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Age-related Sleep Changes and its Implication in Neurodegenerative Diseases

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Abstract: In the article authors discuss the current data on sleep changes with aging focusing on the influence of age-related degenerative changes in orexin-containing and pacemaker brain areas. Pathophysiological mechanisms of sleep disturbances in Parkinson's and Alzheimer's diseases have much in common with normal age neurophysiological changes. Maintenance of the sleep-promoting systems function could positively modify the course of these diseases.

Keywords: Age, Alzheimer's disease, Parkinson's disease, sleep, orexins, sleep disorders.

BACKGROUND

Sleep disorders are commonly underdiagnosed and appear to be a significant source of concern in the geriatric population [1]. Changes in sleep patterns could be considered as a part of normal aging process; however, some of these changes are related to pathology [2, 3]. In addition to negative effect on the quality of life, sleep disorders are associated with increased mortality [2]. The number of medications used for sleep disturbances tends to increase with age, that itself can cause such side effects as falls, cognitive impairment, and sleep disturbances [4, 5].

Difficulties in initiating and maintaining sleep persist in 43% of older population, and are even more widespread among those suffering from psychiatric or somatic disabilities [6, 7]. However, worsening of sleep efficiency and quality has been observed even in healthy people of older ages [8]. Although the ability to initiate and maintain sleep deteriorates, the total amount of sleep needed does not decrease with age [7].

AGING AND SLEEP

Like many other physiological processes, sleep organization passes over several age-related changes through the lifespan. Even healthy aging is characterized by decline of sleep quality that is demonstrated by progressive decrease of sleep efficiency throughout the life span [9, 10]. The rate of this decrease after the age of 60 years consists 3% per decade [11]. The meta-analysis of studies with objective measurements of sleep across the human life span has demonstrated that most of the changes seen in adult sleep patterns except sleep efficiency have occurred between ages from 19 to 60 years, and there were only minimal sleep changes from 60 years and older [10]. A variety of studies have demonstrated four consistently reported age-related changes in polysomnographic sleep macroarchitecture: the decrease of total sleep time, sleep efficiency, slow wave sleep; and increase of wake after sleep onset. Less consistently reported age-related sleep changes were an increase of stage 1 and stage 2 ratio, and decrease of REM sleep ratio. Age-related changes in either sleep latency or REM sleep latency were minimal [9, 10, 12].

The total sleep period, which is defined as the period from sleep onset to the final morning awakening, remains relatively stable across adulthood. However, the total sleep time, *i.e.* the sleep period minus total duration of all night awakenings decreases after age 50 years, reflecting sleep fragmentation on average 27 minutes per each decade [12].

Sleep architecture demonstrates variable changes of different parameters. For the period from early adulthood (16-25 years) to midlife (30-50years) slow wave sleep (SWS) decreases remarkably from 18.9% to 3.4%. This tendency is compensated by an increase of light non-REM sleep (stages I and II) rate from 51.2% to 67.3%. Whereas there are neither significant changes of rapid eye movement (REM) sleep ratio, nor the time spent awake for the period specified [12].

From midlife to older age (over 70 years), no additional decline of the SWS ratio occurs, but percentage of light non-REM sleep and REM sleep ratios progressively decreases (from 60.5% to 50.6% for REM sleep). The decrease of REM sleep duration is associated with the redistribution of REM stages across the sleep period, with a shift of REM stages toward the early part of the night [12].

Older adults have higher wake after sleep onset (WASO) which increases from midlife on average 28 minutes per decade. Actually it is increasing of WASO what mostly determines sleep loss in elderly. Notably, elderly tend to awaken

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less frequently from REM sleep and more often from non-REM sleep than the young [12-14]

Two other commonly held assumptions about the relation of sleep and aging are that older adults usually nap more than younger and report heavier excessive daytime sleepiness (EDS). Although numerous community-based epidemiologic studies have reported prevalence of EDS, among older adults to be as high as 20% to 30%, only few of them have reported of regular napping and its association with sleep complaints [15]. The recent findings indicate that the presence of physical and mental comorbidities is highly associated with the likelihood of the older adult to report regular napping or EDS, while older adults without comorbidities, even those complaining on significant nighttime sleep disturbance, are much less likely to report regular napping or EDS [11].

