J Appl Physiol 129: 1468–1476, 2020.
First published September 24, 2020; doi:10.1152/japplphysiol.00168.2020.

REVIEW | *Physiology of Thermal Therapy*

Heat therapy: possible benefits for cognitive function and the aging brain

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Submitted 6 March 2020; accepted in final form 20 September 2020

Von Schulze AT, Deng F, Morris JK, Geiger PC. Heat therapy: possible benefits for cognitive function and the aging brain. *J Appl Physiol* 129: 1468–1476, 2020. First published September 24, 2020; doi:10.1152/japplphysiol.00168.2020.—Alzheimer's disease (AD) is the most common neurodegenerative disease, yet there are no disease-modifying treatments available and there is no cure. It is becoming apparent that metabolic and vascular conditions such as type 2 diabetes (T2D) and hypertension promote the development and accumulation of Alzheimer's disease-related dementia pathologies. To this end, aerobic exercise, which is a common lifestyle intervention for both metabolic disease and hypertension, is shown to improve brain health during both healthy aging and dementia. However, noncompliance or other barriers to exercise response are common in exercise treatment paradigms. In addition, reduced intracellular proteostasis and mitochondrial function could contribute to the etiology of AD. Specifically, compromised chaperone systems [i.e., heat shock protein (HSP) systems] can contribute to protein aggregates (i.e., β-amyloid plaques and neurofibrillary tangles) and reduced mitochondrial quality control (i.e., mitophagy). Therefore, novel therapies that target whole body metabolism, the vasculature, and chaperone systems (like HSPs) are needed to effectively treat AD. This review focuses on the role of heat therapy in the treatment and prevention of AD. Heat therapy has been independently shown to reduce whole body insulin resistance, improve vascular function, activate interorgan cross talk via endocytic vesicles, and activate HSPs to improve mitochondrial function and proteostasis in a variety of tissues. Thus, heat therapy could offer immense clinical benefit to patients suffering from AD. Importantly, future studies in patients are needed to determine the safety and efficacy of heat therapy in preventing AD.

Alzheimer's disease; cognitive function; heat shock proteins; heat therapy; metabolism

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting over 5 million Americans, with this number expected to balloon to nearly 14 million by 2050 (6). This devastating disease is characterized by worsening memory and social performance and declines in cognitive function (90, 117). Aerobic exercise, like walking and cycling, results in improved brain health during both healthy aging and in dementia models of AD (1, 2, 59). However, not all individuals benefit from exercise. Although controversial (84), this could be due to lack of compliance, nonoptimal intensity, duration or modality timing in relation to meals and effects on the related biomarker response, or an inability to complete exercise regimes due to comorbidity. For example, physical function and motor function continue to decline with age and AD, making it potentially difficult for individuals to exercise enough to receive the known benefits (13). For this reason, alternative therapies and treatments are needed for the decline in cognitive function that occurs with AD and other neurodegenerative diseases. One of these potential treatments is heat therapy.

Heat therapy, via hot water immersion or sauna bathing, has long been associated with tremendous health benefits (27). Recent studies have demonstrated the safety and efficacy of chronic heat therapy in cardiovascular and metabolic adaptations in young, heathy individuals (14) as well as in obese populations (36). In combination with the substantial evidence in preclinical rodent models demonstrating the benefits of heat therapy on vascular health, metabolic outcomes, and mitochondrial function (25, 35, 44, 48, 102), the benefits of heat therapy may also extend to the brain. Our increased understanding of the chaperone and cell signaling roles of heat shock proteins (HSPs) suggests that these highly conserved homeostatic proteins may mediate the beneficial effects of heat therapy. The purpose of this review is to highlight how heat therapy may mitigate the age-dependent declines in metabolism, vascular function, and mitochondrial quality that may be involved in AD etiology.

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The Multifactorial Etiology of Alzheimer's Disease Demands New Therapeutic Approaches

Between 2000 and 2017, deaths from AD have increased by 145% (6). In 2019, AD and other dementias cost the United States ~$290 billion (6). By 2050, those costs could rise to high as $1.1 trillion (6). From a scientific standpoint, β-amyloid (Aβ) protein fragments, or plaques, accumulate outside of neurons and represent a primary brain change associated with AD (107, 122). Toxic amounts of Aβ may contribute to cell death by interfering with synaptic communication between neurons (122). Immune cells in the brain called microglia are activated to clear Aβ, but chronic and potentially neurodegenerative inflammation can occur when microglia fail to clear toxic Aβ (51, 107, 122).

