Endokrynologia Polska
Tom/Volume 63; Numer/Number 6/2012
ISSN 0423–104X

The role of orexin A in metabolic disturbances in patients with acromegaly

Znaczenie oreksyny A w zaburzeniach metabolicznych w akromegalii

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Abstract

Introduction: It has been reported that orexins may play an important role in GH regulation. Orexins participate in the regulation of pituitary hormones secretion, food intake regulation, and the sleep-wake cycle. It has been suggested that a defect of orexin A synthesis could be responsible for disturbances in GH synthesis in patients with acromegaly, and consequently aggravate metabolic disturbances caused by high levels of IGF1.

The aim of this study: The aim of this study was to assess orexin A levels in relation to the activity of the disease and the influence on metabolic profile in patients with acromegaly.

Material and methods: The subjects were 55 acromegalic patients divided into three main groups: a surgically cured acromegalic group (SCA); a well-controlled acromegalic group (WCA); an active acromegalic group (AA); and 29 healthy controls. In all subjects, blood samples were taken to assess the concentration of orexin A, lipids, glucose, insulin and hormones of the pituitary and peripheral glands.

Results: The concentration of orexin A was highest in the control group (CG) and lowest in the WCA group. The differences of orexin A concentration were statistically significant when each group of acromegalics were compared to the CG. There were no significant differences in orexin A concentration among the studied groups of patients with acromegaly. The metabolic disturbances were more often observed in the groups of acromegaly patients. In the AA group, orexin A concentrations correlated negatively with plasma lipids.

Conclusions: The concentration of orexin A is reduced in acromegaly compared to healthy subjects. **(Endokrynol Pol 2012; 63 (6): 463–469)**

Key words: *acromegaly, orexin A, metabolic disturbances*

Streszczenie

Wstęp: Sugeruje się, że oreksyny mogą odgrywać ważną rolę w regulacji wydzielania hormonu wzrostu (GH). Oreksyny biorą udział w regulacji wydzielania hormonów przysadki, regulacji w zakresie pobierania pokarmu i regulacji rytmu sen–czuwanie. Wydaje się, że zaburzenia w syntezie oreksyny A mogą być odpowiedzialne za zaburzenia w syntezie GH u pacjentów z akromegalią, a tym samym mogą nasilać zaburzenia metaboliczne spowodowane przez wysokie wartości IGF1.

Cel pracy: Celem pracy była ocena zaburzeń syntezy oreksyny A u osób chorujących na akromegalię, w korelacji z aktywnością choroby i wpływem na profil metaboliczny u tych pacjentów.

Materiał i metody: W badaniu wzięło udział 55 chorych na akromegalię, których podzielono na trzy podstawowe grupy: chirurgicznie wyleczona akromegalia (SCA), dobrze kontrolowana akromegalia (WCA), aktywna akromegalia (AA), oraz 29 osób stanowiących grupę kontrolną (CG). W każdej z grup oznaczono stężenie oreksyny A, stężenie lipidów, glukozy, insuliny oraz hormony przysadki i gruczołów obwodowych.

Wyniki: Stężenie oreksyny A było największe w grupie CG, a najmniejsze w grupie WCA. Różnice stężeń oreksyny A były istotne statystycznie między wszystkimi grupami chorych na akromegalię a grupą kontrolną. Brak było znamiennych statystycznie różnic stężeń oreksyny A pomiędzy poszczególnymi grupami w obrębie chorych na akromegalię. Zaburzenia metaboliczne były częściej obserwowane w grupach pacjentów z akromegalią. W grupie AA stężenie oreksyny A korelowało ujemnie ze stężeniami lipidów.

Wniosek: Stężenie oreksyny A jest obniżone u chorych na akromegalię w porównaniu z grupą kontrolną. **(Endokrynol Pol 2012; 63 (6): 463–469)**

Słowa kluczowe: *akromegalia, oreksyna A, zaburzenia metaboliczne*

Introduction

Acromegaly is a rare disease caused by GH and IGF1 oversecretion. It is characterised by greater mortality compared to the general population, mainly due to metabolic disturbances and cardio-vascular complications [1–3]. The release of GH is regulated by many substances, and it has been reported that peptides such as orexins play an important role in the regulation of GH secretion [4, 5].

