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Neuroendocrine-Metabolic Dysfunction and Sleep Disturbances in Neurodegenerative Disorders: Focus on Alzheimer's Disease and Melatonin

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Keywords

Alzheimer's disease · Feeding behavior · Sleep · Glymphatic system · Melatonin · Inflammation · Insulin signaling · Aging

Abstract

Alzheimer's disease (AD) is associated with altered eating behavior and metabolic disruption. Amyloid plaques and neurofilament tangles are observed in many hypothalamic nuclei from AD brains. Some of these areas (suprachiasmatic nuclei, lateral hypothalamic area) also play a role in the regulation of the sleep/wake cycle and may explain the comorbidity of eating and sleep disorders observed in AD patients. Inadequate sleep increases the neurodegenerative process, for example, the decrease of slow-wave sleep impairs clearance of β -amyloid peptide (A β) and tau protein from cerebral interstitial fluid. Cerebrospinal fluid (CSF) melatonin levels decrease even in preclinical stages (Braak-1 stage) when patients manifest no cognitive impairment, suggesting that reduction of melatonin in CSF may be an early marker (the cause for which is still unknown) of oncoming AD. Melatonin administration augments glymphatic clearance of A β and reduces generation and deposition of A β in transgenic animal models of AD. It may also set up a new equilibrium

among hypothalamic feeding signals. While melatonin trials performed in the clinical phase of AD have failed to show or showed only modest positive effects on cognition, in the preclinical stage of dementia (minimal cognitive impairment) the effect of melatonin is demonstrable with significant improvement of sleep and quality of life. In this review, we discuss the main aspects of hypothalamic alterations in AD, the association between interrupted sleep and neurodegeneration, and the possible therapeutic effect of melatonin on these processes.

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Introduction

Neurodegenerative diseases are disorders characterized by progressive deterioration of brain structure and function. Degeneration of selective neuron populations gives rise to prominently cognitive symptoms in Alzheimer's disease (AD) and frontotemporal dementia or to predominantly motor symptoms in Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's dis-

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ease. Aside from the habitual existence of neuron loss and brain inflammation, neurodegenerative disorders are also associated with altered eating behavior (hyporexia/anorexia) and metabolic changes such as weight loss (hypoleptinemia), suggesting the participation of hypothalamic neuroendocrine areas involved in feeding behavior. Approximately 50–60% of AD patients manifest eating disturbances [1] and 14–80% show poor nutritional status [2], weight loss being a clinical feature in 20–45% of AD cases [3].

The main symptoms of AD are memory loss associated with language deficiency, personality disorders, and alterations in sensory-motor association functions [4]. The most common form of AD is late onset AD, a multifactorial, heterogeneous disorder associated with genetic factors and environmental risk factors, whereas familial forms of AD (accounting for less than 2–3% of cases) are related to genetic mutations of the amyloid precursor proteins, presenilin 1 and presenilin 2. From a neuropathological perspective, AD is defined by extracellular accumulation of β -amyloid peptide ($A\beta$) in amyloid plaques and the presence of neurofilament tangles formed by fibrillar aggregates of hyperphosphorylated tau proteins [5, 6]. The amounts of $A\beta$ and tau in brain tissue depend on clearance mechanisms related to slow-wave sleep [7]. In this review, we briefly discuss the main aspects of hypothalamic alterations in AD, the association between interrupted sleep and neurodegeneration, and the possible therapeutic effect of melatonin on these processes.

Main Neuroendocrine-Metabolic Dysfunction in AD

The hypothalamus is a key brain structure involved in 2 major pathways that mediate eating behavior: an appetite-stimulating pathway (orexigenic via), and an appetite-suppressing pathway (anorexigenic via) [8]. Neurons located in the hypothalamic arcuate nucleus (ARC) synthesize the orexigenic peptides neuropeptide Y (NPY) and agouti-gene related peptide (AgRP). Their axons form synapses with second-order neurons located in the lateral hypothalamic area (LHA), these cells containing the main orexigenic peptides orexin and melanin-concentrating hormone. The ARC also contains neurons encoding satiety that produce anorexigenic peptides derived from proopiomelanocortin (POMC), which co-exist with cocaine- and amphetamine-regulated transcript-containing neurons. These anorexigenic neurons project to neurons in the hypothalamic paraventricular nucleus and increase

the synthesis of corticotrophin releasing hormone, another powerful anorexigenic peptide.

