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Poor Diet, Stress, and Inactivity Converge to Form a "Perfect Storm" That Drives Alzheimer's Disease Pathogenesis

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Abstract
North American incidence of Alzheimer's disease (AD) is expected to more than double over the coming generation. Although genetic factors surrounding the production and clearance of amyloid-β and phosphorylated tau proteins are known to be responsible for a subset of early-onset AD cases, they do not explain the pathogenesis of the far more prevalent sporadic late-onset variant of the disease. It is thus likely that lifestyle and environmental factors contribute to neurodegenerative processes implicated in the pathogenesis of AD. Herein, we review evidence that (1) excess sucrose consumption induces AD-associated liver pathologies and brain insulin resistance, (2) chronic stress overdrives activity of locus coeruleus neurons, leading to loss of function (a common event in neurodegeneration), (3) high-sugar diets and stress promote the loss of neuroprotective sex hormones in men and women, and (4) Western dietary trends set the stage for a lithium-deficient state. We propose that these factors may intersect as part of a "perfect storm" to contribute to the widespread prevalence of neurodegeneration and AD. In addition, we put forth the argument that exercise and supplementation with trace lithium can counteract many of the deleterious consequences associated with excessive caloric intake and perpetual stress. We conclude that lifestyle and environmental factors likely contribute to AD pathogenesis and that simple lifestyle and dietary changes can help counteract their effects.
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Introduction

Advancements in medicine have led to an increased life expectancy. As such, neurodegenerative diseases are a growing concern. In America, it is estimated that 1 in 9 people over the age of 65 have Alzheimer's disease (AD) or a related dementia. As one of the costliest chronic diseases, approximately 1 in 5 Medicare dollars is spent on AD and dementia. This is expected to be 1 in 3 dollars by mid-century [1], independent of the enormous hourly cost to family and friends involved in caregiving. With our aging population, this disease will bankrupt medical systems throughout the industrialized world over the coming generation. Is modern lifestyle a contributing factor?

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Chronic stress (i.e., depression, anxiety, etc.), increased carbohydrate consumption (i.e., obesity, diabetes), chronic inflammatory conditions (i.e., arthritis, cardiovascular disease), loss of sex hormones (i.e., age, diet, stress), and lack of regular exercise are becoming the norm rather than the exception. The physiological stress response has gone from being an occasional occurrence that evolved to promote survival – via the fight-or-flight response – to a perpetual phenomenon brought on by the fast-paced lifestyle of the industrialized, globally interconnected world. Making matters worse, our reliance on caffeinated beverages and salt-filled fast foods to make it through the day may be stripping our bodies of lithium, a neuroprotective mineral that protects against inflammation and dietary insult. Combined with a lack of time for sleep and exercise, it is quite possible that daily lifestyle factors/decisions result in a predisposition for neurodegeneration.

Accumulation of amyloid-β (Aβ) peptide deposits (plaques), hyperphosphorylated protein tau misfolding (neurofibrillary tangles), and forebrain cholinergic deficits are considered the hallmarks of AD pathology. A lesser known, though increasingly acknowledged, loss of locus coeruleus (LC) noradrenergic neurons in the dorsal pons is associated with all neurodegenerative diseases [2–4]. The LC is the master stress center that plays a fundamental role in regulating output from the hypothalamic-pituitary-adrenal (HPA) axis. The loss of LC neurons in aging and neurodegenerative disease is likely a key factor in the dysfunction of the many cognitive processes involving LC activity [2]. In addition to its role in the HPA axis, norepinephrine regulates central nervous system (CNS) energy utilization [5], modulates thresholds for synaptic plasticity [6], provides neurotrophic [7]/anti-inflammatory [8, 9] support, and aids in the distribution of cerebral blood flow [10–12]. Deficits in any of these capacities can potentially have an impact on cognitive function. Given its role in neurotrophic/anti-inflammatory support and the significant loss observed at autopsy, it is postulated that loss of LC is one of the earliest contributing factors leading to progressive neurodegeneration, thereby raising the question of why we find a consistent loss of LC neurons across all neurodegenerative conditions.

Although genetic factors surrounding processing of amyloid precursor protein (APP) and the microtubule-associated protein tau have been proven responsible for a small subset of early-onset AD patients, limited progress has been made regarding the etiology of sporadic late-onset AD cases. Non-genetic models of sporadic AD have been met with varying levels of success. While contributing valuable insight, these models generally only assess a single stressor that is unable to induce pathology rapidly or robustly enough to be cost-effective or useful. In this review, we will summarize the pathological sequelae associated with multiple stressors ever present in modern lifestyles to help illustrate how these factors coming together as the "perfect storm" may be contributing to the global AD crisis (Fig. 1).

Where Have We Gone Wrong?

The Western Diet

Evolutionary Discordance and the Rise of Agriculture

According to the theories of natural selection and punctuated equilibrium, evolution represents a constant interaction between the genome of a species and the environment in which it resides. Genetic traits are positively or negatively selected in accordance or discordance with constraints applied by a given environment. When environmental pressures remain relatively consistent, genetic traits come to reflect an optimal pool for survival of the population [13, 14]. When rapid and permanent environmental changes occur, individuals within the population experience evolutionary discordance, i.e., failure of the genotype to match the requirements of the environment. Evolutionary discordance has been proposed to manifest phenotypically as disease [14, 15].

Prior to the advent of agricultural practices, human dietary choices were limited to wild plant- and animal-based foods. In contrast, the post-agricultural diet (particularly post-Industrial Revolution) is rich in cereals, refined flour products, dairy, alcohol, and added sugars [16–18]. These modern food sources, which were largely unavailable in pre-agricultural societies, account for much of the daily energy consumed by North Americans. It has thus been proposed that modern human genetic makeup is ill-suited to the present environment. In other words, modern dietary choices may have placed present day individuals in a state of evolutionary discordance that has manifested in obesity, diabetes, cardiovascular diseases, and neurodegenerative conditions [14, 15, 19–21].

