



Orexin and Alzheimer's Disease: A New Perspective

Yoo Hyun Um and Hyun Kook Lim[✉]

Department of Psychiatry, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Orexin's role in human cognition has recently been emphasized and emerging evidences indicate its close relationship with Alzheimer's disease (AD). This review aimed to demonstrate recent research on the relationship between orexin and AD. Orexin's role in stress regulation and memory is discussed, with significant findings related to sexual disparities in stress response, with potential clinical implications pertaining to AD pathology. There are controversies regarding the orexin levels in AD patients, but the role of orexin in the trajectory of AD is still emphasized in recent literatures. Orexin is also accentuated in the context of tau pathology, and orexin as a potential therapeutic target for AD is frequently discussed. Future directions with regard to the relationship between orexin and AD are suggested: 1) consideration for AD trajectory in the measurement of orexin levels, 2) the need for objective measure such as polysomnography and actigraphy, 3) the need for close observation of cognitive profiles of orexin-deficient narcolepsy patients, 4) the need for validation studies by neuroimaging 5) the need for taking account sexual disparities in orexinergic activation, and 6) consideration for orexin's role as a stress regulator. The aforementioned new perspectives could help unravel the relationship between orexin and AD. **Psychiatry Investig 2020;17(7):621-626**

Key Words Orexin, Dementia, Alzheimer's disease, Cognition.

INTRODUCTION

Orexin (also named *hypocretin*) is a neuropeptide, and their function is implemented by two G-protein-coupled receptors. Two subtypes exist, orexin A and orexin B, and they are synthesized by neurons located in lateral hypothalamus and perifornical areas.¹ Orexin has been described in many literatures as a key neuropeptide regulating fundamental brain functions, including arousal, appetite, stress and cognition,²⁻⁶ playing a major role in the homeostatic control of our body state.⁷ Orexin neurons project to various brain regions, including prefrontal cortex, hippocampus, thalamus, hypothalamus, locus coeruleus, raphe nuclei, parabrachial nuclei, central gray and nucleus tractus solitaries, and the aforementioned sites have crucial functions regarding cognitive processes and their consequences.⁸ Orexin has not only been emphasized as an integral research topic in sleep research, but also in neuropsychiatry.^{4,9} Indeed, abundant research reported orexin's in-

tegral role in human cognition and its relationship with Alzheimer's disease (AD). Therefore, in this review, we will demonstrate what has been reported to be the role of orexin in the pathology of AD, and provide future research directions pertaining to this field.

OREXIN AS A STRESS REGULATOR AND ITS RELATIONSHIP WITH COGNITION

With regard to the relationship between orexin and cognition, recent emphasis on orexin's role as a stress regulator should not be dismissed.¹⁰⁻¹² Indeed, a recent study indicated that rats adopted a passive coping behavior after social defeat stress through orexin activation, which induced recognition memory impairments.¹³ Orexinergic blockade in the hippocampus reversed stress-induced anxiety behaviors and memory deficits in rats, which suggested potentials of hippocampal orexins as therapeutic targets to minimize stress-induced impairments.¹⁴ A sexual disparity was noted with regard to orexin's role in stress response, a female rat displaying more vulnerability to repeated stress, demonstrating prominent impairments in habituation and cognitive flexibility, with increased orexin expression when compared with male rats.¹⁵ In rat models, orexin-A was closely related to the expression of corticotropin releasing factor (CRF),¹⁶ and when infusion of orexin-B receptor antagonist was implemented, it significantly reduced stress-

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✉ Correspondence: Hyun Kook Lim, MD, PhD

Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10 63-ro, Yeongdeungpo-gu, Seoul 07345, Republic of Korea

Tel: +82-2-3779-1048, Fax: +82-2-780-6577, E-mail: drblues@catholic.ac.kr

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induced adrenocorticotropin (ACTH).¹⁷ Lower orexin levels were correlated with increased resilience to social stress,¹⁸ while a contrasting result indicated that orexin increased stress resilience by reducing depressive behaviors.¹¹ Orexin-A antagonist inhibited a stress response via fronto-hippocampal circuit, including amygdala.¹⁹ Orexin is also involved in reinforcing norepinephrine-mediated long term potentiation in dentate gyrus, exerting its critical role in attention and memory.²⁰ The hippocampal-amygdala interactions were modulated by orexinergic receptors, with orexinergic receptor blockade in the basolateral amygdala induced long-term potentiation in the dentate gyrus.²¹ Therefore, a mediating role of orexin could exert great influence on the process of emotional learning.²¹ Indeed, orexin was closely related to fear memory, with negative associations between orexin A level and fear extinction.²²

