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Plasma arginine vasopressin level in hypothyroid women in relation to dietary sodium supply

Stężenie argininowazopresyny w osoczu u kobiet z niedoczynnością tarczycy w zależności od zawartości sodu w diecie

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Abstract

Introduction: A disturbed regulation mechanism of arginine vasopressin secretion in response to plasma osmolality and volaemia changes occurs in hypothyroidism. The aim of this study was to determine plasma arginine vasopressin concentration in hypothyroid women under conditions of a low sodium diet and in an upright position.

Material and methods: Twenty-six women with primary hypothyroidism and 24 healthy women (control group) were investigated. In all the patients, the plasma arginine vasopressin and serum sodium and potassium levels, as well as plasma osmolality, were measured first under basal conditions, i.e. after three days of a normal sodium diet (120 mmol sodium per day) in a horizontal position, and next after three days of a low sodium diet (10 mmol Na per day) in an upright position. In hypothyroid patients, the investigations were repeated after a euthyroid state as a result of L-thyroxine treatment had been attained.

Results: An increase of vasopressinaemia, measured under basal conditions as well as after three days of the low sodium diet, was shown in untreated hypothyroid patients compared to the control group. The arginine vasopressin plasma level normalised after a euthyroid state had been attained. As a result of the low sodium diet and the upright position, a significant increase of arginine vasopressin secretion was observed in the control group and hypothyroid women in the euthyroid state. No significant increase of this neuropeptide level in untreated patients was shown while applying the low sodium diet and upright position. Plasma osmolality and natraemia were decreased in the untreated hypothyroid patients. No correlation between vasopressinaemia and plasma osmolality was shown.

Conclusion: The plasma arginine vasopressin level is increased in hypothyroid women, and does not change in the upright position under the influence of a low sodium diet. **(Pol J Endocrinol 2012; 63 (1): 18–21)**

Key words: *hypothyroidism, arginine vasopressin, low sodium diet*

Streszczenie

Wstęp: W niedoczynności tarczycy stwierdzono zaburzenia mechanizmu regulacji uwalniania argininowazopresyny w odpowiedzi na zmiany wolemii i osmolalności osocza. Celem pracy było określenie stężenia argininowazopresyny w osoczu kobiet chorych na niedoczynność tarczycy w warunkach diety ubogosodowej wraz z pionizacją.

Materiał i metody: Badania przeprowadzono u 26 kobiet z pierwotną niedoczynnością tarczycy i 24 kobiet zdrowych (grupa kontrolna). U wszystkich badanych kobiet określono stężenie argininowazopresyny w osoczu, sodu i potasu w surowicy krwi oraz osmolalność osocza, najpierw w warunkach podstawowych, czyli po 3-dniowej diecie normosodowej, zawierającej 120 mmol sodu na dobę, w pozycji leżącej, a następnie po 3-dniowej diecie ubogosodowej (10 mmol Na/dobę) i pionizacji. U chorych na niedoczynność tarczycy badania powtórzono w okresie eutyreozy po leczeniu L-tyroksyną.

Wyniki: W porównaniu do grupy kontrolnej u nieleczonych chorych z niedoczynnością tarczycy wykazano zwiększenie wazopresynemii badanej w warunkach podstawowych i w warunkach diety ubogosodowej wraz z pionizacją. Stężenie hormonu w osoczu uległo normalizacji w okresie eutyreozy po leczeniu substytucyjnym. W następstwie stosowania diety ubogosodowej wraz z pionizacją obserwowano istotne pobudzenie wydzielania argininowazopresyny u kobiet z grupy kontrolnej i leczonych chorych z niedoczynnością tarczycy w okresie eutyreozy. U nieleczonych chorych nie wykazano istotnego wzrostu stężenia tego neuropeptydu, kiedy stosowano dietę ubogosodową wraz z pionizacją. U nieleczonych chorych na niedoczynność tarczycy osmolalność osocza i natremia były obniżone. W badaniach korelacyjnych nie stwierdzono współzmienności pomiędzy wazopresynemią a osmolalnością osocza.