Changing Patterns in the Western Diet

The Western diet is often considered to be a high-fat diet. However, in the early 80s, the United States Department of Agriculture, American Heart Association, and American Medical Association supported a reduction in total dietary fat intake from 40 to 30% with hopes to curb the rising trend in heart disease that was associated with

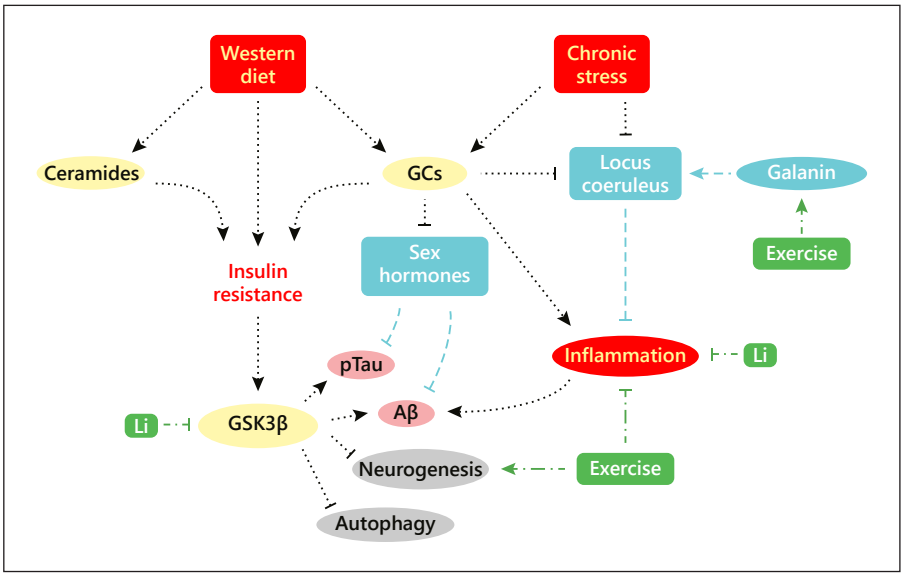

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Fig. 1. High-sugar diets and states of perpetual stress culminate in a "perfect storm" to drive neurodegenerative processes such as increased β-amyloidogenesis and tau protein phosphorylation, depletion of neuroprotective sex hormones, induction and aggravation of neuroinflammation, disruption of glucocorticoid homeostasis, and loss of anti-inflammatory/neuroprotective adrenergic locus coeruleus neurons. Exercise antagonizes many of these processes. Lithium also attenuates many of the noted pathologies, likely through inhibition of GSK3β. Sedentary lifestyles (lack of exercise) coupled with a possible lithium deficiency may thus worsen the deleterious effects of caloric excess and chronic stress.

elevated cholesterol levels. The result was that the reduction in fat intake was replaced with an increase in carbohydrate and sugar consumption, ironically leading to an accelerated increase in heart disease. Thus, the major issue with the Western diet appears to be the excessive consumption of sugars, with fructose being the major contributor to metabolic dysregulation. Humans consumed very little fructose before the mass production of sugar began after WWII. Soft drink consumption has increased from an average 90 servings/year per person in 1942 to approximately 600 servings/year in 2000 [22]. That is the difference of ~2 soft drinks per week to ~2 soft drinks a day. To make matters worse, preschool-aged children are now widely exposed to sugar-sweetened beverages, something that was nonexistent two generations ago.

Excess Caloric Intake Impairs Glucocorticoid and Ceramide Homeostasis

High-sucrose diets have been shown to increase glucocorticoid levels [23, 24], which is associated with a host of pathological effects (Fig. 1). Mice maintained on sugar-sweetened water [25] and diabetic rats [26] display elevated serum corticosterone (analogue of the cortisol found in humans) levels, linking excess sucrose consumption and diabetic states to exaggerated glucocorticoid expression. Chronic glucocorticoid activity exerts several damaging effects on the brain, including quenched antioxidant capacity (increased oxidative damage) [27], potentiation of neuroinflammation [28], induction of brain insulin resistance [26, 29], and activity-mediated LC burnout [30]. In animal models, corticosterone inhibits activation of the insulin receptor while simultaneously reducing expression of its mRNA (reduced protein levels) [26, 31]. Furthermore, glucocorticoids oppose insulin on a functional level, i.e., catabolism versus anabolism [32]. Glucocorticoids also slow the movement of insulin into the CNS from the periphery through inhibition of insulin receptors within the blood-brain barrier (BBB) [33]. Corticosterone/cortisol may thus antagonize the action of insulin on both a functional and molecular level while simultaneously quenching its availability in the brain.

Intriguingly, excessive caloric intake [34–36] and exaggerated glucocorticoid activity [37] have also been implicated in the development of non-alcoholic fatty liver disease (NAFLD). NAFLD is a multifactorial set of conditions with clinical markers of obesity and insulin resistance [38]. Under the umbrella of NAFLD falls non-alcoholic steatohepatitis, a histological subtype characterized by hepatocyte injury and inflammation [38]. Liver steatosis/steatohepatitis and glucocorticoids are known to promote the production of ceramides [39–42] (Fig. 1). Ceramides are known to inhibit insulin signaling and induce oxidative stress and inflammation [43, 44]. As ceramides are lipid soluble and can readily cross the BBB, they are of particular interest in neurodegeneration, as demonstrated by de la Monte et al. [45], who found that peripheral ceramide generation caused sustained impairments in neuronal function and brain insulin signaling. Furthermore, ceramides are often elevated in dementia-associated diseases, including AD [46, 47], suggesting a ceramide-mediated link between high sucrose-induced fatty liver disease and AD pathogenesis.