Peripheral signals interact at the hypothalamic level via receptor-mediated processes to either stimulate or inhibit the orexigenic/anorexigenic pathway. For instance, enhanced circulating levels of white adipose tissue-derived leptin and pancreatic β cell-derived insulin, as well as some gut-derived peptides (e.g., cholecystokinin, glucagon-like peptide 1, peptide YY) inhibit the hypothalamic orexigenic pathway. Conversely, stomach-derived Ghrelin, the only gut-derived orexigenic hormone, closes a feedback mechanism with hypothalamic orexigenic neurons [8]. This mechanism underlies the complexity of individual eating behavior; indeed, most hypothalamic alterations result in undesirable metabolic consequences (Fig. 1).

Several studies support significant hypothalamic atrophy in AD patients [9]. Amyloid plaques and neurofilament tangles are observed in many hypothalamic nuclei from AD brains including paraventricular nucleus, LHA, and tuberomammillary, supraoptic, and suprachiasmatic nuclei (SCN) [10] (Fig. 1). Some of these areas (SCN, LHA) play a role in the regulation of the sleep-wake cycle and may explain the comorbidity of eating and sleep disorders seen in AD patients. Adrenal, thyroid, and gonadal secretion are also dysfunctional in AD patients, dysfunctions that have been claimed to participate in AD physiopathology [10].

However, in AD patients, a dysfunctional hypothalamus induces energy homeostasis derangements and consequent dysmetabolism [11]. Among the altered metabolic pathways, obesity (body mass index higher than 30), insulin resistance (IR; a defective, downstream insulin receptor, insulin-signaling system), type 2 diabetes (fasting glycemia equal to/higher than 7 mM and/or impaired glucose tolerance) and virus infection [12] enhance the risk of AD development [13]. Weight loss in AD patients appears to be associated with both amyloid burden and disease progression [3]. Importantly, weight loss precedes, by approximately 10 years, onset of AD symptomatology [14]. The consensus is that hypothalamic plaques and tangles are present at the early-moderate stage in AD and that weight loss often occurs prior to cognitive derangements. Furthermore, a body mass index decline in older age could indicate a high risk of AD development and a higher rate of AD progression [3].

Although dysmetabolism seems to be related to hypothalamic dysfunction, the signaling pathways involved are not fully understood. A number of factors other than tau and $A\beta$ hypothalamic accumulation could contribute

