REVIEW

Associations between Sleep, Cortisol Regulation, and Diet: Possible Implications for the Risk of Alzheimer Disease[1,2]

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ABSTRACT

Accumulation of proteinaceous amyloid β plaques and tau oligomers may occur several years before the onset of Alzheimer disease (AD). Under normal circumstances, misfolded proteins get cleared by proteasome degradation, autophagy, and the recently discovered brain glymphatic system, an astroglial-mediated interstitial fluid bulk flow. It has been shown that the activity of the glymphatic system is higher during sleep and disengaged or low during wakefulness. As a consequence, poor sleep quality, which is associated with dementia, might negatively affect glymphatic system activity, thus contributing to amyloid accumulation. The diet is another important factor to consider in the regulation of this complex network. Diets characterized by high intakes of refined sugars, salt, animal-derived proteins and fats and by low intakes of fruit and vegetables are associated with a higher risk of AD and can perturb the circadian modulation of cortisol secretion, which is associated with poor sleep quality. For this reason, diets and nutritional interventions aimed at restoring cortisol concentrations may ease sleep disorders and may facilitate brain clearance, consequentially reducing the risk of cognitive impairment and dementia. Here, we describe the associations that exist between sleep, cortisol regulation, and diet and their possible implications for the risk of cognitive impairment and AD. *Adv Nutr* 2016;7:679–89.

Keywords: Alzheimer disease, glymphatic system, sleep, cortisol, hippocampus, Western diet, acidosis, nutritional interventions, supplements

Introduction

Late-onset Alzheimer disease (AD)[8] is a progressive neurodegenerative syndrome, mostly occurring after 65 y of age and characterized by the accumulation of proteinaceous amyloid β (Aβ) plaques and formation of neurofibrillary tangles (1, 2). The disease sequelae often include the development of a progressive cerebral atrophy, cognitive decline, and ultimately death (3).

Formation of both Aβ plaques and neurofibrillary tangles seems to be part of the normal aging process, as revealed by brain immunohistochemical analyses of cognitively normal older people (4).

Aβ and tau oligomers get physiologically cleared by ubiquitination-proteasome degradation, sumoylation, and autophagy (5, 6). If these process results are inefficient, protein aggregates can progressively accumulate, causing neuronal degeneration (6–9).

In addition, the recently discovered glymphatic system, an astroglial-mediated interstitial fluid bulk flow, was shown to play a key role in the regulation of amyloid clearance from the brain by the perivascular space surrounding brain blood vessels (10, 11). This system also plays a role in the brain-wide distribution of growth factors, neuromodulators, glucose, lipids, and amino acids (12). Importantly, the activity of the glymphatic system is higher during sleep and lower (or disengaged) during wakefulness (12). This has special relevance for AD because sleep disorders, such as obstructive sleep apnea (OSA), are associated with the onset of dementia (13–15). In particular, sleep disorders are shown to compromise the normal functioning of the glymphatic system and, as a consequence, contribute to the accumulation of misfolded proteins (16).

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[8] Abbreviations used: Aβ, amyloid β; AD, Alzheimer disease; CAR, cortisol awakening response; DHEAS, dehydroepiandrosterone sulfate; HPA, hypothalamic-pituitary-adrenal; MCI, mild cognitive impairment; OSA, obstructive sleep apnea.

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Western and/or poorly balanced diets, characterized by high intakes of refined sugars, animal-derived proteins, and saturated fats and a concomitant low intake of plant-based foods, are known to be associated with higher risk of AD (17–20) and can increase the secretion of glucocorticoids (e.g., cortisol), catecholamine, and serotonin, causing oxidative stress (21, 22). Deregulated circadian cortisol concentrations are associated with mild cognitive impairment (MCI) and AD, suggesting that glucocorticoids and cortisol, in particular, may play a role in the onset and/or the progression of AD (23).

Deregulated cortisol concentrations are also correlated with poor sleep quality (24), and even partial acute sleep loss may deregulate cortisol release (25). Nutritional interventions aimed at restoring cortisol concentrations may positively influence sleep quality, thus promoting the regulation of brain clearance systems and a reduction of brain amyloids and, consequentially, reduce the risk of cognitive impairment and dementia. Here, we discuss the role of sleep in the regulation of the glymphatic system and amyloid clearance, the associations between deregulated cortisol concentrations and sleep, and the possible implications for the risk of cognitive impairment and AD, highlighting the role of diet in the modulation of these factors.