Although the causative role of Aβ-containing senile plaques in the development of AD is controversial, the presence of these protein aggregates within the extracellular space of brain tissue is closely linked to synaptic nerve loss and progressive cognitive deficits (122). Although multiple phase-III trials have shown target engagement and clearance of Aβ, to date, they have failed to reduce primary outcomes of disease progression (77, 104). These findings have spurred studies examining other factors that likely play a role in AD etiology, such as reduced energy metabolism in the brain. Similarly, it has become increasingly clear that other factors, including an inactive/sedentary lifestyle, low aerobic capacity, and insulin resistance, also impact AD risk [reviewed in (86)]. This understanding highlights the need to pursue alternative metabolic and novel approaches for the prevention and treatment of AD. Moreover, these findings show that an increased focus on mitochondrial function during disease is warranted.

The benefits of heat therapy may occur as a result of heat shock protein (HSP) induction. HSPs are molecular chaperones that function as part of the heat stress response, a conserved mechanism for the body to mitigate cellular stress (16, 57), physical or bioenergetic, and maintain cellular function via regulation of protein folding and degradation under stress (96). HSPs specifically facilitate the folding of new proteins, the refolding of damaged proteins, targeted degradation of nonfunctional proteins/organelles, prevention of oxidative damage, intracellular signaling, and the import/export of proteins into/out of the mitochondria (35, 43, 52, 96, 121). Not surprisingly, changes in the HSP expression profile and cellular localization are linked to numerous disease states. Age-dependent decline in HSPs (characterized by their weight in kilodaltons) can leave neuronal cells open to proteotoxic insults and can increase the risk of AD development (55, 63). In turn, elevated expressions of various HSPs have been shown to improve protein homeostasis in other cells through noncell autonomous processes (114). In this review, we consider the ways in which activation of HSPs with heat therapy could positively impact pathways associated with cognitive decline.

PERIPHERAL METABOLIC DYSFUNCTION AND ALZHEIMER'S DISEASE

Insulin signaling affects a variety of vital cellular processes within the brain, including Aβ trafficking and release, tau phosphorylation, long-term potentiation, and cell survival; such mechanisms may underscore the increased risk for neurodegeneration conferred by insulin resistance (29, 85). Research in animal models has supported the concept that type 2 diabetes (T2D) promotes the development and accumulation of Alzheimer's disease-related dementia pathologies, such as Aβ plaques, tau phosphorylation and neurofibrillary lesions (66), and α-synuclein lesions (103). Common comorbidities of systemic insulin resistance in T2D—such as hyperglycemia, advanced glycation end products, oxidatively damaged proteins/lipids, inflammation, dyslipidemia, atherosclerosis, microvascular disease, renal failure, and hypertension (105)—all have their own complex effects on brain function through a variety of mechanisms independent of insulin signaling (61). In addition, systemic insulin resistance or high circulating level of insulin has been shown to impact the function of the blood-brain barrier by downregulating endothelial insulin receptors and decreasing permeability of the blood-brain barrier to insulin (101). This change in permeability could lead to decreased brain insulin levels and decreased insulin-facilitated neural and glial activity (54).

We have shown that insulin sensitivity—measured by the gold standard assessment, the hyperinsulinemic-euglycemic clamp—is impaired in patients with AD versus cognitively healthy older adults (87). The skeletal muscle is the site of 80–85% of glucose disposal during hyperinsulinemic clamp conditions (31), suggesting that these deficits are due to impaired skeletal muscle metabolism. Skeletal muscle mitochondrial content and respiratory capacity play a critical role in driving whole body aerobic capacity (69, 116), and low aerobic capacity is also a risk factor for AD.