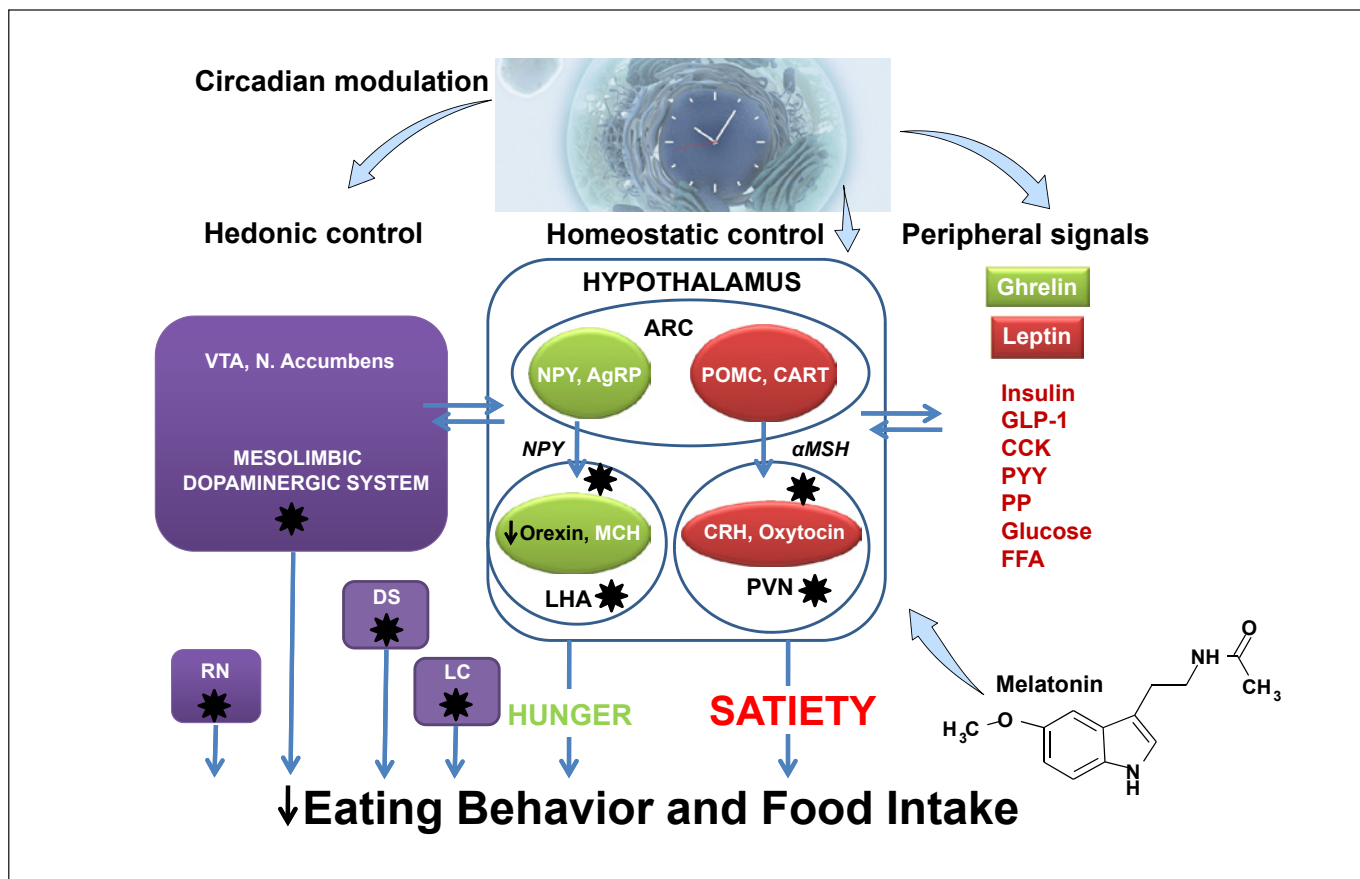


Fig. 1. Possible factors implicated in eating behavior and food intake in AD. Eating behavior is regulated by hedonic, homeostatic and peripheral signals. This scheme represents the main mechanisms, which are disturbed in AD (stars) and may affect eating behavior. The possible role of melatonin on feeding behavior is discussed in the text. VTA, ventral-tegmental area; ARC, arcuate nucleus; DS, dorsal striatum; RN, raphe nuclei; LC, locus coeruleus; PVN, paraventricular nucleus; LHA, lateral hypothalamic area; AgRP, agouti-gene related peptide; NPY, neuropeptide Y; MCH, melanin-concentration hormone; POMC, proopiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; PP, pancreatic polypeptide; PYY, peptide YY; FFA, free fatty acids.

to dysmetabolism in AD patients. Studies support the involvement of leptin-signaling in energy homeostasis changes in AD [10], for example, A β peptide alters ARC NPY neuron response to leptin [15]. Indeed, although not altered, ARC leptin-receptor (leptin-R) gene expression was noticed in transgenic AD mice, the hypoleptinemia characterizing individuals coexists with decreased ARC POMC and cocaine- and amphetamine-regulated transcript mRNA levels, thus indicating a normal function of the anorexigenic pathway; conversely, ARC NPY and AgRP gene expressions are similar in wild-type and AD mice, thus indicating that dysfunctional ARC is limited to NPY-AgRP neurons [15]. This fact was similarly noticed after fasting AD mice and strongly supported by electrophysiological studies [15].

Specifically, ARC lesion favors AD-like lesion development in different experimental models of AD [16, 17]. Weight loss in AD patients could also result from defective sensory (e.g., taste/olfaction) integration or processing [18].

Compelling evidence supports an interrelationship between modified glucose homeostasis and AD pathophysiology, obesity, IR, and diabetes being strong risk factors for AD [13, 19]. Obesity and IR development worsen amyloidogenesis or tau pathology in AD transgenic models [20–22] (Fig. 2). Several studies indicate that brain IR can be enough to promote tau pathology and amyloidogenesis [23]. Interestingly, increased risk of developing diabetes has been reported in AD patients [24], thus supporting the interrelationship between brain lesions and

