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Review

Antiaging Therapies, Cognitive Impairment, and Dementia

Devin Wahl, PhD,[1,2,*] Rozalyn M. Anderson, PhD,[3,4] and David G. Le Couteur, MD, PhD[1,2]

[1]Charles Perkins Centre, [2]Aging and Alzheimers Institute, ANZAC Research Institute, Centre for Education and Research on Ageing, The University of Sydney, Australia. [3]Department of Medicine, School of Medicine and Public Health, University of Wisconsin. [4]Geriatrics Research Education and Clinical Center (GRECC), William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin.

*Address correspondence to: Devin Wahl, PhD, Charles Perkins Centre, The University of Sydney, Johns Hopkins Drive, Camperdown NSW 2006. E-mail: devin.wahl@sydney.edu.au

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Abstract

Aging is a powerful risk factor for the development of many chronic diseases including dementia. Research based on disease models of dementia have yet to yield effective treatments, therefore it is opportune to consider whether the aging process itself might be a potential therapeutic target for the treatment and prevention of dementia. Numerous cellular and molecular pathways have been implicated in the aging process and compounds that target these processes are being developed to slow aging and delay the onset of age-associated conditions. A few particularly promising therapeutic agents have been shown to influence many of the main hallmarks of aging and increase life span in rodents. Here we discuss the evidence that some of these antiaging compounds may beneficially affect brain aging and thereby lower the risk for dementia.

Keywords: Brain aging, Caloric restriction, Health, Cognition, Life span extension

Aging is the most powerful determinant for conditions such as frailty, sarcopenia, and osteopenia, but also for many diseases including arthritis, cardiovascular disease, neurodegenerative diseases, and cancer. One of the most important conditions of old age is dementia which has profound impacts on quality of life, functional capacity, and economic costs. It has been a mantra of dementia research for many decades that dementia is not a part of normal aging. Instead, the search for the pharmacological treatment and prevention of dementia has been driven by disease models that focus on abnormal protein deposition (particularly beta-amyloid [Aβ] and tau). Despite a massive and sustained international effort, no effective pharmacological therapeutics have emerged from this approach (1,2). To date the only treatments that have shown any impact on brain aging and dementia are lifestyle interventions such as diet and exercise that, in parallel to having beneficial effects for the brain, also promote healthy aging.

The cellular and molecular mechanisms that underpin the aging process have been encapsulated by the term "Pillars of Aging" or "Hallmarks of Aging" include the adaptation to stress, epigenetics, inflammation, macromolecular damage, metabolism, proteostasis, and stem cells and regeneration (3). In addition to the well-established 9 hallmarks of aging, scientists have recently argued that "defective autophagy" may be considered a 10th hallmark of aging. Although impaired autophagy shares some overlap with several other aging hallmarks (eg, impaired proteostasis), it covers additional important features of aging and has been implicated in the etiology of neurodegenerative disease (4). Each of these processes provides a potential therapeutic target to delay aging and increase the duration of life in optimal health, often termed health span. The Geroscience concept has been developed in order to emphasize the role of aging in the pathogenesis of age-related diseases, and the possibility that treatments that influence aging might also delay the onset of a suite of age-related conditions and diseases (5). Pharmacological and nutritional interventions (particularly caloric restriction and intermittent fasting) that target aging biology and increase life span in animal models, nearly always delay the onset of age-related disorders from cancer to cognitive impairment (6). Dietary patterns including the Mediterranean diet, traditional Okinawan diet and protein restriction also appear to delay the onset of both age-related disease and dementia in humans (7). The Intervention Testing Program (ITP) was formed to identify agents that could beneficially affect aging and was supported by the National Institute on Aging (8). The goal of this preclinical research initiative was to test nutritional and/or pharmaceutical interventions for their ability extend life span in genetically

heterogeneous mice. Intervention testing is simultaneously replicated at three testing sites across the United States, including the Jackson Laboratory in Bar Harbor Maine, UT Health, San Antonio, and the University of Michigan in Ann Arbor. To date this program has identified and validated several agents that delay aging and increase life span in rodents (see later).

