SHORT REPORT

Nocturnal decrease in vasopressin secretion into plasma in patients with multiple system atrophy

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Abstract

To determine whether the nocturnal decrease in arginine vasopressin (AVP) secretion into the plasma, found in a patient with multiple system atrophy (MSA) reported previously, is a usual finding in MSA, the plasma AVP concentrations in 13 patients with MSA were measured every 4 hours during a 24 hour period. The plasma AVP concentrations in these patients showed significant daily variations and were the lowest during the night. This finding indicates that patients with MSA often exhibit nocturnal decrease in AVP secretion into the plasma. The results suggest the possibility that the system responsible for the daily variations in AVP secretion is involved in MSA.

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Multiple system atrophy (MSA) is a distinct pathological entity characterised by presence of inclusion bodies in glial cells.¹ This neurodegenerative disease is characterised clinically by three adult onset forms—namely, olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome.^{2,3} Most patients with MSA exhibit progressive autonomic failure characterised by orthostatic hypotension, associated with degeneration in the autonomic nervous system. Mathias *et al*⁴ showed that patients with MSA and autonomic failure often exhibited nocturnal polyuria with overnight weight loss, which often accentuated their orthostatic hypotension in the morning. The obvious efficacy of treatment with the vasopressin analogue desmopressin for the nocturnal polyuria, which was established by Mathias and Bannister,^{4,5} suggests that subtle decrease in the plasma concentration of antidiuretic agents during the night could be a predisposing factor for the nocturnal polyuria in MSA; however, the mechanism underlying nocturnal polyuria in patients with MSA remains to be established in detail.

The nocturnal rate of secretion of arginine vasopressin (AVP) into the plasma in healthy people was shown to be higher than the diurnal

rate.^{6,7} The site in the nervous system responsible for the daily variations in AVP secretion is considered to be the suprachiasmatic nucleus of the hypothalamus,^{8,9} which has an essential role in synchronising various physiological functions with the light-dark cycle.¹⁰ As AVP in circulation has a paramount role as an antidiuretic hormone, a decrease in its rate of secretion into the plasma during the night would be expected to result in nocturnal polyuria. Although the functions of episodic AVP secretion into the plasma in MSA have been evaluated previously,¹¹⁻¹³ further investigations on both diurnal and nocturnal AVP secretion are required to ascertain the mechanism of nocturnal polyuria in MSA. We recently reported on a patient with MSA, in which the patient had nocturnal polyuria associated with a decrease in nocturnal AVP secretion, and was successfully treated with nasal administration of desmopressin at night.¹⁴ Detailed neuropathological studies of this patient have shown neuronal loss associated with gliosis in the suprachiasmatic nucleus, which was consistent with the altered regulation of diurnal/nocturnal AVP secretion into the plasma.¹⁵ With this background, this study aimed to determine whether the nocturnal decrease in AVP secretion into the plasma reported in a patient with MSA^{14,15} is a usual finding in MSA.

Methods

SUBJECTS

Thirteen patients with MSA, including the patient in whom the nocturnal decrease in AVP secretion into the plasma was first reported (patient 1), participated in this study (table). They had been admitted to one of three hospitals—the Niigata University Hospital, the Takeda General Hospital, or the National Saigata Hospital—between 1991 and 1998. These hospitals are located at a north latitude between 36 and 38 degrees, and east longitude between 138 and 140 degrees. The clinical diagnosis in the patients was based on the results of neurological examination, including evaluation of autonomic functions, referring to the diagnostic criteria proposed previously.^{2,3} The findings on brain MRI in MSA¹⁶ were of help in our diagnosis. None of the patients had a family history of ataxia, parkinsonism, or dementia. None of them had any electrolyte

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Clinical features of subjects

Patient	Age (y)	Sex	Duration (y)	Cerebellar ataxia	Pyramidal signs	Parkinsonism	OH	Clinical diagnosis
1	67	M	4	+	–	+	2+	SDS
2	48	M	2	+	+	+	1+	SDS
3	58	M	6	+	+	+	1+	SDS
4	65	F	5	+	–	+	1+	SDS
5	66	F	1	+	+	+	–	OPCA
6	54	M	2	+	+	+	2+	OPCA
7	55	M	4	+	+	+	1+	SDS
8	62	M	2	+	–	+	2+	SDS
9	53	M	2	+	+	+	1+	OPCA
10	63	M	4	+	–	+	2+	SDS
11	54	M	5	+	+	+	1+	SND
12	49	F	1	+	+	+	1+	OPCA
13	59	F	1	+	+	+	–	OPCA

