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EDITORIAL

Hypocretin (orexin) pathology in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a growing health problem. It has enormous public health impact. Sleep problems show an early component of this disease. Hypocretin has a major function in sleep-wake cycle. The total number of hypocretin neurons in the normal humans ranges from 51000-83000, located exclusively in the hypothalamus. Deficiency in hypocretins neurotransmission results in narcolepsy, Parkinson's disease, and other neurological and psychological disorders. Cerebrospinal fluid (CSF) hypocretin levels were directly related with t-tau protein amount in AD. Increased hypocretin CSF in AD suggest that hypocretin is involved in the mechanism of AD pathology.

Key words: Hypocretin; Orexin; Alzheimer's disease; Neurological disorders

Core tip: Hypocretin plays an important role in the control of sleep-wake cycle. Increased hypocretin levels in Alzheimer's disease patients suggest hypocretin system is involved during development of the disease symptoms.

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INTRODUCTION

The hypocretins were discovered in 1998 by two groups[1,2]. One group named hypocretins because of hypothalamic origin and similarity with the secretin[1]. The other group named Orexins because these neurotransmitters stimulated food intake[2]. Their projection target suggests hypocretins have a neuromodulatory role in neuroendocrine and homeostatic functions[3,4]. The distribution of hypocretins neurons in human hypothalamus is shown in Figure 1. Hypocretin fibers and receptors are found throughout the brain[3,5,6]. Hypocretins

Table 1 Important findings shows role of hypocretin in Alzheimer's disease

Ref.	Year	Major findings
Friedman *et al*[28]	2007	Increased wake fragmentation found in those with lower hypocretin-1
Kang *et al*[29]	2009	Amyloid-beta dynamics are regulated by hypocretin and the sleep-wake cycle
Fronczek *et al*[27]	2011	40% hypocretin cell loss in Alzheimer's disease
Slats *et al*[30]	2012	Association between hypocretin-1 and amyloid-β42 cerebrospinal fluid levels
Roh *et al*[8]	2014	Modulation of hypocretin and its effects on sleep to modulate Aβ pathology
Liguori *et al*[7]	2014	Increased hypocretin level correlates with sleep disruption and cognitive decline in Alzheimer's disease

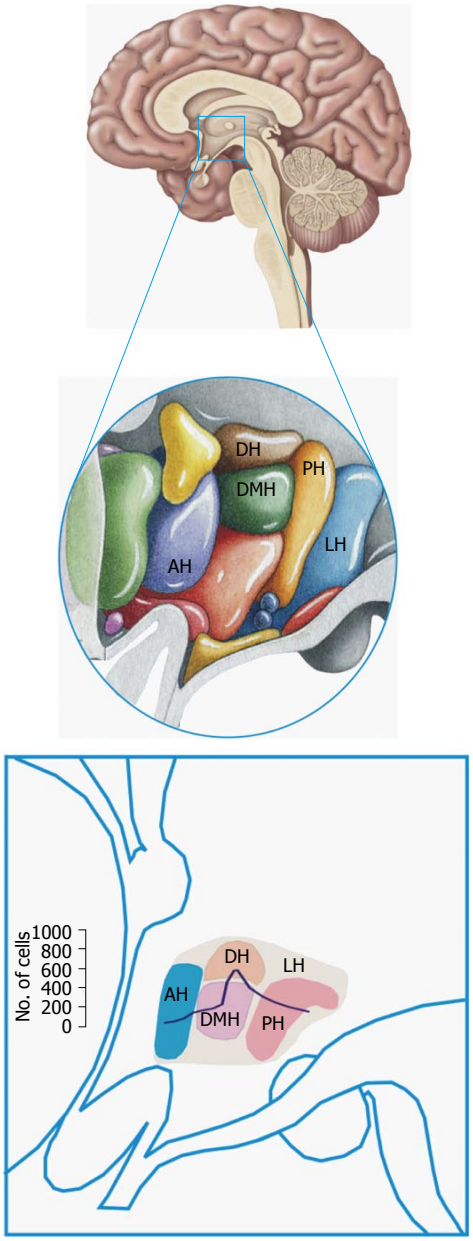

Figure 1 Distribution of hypocretin neurons in human hypothalamus. The normal distribution of hypocretins cells in the hypothalamus is limited to AH, DH, DMH, LH and PH. AH: Anterior hypothalamus; DH: Dorsal hypothalamus; DMH: Dorsomedial hypothalamus; LH: Lateral hypothalamus; PH: Posterior hypothalamus.

loss in narcoleptics opened importance of hypocretin system in health and disease[5]. New findings show the role of hypocretin in the pathogenesis of Alzheimer disease (AD)[7,8].