With these fascinating developments in epidemiology and preclinical aging research, the time is ripe to consider the role of aging biology in the pathogenesis of dementia and age-related cognitive impairment. The rationale for this approach is based on three key observations: first, most of the hallmarks of aging are present in the brains of older people with dementia; second, many of the characteristic features of Alzheimer's pathology can be found in the brains of older people without dementia; and third, there is no cellular process that uniquely differentiates aging biology from current definitions of dementia (9). We have reviewed the aging literature to determine what evidence exists to support the contention that pharmacological treatments that target aging may also have beneficial effects on brain aging and/or the risk of dementia. Several of the compounds we describe in this review have been heavily studied and the results have been replicated numerous times by many groups. Others have been relatively understudied and there is limited research on their health and life span effects (described later). Nonetheless, we focused primarily on compounds that have been tested and replicated by the ITP, and by additional laboratories. We also focused on compounds and treatments that have shown to improve health, primarily in small invertebrate models and rodents. To date, the research into the effects of these treatments on cardiometabolic health is relatively limited and their potential antiaging mechanisms are still under investigation. Nonetheless, there is emerging evidence to suggest that several may show promise to delay aging and reduce dementia.

Compounds Tested by the ITP Associated With Life-Span Extension

To date, six compounds from the ITP have been shown to increase life span in mice (Table 1): aspirin, rapamycin, 17α-estradiol, acarbose, nordihydroguaiaretic acid, and Protandim (PRO) (8). Although the life-span extension benefits of those compounds have been demonstrated in rodents, the mechanisms by which they exert their effects are still being elucidated: some compounds are more effective than others to promote longevity, sex dimorphism is common in the effects of these compounds on longevity, and for some, validation of their efficacy and in depth investigation of mechanisms have only begun recently.

Rapamycin

Rapamycin is an inhibitor of intracellular growth signaling that has been investigated in numerous cell biology and physiology studies and is a major compound of interest in biology of aging research. Rapamycin was isolated from *Streptomyces hygroscopicus* found on Easter Island. In addition to possessing potent antifungal properties, rapamycin suppresses immune responses and inhibits cell growth, including tumor cells, though inhibition of mechanistic target of rapamycin (10). Rapamycin supplementation in adults increased median and maximum life span in genetically heterogeneous male and female mice (11). A subsequent study showed a striking increase in life span by 14% for females and 9% for males even though treatment began when the mice were already of advanced age (12). Several independent groups have shown that rapamycin treatment extends life span in diverse mouse strains, and beneficial effects have been reported across a range of treatment strategies from age of onset (ie, midlife, late-life) to timing of treatment (ie, transient, intermittent) to mode of drug delivery (oral by diet, intraperitoneal injection) (13,14). In mice, rapamycin supplementation is associated with improvements in several age-related changes, including muscle strength, immune function, oral health, mitochondrial function, coordination and balance, nociception, cardiovascular conditions, and brain health (15,16).

Rapamycin supplementation has shown much promise for delaying brain aging and reducing dementia and Parkinson's related pathologies in rodents (17,18). The benefits of rapamycin supplementation, including improved memory and reducing hallmarks of Alzheimer's disease (AD) pathologies, have been seen in most major rodent models of Alzheimer's disease (19). Imaging studies revealed that rapamycin restored brain vasculature and metabolic function in mice carrying the *Apoe* gene, a model of dementia. These beneficial effects were, in part, secondary to an increase in endothelial nitric oxide synthase (20). In mouse models of Alzheimer's disease rapamycin led to reduced Aβ plaques, fewer cortical microlesions and less angiopathy compared to untreated animals (21). Moreover, rapamycin led to increased dendritic outgrowth and neurogenesis,

Table 1. List of Compounds Shown to Increase Longevity in Genetically Heterogeneous Mice by the Intervention Testing Program, Reporting Sex Dimorphism, Evidence for Beneficial Effects on Health and Brain Health in Rodents

ITP	Effects on Longevity and Health (rodents)	Effects on Brain Health (rodents)	Selected References
Aspirin	Increases life span, but only in male mice.	Effective to reduce some hallmarks of dementia in rodents.	(44)
Rapamycin	Increases life span in male and female mice. Decreases age-related pathologies.	Beneficial in rodent models of dementia.	(14)–
17-α Estradiol	Increases life span, but only in male mice.	Improves neuronal mitochondrial function; increases brain-derived neurotrophic factor.	(31,32)
Acarbose	Increases life span in male and female mice (not equivalent). Improves cardiometabolic health.	Improves memory and lowers neuroinflammation.	(36,37)
Nordihydroguaiaretic acid	Increases life span, but only in male mice. Beneficial for cell survival, stress response, and metabolism.	Prevents Aβ toxicity in vitro and in vivo, lowers neuroinflammation.	(48,49)
Protandim	Extends median life span, but only in male mice. Reduces inflammation and fibrosis during aging.	Reduces oxidative stress in vitro	(28,52,54)