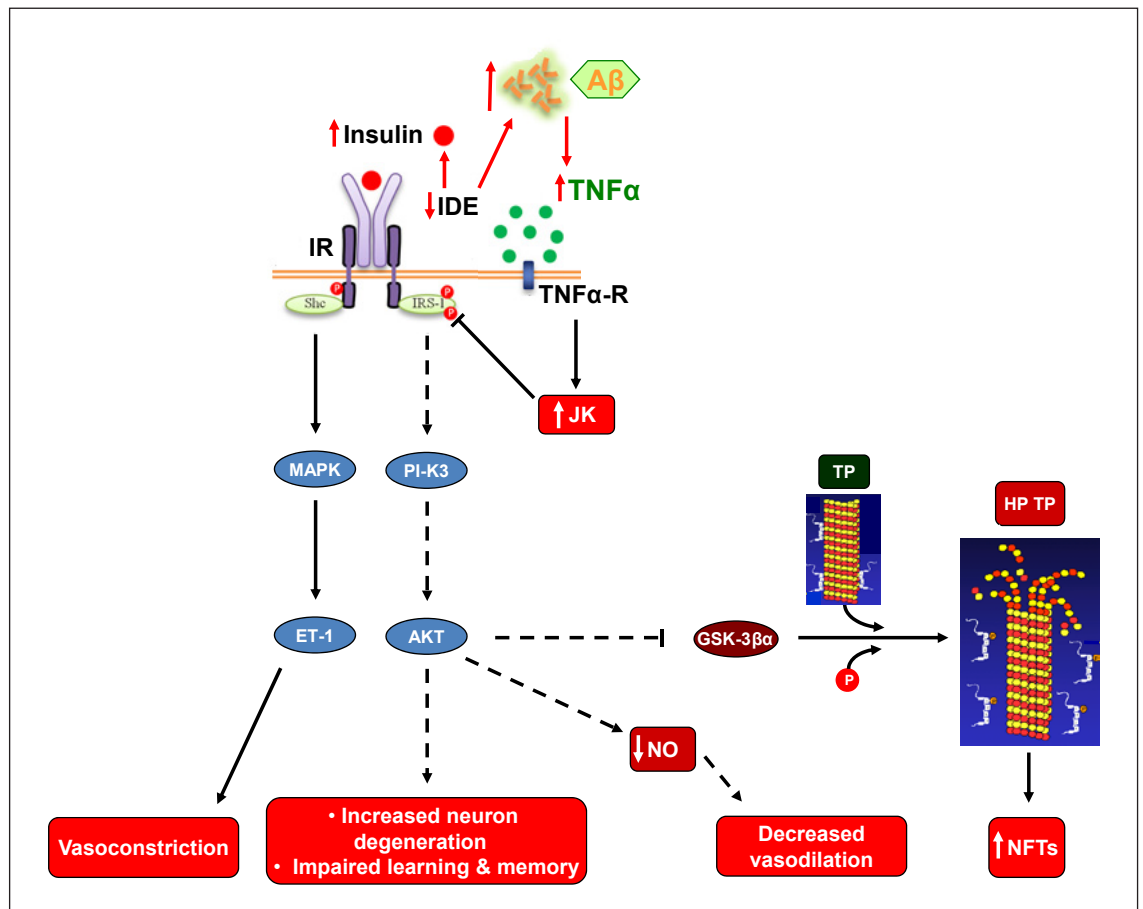


Fig. 2. Disrupted brain insulin-signaling in AD. Amyloid- β ($A\beta$) accumulation enhances tumor necrosis factor- α ($TNF\alpha$) levels and activates c-Jun N-terminal kinase (JNK). As a consequence, serine phosphorylation of insulin substrate receptor-1 (IRS-1) is inhibited. Insulin resistance decreases insulin degrading enzyme (IDE) expression, thus diminishing IDE-induced $A\beta$ degradation. Moreover, reduced brain insulin signaling decreases the inhibition of glycogen synthase kinase-3 β (GSK-3 β) activity on tau protein

(TP) phosphorylation resulting in hyperphosphorylated TP (PP-TP) production and microtubule depolymerization (MTDP), resulting in augmented neurofibrillary tangles (NFTs) deposition. Therefore, impaired insulin signaling results in neuron degeneration and modifies learning and memory. Additionally, IRS-1 deficiency reduces nitric oxide (NO) production and augmented endothelin-1 production, thus decreasing brain blood flow and increasing neuroinflammation.

metabolic disturbances in AD. The AD brain has been claimed as IR, a state correlating with the individual's cognitive score [25]. This observation is in line with the known ability of insulin signaling to promote plasticity and memory that may be relevant for changes in the cerebral cortex or the improved memory observed in humans treated with intranasal insulin [26].