Independent of orexin's role as a stress regulator, orexin's role in cognition and memory and learning is frequently discussed. Orexin-deficient mice exhibited slowed decreased spatial-cue related working memory, when compared to control mice.²³ In a rat model, both types of orexin exerted their effects on spatial learning and memory through orexin 1 receptor, which extends their projection to hippocampal formation.²⁴ Orexin might exert a considerable influence on attention as well, with results on attention-deficit and hyperactivity disorder (ADHD) patients, showing decreased serum orexin A levels in human subjects.²⁵ The relationship between cholinergic transmission and orexin has also been discussed frequently. Activation of basal forebrain by orexinergic neurons, and their critical role in arousal and attention are well-known.²⁶⁻²⁸ Orexinergic neurons and both orexin receptor subtypes are distributed in the basal forebrain, and fine modulation of cholinergic system is mediated through orexinergic control.^{27,28} Such control is suggested to be mediated by gamma oscillations.²⁹ Orexin A is purported to directly influence cholinergic neurotransmission in hippocampus, with lack of response to orexin A noted in aged rats.³⁰ Differentiating disparate olfactory cues is another important role of orexinergic innervation in the basal forebrain.³¹

As with regard to its relationship with medial prefrontal cortex (MPFC), orexinergic receptor signaling was purported to be crucial in potentiating cognitive motivation to eat.³² A recent report proposed that high fat diet fed, orexin-deficient mice exhibit impaired cognition and increased microglial activation when compared with controls.³³ Moreover, hypocretin in MPFC reinforces cortical arousal and attention closely related to limbic states.³⁴ Indeed, orexin is closely associated with dopamine efflux within prefrontal cortex, specifically through dopaminergic neurons in ventral tegmental area.^{35,36}

Orexinergic neurons are lost with aging,³⁷ and its role in age-related cognitive decline is increasingly emphasized. Age-re-

lated cognitive decline and orexin are discussed in consideration for orexin's role in appetite. Age-related loss of orexinergic neurons could contribute to impairments in orexinergic modulation of hippocampal neurochemistry.³⁸ Despite the aforementioned studies that imply important clinical implications, most recent results on the relationship between orexin and cognition have been limited to animal studies. Further human studies are needed to confirm the exact role of orexin in regulating various cognitive pathways.

A CRUCIAL LINK BETWEEN OREXIN AND ALZHEIMER'S DISEASE

A link between orexin and AD has been mostly discussed in the context of explaining the bidirectional relationship between AD and sleep disturbance.³⁹ A recent research suggested that amyloid deposition affects memory by its effect on sleep, but how amyloid affects sleep and consequent memory disruption remains elusive.⁴⁰ Orexin may be an important mediating factor that could explain this ambiguity. However, contradicting results exist regarding the orexin levels in AD patients. A postmortem study concluded that reduced cerebrospinal fluid (CSF) orexin A levels and orexinergic neuronal cell numbers were found in advanced AD patients.⁴¹ Meanwhile, orexin level was increased in moderate to severe AD patients, when compared with mild AD or healthy controls.⁴² Hippocampal overexpression of orexin did not have any association with amyloid beta (A β) deposition, when A β aggregation increased when orexinergic neurons were rescued in amyloid precursor protein (APP)/Presenilin1 (PS1) transgenic mice.⁴³ Moreover, there was no difference in orexin levels between AD patients and healthy controls, and the orexin levels did not reach statistical significance with regard to apolipoprotein E 4 (ApoE4) genotype.⁴⁴ In one study with consideration for a diurnal variation of orexin levels, orexin levels did not differ between AD patients and the control group, and lower A β levels were associated with a higher amplitude of orexin circadian rhythm.⁴⁵ In a recent study on investigation of the relationship between partial sleep deprivation and CSF parameters pertaining to AD-related neurodegeneration, there was a significant increase noted in orexin levels after partial sleep deprivation, while other parameters remained insignificant.⁴⁶