Note: All references are also in the main text.

heightened synaptic plasticity, reduced inflammation, and improved memory in aging mice (22). More recent studies show improved vasculature and improved integrity of the blood brain barrier in Alzheimer's disease models following rapamycin treatment (23,24). These very promising results support the investigation of rapamycin as a potential intervention for common neurodegenerative diseases associated with aging including Alzheimer's disease (25) and Parkinson's disease (26). The first rigorous clinical trial is currently underway to assess the effectiveness of a mild TORC1 inhibitor on Parkinson's disease (http://ir.restorbio.com/news-releases/news-release-details/restorbio-announces-initiation-phase-1b2a-trial-rtb101).

17α-estradiol

Estrogen levels decline in females during aging which is associated with impaired insulin sensitivity and increased visceral fat. 17α-estradiol (17aE) is a weak endogenous steroid with an affinity for estrogen receptors. It is an optical isomer of 17β-estradiol and is approximately 200-fold less active as a hormone than its isomer (27). 17aE reduces inflammation, improves mitochondrial health, preserves metabolic health, and attenuates oxidative damage during aging. Treatment of mice (starting at 10 months of age with 14.4 ppm in chow) with 17aE resulted in an increase in median life span of 19% in male mice (but not female mice) and this was attributed to improved glucose tolerance and insulin sensitivity (28).

It has been proposed that 17aE supplementation may protect the brain from neurodegeneration during aging because there are a large number of estrogen receptors in nervous tissue (29). The ability of 17aE to protect neurons through improved mitochondrial function is one possible mechanism (30). Estrogen exerts positive effects on neuronal mitochondria by preserving their structure and stabilizing Ca^{2+} signaling, thus reducing oxidative damage (31). Estrogen treatment significantly reduced brain inflammation and apoptotic signaling in rats following severe burn injuries (32) and increased brain-derived neurotrophic factor signaling, activated cholinergic neurons, and was associated with improved learning and spatial memory tasks in aging rats (33). In human neurons 17aE inhibited apoptosis directly via the androgen receptor (34). Although estrogen supplementation in females is on the radar as a means to counter age-related cognitive decline (2), and androgen deprivation therapy in older men with prostate cancer might even increase risk of dementia (35), there are currently no trials of 17aE in humans using cognition or memory loss as an outcome.

Acarbose

One of the mainstream ideas in gerontology is that impaired glucose regulation is a driving force behind accelerated aging. The prediction of this model is that sustaining the integrity of glucose metabolism would delay the aging process. Acarbose is a high infinity inhibitor of small intestinal α-glucosidase, and therefore reduces the breakdown of complex carbohydrates into glucose, resulting in decreased glucose absorption (36). The ability of acarbose to lower circulating glucose levels has led to its use as an adjunctive treatment for type 2 diabetes mellitus. In mice, treatment with acarbose increased median life span with greater impact in males than females although the basis for this is not known (37). The beneficial life span effects were associated with heightened insulin sensitivity which was regulated in part by enhanced hepatic mechanistic target of rapamycin complex 2 signaling and increased Protein kinase B (AKT) activity. Impaired glucose metabolism and aberrant insulin signaling, both in the brain and systemically, are thought to contribute to neurodegenerative disease (38). Consistent with this model of brain aging, acarbose reduced key markers of hypothalamic inflammation including $Iba1^+$ microglia, tumor necrosis factor-α, and glial fibrillary acidic protein (39) whereas long-term chronic acarbose treatment (20 mg/kg/d from 3 to 9 months) improved memory during aging in SAMP8 mice (40). To our knowledge there have been no studies on the effects of acarbose supplementation on brain health in humans.

