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Neuropathological investigation of hypocretin expression in brains of dementia with Lewy bodies

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HIGHLIGHTS

- We examined hypocretin immunoreactivity in brains of dementia with Lewy bodies.
- Severe hypocretin loss was seen in the lateral hypothalamus.
- Neurofibrillary tangles were detected in hypocretin neurons in the hypothalamus.
- Hypocretin loss was correlated with neurofibrillary pathology.
- Hypocretin loss was not correlated with Lewy pathology.

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ABSTRACT

Hypocretin (Hcrt) is a neuropeptide synthesized in the lateral hypothalamus (LHT) that plays a key role in maintaining arousal state. In Parkinson's disease (PD), a narcolepsy-like syndrome is commonly seen, and a previous study showed substantial Hcrt neuronal loss in accordance with PD severity. In the present study, we quantitatively examined Hcrt immunoreactivity and α-synuclein and tau pathologies in the LHT and locus coeruleus (LC) in dementia with Lewy bodies (DLB) ($n = 15$), Alzheimer's disease (AD) ($n = 14$), and controls ($n = 7$). In the LHT, substantial Hcrt-positive neurons were detected in controls. In contrast, in DLB and AD, the numbers of both total neurons and Hcrt-positive neurons were significantly reduced. The reduction of the latter was significantly severer in DLB than in AD. In the LC of controls, many Hcrt-positive axonal terminals were found. In contrast, the amount of Hcrt immunoreactivity was significantly reduced both in DLB and AD. In DLB, some Lewy body (LB)-bearing neurons were detected in the LHT, but the Hcrt-positive neurons did not have any LBs. Meanwhile, some tau-positive neurofibrillary tangle (NFT)-bearing neurons were detected in the LHT, and Hcrt-positive neurons occasionally contained NFTs. We observed a significant negative correlation between the number of Hcrt-positive neurons in the LHT and the neurofibrillary stage ($r = -0.67$, $p = 0.0067$), whereas no significant correlation was found between the number of Hcrt-positive neurons and the Lewy stage ($r = -0.47$, $p = 0.077$). This is the first report clarifying the substantial loss of Hcrt neurons in the LHT and of Hcrt axonal terminals in the LC in DLB and the correlation between the severity of Hcrt neuronal loss and progression of neurofibrillary pathology.

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1. Introduction

Hypocretin/orexin (Hcrt) is a neuropeptide synthesized exclusively in the lateral hypothalamus (LHT). Hcrt neurons project widely to regions including the basal forebrain nuclei, brainstem nuclei, and cerebral neocortex. Hcrt also plays a role in maintaining a state of arousal [1]. Previous studies have shown that a mutation is present in the gene encoding the Hcrt-2 receptor in the canine narcolepsy model [2], that a strong correlation exists between Hcrt

Abbreviations: Hcrt, hypocretin; LHT, lateral hypothalamus; LC, locus coeruleus; PD, Parkinson's disease; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; RBD, REM sleep behavioral disorder; SOREM, sleep onset of REM sleep; EDS, excessive daytime sleepiness; SOOS, sudden onset of sleep; MSLT, multiple sleep latency test; NFT, neurofibrillary tangle; LB, Lewy body.

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deficiency and human narcolepsy–cataplexy [3], and that disruption of the Hcrt system is strongly involved in the pathophysiology of narcolepsy [4].

In Parkinson's disease (PD), various types of narcolepsy-like sleep disorders, including REM sleep behavioral disorder (RBD), sleep onset of REM sleep (SOREM), excessive daytime sleepiness (EDS) and sudden onset of sleep (SOOS), are frequently seen [5,6]. In particular, EDS is seen in up to 50% of patients with PD [5]. With the multiple sleep latency test (MSLT), MSLT <5 min, which mimics the narcolepsy pattern, were observed in 50% of PD patients with EDS [7]. Two pathological investigations of the lateral hypothalamic Hcrt neurons in PD showed substantial neuronal loss in accordance with PD severity [8,9]. Other than PD, increased loss of the lateral hypothalamic Hcrt neurons is also seen in the brains of patients with Alzheimer's disease (AD) [10] and post-traumatic injury [11].