High Sugar Intake Lays the Foundation for AD Pathogenesis

A causal link between excessive sucrose consumption and brain insulin resistance is well established [16, 48–50]. The addition of 10% sucrose to the drinking water of mice can lead to glucose intolerance, hyperinsulinemia, and hypercholesterolemia, all symptoms characteristic of insulin resistance [51]. In addition, a high-sugar diet can induce CNS mitochondrial, Aβ, and tau pathologies with cognitive deficits and vascular anomalies similar to those observed in AD transgenic animal models [52–54]. As not all organ systems display the same degree of insulin resistance [55], it is possible that central insulin resistance can precede peripheral establishment, as suggested by Talbot et al. [56], who found that the brain of AD patients can be insulin resistant in the absence of diabetes. The brain is continually on the verge of hypoxia/ischemia due to its extremely high demand for oxygen and energy substrates, supporting the idea of heightened brain sensitivity to even small changes in insulin signaling. Brain insulin resistance leads to hyperactivation of glycogen synthase kinase 3 beta (GSK3β), a serine/threonine kinase responsible for modulating several processes implicated in AD-related neurodegenerative processes, such as hyperphosphorylation of tau [57], increased Aβ production [58], and increased plaque-associated microglial-mediated inflammatory responses [59]. As the insulin signaling pathway is responsible for inhibiting constitutive GSK3β activity [60], even a modest degree of insulin resistance can initiate GSK3β-dependent cellular pathophysiology. Autophagy is regulated, in part, by the GSK3β signaling pathway and shows dysregulation very early in neurodegenerative disease progression [61–63]. This can exacerbate accumulation of both plaques and tangles by slowing their removal. Thus, a diet-induced state of central insulin resistance likely contributes to AD pathogenesis.

In addition, high-sugar diets have been linked to increased production of free radicals, likely as a result of aberrant fructose metabolism. Fructosylation of proteins generates reactive oxygen species that lead to increased cell stress and eventual induction of apoptosis [64]. This increase in free radical production comes from the formation of advanced glycation end products (AGEs) [65] formed when sugars react with amino groups in proteins. AGEs act on receptors for AGEs (RAGE) that are upregulated under high-glucose conditions [66, 67]. Excessive RAGE signaling increases free radical production and exacerbates oxidative damage [66, 68]. When coupled with suppressed antioxidant capacity resultant of high sucrose-induced glucocorticoid activity [27, 69], the cumulative effects of glucocorticoid and RAGE signaling could severely potentiate oxidative damage in the brain. Exaggerated formation of reactive oxygen species has been identified as an early event in neurodegeneration [70].

Finally, the high-sugar diet has been linked to increased BBB permeability. Hargrave et al. [71] found that rats maintained on the Western diet for 90 days exhibited widespread increases in BBB permeability, with the CA1 and CA3 hippocampal cell fields and dentate gyrus of both the ventral and dorsal hippocampus prominently affected. Consequently, the rats demonstrated increased behavioral rigidity and a shift toward hippocampal-independent learning, suggesting a disruption in regular hippocampal performance [71]. The BBB consists of a system of microvascular endothelial cells that serve to control the environment of the brain by facilitating the transport of nutrients and endocrine signals while simultaneously prohibiting the entry of toxic substances. Given the importance of the BBB in protecting the brain from toxins, it is no surprise that damage to the BBB and subsequent increased permeability of the system is strongly linked to the development of AD [72]. In fact, BBB disruption has been found to precede the appearance of clinical symptoms in both elderly human AD patients [73] and transgenic rodent models [74].

Caloric Excess Contributes to Loss of the Neuroprotective Sex Hormones

Depletion of sex hormones in both men and women is known to be associated with increased risk of AD [75, 76]. Estrogens, which decline in women during menopause, are considered neuroprotective as they improve neuronal viability [77] and decrease accumulation of Aβ [78–80]. Additionally, women with AD are shown to have lower estradiol than age-matched controls [81]. As for men, loss of androgens due to aging, fittingly termed andropause, is also considered to increase incidence of AD [82]. Androgens play similar neuroprotective roles to estrogen in preventing neurodegenerative disease. For example, testosterone was shown to inhibit Aβ-induced neurotoxicity in cultured hippocampal neurons through a mechanism independent of estrogen and was suggested to be due to non-genomic activation of androgen receptors [83]. Furthermore, testosterone is shown to attenuate the secretion of neuronal-derived Aβ proteins in rats [84]. Not only do androgens have direct protective effects, but through their conversion to estradiol, can have additional indirect actions that protect against AD. It appears that although estrogen and its receptor may regulate AD pathology by promoting the non-amyloidogenic cleavage of

APP [85] and decreasing tau hyperphosphorylation [86], testosterone decreases AD pathology through an androgen receptor-mediated increase in the endopeptidase neprilysin responsible for clearing Aβ levels in the brain [87] and inhibition of calpain-mediated tau cleavage known to play a role in Aβ-induced toxicity [88]. Although loss of testosterone in males or estrogen in females both increase risk for AD, the earlier and more rapid decline in estrogen in females associated with menopause likely contributes to the increased incidence of AD in postmenopausal females [89]. It is also suggested that proper hormonal supplementation, via selective estrogen or androgen modulators, decreases the risk of development of AD [90–92]. Therefore, factors which affect the rate of decline in these protective hormones may be contributing to the overall increased incidence of AD.

Is the typical Western diet, composed of high quantities of sugars and fats, an accelerating factor in the loss of protective sex hormones? It is no secret that a Western diet is associated with numerous detrimental effects on health that include weight gain, increased risk of cardiovascular disease, and increased free radical production. In men, free and total testosterone levels are depleted in those who consume large amounts of saturated, monounsaturated, or polyunsaturated fatty acids [93, 94]. A high-fat diet in rats was also demonstrated to impair steroidogenesis by damaging Leydig cells, regardless of the age at which the diet was introduced [95]. In addition, reduced protein content in a high-fat diet decreases the antioxidant system and thereby the reduction of testosterone to estradiol [96]. Obesity, an epidemic in those who consume the typical Western diet, appears largely linked to reductions in adrenal steroids and sex hormones [97], whereas weight loss, through either a high-protein or high-carbohydrate (and low-fat) diet, is shown to recover testosterone levels in obese men [98]. Fewer studies consider the role of diet in female loss of sex hormones. Interestingly, it was recently demonstrated that the Western-style diet in postmenopausal women increased serum levels of free estradiol, but did not impact free testosterone levels [99]. However, this study used high consumption of eggs and red meat to simulate a Western diet. These foods are known to be high in cholesterol, the precursor for steroid synthesis. Another study looked at a high-fructose diet in rats and found it decreased adipose testosterone and estrogen in males and females, respectively [100]. As a whole, studies suggest that consumption of a Western-style diet may increase the loss of sex steroids in both men and women, in addition to the normal loss that occurs due to aging (Fig. 1).