Orexins, recently discovered neuropeptides, are synthesised mainly in the posterolateral hypothalamus as well as peripherally. The presence of orexins receptors has been revealed in the pituitary gland at both gene

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and protein levels. It has been shown in gild glands that their expression is modulated during the oestrous cycle and by the steroid milieu [6]. The extent of the orexins and their receptors occurrence indicates their pleiotropic action, of the neurotransmitters as well as neuromodulators. Additionally, due to secretion into the peripheral blood, it has been assumed that they act as hormones [7, 8]. They participate in the regulation of pituitary hormones secretion, food intake regulation, and the sleep-wake cycle [9]. It has been suggested that a defect of orexins synthesis, mainly of orexin A, could be responsible for disturbances in GH synthesis and consequently aggravate metabolic disturbances caused by high IGF1 levels.

The projections of the orexins' fibres come in the area of the classical nuclei, controlling GH secretion such as the periventricular nucleus (mainly expression of somatostatin) and the arcuate nucleus (the expression of GHRH [Growth Hormone-Releasing Hormone]) [10]. It has been shown that in these nuclei the orexins fibres coexist with the neurons showing orexins' receptors expression. The impact of orexins on GH secretion is not clear. Studies to date have reported the suppression as well as the stimulation of GH secretion as a result of the influence of orexins [4, 5, 11].

Chen and Xu, in an experiment using porcine somatotropes, showed that orexin increased *in vitro* GH response to a single injection of orexin B and to the co-administration of orexin A and GHRH. It has been suggested that orexin A increases the sensitivity of somatotropic cells to stimulation by GHRH [4]. On the other hand, other studies have shown that the administration of orexin A caused a decrease in GH secretion in rats [12]. The injection of orexin A in rats has decreased the spontaneous secretion of GH, whereas *in vivo* no changes have been noticed in GH response to GHRH under the influence of orexin A [4]. It has been observed that the intraventricular administration of orexin A leads to a block of releasing of GH and GH response to ghrelin. It is possible that orexin A inhibits endogenous GHRH, and that it has no influence on GH responses to exogenously administered GHRH [5]. Xu et al. reported that orexin A augmented L-type Ca^{2+} current in somatotropes. Moreover, they suggested that orexin might play an important role in the regulation of GHRH-stimulated GH secretion via an increase in the L-type Ca^{2+} current and protein kinase C-mediated signalling pathways [12]. Orexin A may be involved in the regulatory mechanism of nutritional status and GH release [9].

The aim of our case-control study was the analysis of orexin A concentrations in patients with acromegaly in relation to the activity of disease and the influence on metabolic profile in patients with acromegaly.

Material and methods

The study was carried out in 55 patients with acromegaly aged 23–83 years (mean 50.85 ± 5.24), 39 women and 16 men, divided into three main groups according to the minimal GH concentration found during an oral glucose tolerance test (OGTT) and the IGF1 concentration. Normal, according to the age and sex concentration of IGF1 and the level of GH during the OGTT test below 1 μg/L (ng/mL), was considered as a criterion of cure or good disease control. 18 patients with cured acromegaly were included in the surgically cured acromegalic (SCA) group. 17 patients, after failed neurosurgery, who were being treated with a long-acting octeotide, were included in the well-controlled acromegalic (WCA) group. 20 patients who did not meet the criteria for the cure or good control of the disease were included in the active acromegalic (AA) group. In this group, 15 patients had unsuccessful transsphenoidal surgery. Only four patients with acromegaly underwent radiation therapy (two in the AA and one in the WCA and SCA groups). 29 healthy subjects aged 21–77 years (mean 47.86 ± ± 15.76), 23 women and six men, were enrolled to the control group (CG). The CG was sex- and age-matched. 23 patients with acromegaly required hydrocortisone and 22 L-thyroxin replacement. The number of subjects who required hormonal replacement was similar in each group of patients, and there was no statistically significant difference between groups. We did not observe panhypopituitarism in any patient. Thirteen patients with acromegaly and type 2 diabetes mellitus were treated with oral hypoglycaemic agents. Nineteen subjects among the studied received statin therapy: five in the AA, four in the WCA and five each in the SCA and CG groups, respectively. All subjects were recruited from patients of the Department of Endocrinology, Diabetology and Isotope Therapy, Wroclaw Medical University. The protocol of the study was approved by the local Bioethics Committee, and all subjects gave their informed consent.