OPCA=olivopontocerebellar atrophy; SDS=Shy-Drager syndrome; SND=striatonigral degeneration; OH=orthostatic hypotension; –=absent; +=present; 1+=systolic blood pressure decreased by 30 mm Hg on standing; 2+=systolic blood pressure decreased by 50 mm Hg on standing.

disorder, cardiac failure, atrial fibrillation, diabetic mellitus, or renal insufficiency. They had no history of endocrine disturbances; none of them had features suggestive of diabetes insipidus or the syndrome of inappropriate secretion of antidiuretic hormone. None of the patients had any history of epilepsy or psychiatric disturbances, and their usual sleep-wake habits were normal. Informed consent was obtained from all the patients before investigations were performed.

SAMPLING METHODS

Blood samples were obtained from the patients every 4 hours during a 24 hour period, at 0800, 1200, 1600, 2000, 2400, and 0400. To avoid the stress of repeated venepuncture in the patients, all the samples were collected via a heparin lock. Plasma AVP concentrations were determined by radioimmunoassay, and the plasma osmolalities were also measured. The plasma was separated immediately and stored at -70°C until assay. In the assay for AVP, the intra-assay and interassay coefficients of variation were 1.7% and 3.5%, respectively, and the sensitivity of the assay was 0.2 pg/ml. The plasma AVP concentrations of 15 healthy people (age range 34–78 years), in plasma samples obtained with the patients in a supine position, ranged between 0.9 and 3.7 pg/ml. The time of lights out was set at 2100 in our hospitals. The urinary excretion rates and urinary osmolalities were determined in urine samples collected during the day (0800–2100) and in those during the night (2100–0800).

PROTOCOLS

A day before the study was started, the patients were instructed to abstain from smoking and drinking alcohol or caffeine containing beverages, all of which could influence the plasma AVP concentrations. To avoid the episodic changes in AVP secretion, which could result from drinking water, eating, or standing, the following protocol was prepared. On the day of the study, the patients were asked to limit their intake of drinking water to less than 5 ml/kg/h and not to drink water during the hour before blood sampling. Breakfast and lunch were served after the blood samplings at 0800 and 1200, respectively, and the subjects were instructed to finish dinner, which was served at 1800, by 1 hour before blood sampling at 2000.

No other oral intake was permitted. Patients were instructed to lie down in the supine position during the hour before blood sampling. After lights out, the patients were asked to remain in bed whether they were asleep or awake.

No drugs that are known to affect AVP secretion were administered to the subjects before blood sampling—namely, metoclopramide which affects AVP secretion via the cholinergic pathway,¹⁷ and levodopa or naloxone which affect AVP secretion via the dopaminergic or the opioid pathway, respectively.¹⁸ Carbamazepine¹⁹ or other antipsychotic drugs,²⁰ which could possibly affect AVP secretion, were not administered to the patients during the study period.

DATA ANALYSIS

All the values shown are mean (SEM). The plasma AVP concentrations and plasma osmolalities obtained at the different sampling times were compared using analysis of variance (ANOVA) with one way repeated measures. A paired *t* test was used to compare the data of diurnal urine with those of nocturnal urine. *p* Values <0.05 were considered to indicate a significant difference.

Results

The plasma AVP concentrations at each sampling time, starting from 0800, were 3.10 (0.61), 2.54 (0.54), 2.43 (0.54), 2.30 (0.53), 1.83 (0.26), and 2.33 (0.37) pg/ml, respectively, indicating a significant daily variation (ANOVA; $F(5, 60)=3.52$, $p=0.007$), which showed a descent to the lowest mean at 2400 (figure). The plasma osmolalities at each sampling time, starting from 0800, were 290.1 (3.0), 289.2 (2.2), 289.0 (1.6), 290.3 (3.5), 289.1 (2.5), and 290.3 (3.6) mOsm/kg, respectively, showing no significant daily variation (ANOVA, $p=0.979$). The diurnal and nocturnal urinary excretion rates were 51.9 (5.5) and 78.7 (10.9) ml/h, respectively. The diurnal and nocturnal urinary osmolalities were 565.9 (25.0) and 463.8 (26.8) mOsm/kg, respectively. The nocturnal urinary excretion rates were significantly higher than the diurnal urinary excretion rate ($p=0.016$), and the nocturnal urinary osmolalities were significantly lower than the diurnal urinary osmolalities ($p=0.029$).