Aspirin

Aspirin is a nonsteroidal anti-inflammatory drug with documented antioxidant properties. Inflammation and oxidative stress are two major hallmarks of aging, and are probable targets for the effects of aspirin on age-related diseases. ITP studies in genetically heterogeneous mice show that aspirin (21 mg/kg of food) increased median life span, but only in males (41). The lack of life span effects in females could indicate sex dimorphism in drug metabolism, or drug interaction with sex steroids. Several independent rodent studies have demonstrated a positive effect of aspirin on brain aging. A polypill containing aspirin improved synaptic strength and reduced Aβ and tau pathology in a mouse model of AD (42). Aspirin supplementation improved neuronal synaptic transmission and improved memory in a mouse model of surgery-induced cognitive decline (43). Aspirin supplementation for 8 weeks significantly reduced pro-inflammatory cytokines tumor necrosis factor-α and interleukin-1β, and acetylcholinesterase activity in the hippocampus in a mouse model of diabetes (44). The translatability of these effects to humans, however, is in question. A recent review of 14 studies in humans revealed no conclusive evidence that aspirin or nonsteroidal anti-inflammatory drug supplementation is effective for treating Alzheimer's disease (45), and the recently published ASPREE study found no effect of aspirin 100 mg/daily in participants more than 70 years of age on the incidence of dementia (46). Despite some positive animal studies, aspirin does not appear to influence the risk of Alzheimer's disease in humans. Its antiplatelet activity suggested it might have potential as a treatment for vascular dementia, however, here too there was no evidence for any positive effects (47).

Nordihydroguaiaretic Acid

Nordihydroguaiaretic acid (NGDA) has anti-inflammatory and antioxidant properties. The ITP program reported that NGDA treatment (2500 mg/kg of food) led to increased life span in genetically heterogeneous male mice, but not females (41). There have been a few studies on the effects of NGDA on brain aging. Treatment with NGDA improved life span, decreased oxidative stress, reduced neuroinflammation, and improved memory in a fly model of Alzheimer's disease (48). In mammalian models NGDA prevented Aβ neuronal toxicity in vitro and reduced Aβ deposits and cerebral amyloidosis in transgenic mouse models of Alzheimer's disease (49). NGDA supplementation was well tolerated in humans (50), although at this stage studies looking at the effects on NGDA supplementation on cognition have yet to be undertaken.

Protandim

PRO is a mixture of five botanical extracts: curcumin, bacosides, silymarin, withaferin A, and epigallocatechin-3-gallate. It was originally developed as an activator of the transcription factor Nrf2 (encoded by *NFE2L2* gene, nuclear factor erythroid 2-like factor 2). Nrf2 is a "master regulator" of antioxidant activity and modulates responses to stress, inflammation, fibrosis, and cognitive dysfunction during aging (51). Treatment of mice with PRO extended median

life span, but the effect was only seen in males (28). There have not been many studies on the effects of PRO on the brain. A recent in vitro study reported that PRO supplementation promoted oligodendrocyte progenitor cell proliferation under the influence of reactive oxygen species, an effect partly secondary to *Nrf2* activation (52). Long-term (120 days) PRO supplementation (675 mg/d) is well tolerated in humans (53), and PRO supplementation induces superoxide dismutase, reduces lipid peroxidation, and increases plasma antioxidant concentration (54). The effects of PRO on the cognition and brain aging in humans have not been reported.

Compounds Tested by the ITP and Not Found to be Associated With Life-Span Extension

A number of compounds that have been reported to delay aging and/or increase markers of metabolic health in rodents by groups that are independent of the ITP (Table 2). Subsequent testing of some of these compounds by the ITP did not confirm any life extension (eg, resveratrol, oxaloacetic acid, curcumin, simvastatin, 4-hydroxyphenylbutyl nitrone, metformin). Even so, these compounds may still be value as agents to improve brain aging because of their ability to influence cellular processes and pathway that are thought to underlie aging biology.

Resveratrol

Resveratrol has received a lot of attention in aging research, in particular in the context of metabolic health. Resveratrol is a natural polyphenol found in the skin of berries and in limited quantities in red wine. It has been reported to confer many health benefits in a variety of taxa, including reducing cancers, cardiovascular disease, and reducing neurodegeneration (55). Resveratrol supplementation increased the life span of metabolically compromised mice fed a high calorie diet (56), and enhanced longevity was associated with improved mitochondrial function and insulin sensitivity, and reduced incidence of organ pathologies. In mice fed a normal diet; however, resveratrol increased some markers of health but not life span (57). A subsequent meta-analysis of animal studies found that resveratrol, for unknown reasons, only increased life span in lower taxa (58).