Wniosek: U kobiet chorych na niedoczynność tarczycy stężenie argininowazopresyny w osoczu jest zwiększone i nie zmienia się pod wpływem diety ubogosodowej wraz z pionizacją. **(Endokrynol Pol 2012; 63 (1): 18–21)**

Słowa kluczowe: *niedoczynność tarczycy, argininowazopresyna, dieta ubogosodowa*

Introduction

Disturbances in salt and water metabolism occur in hypothyroidism, mainly as impaired free water excretion through the kidneys accompanied by hyponatraemia [1]. In the mechanism of this phenomenon, several factors are taken into consideration, among them the direct effect of thyroid hormones deficiency in the

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sodium-potassium ATP-ase activity attenuation in the proximal renal tubules with a decrease of sodium reabsorption [2] and arginine vasopressin (AVP) influence (through aquaporin 2) on water reabsorption in the renal tubules in the medulla [3].

Hypothyroidism frequently leads to plasma AVP level changes. Previous studies have found ambiguous results: in some, a vasopressinaemia decrease has been shown in hypothyroidism [4–6], while others have shown an increase both in people [7–9] and animals [3]. A few studies have shown that the AVP level in hypothyroidism has been the same as in healthy people [10, 11]. The syndrome of inappropriate AVP secretion in hypothyroidism has also been described [12–14]. Disturbed AVP secretion in response to plasma osmolality and volaemia changes is suggested in hypothyroid patients [5, 7, 9, 11, 15] and experimental animals [4]. Acute water loading has not led to the suppression of AVP secretion [9, 11, 15]. Other studies have shown the attenuation of the influence of increased plasma osmolality on this neurohormone secretion [5]. Significantly higher vasopressinaemia has been observed in animals with experimental hypothyroidism in spite of the lower plasma osmolality [3]. The mechanisms regulating vasopressinaemia in hypothyroidism have not yet been fully explained.

The aim of this study was to establish the plasma AVP level in women with hypothyroidism taking into consideration the upright position and a differentiated diet with low and normal sodium content.

Material and methods

Twenty-six women with primary hypothyroidism, aged 37.1 ± 8.4 (mean ± SD) years, were investigated. The hypothyroidism had been caused by autoimmune thyroid inflammation in 20 women, and by surgical treatment in the other six. It was established that the duration of hypothyroidism symptoms had lasted for 1–50 (mean 15.5) months. The disease was diagnosed on the basis of the clinical picture and TSH, serum free T4 and free T3 concentration measurements. The investigations were repeated after the establishment of a euthyroid state resulting from a mean seven months (range 4–9 months) of substitutional L-thyroxine (Merck Euthyrox N) treatment with a mean daily dose of 155 ± 50 μg. Twenty-four healthy women aged 35.4 ± 7.2 years were designated the control group (C). The patients were hospitalised. The study was approved by the Local Ethics Committee of the Medical University of Silesia. In all the patients, the plasma AVP and serum sodium and potassium levels, as well as plasma osmolality, were measured first under basal conditions, i.e. after three days of a normal sodium diet containing 120 mmol sodium and 70 mmol potassium per day in a horizontal position after an eight-hour sleep. Next, the investigations were undertaken after three days of a low sodium diet (10 mmol Na and 70 mmol K per day) and two hours in the upright position (lsdp).

Blood samples were taken in a fasting state at about 8 am from the ulnar vein. The blood samples with EDTA were immediately whirled in a centrifuge cooled to 4°C. The plasma was stored in a refrigerator at –30°C before measurements were taken.

The AVP plasma level was measured with a radioimmune method using the kit obtained from the Institute for Research, Productions and Applications of Radioisotopes, Prague, Czech Republic. Plasma osmolality was calculated according to the following formula: plasma osmolality [mosm/kg H_2O] = 2 × sodium concentration (mmol/l) + glucose concentration [mmol/l]) + urea concentration [mmol/l] [5]. Heart rate and blood pressure were measured in the morning after a 20 minute rest in the sitting position in hypothyroid patients before treatment, and again after achieving euthyreosis, as well as in the C group. Mean heart rate and blood pressure were calculated on the basis of three consecutive measurements in all cases. Body Mass Index (BMI) was also determined.