Plasma AVP concentrations at six times of the day in 13 patients with MSA. The values shown represent the mean (SEM). The mean plasma AVP concentrations at each sampling time showed significant daily variations (ANOVA; $F(5, 60)=3.52$, $p=0.007$), being the lowest at 2400.

Discussion

This study showed daily variations in AVP secretion into the plasma, with a decreased rate of secretion during the night, in our patients with MSA. The nocturnal rate of secretion of AVP into the plasma in healthy adult subjects (age range 19–45 years) is higher than the diurnal rate,^{6,7} whereas in elderly subjects (age range 60–90 years), the nocturnal rate is the same as the diurnal rate,²¹ suggesting an effect of aging on nocturnal AVP secretion into the plasma. In this study, because the age of the patients ranged between 48 and 67 years, the nocturnal decrease in AVP secretion into the plasma cannot be attributed simply to aging. These results indicate that a nocturnal decrease in AVP secretion into the plasma is a frequent accompaniment of MSA. The increase in nocturnal urinary excretion rate as well as the decrease in nocturnal urinary osmolalities found in this study could be consequences to the nocturnal decrease in AVP secretion into the plasma. Although other hormones controlling urinary volume must also be investigated, our results indicate the possibility that the nocturnal decrease in AVP secretion into the plasma is one of the factors predisposing to nocturnal polyuria in MSA, which has been clearly demonstrated by Mathias and Bannister.^{4,5} Our study further provides a possible rationale behind the efficacy of a previously established treatment method: desmopressin given at night reduces nocturnal polyuria and reverses the overnight weight loss.⁴

The osmoregulatory mechanism responsible for AVP secretion into the plasma,²² which has been reported to be preserved in MSA,¹³ is not considered to be involved in the nocturnal decrease in AVP secretion noted in this study, because no differences in plasma osmolalities were found among the samples obtained at different sampling times. Because in patients with MSA, blood pressure cannot often be maintained within the normal range during the day due to orthostatic hypotension,²³ the plasma AVP concentration during the day was presumed to be raised via the baroregulatory mechanism regulating AVP secretion into the plasma.¹¹ However, the AVP response to orthostatic hypotension is weakened in MSA because the afferent cardiovascular pathways, a

major component of the baroregulatory mechanism regulating AVP secretion, are defective in patients with MSA.¹² This indicates that the daily variations in AVP secretion noted in this study were unlikely to be consequences of the orthostatic hypotension. Furthermore, the patients were instructed to lie down during the hour before blood sampling, thereby excluding the possibility that the upright posture was responsible for the increased plasma AVP concentrations noted in the daytime samples in the present study.

Considering the involvement of the hypothalamic neurons responsible for AVP secretion into the plasma (the supraoptic nuclei and paraventricular nuclei), there was a report of a patient with Shy-Drager syndrome exhibiting diabetes insipidus²⁴; however, none of the patients in this study exhibited any features of this disorder. As the findings presented here reflect an altered pattern of diurnal and nocturnal AVP secretion, the system involved in the regulation of circadian rhythms is probably affected in MSA. We performed a detailed neuropathological examination in patient 1, and found neuronal loss associated with gliosis in the suprachiasmatic nucleus, whereas neurons in the supraoptic nuclei or paraventricular nuclei were well preserved.¹⁵ Taken together, our results indicate the possibility that the nocturnal decrease in AVP secretion into the plasma presented here is associated with the involvement of the suprachiasmatic nucleus. To confirm this speculation, further neuropathological analyses of the suprachiasmatic nucleus on a larger number of patients with MSA would be required. The function of the hypothalamic-pituitary-adrenal axis, which is considered to be mediated by the suprachiasmatic nucleus,²⁵ must also be investigated in MSA.

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