Studies in vitro and in vivo show some promising results of resveratrol treatment in the context of Alzheimer's pathologies (59). There have been several clinical trials of resveratrol and cognition in humans, although the results are mixed as to whether resveratrol may be beneficial to improve cognitive function. A randomized, double blind, placebo controlled, Phase II trial assessed the impact of resveratrol supplementation (1 gm twice daily) in 117 participants with mild-to-severe AD (60). Resveratrol supplementation altered some Alzheimer's disease trajectories, but brain volume loss assessed by MRI was inexplicably increased by resveratrol treatment. Although underpowered for clinical outcomes, it was noted that the Alzheimer's Disease Cooperative Study-Activities of Daily Living score declined less in the resveratrol-treated group. In another placebo-controlled clinical trial in 39 participants with mild-to-moderate Alzheimer's disease, resveratrol (1 g, twice daily for 52 weeks) modulated pro-inflammatory cytokines (possibly by targeting SIRT1) and was associated with better cognitive outcomes assessed by mini-mental status examination and Alzheimer's Disease Cooperative Study-Activities of Daily Living scores, although the number of participants was on the low end (61). On the contrary, a systematic review of four clinical trials involving 225 participants including healthy adults or subjects with mild cognitive impairment concluded overall that resveratrol had no effect on cognition but did improve vigor and reduce fatigue (62). These differing results suggest that more rigorous clinical trials are needed to determine whether resveratrol may reduce dementia.

Curcumin

Curcumin is a naturally occurring phenol found in the Indian spice, turmeric. It has potential roles in increasing vascularity and vascular function, partly through increased nitric oxide availability. One study reported that tetrahydrocurcumin increased life span of male mice (63), but this result was not confirmed by subsequent testing by the ITP. There is evidence to suggest that curcumin supplementation may be beneficial to reduce some hallmarks of dementia in vitro and in rodents. In cultured neural progenitor cells, low concentrations of curcumin stimulated growth and neurogenesis, whereas high concentrations were toxic (64). The same study showed that in adult mice curcumin improved hippocampal synaptic plasticity and resulted in improved hippocampal neurogenesis and neuronal repair. Another study demonstrated that curcumin supplementation improved synapse structure and quality in area CA1 of the hippocampus in APPswe/PS1dE9 double transgenic mice (65). Finally, curcumin supplementation was effective in reducing Aβ generation in APP/PS1 double transgenic mice, partly through the induction of autophagy (66). To date there have been no studies assessing the effects curcumin on cognition in humans. Curcumin has low oral solubility and bioavailability, nonetheless, its ability to influence nitric oxide and lower oxidative stress suggest that is may exert positive effects on vascular endothelial function and brain health in humans (67,68).

4-Hydroxy phenyl N-tert-butylnitrone

4-OH-alpha-phenyl-N-tert-butyl nitrone (4-OH-PBN) is an antioxidant with anti-inflammatory properties that has been used as a therapeutic in a range of age-related disease preclinical studies (69). Beneficial effects of PBN have been reported in particular for stroke and neurodegenerative diseases, with some studies showing effects on life span (70,71) but this was not confirmed by subsequent ITP studies (72). PBN and derivatives have been shown to have positive effects on brain health in vitro and in rodent models (73). PBN supplementation (100 mg/Kg/d for 3 days) improved neurobehavioral scores in a rat model of cerebral ischemia, attributed in part to a reduction in free radical generation (74). Another study demonstrated that free-radical production was attenuated by PBN supplementation in the rat striatum and resulted in increased levels of dopamine (75). In human astrocyte cultures, PBN supplementation significantly attenuated oxidative stress and reactive oxygen species (76). There have not been any human studies of nitrones to determine their effects on the aging brain and safety and tolerability must be first established.

Oxaloacetic Acid

Oxaloacetic acid (OA) is an intermediate of the citric acid cycle and therefore is important for energy regulation and glucose homeostasis. In the nematode model *Caenorhabditis elegans* it was found to increase life span in a manner that was mechanistically linked to nutrient sensing pathways implicated in calorie restriction including FOXO and AMP-activated protein kinase (77). OA was tested for ability to impact mammalian life span as part of the ITP study but did not yield improvements in survival in the cohorts of mice treated. There is some evidence to suggest that OA may promote neuronal

health in rodents (78). OA reduced Aβ neurotoxicity and improved long-term potentiation and synaptic plasticity in the hippocampi of rats (79). Other studies have demonstrated the OA may protect against ischemic injury and stroke in animal models and provide neuroprotection and enhanced infrastructure to neurons in the spinal cord. It was hypothesized that OA may exert its positive effects on neurons by enhancing cell infrastructure and supporting glycolysis and enhanced respiration (80).