Sleep Disorders Are Correlated with the Risk of AD

Lifestyle risk factors associated with AD: a focus on sleep disorders. It was hypothesized that AD might be much more complex than an amyloidosis- and tauopathy-related syndrome. Although advancing age is considered the main risk factor for developing late-onset AD (26–28), strong evidence suggests that AD is strongly correlated with diabetes and the metabolic syndrome (20, 29–35) and cardiovascular diseases (36–49), suggesting the involvement of systemic, metabolic, and multifactorial mechanisms in the etiopathogenesis of AD. Among the risk factors that were implicated in the pathogenesis of type 2 diabetes, metabolic syndrome, and AD, insulin resistance, imbalance of glucocorticoid concentrations, inflammation, dysfunctions of mitochondrial metabolism, oxidative stress, and hyperhomocysteinemia were reported to play a main role (50–52).

In addition, specific dietary patterns can play a role in the onset of neurodegeneration and dementia (18, 19), such as a low intake of plant-derived foods, which was related to a higher risk of diabetes, metabolic syndrome, and dementia (20).

In addition, sleep disorders seem to play an important role in the onset of AD (13–15). Differences in sleep patterns seem more prominent during the early stages of dementia than during later stages (53). However, a 2012 clinical cross-sectional study that involved 431 patients (204 affected by AD, 138 with MCI, 43 with vascular dementia, 25 with frontotemporal dementia, and 21 with Lewy body or Parkinson disease) measured several types of sleep disturbances (i.e., sleep-disordered breathing, rapid eye movement behavior disorder, restless legs syndrome, and excessive daytime sleepiness) and reported that patients affected by MCI or by AD had the same frequency of sleep disturbances of any type (~65% prevalence) (54). Analogously, another epidemiologic study of 236 patients affected by different subtypes of dementia showed that insomnia, in particular, was mostly present in persons affected by AD and that persons affected by MCI had the same frequency of any sleep disturbance as AD patients (55).

Among sleep disorders, OSA is characterized by impaired delivery of oxygen (i.e., hypoxia and hypoxemia), which perturbs neuronal homeostasis, and triggers neuronal degeneration and apoptosis (3). Hypoxia and hypoxemia are correlated with sympathetic activation, neuroinflammation, oxidative stress, and several other pathologic perturbations that cause neurodegeneration (3) and late-onset AD (56).

Sleep restriction can also decrease insulin sensitivity, as reported in healthy subjects (57, 58). Further studies that enrolled higher numbers of participants should be conducted to confirm these observations.

Pharmacologic treatments of sleep disturbances (e.g., melatonin, benzodiazepines, non-benzodiazepine hypnotics, trazodone, and ramelteon) in subjects affected by AD were shown inconclusive and were characterized by uncertainty about the balance of benefits and the risks associated with these treatments, as reported by an analysis of all relevant randomized controlled trials that compared the effects of drugs with placebo (59). Only in the case of a low dose of trazodone (i.e., 50 mg administered at night for 2 wk) was some evidence of efficacy, although larger clinical trials will be needed to allow more definitive conclusions and to establish actual risks and benefits (59).

A recent randomized, double-blind, parallel-group study conducted with 80 patients diagnosed with mild-to-moderate AD, with or without insomnia comorbidity, and receiving standard treatments (i.e., acetylcholinesterase inhibitors, with or without memantine) reported that treatment with prolonged-release melatonin (2 mg, administered nightly for 24 wk, followed by 2 wk of placebo) could improve cognitive functioning and sleep quality compared with placebo, and positive effects were particularly evident in those patients who presented with insomnia comorbidity (60).

However, the use of benzodiazepine might increase the risk of AD, as shown in 1796 subjects with a first diagnosis of AD compared with 7184 matched controls, who started using benzodiazepines ≥5 y before the diagnosis of AD (61). For this reason, long-term use of benzodiazepines should be considered as a possible public health concern (61), and their long-term use should not be encouraged (62).