Modern Society and Perpetual Stress

Changing Patterns in Daily Lifestyle

Threats to homeostasis demand efficient behavioral and physiological responses, which have come to be collectively referred to as fight-or-flight [101, 102]. The fight-or-flight response is mediated, in part, by stimulation of the HPA axis. HPA activity results in the production and release of glucocorticoids (i.e., cortisol) [103].

The stress response can also be triggered by *perceived* threats. Acutely, glucocorticoids associated with the stress response mobilize energy reserves to ensure that adequate resources are in place to deal with current or predicted physical insult/homeostatic challenge [104]. This response is essential to survival. However, chronic glucocorticoid activity is linked to a plethora of negative health consequences [105], such as depression [106, 107], insulin resistance [88, 90], and neurodegeneration [106, 108].

The modern work environment is a stressful one. Deadlines, the threat of firing, and office politics all present as stress-inducing challenges to our overworked minds. In fact, excessive amounts of time spent at work have been positively correlated to perceived psychological stress [109–111] and dysregulated cortisol homeostasis [112]. Unsurprisingly, these same long work hours have been linked to the increasingly common conditions of anxiety, depression, and diabetes [113–115]. Looking at the evidence, it seems not only plausible but probable that working habits are contributing to the widespread stress-fueled deterioration of our health.

Sugar as a Means of Coping with Stress?

Excess sugar consumption is linked to a host of adverse health conditions implicated in the pathogenesis of neurodegeneration [52–54]. Worryingly, stress is associated with increased preference for pleasurable food choices (i.e., high sugar content) [116, 117], even in the absence of hunger [118]. Individuals reporting high levels of chronic stress display exaggerated activity in brain regions involved in reward and motivation when shown images of palatable, high-calorie foods [119]. It is therefore possible that the modern stress-filled lifestyle is intimately related to the burgeoning obesity epidemic; obesogenic feeding disrupts physiological stress responses [23, 24], while chronic stress promotes obesogenic feeding [116, 117, 119].

Is the LC Overdriven in States of Perpetual Stress?

A shared feature of neurodegenerative diseases is the common loss of LC-norepinephrine neurons [2]. The widely studied pathological losses of cholinergic neurons

in the nucleus basalis of Meynert in AD or dopaminergic neurons in the substantia nigra in Parkinson's disease commonly overshadows the greater loss of noradrenergic neurons in the LC [3]. What is driving this early loss of LC neurons? A plausible answer to this may be the cumulative impact of chronic stress, depression, and extended wakefulness (Fig. 1). A fast-paced, high-stress lifestyle increases LC neuron activity and contributes to reduced time and quality of sleep. LC neurons fire at less than 1 Hz during sleep (virtually quiescent during REM), less than 2 Hz during quiet waking, and greater than 2 Hz during active waking [120–123]. LC neurons have long, unmyelinated and highly branched axons that engage in tonic firing at increased rates during wakefulness and in response to glucocorticoids [30]. In addition, LC neurons have very broad action potentials and express low amounts of calcium-binding proteins for buffering of broad action potential-induced calcium influx [124, 125] that can lead to cell death. Modern lifestyles with reduced time for rest and sleep reduce the chance for LC neurons to slow down (i.e., LC loss is observed in stressed animals [126, 127]). The increased/prolonged activity, therefore, is associated with high metabolic demand (necessary to restore ionic gradients along long, unmyelinated, highly branched axons) that can result in increased oxidative stress and activation of apoptotic pathways [128, 129].

Stress Promotes Neuroinflammation

Chronic stress and glucocorticoids can have a profound impact on brain networks [130–134], antioxidant enzyme capacity [69, 135], oxidative injury [136], and neuroinflammation [69, 135, 137, 138]. Elevated glucocorticoid levels have been shown to exert damage to the brain through two primary mechanisms. First, they have been shown to reduce the antioxidant capacity [27]: kainic acid studies conducted by McIntosh et al. [69] demonstrated that neuronal defenses against oxidative challenge were compromised in the brain in response to glucocorticoid exposure. These findings were consistent with an earlier study conducted by the group, leading the researchers to propose that glucocorticoids predispose hippocampal neurons to damage in response to metabolic stressors [27, 69]. Second, exaggerated glucocorticoid activity has been demonstrated to increase the likelihood that systemic inflammation will be propagated into the brain, leading to a neuroinflammatory response [28]. When administered prior to immune challenge (lipopolysaccharide; LPS), glucocorticoids were found to heighten pro-inflammatory responses, including increased expression of TNF-α, IL-1β, and IL-6 and enhanced activation of hippocampal microglia. However, when administered 1 h post-immune challenge, glucocorticoids have been shown to suppress the pro-inflammatory effects of LPS [28], suggesting that chronic glucocorticoid circulation can exacerbate inflammatory responses to stressors. Frank et al. [139] found that hippocampal microglia demonstrated potentiated pro-inflammatory cytokine response to LPS following prior exposure to acute stress. Increased glucocorticoid activity can also exacerbate inflammatory cascades through reduction of the antioxidant capacity of the brain [140]. This loss of antioxidant protection increases the likelihood that systemic inflammation will be propagated into the CNS, resulting in a neuroinflammatory response [28].