Simvastatin

Simvastatin is an HMG CoA reductase inhibitor extensively used to lower blood cholesterol levels. Simvastatin, in combination with an ACE inhibitor, increased life span of long-lived male B6C3F1 mice (81), but subsequent investigation as part of the ITP study did not confirm enhanced longevity in the simvastatin-treated mice (82). Dysregulation of cholesterol homeostasis is thought to contribute to Alzheimer's disease in humans, and statins reduce some of the neuropathological markers of dementia in rodents. Simvastatin (10 or 20 mg/kg for 4 weeks) reduced neurotoxicity, pro-inflammatory cytokines, Aβ plaques, and improved memory as measured by the Morris water maze and Y maze in diabetic mice (83). Simvastatin reduced Aβ neurotoxicity in the hippocampus and dentate gyrus, and upregulated levels of brain-derived neurotropic factor in a mouse model of Alzheimer's disease (84). In amyloid precursor protein mice, simvastatin reduced neuroinflammation, improving cerebral blood flow, reducing Aβ plaques, and attenuated oxidate stress (85).

There have several large-scale studies and meta-analyses in humans that have demonstrated the potential of statins in dementia but contradictory outcomes have also been reported (82). One postmortem study demonstrated that the risk for typical AD pathology (neurite plaques or neurofibrillary tangles) was reduced in humans who used statins (86). Several observational studies have found that statins are associated with reduced risk of dementia in various patient groups (87,88). A meta-analysis of clinical studies of statins indicates that treatment may not have beneficial effects for the prevention of dementia (89). It may be case of need to target the time interval in disease development where interventions are protective at specific time points in disease progression (90).

Metformin

Metformin is extensively used for the treatment of type 2 diabetes mellitus, and although its precise mechanism action is uncertain, AMP-activated kinase is a key downstream effector of metformin. AMP-activated kinase is a nutrient sensing kinase that plays a pivotal role in cellular energetics and has marked effects on aging in many animal models (91). Although initially promising results in mammals were reported, where metformin supplementation (0.1% w/w) initiated at 54 weeks resulted in a 5.83% mean life-span extension in male mice (92), here too the effect was not replicated by the ITP study. Beneficial effects of metformin have on cognition been reported in metabolically compromised animals. Treatment with metformin reduced tau hyperphosphorylation in a mouse model of diabetes and improved spatial memory in the Morris Water Maze (93). In a mouse model of dementia, metformin was associated with increased hippocampal neurogenesis and improved memory (94). In the chronic d-galactose model of brain aging and dementia in rats, metformin treatment reduced Aβ plaques and phosphorylated tau, and increased acetylcholine concentrations (95). In rats fed a high fat diet and injected with Aβ, metformin improved long-term potentiation and beneficial effects were associated with a lower Aβ plaque load (96).

Results of metformin supplementation on human cognition have been mixed. Although many studies have shown that metformin has positive effects on cognition, others have reported no effects or even a negative influence. In one study it was demonstrated that metformin was associated with adverse cognitive outcomes in people with diabetes (97). A meta-analysis of human studies reported that cognitive impairment was reduced in people with diabetes treated with metformin, and six studies showed that dementia incidence was also reduced, but only seen in people with diabetes (98). Another meta-analysis showed that long-term (more than 6 years) metformin use was associated with a lower risk of cognitive decline in people with diabetes (99). More research is needed in order to determine the effects of metformin on dementia. Importantly, the proposed TAME clinical trial (Targeting Aging with Metformin), which aims to determine whether MET influences aging in humans, includes Alzheimer's disease as one of its clinical outcomes (100).

Other Compounds Not Yet Tested by the ITP

The field of aging biology has grown rapidly over the last 20 year and each year new insights are gleaned and new therapeutic pathways with potential for clinical translation are identified. The pace of progress is astonishing and several new leads that have yet to be tested formally by the ITP nonetheless show terrific promise. Many of these compounds or therapies have shown promise to delay aging in invertebrates and small mammals but their influence on human aging has yet to be determined.

NAD Precursors and Derivatives

The discovery of Sirtuins, a family of nicotinamide adenine dinucleotide (NAD) dependent deacetylases and deacylases linked to longevity, has opened an entirely new field within aging research (101,102). The strategy to boost NAD availability as a means to activate Sirtuins has been so successful in preclinical studies it has broken off into an area of its own (103). Derivatives and precursors of NAD^+ have shown promise in enhancing health in mice. NAD^+ levels decline with age and it has been suggested that increasing NAD^+ levels via precursors such as nicotinamide, nicotinamide riboside (NR) (97), or nicotinamide mononucleotide (NMN) may delay aging. In mice, nicotinamide supplementation (0.5 and 1.0 g/kg of diet) did not extend life span but conferred a number of health improvements including prevention of hepatic steatosis in obese mice and reduction of oxidative stress and inflammation (104). NR is well tolerated and is bioavailable in rodents and humans (105). In metabolically compromised mice NR supplementation was associated with enhanced hepatic SIRT1 expression, lower levels of oxidative stress, and improved mitochondrial function (106).