The analyses were performed based on a division into groups. The first division was done on the basis of the activity of the disease. In the second division, the analysis was performed between the AA group, a group of patients with clinically and biochemically compensated acromegaly (WCA + SCA), and the CG. The group of patients with acromegaly (CC + SCA + + WCA) and the CG were isolated in the third division. All patients belonging to the AA and the WCA groups were treated with Octreotide-LAR (long-acting release) at different doses, but most, irrespective of their group, were given the highest dose (30 mg). Five patients in the AA and six in the WCA groups were treated with Octreotide-LAR at 20 mg, and two patients in the AA

Table I. *General characteristics of groups of patients with acromegaly and the control group (basal demographics)*
Tabela I. *Ogólna charakterystyka grup pacjentów z akromegalią i grupy kontrolnej (podstawowe dane)*

Group	Age (years)	Body mass [kg]	Height [m]	BMI [kg/m^2]
AA	50.8 ± 5.2	88.1 ± 21.8*	1.7 ± 0.1$^{\#\,\wedge\,\dagger}$	29.3 ± 5.1
WCA	55.3 ± 12.4	81.4 ± 14.4	1.65 ± 0.09	29.7 ± 4.7*
SCA	54.0 ± 11.5	88.0 ± 14.5*	1.65 ± 0.1	31.7 ± 4.4*
CG	47.8 ± 15.7	74.7 ± 14.9	1.67 ± 0.0	26.8 ± 4.5
WCA + SCA	54.6 ±11.8	84.8 ± 14.6*	1.66 ± 0.09	30.7 ± 4.6*
AA + WCA +SCA	53.2 ± 13.6	86.0 ± 17.5*	1.68 ± 0.11	30.2 ± 4.8*

AA — active acromegaly group; WCA — well-controlled acromegaly group; SCA — surgically cured acromegaly group; CG — control group; $^{*}p < 0.05$ compared to CG group; $^{\#}p < 0.05$ compared to WCA group; $^{\wedge}p < 0.05$ compared to SCA group; $^{\dagger}p < 0.05$ compared to WCA + SCA group

Table II. *Results of hormonal and biochemical analyses in groups of patients with acromegaly and the control group*
Tabela II. *Wyniki badań hormonalnych i biochemicznych w grupach pacjentów z akromegalią i w grupie kontrolnej*

Group	GH 0 min [ng/mL] [μg/L]	GH 120 min [ng/mL] [μg/L]	IGF-1 [ng/mL]	Orexin A [pg/mL]	Fasting glucose [mg%]	TCH [mg/dL]	LDL [mg/dL]	HDL [mg/dL]
AA	11.5 ± 14.93*$^{\#\,\wedge\,\dagger}$	9.65 ± 10.56 *$^{\#\,\wedge\,\dagger}$	540.5 ± 263.9*$^{\#\,\wedge\,\dagger}$	28.5 ± 15.4*	102.6 ± 22.8*$^{\wedge\,\dagger}$	200.6 ± 44.3	127.6 ± 38.4	44.8 ±10.4*
WCA	2.21 ± 2.11*	1.44 ± 1.5*$^{\wedge}$	215.5 ± 129.7	26.7 ± 17.1*	95.7 ± 14.4*$^{\wedge}$	190.9 ± 46.8$^{\wedge}$	110.7 ± 41.7$^{\#}$	55.8 ±15.9
SCA	1.32 ± 2.04	0.98 ± 2.79	164.9 ± 86.1	31.5 ± 11.5*	83.7 ± 10.1*	226.2 ± 37.2*	144.0 ± 40.6*	54.2 ±11.2
CG	1.51 ± 2.82	0.50 ± 1.09	153.9 ± 79.6	39.2 ± 15.4	88.7 ± 10.6	197.2 ± 41.5	108.8 ± 38.9	61.3 ±22.0
WCA + SCA	1.75 ± 2.09*	1.20 ± 2.84 *	189.9 ± 110.9	29.2 ± 15.2*	89.5 ± 13.5	209.1 ± 45.1	127.3 ± 43.9	55.0 ±13.5
AA + WCA + SCA	5.32 ± 10.19*	4.27 ±7.7	317.5 ± 247.4*	28.9 ± 15.1*	94.3 ± 18.4	206.1 ± 44.7	127.4 ± 41.7	53.2 ±12.7