Decades of research indicates that mitochondria from subjects with AD differ from mitochondria from subjects without dementia or cognitive dysfunction (113). Mitochondria appear to mediate the pathology associated with AD. Although it is difficult to assess cerebral mitochondrial function directly, there is evidence that mitochondrial function is also compromised systemically in cognitively impaired subjects (82). Individuals with mild cognitive impairment (MCI) or AD exhibit decreased blood platelet cytochrome oxidase activity and lower mitochondrial respiratory rates in cytoplasmic hybrid lines generated with mitochondrial DNA (mtDNA) from patients with AD compared with those generated with mtDNA from cognitively healthy older adults (108). Mitochondria-produced H_2O_2 emission [otherwise termed reactive oxygen species (ROS)] enhances Aβ production, which can be deposited within mitochondria as a proteostatic measure, but results in mitochondrial deficits (95, 108). Mitochondrial dysfunction in skeletal muscle has also been heavily studied as a primary cause of whole body insulin resistance (41, 72, 127), a recognized risk factor for AD (9, 24, 60, 74, 80, 93, 97, 100, 110, 119, 123, 124). However, the role of skeletal muscle mitochondrial function in AD remains to be elucidated.

Further supporting the role of mitochondrial function in AD, mice transgenic for the human apolipoprotein epsilon 4 (APOE4) gene, the primary genetic risk factor for AD, exhibit blunted mitochondrial respiratory capacity and reduced electron transport complex content in neurons (22). Moreover, both the triple transgenic AD mouse model [which harbors mutations for presenillin1 (PS1), amyloid precursor protein (APP), and tau] (92) and a double transgenic AD mouse model (which harbors mutations for PS1 and APP) (106) display similar mitochondrial respiratory deficits in the skeletal muscle (83, 106). As PS1 and

APP genes are linked to familial AD, whereas APOE4 is linked to the much more common sporadic form of AD, teasing apart the genetic relationship between mitochondrial function and PS1 or APP is of great clinical relevance.

Mitochondrial quality control is regulated by the processes of mitochondrial biogenesis and mitophagy (91). Mitophagy involves the targeting of damaged or superfluous mitochondria to the lysosomes wherein the mitochondrial constituents are degraded and/or recycled (39, 94). Importantly, mitophagy plays a critical role in neuronal function and neuronal survival through the maintenance of a healthy mitochondrial pool and the inhibition of neuronal death (38, 39). Moreover, mitophagy via chaperone-mediated autophagy (CMA) using the cochaperones such as the heat shock cognate 71-kDa protein (HSC70) and the E3 ubiquitin ligase, C-terminus of HSC70-interacting protein (CHIP), is required for neuronal preconditioning to bioenergetic stress (79), and defective CMA is thought to contribute to neurodegenerative disorders (62). Despite this evidence, the role of mitophagy in AD progression is unclear. Using postmortem human AD brain samples, AD can be induced in pluripotent stem cell (iPSC)-derived neurons and transgenic animal models of AD; thus, mitophagy has been directly associated with AD pathology (20). Furthermore, the restoration of mitophagy ameliorates memory loss in both *Caenorhabditis elegans* and two mouse models of AD through the inhibition of Aβ plaques and p-tau (37). It is plausible that a defect in mitophagy induces the accumulation of dysfunctional mitochondria, thereby promoting AD pathology and memory loss, and suggests that it is a target for potential therapy (37).

Potential Benefits of Heat Therapy on Peripheral Metabolism

Growing evidence from preclinical and clinical studies suggests that the heat shock response and/or HSPs could play an important role in preventing insulin resistance and the development of T2D (8). HSP function is tightly coupled to insulin resistance and T2D (44). Specifically, HSP expression declines with T2D in humans, and rodents have increased susceptibility to insulin resistance when the gene for HSP72 is knocked out (25, 35). Conversely, HSP induction via transgenic overexpression, pharmacologic intervention, or heat protects against diet-induced obesity and insulin resistance in rodent studies (25, 48, 102). It is hypothesized that this association is due in part to the anti-inflammatory/antiapoptotic signaling roles of HSPs during disease-induced stress (44). For instance, T2D and insulin resistance increase oxidative stress, instigating c-Jun and NF-κB activation—ultimately increasing inflammation and inhibiting a critical component of the insulin signaling pathway, insulin receptor substrate-1 (IRS-1) (53, 68). HSP72 and HSP25 are shown to reduce c-Jun and NF-κB activity, respectively (44), thus relieving repression on the insulin signaling cascade to allow for proper substrate utilization. Importantly, it remains unknown whether induction of HSPs via heat therapy can modulate systemic metabolism or restore glucose/insulin homeostasis in AD.