A variety of endocrine (reduced growth hormone, changes of cortisol secretion circadian profile), neurometabolic (*e.g*. reduced orexin, melatonin and dopamine levels) and circadian regulation changes also accompany healthy aging. It is expected that the above mentioned alterations could be associated with age-related sleep changes.

There are many factors over and above age-related sleep changes that can contribute to the development of significant sleep disturbances. Most frequent are cardiovascular diseases, arthritis, gastroesophageal reflux disease; neurological and psychiatric comorbidities and side effects of drugs used for its treatment; primary sleep disorders, many of which, like sleep apnea, restless legs syndrome, and rapid eye movement sleep behavior disorder (RBD), tend to occur with increasing frequency in older ages [16].

CHANGES IN CIRCADIAN REGULATION

The circadian rhythms driven by suprachiasmatic nuclei (SCN) provide synchronization of homeostatic processes with environmental changes. It was shown that the chronobiological properties of almost all physiological processes in our body change with age. For instance, the evening decrease of core body temperature and the onset of sleep tend to occur almost 2 hours earlier in older subjects (60-80 years) comparing with younger (20-30 years) [17].

It was suggested that shortening of intrinsic circadian period might result in the advance of the sleep phase and contribute to sleep changes in elderly people [13]. The effect of age on the intrinsic circadian period length seems to be depending on specific (behavior, social, environmental) and genetic backgrounds. The best controlled study performed in humans have not found a significant difference of intrinsic period of the circadian rhythms with average values of 24.18 hours between younger and older subjects [18]. Recent evidences support the old idea of adaptive resonance when intrinsic period is synchronized with the environmental cycle [19]. It is SCN that functions as a reliable chronometer for the organism, so it has to be synchronized to the environmental periodicity [20].

The gradual increase of subjects with early chronotypes with age was found in the epidemiological study in population sample between 20 and 80 years of age. This finding may also be the indicator for phase advanced circadian rhythms in the elderly [21].

The strongest time cue (Zeitgeber) is the daily change of light and darkness. Information about the light intensity is processed and transferred to the SCN by retinal ganglion cells with glutamate and pituitary adenylate cyclase-activating peptide as neurotransmitters [22]. The retinorecipient SCN neurons are activated by light-induced membrane depolarization potential and then increase the frequency of action potential. This activation is followed by an increase of intracellular calcium concentration that influences the expression of genes involved in the rhythm generation [23]. The phase-shifting capacity of light is restricted in the night time providing the correction of the internal clock phase shifting from the circadian cycle.

The ability to synchronize and reset phase is hampered in aged population as it was shown for behavioral, electrical, and molecular rhythms of the SCN [24]. Aging can influence the resetting capacity of the internal clock at many levels from the loss of light perception due to various eye diseases to the breakage of molecular cascades in SCN neurons [20]. *In vitro* studies have revealed that the electrophysiological activity of aged SCN neurons is altered [25]. Recordings from the SCN of mice also show that the amplitude of day-night difference in SCN activity is significantly reduced in older mice [26]. The decline in circadian rhythms amplitude can be explained by decrease of the internal clock output signal and age-induced alterations in neuronal network function, membrane properties and molecular components of circadian pacemaker cells in the SCN.

The age-related changes of the circadian system are followed by reduction of the circadian amplitude of the overall circadian rhythms including sleep–wake cycle and decrease in the amplitude of the EEG slow-waves, K-complexes and sleep spindles. This results in behavioral and physiological fragmentation expressed in nighttime awakenings and daytime naps, lower sleep quality. This decay of circadian control represents the risk factor for developing or aggravating of age-associated neurodegenerative diseases [20] as will be discussed below.

Melatonin is a neurohormone produced in the pineal gland and acting as circadian rhythms modulator. In addition to other biological functions it has antioxidant and free radical scavenger properties [27]. The 24-hour profile of plasma melatonin concentration is primarily controlled by the SCN and follows light-dark and seasonal rhythms. Under normal conditions, low and stable daytime levels are followed by a major circadian rise starting in the evening, between 9 and 11 PM. Secretion of melatonin reach the peak around the middle of the sleep period. Further, melatonin levels progressively return to low daytime values between 8 and 9 AM. The daily pattern of melatonin plasma level is shown on the Fig. (**1**).