Stress Drives Depletion of Sex Hormones

Chronic stress can play a role in accelerating age-related decline in sex hormones (Fig. 1). It was determined that high psychological stress leads to lower testosterone levels in men [97]. In addition, Wang and colleagues [141] demonstrated that chronic stress exacerbated the aging-associated loss of testosterone and Leydig cells in male rats. Stress effects on sex hormones are also known to occur in women as the stress axis also inhibits the secretion of estrogen. So how does stress affect rate of decline? Corticotropin-releasing hormone, elevated in stress, impairs the release of gonadotropin-releasing hormone [142, 143], depleting levels of luteinizing hormone and follicle-stimulating hormone, which are crucial hormones to the production and release of sex steroids in both men and women. In addition, glucocorticoids are shown to inhibit luteinizing hormone release [144] as well as the secretion of estrogen and testosterone by the ovary [145, 146] and testes [147, 148], respectively. Given the prevalence of a chronic stress lifestyle, the impact of such stress on the sex hormones may be contributing to their loss and the eventual development of AD.

A State of Lithium Deficiency

Should Lithium Be Added to the List of Essential Minerals?

Given the integral role played by GSK3β in the pathogenesis of AD and the inhibitory effects of lithium on its action, it is reasonable to question whether the growing AD concern can be partially accounted for by a lack of dietary lithium. Considering that lithium is a trace mineral found in both drinking water and plant matter, it is fair to assume that mammalian species evolved with lithium in the environment and developed some use for it in complex signaling pathways. For example, rats given a

lithium-deficient chow demonstrate suppressed lever-press avoidance behavior compared to rats sustained on a lithium-supplemented diet, suggesting a physiological role for lithium in the regulation of behavior [149]. Factors that limit the availability of lithium or disrupt our handling/retention of it may thus predispose us to neurodegeneration.

Are We Lithium Deficient?

Given that lithium is primarily removed from the body via renal clearance, it is sensible to presume that factors which increase the renal clearance of lithium (rCLi) can contribute to a state of lithium deficiency. Lithium is an alkali metal and monovalent cation that directly competes with sodium for transport across epithelial membranes on account of similar ionic radii [150, 151]. Consequently, lithium and sodium share an intriguing inverse relationship. As the degree of sodium intake increases, so too does rCLi. When sodium concentrations become excessive, transport systems resident within the epithelium become saturated and lithium resorption decreases [152, 153]. Of further concern, a study by Shirley et al. [154] indirectly demonstrated that caffeine, a commonly consumed diuretic, can increase rCLi in healthy males given a 400 mg oral dose of caffeine (~4 cups of coffee). It is therefore reasonable to propose that Western dietary trends, such as excessive salt intake [155] and caffeine consumption, may promote development of a lithium-deficient state.

Medical diuretic use can also influence rCLi [156]. Numerous diuretics such as amiloride, acetazolamide, and furosemide exacerbate lithium clearance through a reduction of proximal- and distal-tubule lithium resorption [152, 156]. A study of 5,092 elderly antihypertensive medication users found that use of thiazide diuretics was inversely correlated with AD incidence [157]. Thiazide diuretics reduce rCLi by increasing the resorption of lithium [156, 158, 159]. While potentially spurious, the inverse relationship between medications that decrease rCLi and AD incidence is worthy of further exploration for the insight it may provide into the connection between lithium and neurodegeneration.

As factors that promote rCLi are becoming increasingly prevalent, epidemiological evidence that associates a lack of dietary lithium with psychiatric illness suggests a plausible scenario for widespread lithium deficiency. In normal and criminal populations, the concentrations of lithium found in the drinking water demonstrates a negative correlation with suicidal and aggressive behaviors [160, 161]. In Texas, mental hospital admission and readmission rates in 27 communities were inversely proportional to the lithium content of residential drinking water [162]. Scalp hair analyses yield similar results. Both children with autism and their mothers demonstrate markedly reduced hair lithium concentrations relative to the general population [163], while a study of American and German adults found that roughly 20% of all individuals have low scalp hair lithium levels, with the lowest concentrations occurring in individuals with learning impairments, cardiovascular disease, and violent criminal behavior [149].

Lithium May Antagonize AD-Related Pathologies

One of the more intriguing capacities of lithium is its putative ability to oppose damages associated with brain insulin resistance. Lithium and the GSK3β cofactor magnesium share similar ionic radii, allowing lithium to act as a competitive inhibitor for the binding of Mg^{2+} at the enzyme's catalytic core [164]. As GSK3β is known to contribute to both Aβ production and aberrant tau phosphorylation [57, 59], a protective role for GSK3β inhibitors (i.e., lithium) against AD pathogenesis likely exists. In culture, lithium consistently reduces tau phosphorylation [165, 166] and Aβ generation [167, 168]. These observations are confirmed in vivo, where lithium attenuates GSK3β-, Aβ-, and phosphorylated tau-driven pathologies [169–174].

Of additional note, lithium appears to support signaling through the canonical Wingless/int (Wnt)/β-catenin pathway – itself a regulator of GSK3β activity – through inhibition of GSK3β. Expression of Wnt3 is associated with increased adult hippocampal neurogenesis [175] and reduced β-amyloidogenic processing of APP [58]. Wnts are glycoproteins responsible for activating developmental and pro-proliferative signaling pathways through interaction with several distinct receptors, including the anti-GSK3β Frizzled (Fzd)-mediated cascade. When Wnt binds to Fzd, the protein Dishevelled (Dvl) is recruited. Activation of Dvl leads to downstream inhibition of GSK3β, preventing the phosphorylation of the GSK3β substrate β-catenin, thereby sparing β-catenin from degradation via the proteasomal pathway [176–178]. Increased endogenous β-catenin expands the population of dividing adult hippocampal progenitor cells [179, 180] and reduces synthesis of β-secretase [58]. Reduced hippocampal neurogenesis is symptomatic of numerous conditions prodromal to AD [181–183]. By increasing the pool of active β-catenin through inhibition of GSK3β [180], lithium may support the anti-Aβ and pro-neurogenesis output of the canonical Wnt/β-catenin pathway.