Mitochondrial dysfunction contributes to the development of metabolic disease (111) and may be a likely target for heat therapy. Our laboratory and others have demonstrated that heat treatment improved skeletal muscle mitochondrial function by improving fatty acid oxidation (48), increasing mitochondrial enzyme activity (23, 48, 115), and increasing mitochondrial biogenesis (76). One way in which induction of the heat shock response may improve mitochondrial function could be through regulation of mitophagy or the targeted degradation of mitochondria through autophagy (35). Evidence suggests that mice lacking HSP72 in skeletal muscle have decreased mitophagy as well as enlarged, dysmorphic mitochondria with reduced respiratory capacity (35). Importantly, mitochondrial dysfunction associated with the lack of HSP72 extends beyond the skeletal muscle and occurs in the liver (7). Thus, it is possible that the activation of HSP72 may improve mitochondrial quality by enhancing the degradation of dysfunctional mitochondria via mitophagy.

Mitophagy could alternatively occur through chaperone-mediated autophagy or CMA, which both use HSC70 and various cochaperones, such as the E3 ubiquitin ligase CHIP, for ubiquitination of organelles/proteins for autophagic or lysosomal removal, respectively (5, 62). Specifically, HSC70 recognizes and binds to the pentapeptide KFERQ-like motifs on target cytosolic or membrane proteins, allows for ubiquitination from its binding partner CHIP, and targets them for degradation via movement to the autophagosome or lysosome upon bioenergetic stress (microautophagy and endosomal microautophagy can also occur) (28, 34). Importantly, ∼45–47% of the human proteome contains the pentapeptide KFERQ-like motifs, and deficiency in CMA contributes to disease states like neurodegenerative disorders (5, 67, 79). This pathway is gaining much interest, as it is reduced with age and appears to heavily regulate whole cell metabolic function and proteostasis. However, the relationship between CMA, proteasomal activity of ubiquitinated substrates, and mitochondrial biogenesis remains ill-defined. Moreover, it is unknown whether heat therapy activates neuronal CMA and can provide positive AD-related outcomes.

HYPERTENSION AND COGNITIVE DECLINE

Cardiovascular disease is a risk factor for both AD and vascular dementia, a form of cognitive decline resulting from small- or large-vessel cerebrovascular disease (64, 125). Together, these conditions account for most dementia cases worldwide (47, 99). Reductions in cerebral blood flow and alterations to the blood-brain barrier have been associated with AD (4, 30, 112), and reductions in regional blood flow are associated with cognitive decline and mild cognitive impairment with AD (73). In addition, more recent studies demonstrate a relationship between cerebrovascular health and AD neuropathological burden even in healthy older adults, suggesting a potential early role for vascular function in the development of neurodegenerative disease (78, 109). Hypertension, which is prevalent in one-third of adults and two-thirds of adults over the age of 65, may play an important role in the development of cognitive decline, AD, and vascular dementia. Given that hypertension is a modifiable risk factor, this makes it a potentially important mechanism for the prevention of age-related cognitive disorders.

Elevated systolic blood pressure is associated with smaller regional and total brain volume as well as decreased brain volume over time (40, 45, 46, 75, 89). Brains of individuals with chronic hypertension demonstrate increased β-amyloid, atrophy, and neurofibrillary tangles and evidence of decreased brain glucose metabolism (10, 98). Vascular remodeling as a result of hypertension is also thought to play a significant role in the development of cognitive dysfunction. Increased arterial stiffness can lead to increased arterial pulse wave velocity and pulse pressure, resulting in endothelial dysfunction. Endothelial dysfunction can also occur as a result of chronic decreases in cerebral blood flow with hypertension. Decreased cerebral blood flow can also result in unmet metabolic demand in vulnerable regions of the brain. Cerebral hypometabolism, a marker of reduced energy metabolism, is one of the earliest biomarkers of AD (12, 88). Brain hypometabolism occurs first in regions of the brain that are normally highly metabolic (19, 49). All these factors could contribute to the etiology of AD, causing increased research emphasis on the role of hypertension in AD progression and prevention.