The obtained results were analysed using Statistica software. It was assessed with the Shapiro–Wilk test whether the analysed parameter featured a distribution deviating from or close to normal. Next, *t*-Student tests for paired and unpaired variables were applied for data from a normal distribution and U-Mann–Whitney and Wilcoxon tests for data not following the normal distribution. The correlation coefficients 'r' were calculated in the correlation studies with the Pearson or Spearman rank tests. The statistical significance of the differences was established at the $p < 0.05$ level.

Results

The characteristics of the investigated patients, including the serum TSH and free thyroid hormones levels, as well as BMI, systolic and diastolic blood pressure and heart rate, are presented in Table I.

In hypothyroid patients before treatment and after achieving euthyreosis, the systolic and diastolic blood pressures were higher than in the C group. In comparison with the C group, an increase of vasopressinaemia measured under basal conditions ($p < 0.001$) and after lsdp ($p < 0.01$) was shown in untreated patients (Table II). The plasma level of AVP returned to normal in euthyreosis as a result of substitutional L-thyroxine treatment. AVP significant secretion stimulation after lsdp was observed in healthy individuals ($p < 0.05$) and treated hypothyroid patients during euthyreosis ($p < 0.01$) (Table II). In the untreated patients after lsdp, no significant increase of this neuropeptide concentration was shown. Plasma

Table I. *Characteristics of the investigated women (x ± SEM)*

Tabela I. *Charakterystyka badanych kobiet (x ± SEM)*

Parameter	Investigated groups			Statistical significance of differences (p)
	Control group (n = 26) C	Hypothyroid patients (n = 24)		
		Before treatment A	After attainment of euthyroid state, B	
Body mass index [kg/m^2]	26.2 ± 0.9	28.2 ± 0.5	26.9 ± 0.8	NS
Serum TSH level [mIU/l]	1.75 ± 0.29	38.42 ± 3.12	2.60 ± 0.41	A:C < 0.001 B:A < 0.001
Serum free T3 level [pmol/l]	5.68 ± 0.39	2.03 ± 0.21	5.53 ± 0.32	A:C < 0.001 B:A < 0.001
Serum free T4 level [pmol/l]	14.62 ± 0.89	5.08 ± 0.62	16.93 ± 1.27	A:C < 0.001 B:A < 0.001
Systolic blood pressure [mm Hg]	115.8 ± 2.6	125.6 ± 3.4	124.7 ± 2.9	A:C < 0.05 B:C < 0.05
Diastolic blood pressure [mm Hg]	78.6 ± 2.3	90.1 ± 2.1	85.3 ± 2.5	A:C < 0.001
Heart rate [beats/min]	78.5 ± 1.6	72.5 ± 1.6	76.9 ± 2.0	A:C < 0.05

NS — not significant

Table II. *Plasma arginine vasopressin (AVP), plasma osmolality and serum electrolytes levels in hypothyroid and healthy women (x ± SEM)*

Tabela II. *Stężenie argininowazopresyny (AVP) i osmolalność osocza oraz stężenie elektrolitów w surowicy kobiet z niedoczynnością tarczycy i zdrowych (x ± SEM)*

Parameter		Investigated groups			Statistical significance of differences (p)
		Control group (n = 24), C	Hypothyroid patients (n = 26)		
			Before treatment, A	After attainment of euthyroid state, B	
Plasma AVP level [pg/ml]	I	2.60 ± 0.18	3.98 ± 0.39	2.61 ± 0.32	A:C < 0.001 B:A < 0.01
	II	3.10 ± 0.21*	4.19 ± 0.36	3.43 ± 0.31**	A:C < 0.01 B:A < 0.05
Plasma osmolality [mosm/kg H_2O]	I	286.1 ± 0.9	282.1 ± 0.8	286.9 ± 1.1	A:C < 0.01 B:A < 0.001
	II	286.4 ± 1.1	282.3 ± 1.1	287.3 ± 1.4	A:C < 0.01 B:A < 0.001
Serum sodium level [mmol/l]	I	139.0 ± 0.5	136.7 ± 0.4	139.2 ± 0.5	A:C < 0.01 B:A < 0.001
	II	139.1 ± 0.5	136.4 ± 0.5	139.3 ± 0.6	A:C < 0.01 B:A < 0.001
Serum potassium level [mmol/l]	I	4.32 ± 0.06	4.47 ± 0.06	4.42 ± 0.05	NS
	II	4.46 ± 0.05	4.58 ± 0.06	4.53 ± 0.07	NS