The potential involvement of brain IR in impaired glucose homeostasis development in AD patients is also supported by the known role of insulin signaling in energy metabolism regulation [27]. The origin of IR in the AD brain seems to be related to both $A\beta$ and tau pathologies [28]. The intracerebroventricular infusion of $A\beta$ oligo-

mers in mice triggers a pre-diabetic state (impaired glucose tolerance) by a hypothalamic-based mechanism [28], and loss of function of tau impairs insulin responsiveness and is associated with altered glucose homeostasis [29]. This is in line with increased brain insulin receptor substrate-1 (IRS-1) inhibition in patients with pure tauopathies [30]. Although the underlying mechanisms remain unclear, $A\beta$ oligomers have been shown to promote insulin receptor internalization [31] as well as activation of c-Jun N-terminal kinase, Protein kinase R, and tumor necrosis factor- α ($TNF-\alpha$) pathways, in turn resulting in IRS-1 function inhibition [28, 32]. These statements are also supported by studies indicating that peripheral glu-

cose dysmetabolism appeared hours (12 h) later than the rapid increase (4 h) in hypothalamic inflammation markers observed after icv administration of A β oligomers in mice [28], thus indicating that glucose dysmetabolism is a consequence of the central effects induced by icv administration of A β oligomers in mice [28]. Moreover, it has also been demonstrated that A β oligomers-induced hypothalamic inflammation in mice, characterized by enhanced brain oxidative stress and TNF- α can be overridden by both antioxidant treatment [28] and when functional TNF- α receptor is absent [33]. Moreover, recent data suggest that apolipoprotein E4 overproduction contributes to intra-endosomal trapping of insulin receptor during late-onset, diabetes-associated AD [34]. Collectively, the data emphasize that glucose homeostasis impairments found in AD patients likely result from hypothalamic damage responsible for abnormal insulin signaling (Fig. 2).

Sleep Disturbances in AD

AD neurodegeneration extends beyond cognitive function to involve key physiological processes, including eating and sleep. The processes involved could serve as biomarkers to aid in the early diagnosis of disease [35]. In the elderly, sleep efficiency decreases to approximately 80% with an increase in sleep onset latency and in percentage of time elapsed in stages N1 and N2 (light slow sleep) and of waking after sleep onset. Other age-related declines are reductions in deep slow-wave sleep (stage N3) and in rapid eye movement (REM) sleep. The electroencephalographic spectral power analysis of polysomnographic data have confirmed that the elderly have reductions in non-REM and REM sleep and a marked decrease in delta activity [36].

The incidence of sleep disorders in patients with AD is close to 70%, and they very often arise before the onset of cognitive deterioration [37]. In relation to non-demented individuals of the same age [38], the sleep architecture of patients with AD indicates a quantitative reduction of both slow-wave sleep and REM and a significant degree of sleep fragmentation that decreases daytime alertness and increases napping. Approximately half of the patients with AD show exacerbation of neuropsychiatric symptoms in the late afternoon/early evening, with agitation, restlessness, and confusion (“sundowning”) [37, 39]. Both sleep disorders and “sundowning” are among the main reasons for institutionalization of these patients [37].

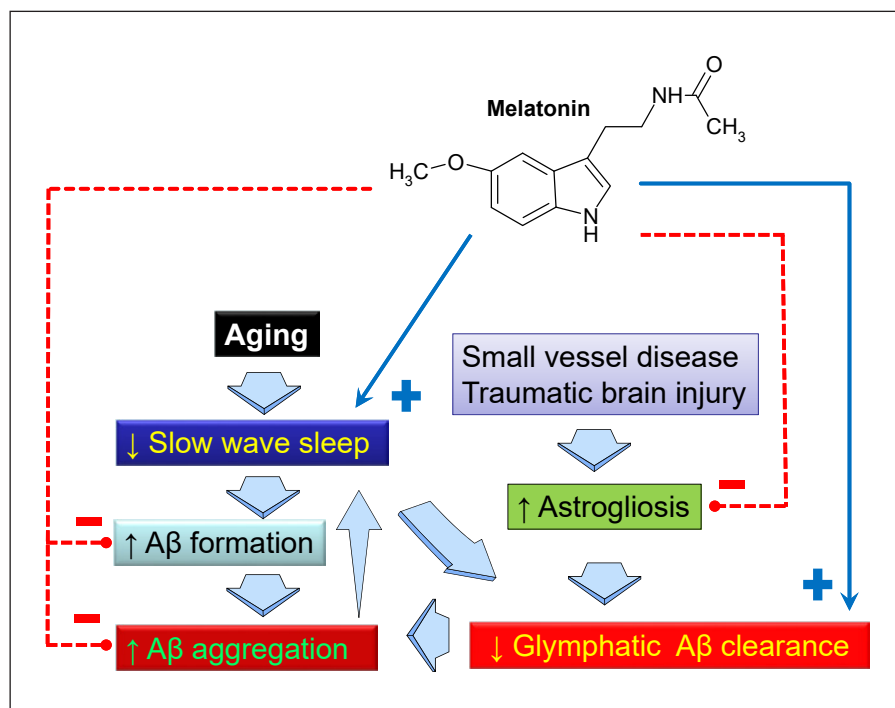
The relation between sleep and neurodegenerative diseases is bidirectional [40]. Neurodegeneration is accompanied by sleep difficulties due to reduction of amplitude and phase changes of circadian rhythms such as that of melatonin secretion, as well as the disturbing influences of neurodegenerative processes on sleep. Conversely, inadequate sleep, in terms of both duration and quality, increases the neurodegenerative process and aggravates the underlying clinical picture [40].