Glymphatic system and role of sleep in the regulation of amyloid clearance. The glymphatic system, which was first described in 2012, is known to control interstitial solute and fluid clearance from the brain. This system is an interstitial fluid bulk that was shown to regulate brain amyloid clearance by the perivascular space that surrounds cerebral blood vessels (10, 11, 63, 64). As a consequence, dysfunctions of the glymphatic systems might play a role in the onset or consolidation of AD and dementia.

The glymphatic system constitutes perivascular tunnels formed by astroglial cells, and its bulk flow is driven by cerebrovascular pulsation and facilitated by aquaporin-dependent astroglial water flux (65). The glymphatic system plays a role not just in the elimination of soluble proteins and metabolites from the brain but also in the brain-wide distribution of growth factors, neuromodulators, glucose, lipids, and amino acids (12). The activity of the glymphatic system was analyzed in rat models (66, 67); however, to date no clinically approved approaches are developed to evaluate the functionality of the glymphatic system in humans.

Interestingly, dysfunctions of the glymphatic system were recently hypothesized to play a role in glaucoma pathogenesis (68), which is characterized by a progressive degeneration of retinal ganglion cells and accumulation of Aβ, which suggests possible associations with AD (69, 70).

The activity of the glymphatic system is higher during sleep or anesthesia and lower or disengaged during wakefulness (12). Accordingly, sleep plays a critical role in ensuring brain metabolic homeostasis and clearance of potentially neurotoxic waste products, such as amyloids (64). This has special relevance for AD, because sleep disorders, such as OSA and insomnia, are associated with the onset of dementia (13–15, 54, 55), as reported in the previous section. As a consequence, sleep disorders might compromise the normal functioning of the glymphatic system and contribute to the accumulation of misfolded proteins in the brain (16). Accordingly, sleep disorders seem to be associated with early deposition of Aβ plaques (71, 72). In particular, OSA was shown to induce Aβ accumulation, hyperphosphorylation of tau, and synaptic dysfunction (56).

Increased stress and decreased sleep were both linked to accumulations of Aβ in animal models (73, 74), and sleep was shown to regulate several synaptic markers in *Drosophila* and possibly the metabolism of a number of central nervous system proteins (75, 76).

In addition, body posture during sleep seems to matter. In particular, lateral position, compared with the supine or prone positions, may increase glymphatic transport, as reported in rats (77). Future studies should be conducted to confirm the possible relevance of these observations in humans.

Impact of sleep disorders on hippocampal volume. Sleep and sleep deprivation exert a bidirectional control on hippocampus-dependent memory consolidation, by modulating signaling pathways that regulate synapsis formation and plasticity (78).

Smaller hippocampal volumes were associated with AD (79–81), neurodegenerative and psychiatric diseases, and mild cognitive impairment (82), and were linked to lower sleep efficiency (82). Accordingly, patients with primary insomnia, compared with control subjects, were characterized by bilateral atrophy of the hippocampus and cognitive impairment (i.e., reduced verbal memory, verbal information processing, and verbal fluency), suggesting that patients affected by chronic sleep disturbances might be at higher risk of cognitive impairment (83).

Both the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles are implicated in adult neurogenesis (84–86), which plays a key role, particularly in the case of the hippocampus, in the maintenance of memory processes and the regulation of emotionality (87). In line with this, it is hypothesized that prolonged sleep restriction or disruption may drive a cumulative decrease of hippocampal neuronal cell proliferation, decrease of neuronal cell survival, and neurogenesis (87).

Some observational studies and preliminary clinical trials have suggested that some modifiable factors, such as cognitive stimulation, physical exercise, and the treatment of general medical conditions associated with reduced hippocampal volume and hippocampal atrophy (e.g., obesity, diabetes, hypertension, hypoxic brain injury, OSA, bipolar disorder, cognitive decline, depression, and head trauma) can reverse hippocampal atrophy or even expand hippocampal size (88).

Diet and Specific Nutrients Can Affect Cortisol Regulation, Sleep Quality, and the Risk of AD

Deregulated cortisol concentrations can play a role in the onset of AD: possible associated mechanisms. Cortisol is a glucocorticoid hormone produced in humans by the adrenal cortex within the adrenal gland in response to stress and low concentration of blood glucose. Its release is mediated by the hypothalamic-pituitary-adrenal (HPA) axis and follows a circadian rhythm characterized by a morning peak [or cortisol awakening response (CAR)], a slow decline throughout the day, and a low or undetectable amount at midnight (89). The hippocampus and other brain structures, such as the amygdala, the prefrontal cortex, and the suprachiasmatic nucleus, play a role in the physiologic regulation of CAR (90).