The role of orexin with regard to the importance of sleep-wake cycle in the trajectory of AD is frequently demonstrated. Orexin has an integral role in promoting wakefulness in mammals, with cessation of its neuronal firing during sleep.³ Increased research is directed to understanding the sleep-wake cycle and its control of A β levels in brain interstitial fluid.⁴⁷ Soluble A β has been purported to be a major culprit for inducing neurotoxic effects resulting in synaptic loss and dysfunc-

tion, and the sleep-wake cycle is predicted to play a major role in the clearance of soluble A β .⁴⁸ Orexinergic signaling has been suggested as a major pathway for hippocampal circadian oscillation that is suspected to exert a considerable influence on the expression of AD-risk genes that play a major role in production and transport of A β .⁴⁹ Excessive orexinergic signaling is purported to be a culprit for causing sleep-wake cycle disruption that hastens A β deposition.⁵⁰ In line with this proposition, interstitial fluid A β levels increased with orexin infusion and decreased with orexin antagonist in one study.⁵¹ There was a study where orexin disrupted degradation of A β by microglia.⁵²

Orexin is also discussed in the context of tau pathology,⁵³ with orexin levels proportionally increased with total tau protein (T-tau) levels in AD patients. Moreover, orexin showed a positive relationship with phosphorylated tau (P-tau) levels in cognitively normal elderly subjects, even when controlled for years of education and ApoE4 status.⁴² In a mouse model, orexin knockdown resulted in inhibition of T-tau and P-tau levels, with adenosine A receptor showing a close expression level with orexin.⁵⁴ Tau proteins usually represent brain neuronal injury subsequent to AD pathology, and how orexin exerts its influence on tau-mediated neuronal injury remains ambiguous. Many possible mechanisms were proposed through which orexin exerts pernicious effects that hasten AD pathology. In an AD mice model, orexin A aggravated mitochondrial impairment.⁵⁵ Genetic vulnerability might be another culprit, with one study suggesting orexin receptor 2 gene could be a risk factor for AD.⁵⁶ With regard to neuronal injury and orexin, a few of recent findings present a potential candidate for future research directions. Orexin has been suggested as one important potential neuropeptide in the modulation of the metaplasticity in the brain, with evidences for fine modulation of long-term potentiation and long-term depression in animal models.⁵⁷ Recently, orexinergic innervations were discovered in the adult rat subventricular zone, which is the site for active neurogenesis.⁵⁸

OREXIN AS A POTENTIAL THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

Orexin, with key previously published findings on its relationship with AD, has been discussed as a potential therapeutic target for AD. Orexin A and B treatment both regulated the hippocampal oscillator, which is suggested to play a major role the circadian control of Alzheimer's disease-risk genes.⁴⁹ With regard to emphasis on understanding of orexin in consideration for its role in sleep modulation,⁴³ orexin antagonist is an interesting target of research in patients at risk or suffering from

AD. Suvorexant, an orexin antagonist approved by FDA with indications on insomnia patients, can be utilized in future clinical trials to unravel A β dynamics.⁴⁷ Indeed, almorexant, another type orexin antagonist, reduced interstitial A β levels during the light period.⁵¹ Delivery methods of therapeutic effects of orexin are another matter in discussion. Orexin gene delivery through lentiviral vector was suggested as a study modality to explore the relationship between orexin and AD, and such method could be applied to the development of new therapeutic agents.⁵⁹ Intranasal delivery is another option, with a recent review demonstrating intranasal administration of orexin effectively increasing neuronal activation in an animal model.⁶⁰

FUTURE DIRECTIONS IN RESEARCH ON THE RELATIONSHIP BETWEEN ALZHEIMER'S DISEASE AND OREXIN

Several important considerations are necessary in the future research regarding the link between AD and orexin. First, orexin level changes with regard to AD trajectory will be conducive to understanding the interactive link between orexin and AD pathology. Indeed, a recent research on change of CSF tau, neurofilament light and YKL-40 levels compared between groups in different phases of AD trajectory provided a valuable insight into a potential CSF biomarker that could be utilized in clinical settings.⁶¹ The same approach could be applied to orexin measured from CSF, thus understanding how orexin affects the AD pathology longitudinally.

