUSIONS

Based on the available evidence, it seems likely that developing novel strategies to target central, exercise-relevant energy-sensing pathways is a particularly promising direction for future research aimed at promoting healthy brain aging. New strategies like those outlined above will need to be tested in preclinical models and then carefully controlled clinical studies for feasibility, safety, and efficacy — but given the importance of

healthy brain aging and dementia prevention, we suspect that such endeavors will be well worth the effort.

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