High diurnal salivary cortisol concentrations were described in subjects affected by amnestic MCI (91, 92), in cognitively normal elderly individuals who experienced subjective memory complaints (93), in nondepressed community-dwelling elderly people (94), especially if homozygous for the apoE ε4 allele (95), and in subjects affected by AD and their caregivers (96–98).

Conversely, another study reported that subjects affected by MCI had cortisol concentrations similar to concentrations of the normal elderly group, but lower than young controls (99). Possible conflicting data might be due to differences in study design, such as the time of sampling (i.e., daytime compared with nighttime) and even the season, because cortisol concentrations can change according to seasons (100).

The hippocampus contains a high concentration of corticosteroid receptors and, for this reason, is particularly responsive to cortisol (81), dehydroepiandrosterone sulfate (DHEAS), and other stress hormones that are known to regulate hippocampal plasticity, excitability, long-term potentiation, and depression (101). Opposite to acute glucocorticoid elevations, which were shown to play protective effects (102), chronic release of high glucocorticoid and high nocturnal cortisol concentrations were associated with smaller hippocampal volumes (103, 104). In addition, high cortisol concentrations, in association with reduced hippocampal volumes and cognitive

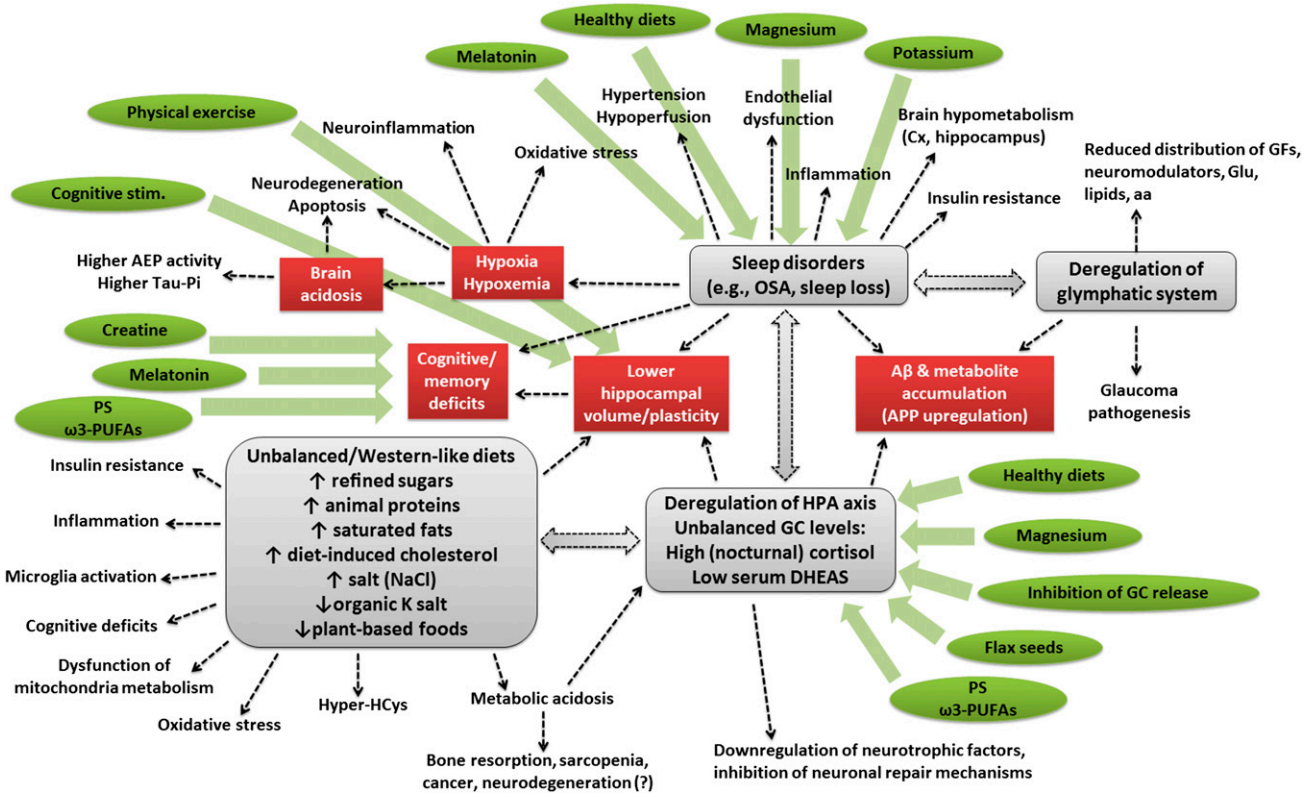

FIGURE 1 Schematic representation of the complex network underlying the onset of cognitive impairment and eventually AD. Imbalanced, Western-like, high-fat diets elicit deregulation of the HPA axis and of GC (e.g., cortisol) release and lower hippocampal volumes, besides inducing a plethora of other effects (e.g., insulin resistance, inflammation, microglia activation, cognitive impairments, dysfunction of mitochondria metabolism, oxidative stress, hyperhomocysteinemia, and metabolic acidosis), which typically characterize type 2 diabetes, metabolic syndrome, and AD. Deregulation of cortisol release can affect sleep quality, reduce hippocampal volume, promote the accumulation of Aβ plaques and other metabolites, downregulate the synthesis of neurotrophic factors, and inhibit neuronal repair mechanisms. Sleep disorders may themselves compromise cortisol release; reduce hippocampal volume and plasticity; induce cognitive and memory deficits; elicit hypoxia and hypoxemia (which is responsible for increased brain acidosis, neuronal degeneration, inflammation, oxidative stress, induction of asparaginyl