Several studies indicate that NAD precursors and derivatives show promise for brain aging (102,107). Nicotinamide treatment significantly reduced Alzheimer's pathologies in mice (108), including lowering levels of amyloid precursor protein (109) and presenilin 1 in the brains of Aβ-injected mice (110). Another study demonstrated that NMN supplementation was sufficient to induce neuronal mitophagy and ameliorate cognitive decline in a *C. elegans* model of Alzheimer's disease (107,111). In a fly model of Parkinson's disease NR supplementation reduced dopaminergic neuron loss and improved motor skills (112). In a DNA repair-deficient mouse model of Alzheimer's disease, NR supplementation reduced phosphorylated tau levels and improved cognitive function (113). NMN reduced Aβ oligomers and improved spatial memory in a rat model of Alzheimer's disease, and improved neuron survival, partly by reducing reactive oxygen species

(114). NMN treatment also improved mitochondrial respiration in a mouse model of Alzheimer's disease (109). Interest in use of the NAD/Sirtuin pathway specifically for brain aging has grown considerably in recent years and it seems only a matter of time before treatments based on this biology are available in clinics (115). In one study of NR supplementation in humans, treatment was associated with improvement in markers of cardiovascular health (116). As yet, there have not been any studies on cognitive function in humans.

Spermidine

Spermidine is a natural dietary polyamine that promotes cardioprotection and increases health span and life span in flies and rodents (117). Spermidine is found soybeans, nuts, and some fruits and vegetables and is safe and well tolerated. This polyamine is thought to promote health partly through its effects on cardiac autophagy and mitophagy, and improved mitochondrial function. Polyamine levels decline during normal aging and in the brain spermidine levels decline rapidly during Alzheimer's disease (as much as 70% in the temporal lobes) (118). In aging flies, spermidine treatment is associated with improved memory and this effect is linked to enhanced autophagy in neuronal tissue (119). In rats, spermidine treatment (5 and 10 mg/kg) improved motor performance and attenuated pro-inflammatory cytokines and oxidative stress in the striatum (120). A single striatal injection of spermidine improved novel object recognition memory in a rodent model of Huntington's disease (121). There have been several studies of spermidine treatment in humans. Long-term supplementation with spermidine (1.2 mg/d) is safe and well tolerated in older humans (122). High levels of dietary spermidine intake as measured by food questionnaires correlated with reduced blood pressure and lower cardiovascular disease (123), and supplementation (1.2 mg/d for 3 months) was associated with improved memory performance in older adults (60–80 years) with subjective cognitive decline (124). Rigorous clinical trials testing the benefits of spermidine on cognition and memory loss have yet to be conducted.

Senolytics

Cellular senescence increases with age and plays a role in tissue damage, inflammation, and reduced physical function. Senescent cells accumulate in many diseases that occur during aging including osteoarthritis, cardiac dysfunction, frailty, and diabetes (125). The "main hallmarks" of senescence include the hindrance of cell proliferation and reduced apoptosis, both of which lead to altered cellular metabolism (126). Most research on senolytic compounds has been conducted in invertebrates and lower-order mammals; the safety and tolerability in humans must be determined before commencing large-scale clinical trials (127).

Senolytic drugs, which were designed to selectively induce apoptosis of senescent cells, have shown promise to improve markers of cardiometabolic health and reduce age-related disease (128). One landmark study demonstrated that a "senolytic cocktail" containing quercetin and dasatinib significantly increased the survival and improved physical function of senescent cell-transplanted young mice and also naturally aged mice. The results of that study suggest that senolytic compounds improve health and increase life span, even if administered in old age (129). There is limited evidence to suggest that senolytic compounds may be effective in neurodegeneration, although it has been shown that the main hallmarks of Alzheimer's, including tau protein aggregation, are associated with neuronal senescence (130). One recent and landmark study demonstrated that senolytic therapy was sufficient to remove Aβ plaques, reduce neuroinflammation, and improve memory in a mouse model of AD, which was largely attributed to the removal of senescent cells (131). Therefore, senolytic