The levels of melatonin secretion in human change during the lifespan. In the fetal period, fetus uses maternal melatonin which crosses the placenta. Melatonin secretion increases from birth reaching the peak around puberty, and then progressively declines in middle-aged and elderly individuals [29] reaching the lowest values after the age of 55. The daytime melatonin levels are similar in older and younger subjects. However nocturnal elevation of melatonin

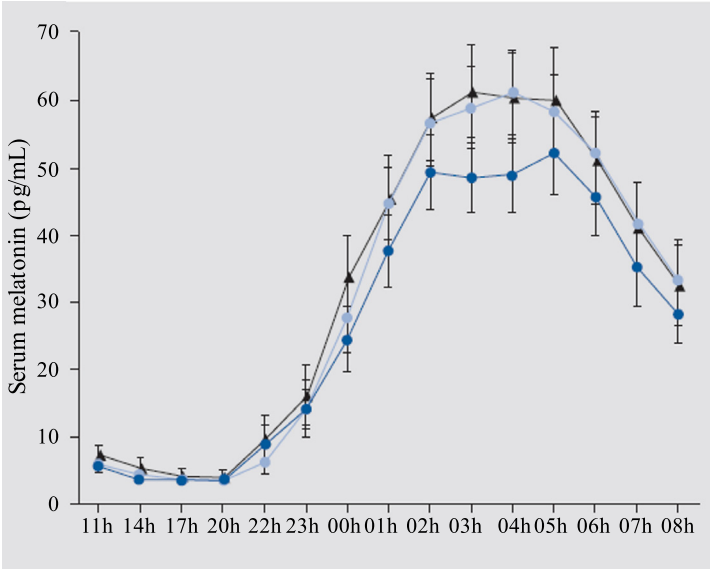

Fig. (1). Reproducibility of the circadian patterns of melatonin in young healthy men. Reproduced with permission from [28]. Three different 24-h cycles of melatonin secretion are presented.

concentration is compromised in the elderly (64-81 years) [30] and subsequently the functional effects of melatonin are gradually impaired [31, 32]. Meanwhile the timing of sleep and the peak phase of the circadian melatonin rhythm were reported to occur earlier in older subjects (60-75 years) that supports the idea of shortening of intrinsic circadian period [33].

The mechanism of melatonin levels declining with age has not yet been fully explained. Age-related decline of rhythmic melatonin production is also attributed to degenerative changes of the neural structures controlling the pineal gland (*e.g*. hypothalamus), rather than to the degeneration of pineal tissue per se [34]. There are some hypotheses explaining this declining mechanism: decrease of beta-adrenergic receptors in the pinealocytes [35], decreased activity of aralkylamine N-acetyltransferase, the key enzyme responsible for melatonin synthesis [36], effect of extremely low frequency of magnetic field [37] and increased clearance of plasma melatonin [38].

Difficulties in solving this problem are caused by differences between pineal gland structure and localization in human and rodents and discrepancy between melatonin levels and presence of sleep disturbances in humans. Some authors reject the age-related melatonin declining [39]. In contrast the recent review of Belancio *et al*. (2015) proves that melatonin levels actually decline in elderly. The authors suggest that light at night (*e.g*. in shift workers) affects significantly the integrity of the cellular genome and metabolic function that is strongly associated with suppression of circadian melatonin production. This suggestion is based on the idea that loss of synchronized oscillation of biological processes along the life span is accompanied by a continuous decline in their amplitude [40]. That idea is proved by the other independent study of subjects of 65-80 years, where such behavior factor as midday exposure to environmental light has shown positive relation to the nocturnal melatonin secretion [38].

The age-related decline of melatonin secretion has been suggested to be the one of the major reasons for increase of sleep disruption in older people. In the study on the relationship between timing of plasma melatonin rhythm and timing of the habitual sleep/wake episode in a group of healthy young and older subjects, J. Duffy *et al*. (2002) observed that the older subjects (60-80 years) were falling asleep and waking earlier relative to their nocturnal melatonin peak secretion and further reduction as compared to younger subjects (20-30 years) [41]. This finding indicates that aging is associated not only with an advance of sleep timing and the timing of circadian rhythms but also with the change of the internal synchronization of the sleep-wake cycle and the output of the circadian pacemaker. In healthy older subjects, the relative timing of the melatonin rhythm with respect to sleep may not play a causal role in sleep disruption.

Meanwhile Singer *et al*. (2003) by the data of the large multicenter placebo-controlled study criticize the possibility of clinical application of melatonin for sleep disturbances. This study based on actigraphy has revealed not any significant positive trend in patients with nighttime symptoms of Alzheimer's disease after the treatment with melatonin [42].