endopeptidase activity, and increase of phospho-tau); increase hypertension and hypoperfusion, endothelial dysfunctions, inflammation, cortical and hippocampal hypometabolism, and insulin resistance; and reduce the functionality of the glymphatic system. Deregulations of the glymphatic system can cause accumulation of Aβ plaques and other metabolites; reduce the distribution of growth factors, neuromodulators, glucose, lipids, and amino acids; and can contribute to glaucoma pathogenesis. Some dietary interventions and supplements (indicated in green), such as plant-based and Mediterranean (healthy) diets, PS and ω-3 PUFAs, melatonin, creatine, magnesium, potassium, flax seed cultivars, and inhibitors of GC release, in combination with cognitive stimulation and physical exercise, can soothe ≥1 of these risk factors and, for this reason, might be considered as nonpharmacologic interventions aimed at preventing the risk of AD or reducing its symptoms. Aβ, amyloid β; AD, Alzheimer disease; AEP, asparaginyl endopeptidase; APP, amyloid precursor protein; Cx, cortex; DHEAS, dehydroepiandrosterone sulfate; GC, glucocorticoid; GF, growth factor; Glu, glucose; HPA, hypothalamic-pituitary-adrenal; Hyper-HCys, hyperhomocysteinemia; OSA, obstructive sleep anea; PS, phosphatidylserine.

decline, were observed in patients with AD (105, 106), eventually presenting a parallel reduction of DHEAS secretion (101). Accordingly, plasma cortisol and apo A-II, as well as several other cerebrospinal fluid markers (e.g., fibroblast growth factor 4, heart-type FA binding protein, calcitonin, and tumor necrosis factor-related apoptosis-inducing ligand receptor 3) could serve as useful biomarkers to predict midterm progression from MCI to AD, as shown in a recent cohort study that enrolled 928 patients with MCI at baseline (107). Analogously, high cerebrospinal fluid cortisol concentrations were found associated with more rapid clinical worsening and cognitive decline in MCI-AD, suggesting that dysregulation of the HPA axis may occur at early (MCI) stage of AD, possibly accelerating disease progression (23). In addition, high concentrations of morning basal cortisol were associated with lower cognitive functions in postmenopausal women (108).

Activation of plasma macrophages and brain microglia can cause release of proinflammatory cytokines, leading to hypersecretion of cortisol, possibly contributing to the progress from depression to dementia (109). High cortisol concentrations can also downregulate the synthesis of neurotrophic factors and inhibit neuronal repair mechanisms (109).

