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PSYCHOGERIATRIC NOTE

Plasma orexin-A levels in patients with delirium

The pathophysiology of delirium remains poorly understood. Recently, the sleep medication suvorexant, an orexin receptor antagonist, showed a preventive effect on delirium.[1] However, it remains unclear whether regulation of orexin by suvorexant directly affects the development of delirium. Although measuring orexin levels in cerebrospinal fluid (CSF) is ideal, it is often difficult to perform a lumbar puncture in patients with delirium because of safety risks; additionally, doing so presents ethical problems. A few studies have demonstrated a correlation between orexin-A levels in CSF and in plasma samples.[2] This prospective cohort study aimed to evaluate the association between plasma orexin-A levels and delirium.

We enrolled 70 patients aged ≥65 years who were admitted to the geriatric ward of Nagoya University Hospital between 1 December 2017 and 31 January 2018. Exclusion criteria were as follows: (i) currently taking suvorexant; (ii) having a fixed schedule for discharge within 10 days of admission; or (iii) severe disturbance of consciousness (Glasgow Coma Scale score ≤8). Written informed consent was obtained from participants or their family members. This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

Each patient underwent blood sampling and evaluation for delirium on days 2–4. Fasting blood was collected between 0700 and 0800 hours in a 3-mL tube containing ethylene diamine tetra-acetic acid disodium and aprotinin. After blood sampling, the tubes were stored in a refrigerator at 4°C. Within 2 h, the blood was centrifuged for 10 min at 3000 rpm at room temperature. The obtained plasma was stored at −80°C until analysis. Plasma orexin-A levels were measured by SRL Inc. (Tokyo, Japan) with a commercially available radioimmunoassay kit (Peninsula Laboratories International, Inc., San Carlos, CA, USA). Within 1 h after blood sampling, two geriatricians independently diagnosed delirium based on the criteria of *the Diagnostic and Statistical Manual of Mental Disorders*, 5th edition. We assessed the severity of delirium with the Japanese version of the Memorial Delirium Assessment Scale.[3] The Delirium Symptom Interview was used to subtype patients as hyperactive, hypoactive, or mixed.[4]

We compared baseline characteristics and plasma orexin-A levels between patients with and without delirium using the χ^2 test, Fisher's exact test, *t*-test, or Mann–Whitney test. The association of plasma orexin-A levels with primary diagnosis was evaluated by using the Kruskal–Wallis test. We also evaluated the association of orexin-A levels with delirium severity (Pearson's correlation coefficient) and delirium subtypes (one-way ANOVA). On days 10–12, patients underwent re-evaluation and blood sampling. Differences in orexin-A levels between the first and second blood samples were examined (paired *t*-test). Any missing data were not imputed. A *P*-value <0.05 was considered statistically significant. All analyses were performed with SPSS version 25 (IBM, Armonk, NY, USA). We calculated the sample size by predicting that 20% of patients would develop delirium and by referencing studies that examined plasma orexin-A levels in patients with other diseases.[5,6] Accordingly, we determined that we would need 14–63 patients (*t*-test, $\alpha = 0.05$, $\beta = 0.80$).

Among the 93 consecutive older patients admitted during the study period, 23 were excluded based on the exclusion criteria, leaving 70 patients for inclusion (Fig. S1). The primary diagnoses were infectious disease ($n = 16$), cardiac disease ($n = 8$), stroke ($n = 7$), dementia ($n = 6$), gastrointestinal system disorders ($n = 5$), neurological disorders other than stroke ($n = 5$), and others ($n = 23$). Delirium developed in 15 patients (21.4%). There was no significant difference in the levels of orexin-A between patients with and without delirium ($P = 0.100$) (Table 1). The primary diagnosis was not associated with orexin-A levels ($P = 0.673$). Orexin-A levels had no association with delirium severity ($n = 15$, $P = 0.631$) or delirium subtype ($P = 0.434$) (Fig. S2). Also, there was no difference in orexin-A levels in patients with delirium before and after amelioration ($P = 0.313$) (Table S1).

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Table 1 Participant characteristics and mean plasma orexin-A levels

	All patients (n = 70)	Delirium		P-value[†]
		Yes	No	
Patients, n (%)		15 (21)	55 (79)	
Age (years), mean ± SD	84.8 ± 6.1	84.6 ± 7.1	84.8 ± 5.9	0.91
Male sex, n (%)	35 (50)	8 (53)	27 (49)	0.77
Dementia, n (%)	38 (54)	13 (87)	25 (46)	0.005
Total number of medications[‡], median (IQR)	5 (2–8)	2 (1–6)	5 (2–9)	0.12
Use of psychotropic medications[‡], n (%)	5 (7)	1 (7)	4 (7)	0.71
Use of benzodiazepines[‡], n (%)	10 (14)	1 (7)	9 (16)	0.31
Length of fasting (days), median (IQR)	0 (0–1)	1 (0–3)	0 (0–0)	<0.001
Barthel index[§], median (IQR)	90 (30–100)	30 (5–85)	95 (60–100)	0.001
Lawton IADL score[¶], median (IQR)	3 (0–7)	0 (0–2)	4 (1–7)	0.006
IQCODE-sf[††], median (IQR)	3.7 (3.2–4.5)	4.2 (3.9–4.9)	3.6 (3.1–4.3)	0.008
CCI[‡‡], median (IQR)	2 (1–3)	3 (2–3)	2 (1–3)	0.09
APS component of APACHE II[§§], median (IQR)	3 (2–6)	5 (3–7)	3 (2–6)	0.07
MDAS[¶¶], median (IQR)	6 (3–14)	16 (13–17)	4 (2–10)	<0.001
Orexin-A in plasma (pg/mL), mean ± SD	90.8 ± 29.0	102.1 ± 25.5	88.0 ± 29.7	0.100

[†]Delirium versus no delirium. [‡]Medication on the day before blood sampling. [§]Barthel index ranges from 0 to 100; a higher score indicates higher function. [¶]Lawton IADL score ranges from 0 to 8; a higher score indicates higher function. [††]IQCODE-sf ranges from 1 to 5; a higher score indicates severe pre-existing cognitive impairment. [‡‡]CCI ranges from 0 to 37; a higher score indicates having more comorbidities. [§§]APS component of APACHE II ranges from 0 to 56; a higher score indicates severe physical illness. [¶¶]MDAS ranges from 0 to 30; a higher score indicates severe delirium. APS component of APACHE II, Acute Physiology Score component of the Acute Physiology and Chronic Health Evaluation II; CCI, Charlson Comorbidity Index; IADL, instrumental activity of daily living; IQCODE-sf, Informant Questionnaire on Cognitive Decline-short form; IQR, interquartile range; MDAS, Memorial Delirium Assessment Scale.

The present study revealed there was no difference in plasma orexin-A levels between patients with and without delirium. Although the study also showed that plasma orexin-A levels did not have any association with delirium severity, subtypes or clinical course, the sample size of these secondary analyses was too small so we are unable to draw any conclusions about them. Orexin-A in CSF can be associated with delirium, but plasma orexin-A levels may not reflect CSF orexin-A levels. Orexin-A is apparently secreted not only by the brain but also by the intestine,[7] and the amount of orexin-A from the intestine, as well as plasma orexin-A levels, could be altered by physical stress. Studies comparing CSF orexin, not plasma orexin, between patients with and without delirium would provide crucial data.

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DISCLOSURE

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The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

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Figure S1 Patient selection flow chart.

Figure S2 Plasma orexin-A levels in the four patient groups (n = 70).

Table S1 Mean plasma orexin-A levels at the first and second blood sampling of the four patient groups (n = 47).

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