Several studies have shown that sleep disruption is a major contributor to neuropathology. Sleep deprivation for one night [41] or interruption of non-REM sleep [42] in healthy subjects has been shown to increase levels of A β_{1-42} and A β_{1-40} in cerebrospinal fluid (CSF). In mice, sleep deprivation caused increases in A β peptides in brain interstitial fluid [43], and a direct relationship was established between A β and wakefulness. Injections of orexin, the major neuropeptide related to wakefulness, led to increases in A β , whereas the orexin antagonist almorexant decreased A β levels [43]. A significant relationship between sleep disruption and tau pathology may also occur, as shown by the impaired memory, tau metabolism, and synaptic integrity found in a sleep-deprived mouse model of AD [44].

The feasible link between sleep disruption and impaired A β and tau clearance is a dysfunctional glymphatic system (Fig. 3). The glymphatic hypothesis [45, 46] holds that the movements of solutes in brain extracellular space (ECS) occur by exchange of water driven by perivascular astrocytes through aquaporin-4 (AQP4) channels and by changes in vascular lumen. AQP4 is expressed predominantly in the feet of astrocytes and the passage of water through AQP4 is responsible for an exchange of fluids actively driven between para-arterial and paravenous spaces via a convective flow of interstitial fluid. It has been assumed that arteriolar pulsations, as well as venular collapse dependent on respiration contribute to this convective flow [47]. Exchange of solutes between CSF and interstitial fluid occurs mainly during slow-wave sleep when the cortical interstitial space increases by over 60%, providing a low resistance route for the movement of CSF and interstitial fluid in the brain parenchyma [45, 46].

The concept of A β clearance by the glymphatic system received support from the observation that elimination of radiolabeled A β peptide injected is strongly reduced in knockout mice for AQP4 channels [45]. In fact, the location of AQP4 in the feet of perivascular astrocytes is known to be highly altered in AD [48], and from this point of view, AD development and progression may be

Fig. 3. Sleep disruption, particularly of slow-wave sleep, and altered feeding behavior, are frequent features in AD. Reduced slow-wave activity impairs glymphatic amyloid- β ($A\beta$) clearance, which is greatest in the sleeping brain. Metabolic demand increases with loss of slow-wave sleep, augmenting $A\beta$ formation. Astrogliosis associated with aging, small vessel disease, traumatic brain injury, or amyloid plaques is associated with impaired glymphatic pathway function, possibly via impairment of perivascular aquaporin-4 localization. The presence of $A\beta$ aggregates specifically inhibits slow-wave activity. Melatonin counteracts most of the dysfunctions observed and may improve feeding behavior signaling at the hypothalamic level.



due to failure of $A\beta$ clearance, which is aggravated by sleep disturbance [49]. Another aspect related to AD refers to the clearance of apolipoprotein E from the ECS, since sleep deprivation was found to suppress this process [50] as well as elimination of tau protein from ECS [51]. Although the glymphatic hypothesis remains a matter of controversy [52], the role of normal sleep for correct cerebral clearance of toxic products can be considered well established (Fig. 3).

Melatonin in AD

Severe disruption of the circadian system occurs in AD, indicated by alterations in numerous body rhythms, such as body temperature, plasma glucocorticoids and plasma melatonin. An emerging symptom of this circadian disruption is “sundowning,” a chronobiological phenomenon observed in patients with AD along with sleep and wakefulness disorder. Chronotherapeutic interventions such as exposure to bright light and timed melatonin administration in selected circadian phases alleviated “sundowning” and improved sleep-wake patterns in patients with AD [53, 54].