High concentrations of glucocorticoids and, in particular, cortisol were reported in subjects affected by other

hypercortisolemic diseases, such as Cushing disease and depression. Elevated cortisol concentrations in Cushing disease were found associated with cognitive decline, in particular with a reduction of verbal learning, several subtests of learning, delayed recall, and visual–spatial ability, as shown in 48 patients with a first episode of acute, untreated Cushing disease compared with 38 healthy control subjects, suggesting an impairment of both the neocortex and hippocampus (110).

However, although individuals affected by Cushing disease and depression present constantly elevated concentrations of cortisol, mild-to-moderate AD stages are generally characterized by hyperactivity of the HPA axis, a perturbation of the circadian rhythm of cortisol release, and an insufficiency of glucocorticoid receptor signaling (111).

In addition, it was reported that high glucocorticoid and cortisol concentrations may contribute to amyloid formation and may potentiate their toxicity (112, 113). Conversely, DHEA and DHEAS or even inhibition of glucocorticoid release may have neuroprotective effects (113–115).

Glucocorticoids were reported to elevate Aβ production by increasing amyloid precursor protein expression also in primary cultures of astrocytes (116), and activated astrocytes were shown to contribute to Aβ production (117).

Moreover, deregulated cortisol concentrations were shown correlated with diminished sleep quality and insomnia (24), which are associated with AD (55), as we commented in the previous paragraph. However, even partial acute sleep loss can alter the negative glucocorticoid feedback regulation, inducing elevation of cortisol the next evening (25).

Importantly, Western diet and, more in general, low-quality dietary patterns, characterized by high consumption of meat, saturated fat, and refined sugars, are known to be associated with obesity, diabetes, lower cognitive function, reduction of hippocampal volumes, and AD (118). In the next sections we discuss how specific dietary patterns and nutritional interventions can affect cortisol regulation, possibly affecting sleep quality, which might have implications for the risk of cognitive impairment and AD.

Effects of diet in the modulation of circadian cortisol concentrations. Dietary composition plays an important role in the regulation of glucocorticoid and cortisol release. In particular, Western-like diets, characterized by high intakes of refined carbohydrates, animal proteins, and saturated fats and low intake of plant-based nutrients, fibers, and antioxidants, which are associated with a higher risk of AD (17–20), can upregulate the release of cortisol, catecholamine, and serotonin, causing oxidative stress (21, 22).

It was reported that an isocaloric high-protein diet can increase the amount of cortisol and also of lean body mass, total ghrelin (also known as the "hunger hormone"), growth hormone, and testosterone, as shown in untrained healthy young men (119). In addition, increased intakes of saturated fats were reported to elevate salivary cortisol, as shown in subjects at risk of psychosis (120).

Diets characterized by intakes high in fat and low in fruit and vegetables can decrease CAR and can deregulate cortisol diurnal profile, as reported by an observational study of 24 young adults (aged 18–22 y), who were compared with 48 community-dwelling older adults (aged 65–88 y) (121).

It should be considered that the association between diet and glucocorticoid release is bidirectional; that is, not only the diet can influence glucocorticoid and cortisol release, but also deregulated glucocorticoid and cortisol concentrations can increase the craving for and consumption of low-quality foods, rich in calories, sugar, and fat (102, 122).

Furthermore, Western-like diets, typically rich in animal proteins and salt and deficient in fruit and vegetables, are typically acidogenic; that is, they can cause a subclinical or low-grade state of metabolic acidosis (123, 124). This metabolic acidosis is responsible for increased bone resorption and loss of calcium from bone tissue (22), loss of muscular mass, sarcopenia, negative nitrogen balance (125), and cancer formation (124). In addition, conditions of brain acidosis occur on brain ischemia and hypoxia (126), particularly in association with hyperglycemia and diabetes (127). Under acidic conditions, some AD-related enzymes have shown altered activities, such as the asparaginyl endopeptidase, which results more active in the presence of acidosis, consequentially leading to tau hyperphosphorylation, as shown in histopathologically confirmed AD brain tissues and in SH-SY5Y cells in vitro (127). In addition, brain acidosis can cause endothelial cell and cholinergic neuron degeneration, as shown in an organotypic brain slice model made with brain capillary endothelial cells and cholinergic neurons cultured in medium at pH < 6.6 (128).