METABOLIC CHANGES

Normal aging is accompanied by changes in many hypothalamic functions including circadian rhythms, the autonomic and endocrine tone [43].

Secretion of corticosteroid cortisol is synchronized with the sleep-wake homeostasis. Sleep onset is consistently followed by the simultaneous decrease of the level of cortisol [44]. Final morning awakening and transient awakenings during the sleep period increase the cortisol secretion. It was proved in the study of cortisol profiles recorded during nocturnal sleep: all transient awakenings that interrupted sleep for at least 10 minutes were followed by significant cortisol pulses within the next 20 minutes [45]. Chronic insomnia with a reduction of total sleep time is strongly associated

with an elevation of evening and nocturnal cortisol levels [46]. However, none of these studies have determined whether a hyperactivity of the corticotropic axis resulted from the brain activity, or *vice versa*.

In healthy subjects the circadian rhythm of cortisol secretion persists throughout the aging process, and is still present in very old individuals. However, after the age of 50 years, aging is associated with significant alterations of cortisol profile: evening cortisol levels increase progressively and late evening levels are markedly higher in healthy subjects older than 70 years than in young adults [47]. In the elderly, the quiescent period of hormone secretion starts later and ends earlier; it is more fragmented, and markedly shortened. Alterations are more pronounced in women than in men: between 25 and 65 years of age, the reduction of the quiescent period duration in men is less than 3 hours but averages approximately 4,5 hours in women [47]. Interestingly the age-related increase of evening cortisol concentrations and the age-related decline of REM sleep occur in a mirror manner. Thus, age-related alterations of sleep quality could contribute or result from the alterations of the corticotropic axis observed in the elderly.

Other aspects related to hypothalamic activity during aging are the changes of energy homeostasis and metabolism mainly characterized by increased body mass and glucose intolerance. Well-controlled laboratory studies indicate that both short (for 1 to 7 days) and prolonged (at least 6 months) partial sleep restriction results in increased insulin resistance [48, 49]. These observations are consistent with data obtained in multiple epidemiologic studies, revealing the association between short sleep duration and the risk of diabetes mellitus [50]. Aging is associated with the impairment of glucose tolerance, reflecting the decline of insulin secretion and insulin receptors sensitivity. The similarity between these effects of aging and sleep restriction suggests that the age-related sleep disorders can accelerate deterioration of glucose metabolism progressing with age [51].

ROLE OF OREXIN

Orexins A and B /hypocretins-1 and -2 are the neuropeptides, regulating various functions, such as arousal, whole-body energy metabolism, reward seeking, and autonomic functions such as ventilation, blood pressure, heart rate. Although orexin-producing neurons are concentrated in small area in lateral–posterior–perifornical hypothalamus, orexin receptors are widely distributed in a brain in site-specific manner and have different affinity profile: orexin receptor-1 preferentially binds the orexin A, while orexin receptor-2 has equal affinity for both substances.

Orexinergic axons accumulate in the sleep-wake cycle centers where they increase the firing rate of the histaminergic neurons playing a prominent role in arousal. Thus, mutations of orexin receptor-2 gene are responsible for hereditary narcolepsy in dogs while in humans this pathology seems to develops as a consequence of autoimmune damage of orexin neurons [52]. Orexin A is thought to be widely involved in the regulation of food intake as its injection stimulates feeding behavior in rats. In addition orexins are linked to promotion of energy expenditure in rodents [53].

Importance of orexin signaling is well demonstrated by diseases associated with its deterioration. It is known that abnormalities of orexin signaling pathways underlie the pathophysiology of sleep disorders [54-56]. Decrease of central orexin signaling is associated with age-related anorexia [57], obesity [58] and variety of neurological disorders [59].

The recent study has shown a 23% reduction of orexin neurons number from infancy to late adulthood, with a 10% decline occurring between early and late adulthood [60]. These findings as well as data from multiple animal and human studies support the hypothesis that decline of either orexin neurons or orexin sensitivity in older individuals contributes to some aspects of age-related sleep changes.

The most recognized orexin function related to sleep is promotion of arousal and stabilization of the sleep/wake cycle [61]. Age-related decrease of orexin production can negatively affect sleep duration and sleep quality, what is suggested to be the risk factor for the insomnia and contribute to growing prevalence of other sleep disorders with age.