AA — active acromegaly group; WCA — well-controlled acromegaly group; SCA — surgically cured acromegaly group; CG — control group; $^{*}p < 0.05$ compared to CG group; $^{\#}p < 0.05$ compared to WCA group; $^{\wedge}p < 0.05$ compared to SCA group; $^{\dagger}p < 0.05$ compared to WCA+SCA group

group at 10 mg. These patients did not tolerate higher doses. Body weight was highest in the AA and lowest in the CG groups. The difference was statistically significant when the AA, the SCA, the WCA + SCA and the AA + WCA + SCA groups were compared to the CG group ($p < 0.014$; $p < 0.005$, $p < 0.009$, $p < 0.004$, respectively). Mean BMI was highest in the SCA and lowest in the CG groups. The difference was statistcally significant when the WCA, SCA, WCA + SCA and the AA + WCA + SCA groups were compared to the CG group ($p < 0.003$; $p < 0.001$, $p < 0.001$, $p < 0.003$, respectively). General characteristics of the subjects are set out in Tables I and II.

Body weight, height and blood pressure were measured in all patients who participated in the study. Pituitary, thyroid and adrenal glands function was assessed on the basis of hormones levels. The GH, PRL, LH, FSH, oestradiol (E_2), total testosterone (T), ACTH, and insulin concentrations were analysed by the chemiluminescent method using Immulite 2000 kits (DPC, Germany or USA, Siemens, USA). Normal ranges were: GH: 0.06–5 μg/L (ng/mL), PRL: women 1.9–25 ng/mL, men: 2.5–17 ng/mL, LH: postmenopausal women 11.3–39.8 mIU/mL, women in follicular phase 1.1–11.6 mIU/mL, men 0.8–7.6 mIU/mL, FSH: postmenopausal women 9.7–111 mIU/mL, women in follicular phase 2.8–11.3 mIU/mL, men 0.7–11.1 mUI/mL, E_2: postmenopausal women 30–140 pg/mL, women in follicular phase 0–160 pg/mL, T: women 0.2–0.8 ng/mL, men 1.29–7.67 ng/mL, ACTH: 0–46 pg/mL, insulin: 6.0–27.9 μIU/mL. Serum IGF1 level was assessed by radioimmunologic assay using IGF-1-D-RIT-CT kit (BioSource Europe S.A., Nivelles, Belgium), normal range: according to the age and sex.

Biochemical tests including lipids, insulin and glucose were also performed. Total Cholesterol (TCH), High Density Lipoprotein Cholesterol (HDL), and triglycerides (TG) were studied by immunoenzymometric assay using Cholesterol RTU kit, HDL Cholesterol Direct kit and Triglicerides Enzymatique PAP 150 (BioMerieux s.a., France), respectively. Normal ranges: TCH 130–200

mg/dL, HDL women 31–85 mg/dL, men 30–70 mg/dL, TG women 35–131.3 mg/dL, men 43.8–183.8 mg/dL. For each patient, the level of orexin A was measured in the plasma, fasting by immunoradiometric method using Orexin A-Magnetic Bead RIA kit (Phoenix Pharmaceuticals, USA). The lowest level of detection was 18.8 pg/mL. In addition, OGTT (75 g) was performed in acromegalic patients. During this test, the levels of GH, glucose and insulin were measured before and 1 and 2 hours after the glucose ingestion. Body mass index, homeostasis assessment model insulin resistance index (HOMA-IR), and the quantitative insulin-sensitivity check index (QUICKI) were calculated. The study of the body composition was performed by the dual-energy X-ray absorptiometry (DXA) method using an Hologic DPX densitometer.