The pineal methoxyindole melatonin is a synchronizer of the SCN clockwork [55]. In mammals, melatonin is

synthesized in the pineal gland in a rhythmic manner, with high levels during nighttime and low levels during daytime. Melatonin phase-shifts circadian rhythms in the SCN by acting on MT_1 and MT_2 melatonin receptors expressed in SCN neurons, thus creating a reciprocal interaction between the SCN and the pineal gland. The circadian rhythm in the secretion of melatonin has been shown to be responsible for the sleep/wake rhythm in both normal and blind subjects (i.e., in the absence of the synchronizing effect of light) [56].

Melatonin exhibits an amazing phylogenetic conservation from unicellular organisms to higher vertebrates that strongly suggests a cytoprotective function. Experimental treatment with melatonin has been demonstrated to be neuroprotective in aging and AD animal models, as its administration decreased the accumulation of $A\beta$ and hyperphosphorylated tau, improved neuroplasticity and neuron survival, prevented learning and memory impairment, and ameliorated anxiety and depression-like behavior (see [57, 58]).

Early work of Pappolla et al. indicated that melatonin efficiently reduces the generation and deposition of $A\beta$ [59–62] (Fig. 3). Melatonin administration also increases $A\beta$ glymphatic clearance [63]. Since melatonin inhibits only the first stages of $A\beta$ aggregation (nucleation phase) but does not revert oligomers or fibrils once they are

formed, its therapeutic application in AD prevention should be considered [64]. Concerning tau, melatonin was effective to inhibit A β -induced tau protein hyperphosphorylation via PI3K/Akt/GSK3 β signaling in murine hippocampus [65].

The imbalance between inflammatory and anti-inflammatory signals is a hallmark of the neurodegenerative process that contributes to AD progression. The term “inflammaging” was introduced to underscore the importance of inflammation in senescence and its role in the development of age-related diseases [66]. Reversal of inflammation by melatonin occurs at different levels. Melatonin is effective in suppressing IR, a hallmark of the metabolic syndrome, by reversing the blockade of a key step in transduction of insulin signals, that is, reduced phosphorylation of IRS-1 [67]. Another important aspect of anti-inflammatory activity of melatonin is its role as an immunological buffer, comprising both proinflammatory and anti-inflammatory effects. In several conditions such as senescence and cancer, the anti-inflammatory aspects of melatonin prevail [68].

As for appetite regulation, the possible involvement of melatonin has been studied for years. Melatonin regulates food intake in rats [69], mice [70], hamsters [71], pigs [72], and several submammalian species such as goldfish [73], rainbow trout [74], and zebrafish [75]. In rat, conflicting responses include reduction, increase, or no effect on food consumption [76, 77]. A decrease in fat mass and body weight has been reported in rats [77–79], whereas melatonin increases fat mass in gray mouse lemurs [80], Syrian hamster [71], raccoon dog [81], and garden dormouse [82].

In a study evaluating gene expression of NPY, leptin-R, POMC, prolactin-releasing peptide (PrRP), insulin receptor, IRS-1, and IRS-2 in the medial basal hypothalamus of obese rats, we reported that treatment for 10 weeks with 2.3 mg/kg melatonin, suppressed augmented medial basal hypothalamus mRNA levels of NPY, leptin-R, PrRP, insulin-R, IRS-1, and IRS-2 [83]. These results suggested that melatonin administration might be able to set up a new equilibrium among hypothalamic feeding signals (Fig. 1, 3). Remarkably, melatonin reduced gene expression of both the strong orexinergic signal NPY and the anorexigenic signal PrRP, as well as that of receptors for anorexigenic signals such as leptin and insulin, and of insulin intracellular signaling (IRS-1, IRS-2) [83]. Whether this effect is relevant for clinically demonstrated activity of melatonin in AD patients deserves further exploration.

Melatonin trials performed in the clinical phase of AD have failed to show [84] or show only modest positive ef-

fects on cognition [85, 86]. Based on preclinical data, melatonin is more likely to prevent the aggregation of A β rather than to reverse neuropathology in the clinically manifest phases of the disease. Normal aging is characterized by a decline in cognitive abilities which includes reasoning, memory, and semantic fluency, already detectable in the 5th decade of life. There is evidence of a preclinical stage in dementia in which cognitive performance is limited compared to normal aging (minimal cognitive impairment [MCI]) [87]. In community-based studies, close to 30% of a sample of older people living in the community showed performance deficits not explained by changes related to age, education level, mood, or health condition [88]. This finding strongly suggests the existence of early pathological changes: a state of transition that occurs between normal aging and early AD. Analysis of published data on melatonin administration in the early stages of cognitive decline consistently showed that melatonin, taken every night before retiring, improves quality of sleep and cognitive performance in this phase of the disease (see [89]). In MCI patients, the effect of melatonin is demonstrable, with significant improvement of sleep and quality of life and reduction of cognitive impairment [90].