Many prior studies have shown that orexin-containing neurons may be important mediators of cognitive performance. These cells, apparently, connect directly with basal forebrain cholinergic neurons [62], and orexin appears to mediate long-term potentiation in the dentate gyrus of the hippocampus [63]. It was shown, that substances blocking orexin receptor-1 can cause deterioration in performance of operant, attentional and spatial memory tests in rats [64-67]. In opposite, modafinil, that activates orexin neurons, improves attention in rats [68].

Whereas the loss of orexin neurons during aging contributes to decline of sleep features, energy expenditure, and cognition, the therapies increasing orexin signaling could have beneficial impact on all of these factors.

AGE-RELATED NEURODEGENERATIVE DISEASES

Age-related cognitive decline is common in older adults, with incidence of diagnosis increasing from 4% to 36% between 65 and 85 years of age [69].

Alzheimer's disease (AD) is a neurodegenerative disorder which affects multiple brain areas and types of neurons, very likely including the primary sleep-regulating systems. AD is characterized by cognitive impairment from mild cognitive decline to dementia. However, sleep disturbances and a disturbed sleep-wake pattern are also considered as the major feature of AD, correlated with a severity of dementia [70, 71]. Up to 82% of AD patients get up during the night and 34% wake up at night thinking it is daytime [72]. Other features of sleep-wake cycle disorders in AD patients are excessive daytime sleepiness, daytime napping, REM sleep dysregulation and circadian rhythm disturbances [73]. Sleep disturbances appear to occur early in the course of the disease and may predict amyloid-beta (Aβ) plaque pathology and precede subsequent development of clinical dementia [74, 75].

There are promising data that circadian clock lesion contributes to the pathogenesis of age-related neurodegenerative diseases. Disrupted circadian rhythms and melatonin secre-

tion in AD have been reported by several authors [76, 77]. A proposed mechanism of circadian dysfunction in AD is the degeneration of SCN with critical loss of vasopressin and vasoactive intestinal peptide-expressing neurons [78, 79]. Circadian oscillation of clock genes in the human pineal gland in AD patients turns disrupted even at early stages of AD that is reflected by loss of rhythmic melatonin secretion [80, 81]. Thus, at AD there is evidence of disturbance of clock gene expression rhythms which appears to develop early in the course of disease [82]. Melatonin is known to have antioxidant and neuroprotective properties, thus the age-dependent decline of its production has some responsibility for neurodegeneration [29]. Conclusively, further studies of circadian function in prodromal AD and its relation to the risk or progression of the disease are needed.

The second most common age-related neurodegenerative condition, Parkinson's disease (PD), demonstrates disrupted circadian rhythms and sleep-wake disturbances in humans and mouse models [83]. Multiple factors and conditions related to PD are implicated in the development of sleep disturbances in these patients [84]. Disease-related pathological changes include impairment of thalamocortical arousal network and degeneration of sleep-wake and REM sleep brainstem centers, resulting in loss of dopamine, norepinephrine and serotonin neurons, all of which have alerting properties, and subsequent development of excessive daytime sleepiness and insomnia [85]. Additionally, sleep architecture may be altered in PD due to degeneration of basal forebrain and brainstem cholinergic neurons, including the pedunculopontine nucleus and peri-locus coeruleus area that causes reduction of REM sleep and development of RBD that affects consistency and depth of sleep . A loss of serotonergic neurons in raphe nucleus is associated with a decreased percentage of slow wave sleep [86]. Sleep disturbances at PD can also be a consequence of nocturnal motor symptoms, affective symptoms, dementia, medications, disorders of sleep-wake circadian rhythm, and comorbid primary sleep disorders like sleep apnea syndrome or restless leg syndrome [87].

The orexin system is affected in both Parkinson's [88-90], and Alzheimer's diseases [91, 92], multiple system atrophy [93] and other neurological disorders [59]. While many studies were focused on the importance of orexin loss in disease-related sleep disturbances, it is more interesting to consider the role of orexin in pathogenesis of these neurodegenerative diseases.

Along with the normal orexin decline during aging process, additional loss of orexin neurons may have contribution in pathogenesis of several progressive neurodegenerative conditions, including AD and PD [88, 89, 92] which are characterized both by sleep disturbances and cognitive deficit. While the underlying cause of orexin neurons loss in these disorders is unknown, it is possible that the neurodegeneration greatly accelerates normal age-related reduction of amount of the orexin producing neurons. Orexin deficit can promote cognitive decline in both normal aging and in neurodegenerative disease through direct involvement of the neuropeptide in cognition, or indirectly through effects on sleep and activity.