Statistical analysis was done by computer program Statistica for Windows, version 7.0. Parameter distributions were assessed using Shapiro-Wilk's test. When a distribution was normal with equal statistical variance, Student's t-test was used to assess statistically significant differences. Mann-Whitney's U-test was used to assess statistically significant differences for other parameters. Pearson's test or the Spearman's rank correlation test R was used to assess the correlation between traits, depending on the kind of distribution. As a level, a statistically significant p value < 0.05 was used.

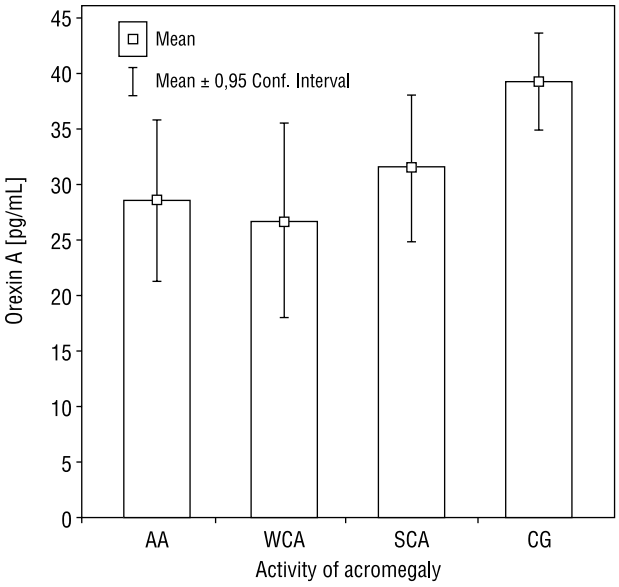

Figure 1. *Concentration of orexin A in relation to the activity of acromegaly. AA — active acromegaly group; WCA — well-controlled acromegaly group; SCA — surgically cured acromegaly group; CG — control group; (AA v. CG, WCA v. CG, SCA v. CG, $p < 0.008$; $p < 0.005$; $p < 0.039$, respectively)*

Rycina 1. *Stężenia oreksyny A w zależności od aktywności akromegalii: AA — grupa z aktywną akromegalią, WCA — grupa z dobrze kontrolowaną akromegalią, SCA — grupa z chirurgicznie wyleczoną akromegalią, CG — grupa kontrolna (AA v. CG, WCA v. CG, SCA v. CG, $p < 0.008$; $p < 0.005$; $p < 0.039$, odpowiednio)*