Dementia with Lewy bodies (DLB) is the main clinicopathological entity of Lewy body disease, which also includes PD. Clinically, DLB is characterized by core features including visual hallucinations, cognitive fluctuation, and parkinsonism, and frequently shows sleep disorders including RBD, EDS, and SOOS. In DLB, Lewy pathology is commonly accompanied with AD pathology [14]. Concerning Hcrt pathology, only one study has been reported by Lessig et al. [12]. They showed reduced Hcrt immunoreactivity in the temporal neocortex, which was correlated with α-synuclein accumulation. However, they did not investigate the LHT where Hcrt neurons are found.

In the present study, we examined Hcrt immunoreactivity in the brains of DLB, specifically in the LHT and locus coeruleus (LC), where Hcrt neurons richly project. Furthermore, we also investigated the relationship between Hcrt immunoreactivity and severity of Lewy pathology or concomitant AD pathology.

2. Materials and methods

2.1. Brains

We examined 15 brains from DLB cases (11 males and four females, mean age 75.7 years, mean brain weight 1.133 g), 14 brains from AD cases (eight males and six females, mean age 80.9 years, mean brain weight 1.021 g), and 7 brains from control cases (four males and three females, mean age 74.1 years, mean brain weight 1.276 g), which were preserved in our center. These included the same materials that we previously used [13]. DLB and AD cases fulfilled the pathological criteria for DLB [14] and AD [15,16], respectively. Pathological subdivisions of these brain cases are shown in Table 1. All autopsies were performed with written consent, and the present study was approved by the local ethics committee of our center.

2.2. Hcrt, α-synuclein, amyloid, and tau immunohistochemistry

Brains were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) and embedded in paraffin. Thereafter, (1) six-micrometer-thick three coronal sections were cut on the cerebral hemisphere from the level where the fornix touches the paraventricular nucleus to the level where the fornix touches the mammillary body and (2) six-micrometer-thick three

Table 1
Neuropathological characteristics of brains.

Group	Case	Sex	Age, years	Brain weight (g)	Lewy body type pathology	Lewy stage	NFT stage	Amyloid stage	Likelihood
DLB	1	M	50	1050	Diffuse	IV	II	0	High
	2	M	81	1400	Lim	II	II	0	High
	3	M	71	1320	Diffuse	III	III	B	High
	4	M	74	1300	Diffuse	II	III	C	High
	5	F	77	900	Diffuse	III	III	C	High
	6	F	79	1173	Diffuse	III	III	C	High
	7	M	84	1140	Lim	II	III	C	Intermediate
	8	M	78	1230	Diffuse	III	IV	C	High
	9	M	79	1060	Diffuse	III	IV	B	High
	10	M	84	1060	Diffuse	II	IV	B	High
	11	M	88	1145	Lim	II	IV	C	Intermediate
	12	M	67	1030	Diffuse	IV	V	C	Intermediate
	13	F	62	980	Diffuse	III	VI	C	Intermediate
	14	M	79	1165	Diffuse	IV	VI	C	Intermediate
	15	F	82	1050	Diffuse	IV	VI	C	Intermediate
AD	1	F	89	930	–	–	IV	C	–
	2	F	83	940	–	–	IV	C	–
	3	M	83	1110	–	–	IV	C	–
	4	M	65	1070	–	–	IV	C	–
	5	F	85	1130	–	–	IV	C	–
	6	F	79	950	–	–	IV	C	–
	7	F	85	975	–	–	V	C	–
	8	M	79	802	–	–	V	C	–
	9	M	76	1190	–	–	V	C	–
	10	M	86	950	–	–	V	C	–
	11	M	81	1020	–	–	V	C	–
	12	F	81	1070	–	–	V	C	–
	13	M	83	940	–	–	VI	C	–
	14	M	77	900	–	–	VI	C	–
Cont	1	F	64	1320	–	–	I	0	–
	2	F	65	1350	–	–	I	0	–
	3	M	68	1350	–	–	I	0	–
	4	F	79	1160	–	–	I	0	–
	5	M	79	1259	–	–	I	0	–
	6	M	80	1260	–	–	II	0	–
	7	M	84	1230	–	–	II	0	–

DLB: DLB group; AD: AD group; cont: control group; Lewy pathology type: McKeith et al. [14]; diffuse: diffuse neocortical type; lim: limbic type; Lewy stage: Braak et al. [18]; NFT stage: Braak et al. [15]; amyloid stage: CERAD by Mirra et al. [16]; likelihood: McKeith et al. [14].

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