HYPOCRETIN AND NEUROLOGICAL DISORDERS

Narcoleptic patients have low or undetectable cerebrospinal fluid (CSF) hypocretin[9]. The pathological studies revealed 85%-95% loss of hypocretins cells in narcoleptics with cataplexy[10]. Maximum cell loss was occurred in the posterior and tuberomammillary nucleus[11,12]. Decreased CSF hypocretin were reported in, idiopathic hypersomnia, hypothalamic neoplasms and acute disseminated encephalomyelitis[13-17]. Higher CSF hypocretin were found in restless legs syndrome[18]. Lower hypocretin CSF were reported in patients with multiple sclerosis[16], Niemann Pick disease type C[19] and Whipple's disease[20]. Hypocretin cell loss was found in Parkinson disease patients[21,22]. Benarroch *et al*[23] reported 70% loss of hypocretins cells in multiple system atrophy patients. In Huntington's disease 30% loss of hypocretins cells occurred[24]. Bauman *et al*[25] found hypocretins cell loss in TBI patients with severe injury. There was reduced fluctuations of hypocretins CSF in depression patients[26].

DYSREGULATION OF HYPOCRETIN SYSTEM IN AD

Number of hypocretins cells in AD patients were reduced by 40%[27]. AD patients with lower hypocretins-1 showed increased wake fragmentation[28]. Kang *et al*[29] reported the role of hypocretins and sleep in amyloid beta dynamics. The link between mean amyloid beta 42 and hypocretins suggests a relationship between AD pathology and hypocretin disturbance. The important findings related to the role of hypocretins in AD are summarised in Table 1. With symptom progress AD patients had increased hypocretins levels. The hypocretin levels in AD were associated with tau protein and sleep impairment. Hypocretin output and function seem to be over expressed with disease[8]. A few literature reports showing that[30,31] there was no decrease in CSF hypocretin levels. These studies considered smaller samples including some cases, patients receiving psychiatric medications, which may influence hypocretin neuronal activity and output. Liguori *et al*[7], results are in contrast to Fronczek *et al*[27], study reporting decreased

hypocrein neurons and CSF levels in AD patients. This difference may be related to the fact that Ligouri *et al*[7], performed *in vivo* study, whereas Fronczek *et al*[27], were used pathological tissues from advanced AD patients. Roh *et al*[8], found that hypocretin knockout animals slept for longer time and lower amyloid-beta. These studies show the importance of hypocretin system in AD.

AD AND NARCOLEPY

The core sleep problems in AD and narcoleptic patients are partly resemble. Hypocretin may have an important function in the pathological mechanism of AD. In narcoleptic patients with cataplexy have 90% of hypocretins cell loss and undetectable level of CSF hypocretin. If hypocretins mediates AD symptom progress, narcolepsy patients should be protected against AD pathology. The neuropatholgical records of twelve narcolepsy with cataplexy showed that thirty three percentages of these narcoleptics had AD pathology which is comparable to the prevalence in general population[32]. This report shows that severe loss of hypocretin neurotransmitter does not protect from AD.

HYPOCRETIN AS A CSF BIOMARKER

Higher CSF t-tau protein levels mark the AD neurodegeneration. Increased t-tau levels represent a sign of rapid cognitive decline because they have been faster more pronounced neuronal degeneration, supporting the transition from early to more advanced disease stages[33]. CSF hypocretin levels were directly correlated with t-tau protein levels in AD[8,34] . This finding suggests that higher hypocretin levels may be related to rapid tau-mediated degeneration in AD. The pathogenesis of AD may therefore involve dysregulation of the hypocretins system, with over expression of hypocretins output and function.

CONCLUSION

With a rising prevalence of AD around the world, there is an urgent need to identify opportunities for prevention and treatment of the disease. Hypocretin may have a role in the pathological process leading to AD. The pathogenesis of AD may therefore involve dysregulation of the hypocretins system, with over expression of hypocretins output and function, manifested as sleep disturbance and associated with progressive neurodegeneration. Further studies on the importance of hypocretin during the process of AD could lead to new preventive and therapeutic findings.

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