Importantly, acid-base balance can also influence adrenal hormone production of cortisol. Indeed, a reduction of bicarbonate concentrations can stimulate the kidneys to upregulate glutaminase activity and to produce cortisol (129). In this regard, a protein-rich diet, low in organic potassium salts, was reported to cause a moderate metabolic acidosis associated with an increase in cortisol production and a consequential increased risk of insulin resistance and type 2 diabetes (130). Accordingly, some studies have reported that a transiently induced metabolic acidosis, as a consequence of a high protein meal intake, can enhance serum and salivary cortisol concentrations in a dose-dependent manner (131).

Considering these bidirectional mechanisms and the important role played by cortisol on sleep regulation, it is conceivable that unbalanced/Western-like diets, by inducing metabolic and brain acidosis, might lead to an alteration of the circadian rhythm of cortisol release, which may affect sleep quality. These effects might be implicated in the onset of AD and cognitive impairment (**Figure 1**). However, to our knowledge to date no studies directly assess these associations in large cohorts of elderly, MCI, or AD subjects. In the next section we highlight how specific nutritional interventions or supplements can positively modulate cortisol concentrations and ameliorate sleep quality.

Effects of dietary and nutritional interventions on cortisol regulation, sleep quality, and cognitive functions. Specific dietary and nutritional interventions might reverse metabolic acidosis, possibly restoring cortisol regulation, sleep quality and, consequentially, may preserve cognitive functions or reduce cognitive impairments.

High adherence to a healthy, well-balanced diet characterized by adequate intakes of fruits, vegetables, whole grains, and fish and moderate/low consumption of saturated fat, *trans* fat, dietary cholesterol, refined sugars, and salt, as recommended by the American Heart Association, was reported to reduce urinary cortisol concentrations and to elevate serum DHEAS in women, although reducing urinary norepinephrine values in men, as shown in 1318 Puerto Rican adult subjects living in Boston, MA (132).

Analogously, adherence to a Mediterranean diet, with a high intake of MUFAs, seems to positively modulate the HPA axis and cortisol regulation and induce lower abdominal fat distribution, as reported in a cohort of women from a Mediterranean area (Murcia, Spain) (133). In addition, Mediterranean dietary intervention composed of predominantly plant-based foods (i.e., vegetables, fruits, olive oil, legumes, whole-grain cereals, nuts, and seeds) and fish and a low intake of processed foods, dairy products, red meat, and vegetable oils induced an amelioration of cognitive performances, a reduction of inflammation, and oxidative stress and improved psychological well-being factors (e.g., sleep, stress, anxiety, and depression), as shown in elderly healthy Australians (134).

On the contrary, high-fat diets can have a profound impact on microglia activation and the maintenance of cognitive functions. High-fat diets can induce hippocampal inflammatory cytokine production, loss of synaptic protein expression, impairment of hippocampus-dependent memory, and reduction of long-term potentiation in mice (135). Similarly, diet-induced hypercholesterolemia was found to increase both Aβ and phospho-tau and induce microglial activation in $A\beta_{25–35}$-injected mice, resulting in spatial learning and memory deficits (136). However, because most of these studies were conducted in animal models, it will be important to confirm these results in humans.

Moreover, specific nutrients and supplements were reported to positively affect cortisol regulation and, for this reason, might be suitable to improve sleep quality. For instance, flax seed cultivars, in particular Linola 989, the strain with the highest content of lignan and the lowest content of α-linolenic acid, were reported to reduce responses to stress and plasma cortisol concentrations in 35 postmenopausal women with vascular disease (137). However, the possible effects of flax seed cultivars on sleep regulation and quality were not reported in this study.

Supplementations with the phospholipid phosphatidylserine, together with omega-3 PUFAs 3 times/d for 12 wk were shown to reduce cortisol basal concentrations and to regulate circadian rhythm of salivary cortisol, reducing symptoms in elderly subjects with major depression (138). For this reason, phosphatidylserine alone or in combination with ω-3 PUFAs might positively regulate sleep quality, preserving or increasing brain functions (139). A study reported that bovine cortex-derived phosphatidylserine supplementation for 12 wk induced an improvement of both standard and computerized neuropsychological performance tests in elderly patients with MCI, compared with control subjects who were administered a placebo (140). Similar results were observed with different phosphatidylserine preparations, alternative to the use of bovine cortex-derived phosphatidylserine that might raise concerns of prion transmission. In this regard, a phosphatidylserine preparation that contained ω-3 PUFAs attached to the phosphatidylserine backbone and supplemented for a period of 6 wk (141), or for 7 and 15 wk (142), was proven effective in nondemented elderly subjects with memory complaints. Analogous effects were described with a soybean-derived phosphatidylserine, administered daily for 12 wk to elderly volunteers with memory complaints (143).