Lithium may even attenuate the neuroinflammatory responses believed to be at the root of a host of neurodegenerative conditions, including AD [184–188]. GSK3β plays an integral role in the induction of pro-inflammatory microglial activation [189]. Several studies have demonstrated that lithium can block LPS-induced induction of M1 (pro-inflammatory) microglial phenotypes [190, 191], likely through mechanisms reliant on inhibition of GSK3β.

It should be noted that lithium has demonstrated little to no efficacy as a frontline treatment in AD [192–194]. However, there is evidence to suggest that lithium is best suited for prophylaxis, as evidenced by improvements in clinical biomarker expression and cognitive decline in amnestic mild cognitive impairment patients – a condition often prodromal to AD – following long-term treatment with low-dose lithium orotate [195]. Furthermore, in a sample of elderly bipolar disorder patients, AD prevalence was found to be 5% (3/66) in those on lithium and 33% (16/48) in those who were not [196].

In summary, through inhibition of GSK3β (primarily), prophylactic supplementation with lithium may attenuate Aβ, phospho-tau, and neuroinflammatory phenotypes resultant of Western dietary trends and stress-filled, sedentary lifestyles.

What Can We Do?

Exercise Interacts with Many Factors That Drive AD Pathology

Exercise and AD

The rise in AD that plagues society is possibly a result of combining the previously discussed factors, but fortunately we are not cemented to this fate as literature presently exists that supports a preventive role for exercise in AD. It was recently demonstrated that 6–12 months of exercise in seniors with dementia or mild cognitive impairment improved both memory and the volume of the hippocampus compared to sedentary controls [197]. Furthermore, treadmill exercise in rats injected with Aβ is shown to prevent loss of cognitive function [198]. Alternatively, lack of exercise is implicated in development of AD and dementia [199]. In addition to the behavioral improvements exercise promotes in AD, it is also demonstrated to interact with the development of Aβ plaques. For example, voluntary exercise for a period of 5 months in a transgenic mouse model, TgCRND8, resulted in decreased Aβ plaques [200]. The mechanism involved in this phenomenon is associated with changes in APP processing. Clearly, exercise can improve physiological and behavioral outcomes in AD patients, but might exercise also interact with the factors discussed in this review? Can exercise delay or prevent AD onset by antagonizing the factors associated with its induction?

Exercise and the Western Diet

As previously discussed, a high-carbohydrate or high-fat diet is associated with various detrimental effects on health; however, these can be reversed with regular exercise. Exercise training in overweight and previously sedentary adults improved metabolism of both glucose and fats [201]. It was previously shown that exercising could compensate for the resulting insulin resistance caused by consumption of a high-fat diet in rats [202]. This compensation resulted from increases in muscle glucose uptake and storage rather than remedying the underlying development of diet-driven insulin resistance. Interestingly, exercise training in obese women with no effect on weight, inflammatory markers, or adiponectin has still been shown to increase insulin sensitivity [203]. High-fructose diet effects are also ameliorated by exercise, as shown by Botezelli and colleagues [204], who found that swim exercise introduced both early and late into the diet protocol prevented development of insulin resistance and generation of NAFLD. In addition to affecting insulin resistance and weight, exercise is also known to impact factors in the brain which protect against the effects of a high-fat diet. These include brain-derived neurotrophic factor (BDNF), CREB, and synapsin [205]. Elevation of BDNF is achieved by increased transcription of mRNA for BDNF and a reduction in reactive oxygen species. Exercise also decreases the generation of free radicals that is associated with consumption of a high-fat diet [205]. Obesity, a common result of the Western diet, results in dysfunction in mitochondria and thereby oxidative stress. Exercise, through an unknown mechanism, attenuates this obesity-induced dysfunction in skeletal muscle mitochondria and prevents the generation of oxidative stress [206]. Thus, exercise can be used to combat the AD-inducing effects of a high-carb or high-fat diet.

Exercise and Chronic Stress

Exercise, in addition to its benefits in weight loss and diabetes, exhibits profound improvements in stress and depression. Exercise is already commonly touted as a treatment for anxiety [207] and depressive disorders [208, 209]. Multiple mechanisms associated with exercise can produce these improvements in mood. Of particular note is the upregulation of galanin that occurs in LC neu-

rons following exercise [210, 211] (Fig. 1). Galanin, a peptide thought to be neuroprotective and capable of stimulating neurogenesis, is released from LC-noradrenergic neurons during phasic burst firing [212–214]. As the LC is the main source of norepinephrine for the brain, it plays an important role in mood regulation. For instance, many medications that affect mood and are used to treat depression are enhancers of norepinephrine levels (in addition to serotonin).

Beyond protection of the LC, galanin abates Aβ-induced activation of p53, Bax, and caspase-3, which belong to the apoptotic cascade [215]. In human primary neurons, galanin, via GAL-2 receptor, downregulates Bax [216]. Galanin reduction is associated with diabetes [217], stress, and depression and may represent a means by which these risk factors contribute to AD pathogenesis.

Exercise also improves mood via other routes. One such alternative mechanism is the increase of dopamine in the reward system. For example, in the prefrontal cortex, increases in dopamine and the D2 receptor [218] following exercise led to antidepressant-like effects in rats. Finally, the major neurotransmitter for mood, serotonin, is demonstrated to be increased in senior men who exercise [219]. Therefore, chronic stress and depression are effectively attenuated via introduction of exercise.

Finally, and perhaps most importantly, regular exercise has been shown to reduce the degree of HPA activation in response to non-exercise-related stress [220]. As discussed previously, adaptive responses to real and perceived stressors involve induction of both the HPA axis and sympathetic nervous system. The result of this adaptation, known as allostasis, is the mobilization of lipids from adipose tissue and glucose from hepatic glycogen stores. The degree and frequency of the stress response contributes to allostatic load ("wear-and-tear" as the result of stress). How quickly allostatic load accumulates is thought to depend on two primary factors: (1) mental fitness, i.e., how an animal perceives stress, and (2) physical fitness [221]. Not surprisingly, sedentary individuals with poor physical fitness demonstrate increased allostatic load relative to their peers [222]. Poor physical fitness also correlates with increased incidence of stress-related health complications [221, 223].