Second, quantification of orexin levels, along with objective sleep studies including polysomnography and actigraphy, should be used to accurately reflect the sleep-wake cycle and sleep patterns among elderly population. Third, cognitive profiles and longitudinal observation of narcolepsy patients, with consideration for the incidence of AD in this particular group will be integral to understanding the link between AD and orexin. In sleep research, orexin has remained a central research arena for narcolepsy, with key findings that reported its major relationship with pathophysiology of narcolepsy. Mutations in orexin receptor gene were discovered in canine narcolepsy cases,⁶² and subsequent reports demonstrated deficient orexin level in narcolepsy patients.⁶³ In a recent report, when compared with controls, type 1 narcolepsy patients exhibited reduced amyloid deposition.⁶⁴ Moreover, neurodegenerative CSF biomarkers, including A β , T-tau and P-tau levels were reduced in narcolepsy patients, when compared with healthy individuals.⁶⁵ Whether narcolepsy patients' orexin-deficient status is a protective factor for AD should be explored in further studies.

Fourth, orexin level studies should be implemented along

with validation studies with utilization of neuroimaging modalities. Indeed, a recent paper published an article defining cutoff values of CSF biomarkers defined by positron emission tomography (PET) status.⁶⁶ Orexin levels measured in different phases of AD trajectory, with their relationship with PET and neural networks manifested by magnetic resonance imaging (MRI) will provide a novel insight into the relationship between AD and orexin.

Fifth, the relationship between orexin and female hormones will provide an interesting research arena in exploring the link between AD and orexin. Female sex is a well-known risk factor for AD, and searching for gender-specific predictors of AD is a major research field that deserves more clinical attention.⁶⁷ As mentioned before earlier in this article, a sexual disparity was noted in orexin expression levels, demonstrated in rats, with female displaying more vulnerability to stress and increased orexin activation.¹⁵ Neuroprotective effects of estrogen, inherent vulnerability of female brain to AD, and a recent research findings of estrogen receptor localization of neurofibrillary tangles are all intriguing topics under discussion,^{68,69} but most previous studies on the effects of estrogen replacement therapy on AD prevention are disappointing.⁷⁰ The relationship between sleep and estrogen has been reported frequently,⁷¹⁻⁷⁴ and in consideration for the integral role of orexin during wake and sleep states, investigations on the mediating role of orexin in AD pathology and sleep in female patients are needed. Inhibitory effects of estrogen on orexin A was reported in one study,⁷⁵ and orexin A was reported to be responsible for progesterone secretion in a sheep model. How female hormones, sleep and AD pathology interact could be a new pathway to understanding AD trajectory.

Lastly, orexin plays a critical role as a stress regulator, and the relationship between orexin and cognition is often in the context of stress. A recent review reported accumulated evidences supporting oxidative stress evoked by prolonged wakefulness, increasing neuronal oxidative damage.⁷⁶ Orexin a wake promoter, and the relationship between reactive oxygen species and orexin levels in normal controls without AD pathology, preclinical dementia, mild cognitive impairment, AD patients will be conducive to unravelling the orexin's role as a stress regulator and its impact on cognition.

CONCLUSION

In this review, we have presented recent, updated evidences for the relationship between orexin and AD pathology. Many previous literatures suggested sleep as a modifiable risk factor for AD,⁷⁷⁻⁸⁰ with emphasis on early intervention for those in the AD trajectory. However, still, there is no clear-cut model to understand the role of sleep in the course of AD pathology.

Orexin, a major neurotransmitter regulating sleep, stress and appetite, may have a direct or indirect effect that could help uncover the relationship between sleep and AD. Further well-designed prospective studies are needed to explicate the link between orexin, sleep and cognition, adopting more diverse research methods and multifaceted understanding of orexin.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

All authors have contributed to the present review with equal efforts.

ORCID iDs

Yoo Hyun Um <https://orcid.org/0000-0002-3403-4140>
Hyun Kook Lim <https://orcid.org/0000-0001-8742-3409>

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