CSF melatonin levels decrease even in preclinical stages of AD when patients manifest no cognitive impairment, suggesting that reduction in CSF melatonin may be an early trigger and marker for AD [91, 92]. Although it is not known whether the relative melatonin deficiency is a consequence or a cause of neurodegeneration, it seems clear that loss of melatonin aggravates the disease and that early circadian disruption may be an important deficit to be considered. A recent study observed significant differences in melatonin levels between MCI and AD patients, with a negative correlation between neuropsychological assessment of dementia and melatonin levels [93]. Two meta-analyses endorsed the view that melatonin therapy is effective in improving sleep in patients with dementia [94, 95]. Moreover, the melatoninergic agonist ramelteon was reported to be effective to treat delirium, an acute state of mental confusion that may lead to many adverse sequelae in intensive care unit elderly patients [96].

Conclusions and Remarks

Evidence discussed here supports a significant hypothalamic alteration in AD patients resulting in energy homeostasis disorders and dysmetabolism, weight loss being as-

sociated with disease progression. In fact, obesity, IR, and type 2 diabetes are important risk factors for AD development. In addition, the incidence of sleep disorders in patients with AD is close to 70%, about 50 % of patients with AD showing exacerbation of neuropsychiatric symptoms in the late afternoon- early evening (“sundowning”). This disruption of the sleep-wake cycle affects normal cerebral perivascular and non-perivascular removal of toxic waste by affecting directional and nondirectional CSF flow.

Melatonin combines 2 properties for application in human medicine: chronobiotic and cytoprotection. Many published studies support a significant chronobiologic regulatory effect of melatonin on sleep. In a meta-analysis including 19 studies involving 1683 subjects, melatonin showed significant efficacy in reducing sleep latency and also increased total sleep time [97]. Trials of longer duration and the use of higher doses of melatonin demonstrated greater effects. Several consensus statements also support this role of melatonin. For example, the British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders concluded that “melatonin should be the choice hypnotic for insomniacs over 55 years of age” [98]. In 2007, a sustained release form of 2-mg melatonin (Circadin[®], Neurim, Tel-Aviv) was approved by the European Medicines Agency (EMA) for treatment of insomnia in elderly people. The fact that melatonin does not show evidence of dependency, isolation, rebound insomnia, or negative influence on alertness during the day was emphasized by the EMA and also the US Food and Drug Administration, for the melatonin analogs ramelteon (Rozerem[®], Takeda) and tasimelteon (Hetlioz[®], Vanda).

Concerning cytoprotection, almost every cell in the human body contains melatonin in quantities much higher than those circulating in blood derived from the pineal gland. To modify intracellular melatonin levels doses much higher than those utilized as a chronobiotic are required (i.e., in the 40–100 mg/day range) [99]. In view of studies in animal models of AD, it has become ap-

parent that several potentially useful effects of melatonin such as prevention of A β formation of tau phosphorylation require doses of melatonin in the order of >100 mg/day as the equivalent human dose. If we expect melatonin to be effective in improving health, especially in elderly people, it is likely that the low doses of melatonin commonly administered up to the present (under 10 mg/day) are not beneficial. Published reports indicate that melatonin is a safe drug with low toxicity (for references see [67]). In 2 dose-escalation studies of melatonin in healthy volunteers, tolerability and pharmacokinetics of up to 100 mg oral doses of melatonin were assessed with no adverse effects detected [100, 101]. However, the safety of melatonin in long-term treatment remains to be settled.

Melatonin enrichment of food could offer a strategy to reach amounts providing effective cytoprotection in AD. Therefore, one area of interest is the development of functional foods containing high levels of melatonin. Melatonin is widely used as a food supplement, dietetic product, and drug in many countries worldwide. The European Food Safety Authority has admitted the health claim that melatonin reduces sleep onset latency [102]. Melatonin-rich food and bioextracts can therefore now be developed to serve as nutritional supplements, dietetic products, and drugs.

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Disclosure Statement

The authors declare they have no conflicts of interest to disclose.

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