Table 2. List of Compounds Shown to Improve Health in Rodents With Current Evidence for Beneficial Effects on the Brain

Compound	Effects on Longevity and Health (rodents)	Effects on Brain (rodents)	Selected References
Resveratrol	Increases life span in male mice fed a high fat diet. Reduces cancers, cardiovascular disease, improves mitochondrial health, and prevents inflammation.	Reduces hallmarks of brain aging. Attenuates oxidative damage, improves mitochondrial health, reduces inflammation.	(56,61)
Nicotinamide	Prevents hepatic steatosis and reduces oxidative stress and inflammation.	Reduces hallmarks of dementia including tau levels and amyloid precursor protein. Improves cognitive function in mice.	(104,109,113)
Metformin	Increases life span in male mice. Confers health benefits including reducing cardiovascular disease.	Reduces hallmarks of dementia, improves neurogenesis and memory.	(92,93)
Curcumin	Life span effects not known but reduces infection, oxidative stress, and improves cardiovascular health.	Stimulates neurogenesis, hippocampus neuroplasticity, and neuronal repair mechanisms. Alleviates oxidative stress.	(65,66)
4-OH-alpha-phenyl-N-tert-butyl nitrone	Effects on life span not known. Reduces reactive oxygen species and free radicals.	Improves cognitive performance and decreased oxidative damage.	(73,76)
Oxaloacetic acid	Inhibits cellular stress and reactive oxygen species.	Reduced hallmarks of dementia and protects against stroke, improves glycolysis, and enhances respiration.	(78,79)
Simvastatin	Increases the life span of male mice. Reduces the risk of vascular disease and lowers blood pressure and cholesterol.	Reduced hallmarks of dementia, neurotoxicity, inflammation, and improves spatial memory.	(85)
Spermidine	Increases life span in rodents. Increases cardiac autophagy and mitophagy.	Improves motor function and memory. Attenuates pro-inflammatory cytokines in the striatum. Improves memory.	(119,122)
Senolytics	Increases life span and physical function in male mice.	Attenuates inflammation, removes Aβ plaques, improves memory.	(129,131)

Note: All references are also in the main text.

therapy may provide an exciting and promising avenue for treating dementia and other neurogenerative diseases (132).

Parabiosis

Although much of this review has focused on compounds that may delay aging, there is an emerging interest in the ability of parabiosis, which is commonly defined as a shared blood supply between two surgically connected animals, to delay aging and age-associated disease (133,134). In aging research, parabiosis connects the circulatory systems of a young an old animal to determine whether certain factors in the young blood may positively influence or "rejuvenate" the old blood (135). Several studies have shown that factors in young blood can improve markers of brain health in old mice, including remodeling cerebral vasculature, improving cerebrovascular metabolism, and enhancing neurogenesis (136). The exposure of old mice to young blood resulted in improved hippocampus health, including genetic markers of plasticity, increased dendritic spine density, and improved spatial and fear conditioning memory (137). Taken together, these results suggest that insights gleaned from parabiosis studies may well contribute to the development of novel therapeutic interventions and additional compounds for the treatment of neurodegenerative disease.

Conclusions

Despite extensive research over several decades, effective pharmacological approaches for the prevention of dementia remain elusive. Although aging is the most powerful risk factor for dementia, the traditional view was that aging is not a modifiable risk factor. Recent biology of aging research challenges this perspective. Numerous preclinical studies in rodents and nonhuman primates have shown that aging is indeed modifiable and a growing body of evidence indicates that aging can be influenced by pharmacological interventions. Several of these pharmacological agents have been studied quite extensively and results have been replicated in many laboratories, and under a variety of settings. Others have been relatively understudied and more research is necessary to determine their mechanisms of action and influence on aging and life span. The major challenge at this stage is bringing this preclinical promise to clinical application through translational studies, and to establish the safety and tolerability of these compounds in humans. In this review, we found only a limited number of studies that consider brain aging as a primary cause for dementia, and fewer still that apply antiaging interventions as a means to delay or offset entirely age-related memory loss and cognitive decline. Our assessment of the current literature indicates that a thorough evaluation of novel antiaging compounds for their ability to specifically impact brain aging and dementia is warranted and that closer interactions among investigators of aging biology and clinical neurobiology would likely benefit the field of geriatrics and gerontology enormously.

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