The stress response is regulated by a negative feedback loop through the hippocampus and HPA that attenuates HPA activity following sufficient interaction between glucocorticoids and their receptors in the hippocampus [224, 225]. Chronic elevations in glucocorticoids, as observed due to perpetual stress [182] and/or high-sugar feeding [23, 24], decrease glucocorticoid receptor density in the hippocampus, thereby blunting negative feedback inhibition of the HPA axis and prolonging the duration of the stress response [226]. Of concern, LC neurons engage in tonic firing at increased rates during wakefulness [120–123] and in response to HPA activation [30], which supports the idea that excessive corticotropin-releasing factor (CRF) signaling in the LC contributes to "activity-mediated burnout" of resident noradrenergic neurons; CRF promotes LC activity during stress [227]. Given that high-sucrose diets and chronic stress are known to reduce glucocorticoid-mediated negative feedback of HPA output, it is likely that CRF-induced elevations in LC basal firing rates would proceed unchecked under such conditions, culminating in neuronal damage and possible apoptosis [128, 129]. Sedentarism, chronic stress (CRF-induced firing), and insufficient sleep (increased basal firing rate) might thus constitute a means by which lifestyle factors drive the LC atrophy implicated in a host of neurodegenerative conditions.

In contrast, regular exercise improves both behavioral and physiological responses to non-exercise-related stressors [228–230]. This positive effect of exercise may be mediated by modulation of HPA reactivity. Aerobic exercise protects against stress/diet-induced reductions in hippocampal glucocorticoid receptor expression, preserving the integrity of the negative feedback loop responsible for stress response cessation [220, 225]. In addition, as mentioned previously, exercise increases galanin expression in the LC [211]. Galanin is known to act in an autocrine manner to desensitize LC neurons through amplification of hyperpolarization following spike discharge [212, 231]. Therefore, it is possible that exercise could prevent the activity-mediated burnout of the LC associated with chronic stress, i.e., exercise increases galanin levels, which in turn dampen the basal firing rate of LC neurons. In short, exercise may protect against stress-induced LC neuronal loss by (1) attenuating the duration and severity of allostasis through maintaining efficacy of the negative feedback loops involved in stress response cessation, and (2) clamping down on LC overactivity via upregulation of local galanin expression.

Exercise and Inflammation

AD is linked to aberrant regulation of inflammatory processes. Intriguingly, exercise has demonstrated body fat-independent anti-inflammatory capabilities [232, 233]. Treadmill exercise in high fat-fed rats blocks the increase in pro-inflammatory mediators, such as TNF-α, IL-1β, and cyclooxygenase-2, associated with obesogenic feeding [234]. These anti-inflammatory effects are ob-

served in humans as well. Physically fit individuals demonstrate increased expression of IL-10 [235, 236] (anti-inflammatory) and decreased levels of the pro-inflammatory mediators IL-6 and TNF-α [235, 237–240] relative to their sedentary peers. Exercise has also been shown to blunt the response mounted to LPS, a known inducer of systemic inflammation [241]. As exercise decreases inflammatory burden in individuals suffering from chronic systemic inflammation, it may protect against induction of neuroinflammation (and thus AD) (Fig. 1); peripheral inflammation leads to central inflammation [242–244].

Exercise and the Loss of Sex Hormones

The loss of sex hormones can be slowed or prevented by introducing exercise. For example, testosterone production from the testes in OLETF rats is demonstrated to increase following training with aerobic exercise [245]. Exercise also attenuated obesity-augmented hypogonadism in male rats [246]. While exercise increases BDNF in the hippocampus, the degree of improvement appears to depend on the presence of estradiol [247]. It was shown that exercise-induced increases in BDNF are absent when estrogen is not present. Interestingly, voluntary activity was also shown to be reduced in rats that were without estrogen [247]. This study demonstrates an important relationship between exercise and estrogen in brain health. More evidence of the interaction between exercise and estrogen comes from a study by Erickson and colleagues [248], who demonstrated that exercise with hormone replacement therapy ameliorated decline in brain function and loss of brain tissue that occurs with long-term use of hormone replacements. Furthermore, as discussed in previous sections, decline in sex hormones is accelerated by the Western diet and chronic stress. Given that exercise also disrupts these factors, it is reasonable to assume that sex hormone decline is also indirectly improved.

Lithium Supplementation May Delay or Prevent AD Onset

Lithium as a Prophylactic in AD

Lithium salts have a well-established role in the treatment of major affective disorders, notably mania. Interestingly, a comparison of the prevalence of AD in elderly bipolar disorder patients found that AD was diagnosed in just 5% of patients undergoing lithium therapy, in contrast to a rate of 33% in those not on the medication [196]. While efforts to treat AD with lithium have failed to yield significant reductions in disease-related biomarkers or notable benefits to cognitive performance [192, 193], there is reason to believe that the element may have prophylactic benefit in individuals considered high-risk for disease development. Long-term lithium treatment (>300 mg of $LiCO_3$/day) in 45 individuals with amnestic mild cognitive impairment yielded a significant decrease in cerebrospinal fluid concentrations of phospho-tau and a marked increase in cognitive performance relative to placebo [195]. Furthermore, lithium demonstrates prophylactic potential even at subtherapeutic dosage. Microdose lithium (0.3 mg of $LiCO_3$/day) prevented cognitive decline in AD patients over a 15-month period. Significant differences between the treatment and control groups were observed as early as the third month, with the gap broadening progressively [249]. While inconclusive, these findings suggest lithium may have the potential to slow or even halt the progression from prodromal stages to AD (Fig. 1).