Potential Benefits of Heat Therapy on Hypertension and Vascular Dysfunction

Prior research demonstrates that acute heating, either by sauna or water immersion, results in increased cardiac output and a redistribution of blood flow to the periphery (14). Shifts in blood flow with heat favor a beneficial shear pattern that enhances vascular remodeling and endothelial function (14, 18, 118). In murine models, 30-day heat acclimation affords protection from ischemia/reperfusion (I/R) injury such that cardiac myocytes are better able to survive I/R stress (81). In humans, acute hot tub use appears to temporarily protect tissue from I/R stress (15), but this effect has not been examined in a chronic heat intervention.

HSPs have demonstrated roles in cardiovascular protection. HSP25 can downregulate an early step in the formation of atherosclerotic plaques (26), whereas HSP72 has been shown to inhibit angiotensin II and decrease vascular smooth muscle hypertrophy (129). In addition, HSP90 plays an important role in NO synthase stability (11). Future studies are needed to demonstrate the effects of chronic heat therapy on vascular function and hypertension in AD patients as well as to determine HSP-driven adaptations that may occur in this population.

Heat-Mediated Extracellular Vesicle Organ Cross Talk May Benefit the Brain

One possible mechanism by which heat therapy may benefit the brain is by facilitating the delivery of molecular mediators within extracellular vesicles (EVs; exosomes and microvesicles). Although it has been shown that exercise increases brain HSP content (17), HT-induced increases in neuronal HSP content in humans remain unknown. EVs, which are shown to carry molecules/proteins across the blood-brain barrier (21), are likely an additional mechanism to increase the neuronal HSP content. EVs are bilayer-phospholipid enclosed vesicles that carry protein and mi-RNA cargo throughout circulation, whose contents will ultimately be delivered into the cytoplasm of target cells due to their hydrophobic membrane (21). EVs have been shown to act as key regulators of nerve regeneration, synaptic function, and behavior (32, 126). Importantly, when directly injected into the brain, EVs can effectively eliminate protein aggregates like Aβ (126). Despite this, very little is known about how EV content or biological function change in the context of aging, AD, or exercise training or with chronic heat. However, it has been established that HSPs can travel in EVs, and recent studies showed that their expression was elevated following acute exercise (42, 120). In addition to their roles in mediating inflammation, interacting with the insulin signaling pathway, and modulating mitochondrial quality control, HSPs are essential for the maintenance of protein structure and stability in most tissues, including neurons. In this way, EVs and their HSP cargo could provide a mechanism for interorgan cross talk—specifically regarding stress sensing, metabolic function, and proteostasis.

In the context of the brain and neuronal cells, EVs are postulated to remove and discard unwanted proteins, RNAs, and lipids via microglia intercellular-dependent mechanisms (32). A recent study characterized the proteome of brain-derived EVs from control and AD cohorts (33). Not surprisingly, the AD EVs contained more phosphorylated tau cargo, and pathway analysis showed gene enrichment for APP signaling, Prion disease ontology, and stress-activated p38 MAPK cascade (33). These novel findings demonstrated that despite their biophysiological similarities, there were significant differences in the protein signatures of EVs derived from AD as compared with control brains. Although previous studies have considered the role of EVs in AD pathology and as disease biomarkers, we are proposing a conceptually novel mechanism, whereby the autophagosomal capacity of EVs and the cargo they contain can be targeted for the prevention and treatment of AD. Specifically, the EV system could be leveraged for both proteostatic and metabolic maintenance (HSPs as cargo from other tissues) and degradation via microglial EV formation and export of aggregates (i.e., p-tau). In this way, we would be restoring the normal interorgan cross talk that may be aberrant in AD.

Current Evidence if Heat Therapy Benefits in Humans

A growing number of research studies are examining the benefits of repeated heat bouts in health and disease. Research from Hooper (56) in 1999 first examined the potential effects of hot water immersion on blood glucose regulation. With significant reductions in blood glucose and hemoglobin A1C after 3 wk of heat therapy, these findings were attributed to increased blood flow and glucose clearance. However, Minson and colleagues (14) only recently demonstrated the efficacy of repeated bouts of hot water immersion on cardiovascular outcomes. They found that 8 wk of heat therapy resulted in improved endothelial function, arterial stiffness, wall thickness, and blood pressure in young, healthy individuals. A more recent study from the Minson laboratory demonstrated that 30 sessions of hot water immersion over 8–10 wk were effective at reducing metabolic risk in obese women with polycystic ovarian syndrome (36). Like Hooper's initial hot tub study, Minson et al. showed that repeated heat therapy resulted in significant reductions in fasting glucose and improved glucose clearance following an oral glucose tolerance test. Importantly, these findings collectively demonstrate the validity of chronic heat therapy as a clinical treatment to improve glucose metabolism in obese and/or insulin-resistant individuals, both known risk factors for AD. However, it remains to be tested whether improved glucose control and improved insulin sensitivity could impact cognitive decline in individuals with mild cognitive impairment or AD.