Orexin receptor-2 polymorphism has been identified as potential risk factor for development of AD [94]. Relation of orexin downregulation and PD seems to be even more evident from findings of Thannickal *et al*. (2007) who examined brains of patients suffered from PD. They have revealed significant losses of orexin and melanin concentrating hormone neurons of hypothalamus, which are strongly correlated with the clinical stage of PD, not with disease duration [89]. These findings may explain narcolepsy-like symptoms of PD *i.e*. excessive daytime sleepiness and night insomnia and, partially, autonomic dysfunction due to fail of autonomic function of orexin. It was also shown that antiparkinsonian agents can selectively damage orexin neurons aggravating the sleep disturbances [95].

There are many evidences linking the development of AD and PD with oxidative stress and brain mitochondrial dysfunction. In recent *in vitro* and *in vivo* studies, Nixon *et al*. (2015) have shown that orexin has neuroprotective effect, reducing neuronal damage caused by ischemia or oxidative stress in hypothalamic, hippocampal, and cortical tissue [61].

One explanation of this protective effect of orexin is upregulation of hypoxia-inducible factor 1 alpha (HIF-1α) that increases resistance to oxidative stress [96]. HIF-1α is a transcription factor that alters mitochondrial activity by increasing adenosine triphosphate production through oxidative phosphorylation, and affects expression of transferrin gene which is important for iron metabolism in the brain. The increased oxidative stress and dysfunction in brain iron metabolism are involved in the development of both AD and PD [97].

In case of PD, HIF-1α activatiors are proposed as potential therapeutic agents, and orexin has recently been shown to protect against the parkinsonian neurotoxin 1-methyl-4-phenylpyridinium ion-induced toxicity through induction of HIF-1α in a dopamine-producing neuronal cell line [96].

There are different opinions about the role of HIF-1α in the pathophysiology of AD. Investigation of chronic inflammation processes in a mouse model of AD has shown no changes of both HIF-1α gene expression and amount of HIF-1α in the brain [98], on the contrary the other study with postmortem brain section of AD patients has found the increase of HIF-1α concentration [99]. Nevertheless, the supporters of both points of view agree that therapy agents activating the HIF pathway may be beneficial for neurological disorders that involve metabolic stress, such as Alzheimer's disease.

Taken as a whole, these results suggest that orexin might protect against development of neurodegenerative disease, and that orexin loss in AD and PD might exacerbate disease progression by increasing susceptibility to oxidative damage [61].

The interest to age-related changes of sleep has been greatly enhanced by recent discovery of the role of sleep in the brain clearance from the waste proteins like amyloid beta, tau-proteins and synucleins involved in the pathogenesis of neurodegenerative diseases [100]. Thus, not only underlying mechanisms of neurodegenerative diseases cause

both sleep and cognitive impairment but sleep loss itself can accelerate progression of these age-related diseases.

CONCLUSION

Normal process of aging implies qualitative changes of sleep and decreasing of sleep-wake rhythm amplitude. Association between sleep disturbances and cognitive impairment especially in neurodegenerative disorders prompts suggestions that neurodegeneration underlies both sleep and cognitive disturbances. More or less severe degeneration determines normal or pathological (*e.g*. neurodegenerative disorders) course of aging respectively. Meanwhile some authors suggest that good sleep itself has protective effect on brain function especially on the processes of cognition. From this point of view the age-dependent weakening of circadian clock driving force due to the loss of neurons of SCN and decrease of nocturnal secretion of melatonin could be considered as the factors involved into development of clinical features and probably processes of neurodegeneration in such diseases as AD or PD.

Orexin plays an important role in both sleep-wake cycle and cognitive functions. Furthermore declining of its transmission correlates with AD and PD symptoms severity. These findings open a large field for further investigations of therapy implication of orexin or its pathways. The same can be said about melatonin in spite of multiple and contradictory opinions about its role in the pathogenesis of neurodegeneration.

Metabolic changes developing with age from one side – reflect central neurohormonal degeneration but from the other – worsen this degeneration through the hyperglycemia and peripheral vascular diseases. Mechanisms of interaction of sleep and neurodegerative disorders still have to be investigated. Better understanding of these links could lead to the development of new effective treatment agents.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

Declared none.

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