I — normal sodium diet; II — low sodium diet and upright position; in comparison with the values under basal conditions: *p < 0.05, **p < 0.01; NS — not significant

osmolality and natraemia in the untreated hypothyroid patients were lower than after treatment and in the C group, independently of the dietary sodium supply (Table II). The plasma level of AVP in hypothyroid women was negatively correlated with the serum free T3 concentration ($r = –0.44$; $p < 0.05$). No correlation was found between vasopressinaemia and plasma osmolality.

Discussion

A literature survey shows that in hypothyroid patients and experimental animals with deficient thyroid hormones, the plasma AVP level has proved to be ambiguous, from increased through normal to decreased. The ambiguities in the results of these studies have not yet

been fully explained. On the basis of the presented investigations, the plasma AVP level measured under basal conditions and after the lsdp was higher in the hypothyroid women than in the healthy ones. The vasopressinaemia increase measured under basal conditions has also been seen in other studies dealing with hypothyroid patients [7–9] and experimental animals [3].

In the literature there are also casuistical descriptions of severe hypothyroidism, often with accompanying myxoedema coma and high AVP plasma level as well as decreased natraemia and osmolality, indicative of the Syndrome of Inappropriate AVP secretion (SIAVP) [12–14]. However, other studies have shown that in hypothyroidism, a vasopressinaemia increase has not been observed [10, 11] and it has even been seen to decrease [4–6]. The different directions of blood AVP level changes in hypothyroidism may indicate the contribution of many factors to the complex mechanism of production, secretion and degradation of this hormone in the conditions of thyroid hormones deficiency.

In hypothyroid patients, Laczi et al. [7] have shown a decrease of the plasma osmolality threshold conditioning the AVP secretion. Iwasaki et al. [5] have observed a substantially lower vasopressinaemia increase, as a result of the induced plasma hyperosmolality, than in patients with normal thyroid function. A similar reduction of the plasma AVP level increase after hypovolaemic stimulation has been observed in experimental hypothyroidism in animals [4]. A similar mechanism regulating the AVP secretion into blood circulation may have also occurred in our own research, because the vasopressinaemia in the investigated hypothyroid women was increased in spite of the fact that the plasma osmolality was lower than the one shown in the patients with euthyreosis. In our study, it has been shown that in respect to the results obtained under basal conditions, no significant vasopressinaemia changes occurred as a result of the lsdp of short duration in the investigated hypothyroid women compared to the euthyroid patients treated with L-thyroxine and healthy individuals showing an increased secretion of this hormone. Assuming that applying the low sodium diet leads to volaemia reduction, the AVP secretion stimulation should have been expected. The lack of hypothalamic-pituitary system response, involving the AVP secretion, to applying the lsdp in hypothyroid women may be connected to the disturbed sensitivity of this system to the volaemia changes. AVP secretion inhibition did not occur as a result of increased volaemia and reduced plasma osmolality under conditions of thyroid hormones deficiency in people [15] or experimental animals [3]. In this investigation it was shown that a lack of significant correlation between plasma osmolality and vasopressinaemia in hypothyroid women may be indicative of the disturbed AVP secretion osmoregulation. Other investigators [11] have shown a similar lack of correlation between the plasma AVP level and its osmolality in hypothyroid patients. Moreover, they have not observed the neurohormone secretion inhibition as a result of the osmolality reduction induced in these patients with acute water load. Salomez-Granier et al. [16] have even shown a negative correlation between the plasma osmolality and vasopressinaemia in hypothyroid patients, which may contradict the physiological AVP secretion osmoregulation.

The normalisation of AVP concentration and its significantly increased secretion occurred in euthyreosis as a result of the hormonal L-thyroxine substitution after applying the lsdp. It should be pointed out that in the studies of Ota et al. [11], the restoration of normal AVP secretion inhibition was observed in the treated hypothyroid patients after an acute water load.

Conclusion

In hypothyroid women, the plasma arginine vasopressin level is increased and remains unaltered after the application of a low sodium diet and in the upright position.

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