Despite lack of data available in AD cohorts, a recent study did demonstrate the safety and adherence of heat therapy in aged individuals. In this 12-wk study, heat therapy via hot water immersion and supervised exercise both improved walking distance and resting blood pressure in patients with peripheral arterial disease (PAD) (3). Like the work of Minson et al. in younger healthy cohorts, this study demonstrates that heat therapy improves functional ability and cardiovascular outcomes in aged individuals (mean age of heat group = 76 ± 8 yr). Importantly, adherence to heat therapy was excellent and the heat was well tolerated in this population.

Although many of the studies cited in this review use hot water immersion as the primary modality of heat therapy, sauna therapy has also been shown to have an impact on cardiovascular health. Two weeks of 60°C far-infrared sauna 6 days/week significantly improved endothelial function in men with elevated cardiovascular risk (58) and in men with congestive heart failure (65). Evidence from large prospective studies also indicate that increased frequency and duration of heat (sauna) exposure reduce cardiovascular morbidity risk of incident hypertension (128) and mortality (70). Importantly, a population-based prospective cohort study of 2,315 healthy men aged 42–60 yr at baseline demonstrated that moderate-to-high frequency of sauna bathing (2–3 times/week and 4–7 times/week, respectively) was associated with lowered risks of dementia and AD (71). These data support the rationale for conducting larger-scale hot water immersion therapy studies in AD.

Finally, a recent study by Hafen et al. (50) demonstrated the first evidence that mitochondrial adaptation can occur in human skeletal muscle in response to repeated exposures to mild heat stress. These investigators used local, deep-tissue heating of the vastus lateralis via pulsed shortwave diathermy in young men and women for 2 h (6 consecutive days). Increases in HSP72 and HSP90 corresponded with increased maximal coupled and uncoupled respiratory capacity. Although these data are encouraging, they also highlight the need for new studies in additional populations and with other heat treatment modalities, as there are surely differences in whole body versus tissue-specific heating. Importantly, one modality may better impact whole body metabolic outcomes and increase patient ease-of-treatment/compliance.

Considerations for Future Work Examining Heat Therapy in Humans

An important consideration regarding published HT literature is that the core temperature used differs between animal and human studies. Animal studies have typically been performed between 41°C and 42°C (7, 48, 102), whereas human studies have typically settled around 38.5°C (14, 25). Mechanistic outcomes in human studies have thus far also been limited; for instance, it remains unclear as to whether there are increases in local HSP content versus translocated HSP content via EV. This is a potential focus of future studies. Negative effects of heat treatment in our studies have been mild and limited to anecdotal reports of dehydration and headache, which resolved within 24 h post treatment. No deleterious events have been observed beyond 24 h.