A Case for Lithium Orotate

Given the reported capacity of lithium to attenuate the progressive cognitive decline observed in AD, the lack of research surrounding lithium as a prophylactic agent is perplexing. Much of the hesitation surrounding use of lithium salts stems from the narrow therapeutic index for lithium carbonate. While these concerns are valid, they arise from the likely incorrect assumption that all lithium salts work the in the same manner. In the late 1970s, King et al. [250] noted that lithium orotate resulted in greater serum and brain concentrations of elemental lithium than did equivalent lithium carbonate dosages. These increased serum concentrations may be related to reduced kidney filtration rate [251] and/or increased delivery of lithium across cell membranes as a neutral non-dissociated lithium orotate complex [252, 253]. As such, lithium orotate can achieve therapeutic brain lithium concentrations at markedly reduced dosages compared to conventional lithium compounds, expanding its safety profile. A PubMed search for "lithium orotate" will bring up nine results. Of these, the most recent three imply that lithium orotate is toxic in some manner [254–256]. However, upon closer inspection, no real toxicity occurred despite taking 18 times the suggested dose [256]. Considering the reduced dose requirements of lithium orotate, it warrants further study as a potentially safe treatment for a host of neurological illnesses, AD included.

Conclusion

Altogether, the evidence summarized in this review presents a profound role for dietary and lifestyle decisions in the preservation or deterioration of neurological health

Table 1. Exercise is a potent attenuator of many AD-associated pathological processes

	Western diet	Chronic stress	Exercise	Lithium supplementation	AD phenotype
HPA/GC dysregulation	↑ 23–26	↑ 112, 182, 202–204, 210	↓ 211, 212, 220, 228–230, 231	–	261–265
Ceramide production	↑ 39–42	↑ 243	↓ 189	–	46, 47
Insulin resistance	↑ 16, 26, 29, 44, 48–51	↑ 257–260	↓ 202–204	↓ 164, 170	52–54, 57–60
Loss of locus coeruleus	↑ 30	↑ 30, 112, 120–129	↓ 210, 211	–	2–4
Inflammation	↑ 28, 59, 138	↑ 28, 69, 135–140	↓ 232–241	↓ 184–188, 190, 191	70, 184–188
Aβ and/or pTau production	↑ 52–54, 57, 58	↑ 261–264	↓ 198, 200, 215	↓ 58, 165–174, 195	57, 58
Loss of sex hormones	↑ 93–97, 99, 100	↑ 97, 141–148	↓ 245, 246	–	75, 76, 81, 82

While chronic stress, Western diet, and lithium deficiency alone are unlikely to precipitate AD, they may act in a synergistic manner to drive disease pathogenesis. The relationship between the pathological processes associated with each factor and AD are captured in the "AD phenotype" box. Exercise shows potential to combat the AD-related pathologies associated with these factors.

throughout the life span (Table 1). Excess caloric intake (sucrose, in particular) disrupts glucocorticoid [23, 24] and ceramide homeostasis [39–42], which in turn contributes to central insulin resistance, neuroinflammation, and brain oxidative stress [28, 29, 43, 44, 100]. These events/states are directly linked to the β-amyloidogenic processing of APP and hyperphosphorylation of microtubule-associated tau proteins [52–54, 57, 58], the hallmark processes of AD-like neurodegeneration. Of note, increased consumption of palatable, high-caloric density foods is likely a coping mechanism for chronic stress [116, 117, 119], a widespread issue in modern society.

In addition to promoting increased sugar intake, perpetual stress perturbs physiological HPA function, leading to dysregulated glucocorticoid activity. Both chronic stress – likely through central mechanisms – and excess glucocorticoid signaling overdrive the LC by increasing the basal firing rate of resident adrenergic neurons [30]. Over time, this increase in basal activity induces a state of "activity-mediated burnout" which culminates in a loss of function [128, 129]. As adrenergic output from the LC is highly anti-inflammatory and neuroprotective, its loss will likely exacerbate central damages inflicted by other stressors (i.e., caloric excess).

Making matters worse, our society may be lithium deficient. Excess salt and caffeine consumption increase rCLi, potentially leading to a lithium-deficient state. Low levels of lithium in scalp hair, which correlates with insufficient lithium intake, are associated with autism [163], violent behavior, and suicidal ideation [149]. Similar trends are observed in communities lacking lithium in the drinking water [160, 161]. Lithium is a potent inhibitor of GSK3β [164], whose aberrant activity is a central mediator of the deleterious effects of insulin resistance [60] (i.e., GSK3β phosphorylates tau [57, 59]) and ultimately AD. As such, lithium deficiency likely worsens the neurological damages associated with high sugar intake and chronic stress.

While AD is viewed as an inevitable event that affects random individuals, the evidence provided in this review highlights ways in which AD onset may potentially be delayed or even avoided. First, exercise counteracts many of the deleterious effects associated with chronic stress and the Western diet. Aerobic exercise in rodent models attenuates insulin resistance, inflammation, and free radical production in response to obesogenic feeding [202–205]. Furthermore, exercise protects the LC from stress-induced degeneration by restoring appropriate HPA function [220, 228–230] and increasing expression of the neuroprotectant galanin [210]. Second, treatment with low doses of lithium carbonate prevents cognitive decline for individuals with amnestic mild cognitive impairment [195] or AD [249], suggesting a prophylactic role for lithium against neurodegeneration despite a demonstrated lack of efficacy as a frontline treatment [192–194]. To sum up, exercise and lithium supplementation (correcting for deficiency) represent means by which we may take control of our own health and potentially prevent the events that lead to AD pathogenesis.

People are exposed to differing sets of stressors throughout their life span. Thus, differing levels of physical activity, lithium concentration in the drinking water, socioeconomic status, stress, and access to healthy food may in part explain why not all individuals develop AD.

In closing, diet, stress, physical activity, and lithium intake are factors within our control that likely contribute to neurodegenerative processes associated with AD pathogenesis.

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Author Contributions

A.G.P., C.A.W., and L.K.B. were involved in writing and editing the manuscript.

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