Results

The concentration of orexin A was highest in the CG and lowest in the WCA groups (Table II). The differences of orexin A levels were statistically significant when each group of patients with acromegaly was compared to the CG. There were no significant differences of orexin A concentration among the studied groups of patients with acromegaly (Fig. 1). The differences of orexin A were also statistically significant when we used the division numbers 2 and 3 and compared the group of patients with acromegaly to the CG (WCA + SCA *v.* CG, AA + WCA+SCA *v.* CG; $p < 0.005$; $p < 0.004$, respectively). A tendency to a negative correlation between orexin A concentration and the level of GH at 0 and 60 minutes during the OGTT was observed. It was statistically significant in the AA group ($p < 0.052$; $p < 0.003$, respectively). Metabolic disturbances were more often observed in groups of patients with acromegaly. TCH and LDL-cholesterol levels were highest in the SCA and lowest in the WCA groups. The difference was statistically significant when the SCA was compared to the WCA and CG groups ($p < 0.007$; $p < 0.02$, respectively). It was on the border of statistical significance between the AA and SCA groups ($p < 0.092$). HDL cholesterol was highest in the CG and lowest in the AA groups and it was statistically significant ($p < 0.045$) (Table II). TG levels were highest in the AA and lowest in the WCA groups. However, there was no statistically significant difference among the studied groups. The mean of body fat mass was highest in the WCA and lowest in the AA group. The differences were statistically significant when the following groups were compared: AA *v.* WCA, AA *v.* WCA+SCA, WCA+SCA *v.* CG ($p < 0.0016$; $p < 0.006$; $p < 0.0035$, respectively). The mean of the percentage of body fat was significantly lower in the AA group compared to the WCA ($p < 0.002$). The mean of the lean body mass was highest in the AA group and lowest in the CG group. The differences were statistically significant when the following groups were compared: AA *v.* CG, SCA *v.* CG, AA *v.* WCA, WCA + SCA *v.* CG, AA + WCA + SCA *v.* CG ($p < 0.005$; $p < 0.01$; $p < 0.05$, $p < 0.014$, $p < 0.003$, respectively). Fasting glucose levels were highest in the AA group. The differences were statistically significant when the following groups were compared: AA *v.* CG, SCA *v.* CG, AA *v.* SCA, WCA *v.* SCA, AA *v.* WCA + SCA ($p < 0.03$; $p < 0.05$; $p < 0.002$; $p < 0.012$; $p < 0.025$, respectively). Prolactin levels were higher in all groups of patients with acromegaly than in controls. There were no such differences between groups of subjects in other hormones (FSH, LH, ACTH, T, E_2) studied (not shown).

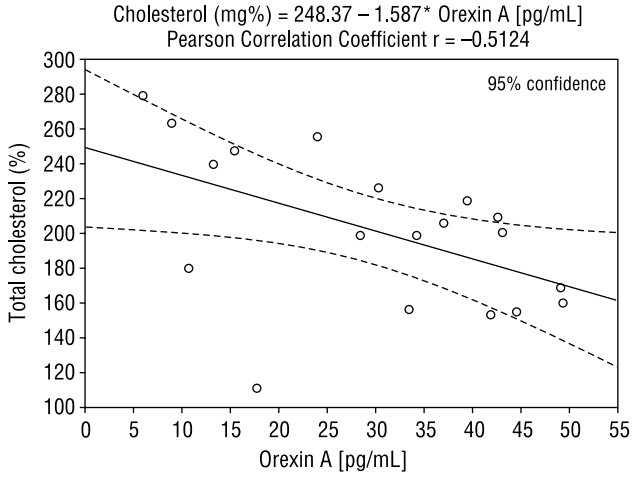

Figure 2. *Correlation between orexin A and total cholesterol in the active acromegaly (AA) group*

Rycina 2. *Zależność między stężeniami oreksyny A i całkowitego cholesterolu w grupie z aktywną akromegalią (AA)*

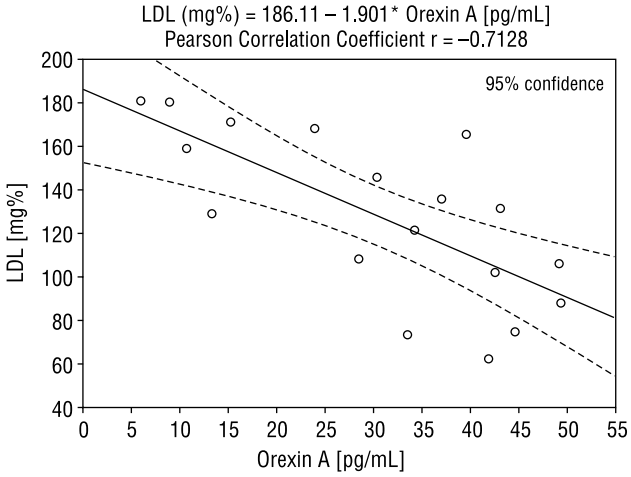

Figure 3. *Correlation between orexin A and LDL in the active acromegaly (AA) group*