In addition, magnesium deficiency is strongly correlated with insomnia, and deficit of magnesium, coupled with excess of calcium, may cause major depression and mental health problems (144). A 2012 clinical trial conducted in 46 elderly subjects showed that daily supplementation of 500 mg Mg compared with placebo for 8 wk significantly increased sleep time, sleep efficiency, the concentration of serum renin, and melatonin and significantly decreased serum cortisol concentration (145).

In addition, potassium is important to guarantee sleep duration, as reported in young men taking oral potassium chloride supplements for 1 wk compared with identical placebo capsules (146). Direct effects of potassium supplementation on cortisol regulation were not reported in this study, although there is evidence that potassium supplementation can elevate serum cortisol (147).

Sleep deprivation can cause a decrease of creatine in the brain, negatively affecting cognitive and psychomotor performance, and mood state. Therefore, creatine supplementations might help reduce these negative effects. In this regard, double-blinded intervention studies assessed the effects elicited by creatine monohydrate (5 g supplemented 4 times/d for 1 wk) compared with placebo and showed that after 24-h sleep deprivation, with mild or moderate exercise, creatine supplementation ameliorated cognitive and psychomotor performance and eventually mood state, although plasma concentrations of catecholamines and cortisol did not differ in the 2 groups (148, 149).

Further Considerations

The risk of dementia and sporadic/late-onset AD is strongly associated with lifestyle factors. In particular, diet, sleep quality, and circadian cortisol regulation, which have been indicated as possible risk factors for AD (13–15, 18–20, 53, 96, 97), are known to be interconnected by regulatory patterns. Another important aspect in this complex network is the recently discovered glymphatic system, which is known to play a role in the clearance of misfolded proteins

from the brain and is known to be functional during sleep (10–12, 63–65).

Perturbations of either one of these variables might have an impact on the others and were found to be associated with hippocampal volume reduction (82, 83, 90) and consequentially cognitive impairment and/or AD (79–81).

Considering the pivotal role played by diet in the initiation or consolidation of cognitive impairment and dementia (17–20), it is conceivable that poorly balanced nutritional patterns, with high intakes of refined sugar, animal products, high-calorie foods, and saturated fats, by negatively influencing the circadian rhythm of cortisol release, might perturb sleep quality, thus contributing to the impairment of amyloid clearance pathways (e.g., the glymphatic system), the accumulation of amyloids, and the reduction of hippocampal volumes (Figure 1). However, it should be considered that to date no studies describe a direct effect of deregulated cortisol concentrations on the glymphatic system.

In addition, considering that there are no clinically approved approaches to evaluate the functionality of the glymphatic pathway in humans, current and future research efforts should aim at assessing, by mean of neuroimaging readouts, the effects of dietary interventions in the regulation of the glymphatic system, Aβ clearance, and brain metabolism in MCI and AD patients.

Another aspect to consider that deserves further extensive dissertation is the role of physical activity in the regulation of circadian cortisol rhythm, sleep, cognition, and the prevention of AD, as recently indicated (91).

In addition, intervention strategies aimed at modulating endogenous neurogenesis through the use of neural stem cell-based therapies (150), lifestyle intervention strategies, or pro-neurogenic factors (151, 152) may help promote the regenerative and recovery process in the aging brain (153).

In conclusion, multidisciplinary approaches that involve strategies aimed at promoting healthy lifestyle and that reduce comorbidity-related neurotoxicity and neurodegeneration could be successful in delaying the onset of cognitive impairment and dementia, as recently shown (154). Similar initiatives are currently encouraged and supported both in Europe (155, 156) and in the United States (157). Further research is clearly needed to define intervention strategies aimed at ameliorating diet and sleep quality and to provide recommendations to implement preventative and therapeutic strategies.

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