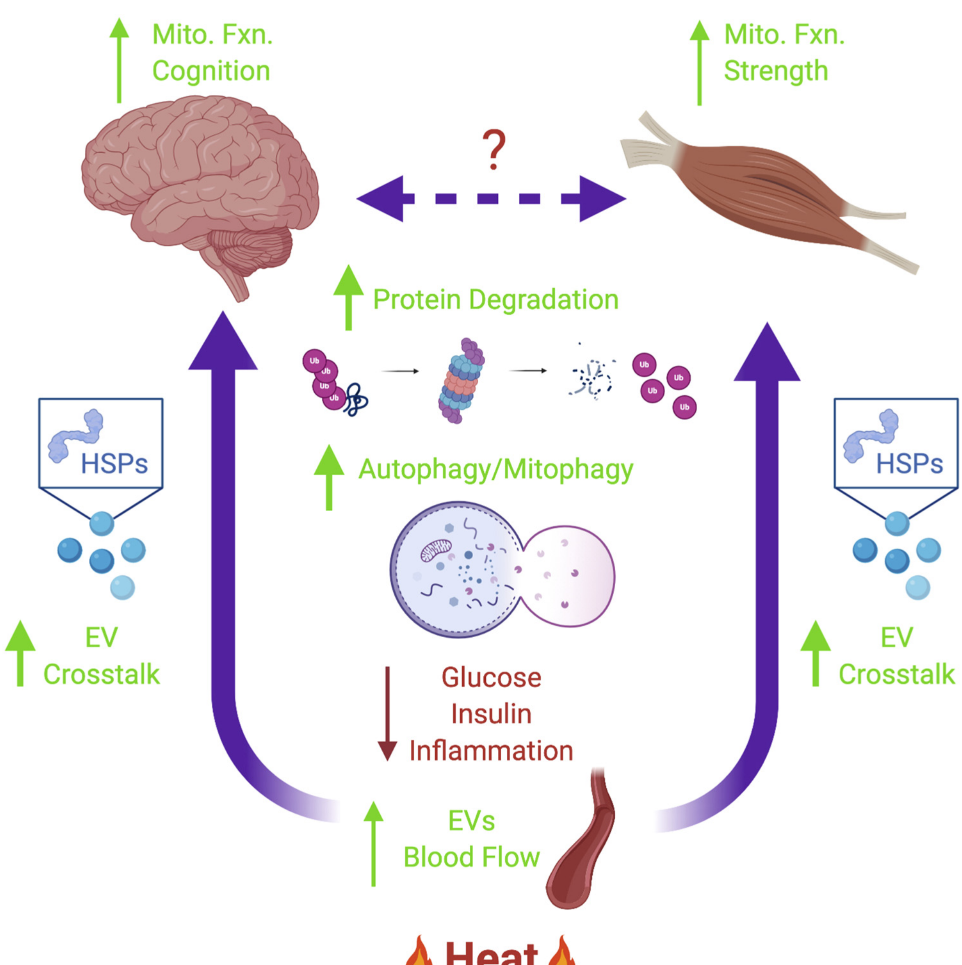

Fig. 1. The role of heat therapy in preventing AD. Heat therapy increases peripheral blood flow and may increase interorgan cross talk via endocytic vesicle (EV) formation and transport—although interorgan cross talk remains ill-defined. EVs may contain heat shock proteins (HSPs) that can improve mitochondrial function (increase mitophagy/respiratory function), reduce inflammation, and restore proteostasis [increase aggregate degradation via chaperone-mediated autophagy (CMA), chaperone-assisted selective autophagy (CSA), or the proteasome). Combined, these effects can improve whole body metabolic homeostasis (reducing blood glucose and insulin) and improve tissue-specific outcomes such as cognitive function or strength. AD, Alzheimer's disease.

Summary

AD is the most common neurodegenerative disease, yet there are no disease-modifying treatments available and there is no cure. We believe that heat therapy can be of tremendous clinical benefit to patients with AD (Fig. 1). Specifically, we and others have shown that heat therapy prevents obesity and insulin resistance and restores target blood glucose and insulin levels—all risk factors associated with AD. Moreover, it is well established that heat therapy increases blood flow and vascular compliance, in addition to potentially increasing interorgan cross talk via EV transport/formation. Finally, we propose that HSPs induced via heat therapy are critical for proteostasis (protein aggregate degradation), mitochondrial function (mitophagy, mitochondrial respiratory capacity, and mitochondrial health), cross talk (stress sensing in distant organs such as the brain), and general cell health (inhibition of c-Jun and NF-κB signaling). Overall, emerging research indicates that heat and HSP induction show immense therapeutic potential in nearly all diseases with an inflammatory, proteostatic, and/or metabolic component—making heat therapy a logical and important research focus for the prevention of chronic disease.

GRANTS

Research support was provided by the Madison and Lila Self Graduate Fellowship (to A. T. Von Schulze). Work performed by A. T. Von Schulze, F. Deng, and P. C. Geiger was supported by the National Institutes of Health Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the NIH under Grant number P20 GM103418, the University of Kansas Alzheimer's Disease Center P30 AG035982, and the National Institute on Aging AG066488.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.C.G. conceived and designed research; A.T.V.S. prepared figures; A.T.V.S. and P.C.G. drafted manuscript; A.T.V.S., F.D., J.K.M., and P.C.G. edited and revised manuscript; A.T.V.S., F.D., J.K.M., and P.C.G. approved final version of manuscript.

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