Rycina 3. *Zależność między stężeniami oreksyny A i LDL cholesterolu w grupie z aktywną akromegalią (AA)*

In the AA group, orexin A concentrations correlated negatively with lipids: TCH and LDL (Fig. 2 and 3). In the other groups, a tendency to a negative correlation between the above parameters was observed but they were not statistically significant. Orexin A positively correlated with the mean of body fat mass and the percentage of the body fat in the AA and the WCA groups ($r = 0.569$, $p < 0.01$; $r = 0.583$, $p < 0.02$, respectively). In the WCA group, orexin A correlated negatively with the dose of Octreotide -LAR ($r = –0.601$, $p < 0.01$). In each group of patients with acromegaly, a tendency to negative correlations between orexin A and glucose, insulin and HOMA index were observed.

Discussion

The influence of the somatotropic axis on the secretion of orexin A is not clear. We could not find any previous reports on orexin A metabolism in acromegaly. The current study is the first aimed at the assessment of orexin A concentrations in patients with acromegaly in relation to the activity of disease and the metabolic profiles in patients with acromegaly.

Most of the performed experimental studies have indicated the influence of orexins, especially of orexin A, on the secretion of GH. Since the discovery that orexin neurons occur in the arcuate nucleus, where there are huge numbers of GHRH neurons, it is supposed that orexin inhibits the endogenous GHRH tension. Consequently, it leads to a decrease in GH and IGF1 secretion. This might explain the inhibitory effect of orexin A on the basal secretion of GH and the lack of influence on GH response to the administration of exogenous GHRH [4, 5].

We have observed that orexin A concentration was highest in controls and lowest in the WCA group. The difference in the concentration of orexin A was statistically significant when each group of patients with acromegaly was compared to the CG. This was independent of the kind of division carried out. There were no significant differences of orexin A concentration among the studied groups of patients with acromegaly. This may indicate the disorders of orexin A metabolism in patients suffering from acromegaly. Moreover, reduced levels of orexin A in both the WCA and SCA groups suggest that abnormal orexin A secretion is sustainable. The confirmation of an inhibitory influence of orexin A on GH secretion may be the negative correlation between GH and orexin A concentrations. This was statistically significant in the AA group. In the other groups, we observed a trend toward a negative relationship between these parameters. The lowest concentration of orexin A was observed in the WCA group, which may be associated with the additional effects of somatostatin analogues on the metabolism of orexin A. In our study, we showed a statistically significant negative correlation between orexin A and the dose of octreotide. This observation requires further study. We do not know how somatostatin analogues may affect the orexin-GHRH pathway.

In each group of patients with acromegaly, we observed a tendency to a negative correlation between the concentration of orexin A and the concentrations of glucose and insulin at 120 min of the OGTT and the HOMA index. It is known that insulin has an antagonistic effect in relation to orexin A and the correlation between these parameters is negative, as observed in previous studies [14]. In acromegaly, deficiency of orexin

A may be the consequence of GH hypersecretion as well as the excessive secretion of insulin. Hypothetically, these results may suggest that the deficiency of orexin A may influence the disorder of carbohydrate metabolism in acromegaly.

Lipids disorders are very common in acromegaly. The influence of GH on lipids metabolism is associated with increased lipolysis. In addition, it causes the redistribution of body fat, increasing the amount of visceral fat [15]. Moreover, the abnormalities of lipids are aggravated by insulin resistance, which changes the activity of lipoprotein lipase [16]. This leads to an increase of triglycerides levels, a decrease in HDL synthesis, and a rearrangement of the quality of LDL cholesterol. This causes a change in lipids profile for the atherogenic one.

The highest triglycerides concentration was observed in the AA and the lowest in the WCA groups, in which we also noticed the smallest HOMA index. The WCA group was characterised by the lowest level of TCH and LDL cholesterol, and the difference compared to the SCA group was statistically significant. This confirmed the dependence of lipids disturbances on insulin resistance [17–19] and their amelioration while being treated with somatostatin analogues. The changes in the lipid profile observed in the WCA group are consistent with observations made by others [20, 21]. The highest concentrations of TCH and LDL cholesterol were observed in the SCA group. Our results are similar to other reports which have suggested that effective treatment of acromegaly is not always connected to a reversion to a normal lipids profile [22]. HDL cholesterol concentration was highest in the CG and lowest in the AA groups. The WCA group was characterised by a higher level of HDL, compared to the AA and SCA groups, which is related to the influence of somatostatin analogues. Analysis of the modification in lipids profile based on division number 3 (AA + SCA + WCA) *v.* the CG, revealed that groups of patients with acromegaly had higher levels of TCH, LDL cholesterol and triglycerides and a lower level of HDL cholesterol. In the cases of LDL and HDL cholesterol, the differences were on the border of statistical significance. The changes in lipid profile in patients with acromegaly are consistent with previous observations indicating that levels of triglycerides and TCH remain unchanged or increase [23–25], whereas HDL cholesterol remains unchanged or decreases [24, 26].

The alterations in lipids were correlated with the concentration of orexin A. The modifications in lipids profile were the greatest in the AA group. We noticed a statistically significant correlation between orexin A and TCH and LDL cholesterol. This may suggest the dependence of lipids metabolism on orexin A. It is known that orexin A participates in the regulation of food intake and energy expenditure [9].

The changes in lipids profile in acromegaly are similar to those observed in patients with narcolepsy with known orexins deficiency [27, 28]. A lot of the metabolic disturbances were observed in patients with narcolepsy. These changes are independent of BMI or the food intake and they are the result of orexins deficiency. It has been shown that significant metabolic disturbances occurred, despite the lack of increase in BMI and hypophagia. These disturbances were the increase in the level of TCH and triglycerides and the decrease in HDL cholesterol, accompanied by significant insulin resistance and increased glucose level. This suggests the direct effect of orexin on numerous metabolic processes [29, 30]. Although the mechanism of disturbances of metabolism of orexins in patients with acromegaly is different than in patients with narcolepsy, the influence on lipids metabolism appears to be similar. For this reason, we suppose that the deficiency of orexin A may increase the metabolic disturbances occurring in the course of acromegaly in the same way as in patients with narcolepsy.

Acromegaly is also associated with a decrease in fat mass and an increase in lean body mass. This is a result of the lipolytic effect of GH [31, 32]. The highest lean body mass was observed in the AA and the smallest in the CG groups, and the difference was statistically significant. The AA group was also characterised by the smallest value of fat mass and body fat percentage. The highest values of these parameters were observed in the WCA group. This indicates that good control of acromegaly, by using somatostatin analogues, may eliminate the effect of GH. Matsumar et al. showed a positive correlation of orexin A with BMI and fat body mass in healthy subjects [33]. The level of orexin A decreases in patients with obesity and its correlation with BMI is negative [31]. In our study, body weight and BMI in the groups of patients with acromegaly were higher than in the CG group, regardless of the division. We did not observe pathologic obesity among the patients, so the correlation of orexin A with BMI should be correct. So, in theory, higher BMI in patients with acromegaly groups should correlate with higher levels of orexin A in these groups.

The data presented in this paper requires more analysis, including factors that may impact upon the relationship between the levels of orexin A and GH in acromegaly. The limitations of the presented research are the varying duration of the disease in patients, as well as the duration of the therapy with somatostatin analogues, which could affect the results. The relationships between orexin A and the concentrations of GH, IGF1 should be assessed before and after treatment (surgical as well as pharmacological) to eliminate their influence on the results.

Conclusions

The concentration of orexin A is reduced in patients suffering from acromegaly compared to healthy subjects. We suppose that orexin A deficiency may increase the metabolic abnormalities in patients with acromegaly, especially regarding the impact on the metabolism of lipids. This hypothesis requires further study.

Acknowledgments

The study was supported by Wroclaw Medical University grant No. 1827.

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