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Orexigenic and Anorexigenic Peptides in Restrictive Type of Anorexia Nervosa

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1. Introduction

1.1 Subtypes of Anorexia Nervosa (AN)

Current diagnostic criteria distinguish between two subtypes of Anorexia Nervosa (AN): the restrictive anorexia nervosa (AN-R) and binge/purging anorexia nervosa (AN-B), according to DSM-IV (APA, 1994). These two subtypes may be differentiated by various kind of anorexigenic-orexigenic dysregulation. Among other symptoms, AN is a disorder characterized by abnormal eating behavior and by weight changes which are reflected in multiple endocrine and metabolic abnormalities. Among them, dysregulation of anorexigenic and orexigenic signaling seem to play a prominent role. A number of orexigenic peptides have been identified such as ghrelin, neuropeptide Y, and melanin-concentrating hormone.

1.2 Ghrelin – the orexigenic peptide

Ghrelin is a 28-amino acid peptide discovered by Kojima et al. in 1999 (Kojima et al., 1999). Its biological activity depends on the post- translational acylation of serine 3 with octanoic acid. Ghrelin is mainly secreted by A-like cells in the fundus of stomach, but it is also produced in small quantities in the hippocampus, pancreas, intestines, male gonads, placenta and pituitary gland (Lazarczyk et al., 2003). It is known that ghrelin influences the motility in the gastrointestinal system, secretion of hydrochloric acid and endo- and exogenous pancreas functions (Murray et al., 2003;ang Broglio et al., 2001). It stimulates the secretion of such hormones as growth hormone, cortisol, prolactin, aldosterone, and adrenocorticotropic hormone (Lazarczyk et al., 2203; Murray et al., 2003; Broglio et al., 2001; Wren et al., 2000; Warzecha et al., 2006; Dembinski et al., 2005). It also influences the cardiovascular system by reducing blood pressure and increasing cardiac output (Kojima et

al., 1999). Ghrelin affects the proliferation of cancer cells, and it is known that resistance to ghrelin can be responsible for cancer cachexia (Ziegman et al., 2003). The highest increase of the plasma ghrelin concentration is observed before food intake. After feeding the ghrelin plasma level decreases within 2 h (Neary et al., 2003). Starvation and/or malnutrition results in an increase of ghrelin level (Ziegman et al., 2003).

1.3 Orexin A (OXA, hypocretine-1) – the orexigenic peptide

Orexin A (OXA, hypocretine-1) has been isolated from rat hypothalamus and named for its ability to stimulate feeding when injected into the brain (Sakurai et al., 1998 and Kirchgessner 2002). Orexin A is expressed in the lateral hypothalamic area, which has been described as the "feeding center", and this peptide was initially characterized as an orexigenic (appetite-stimulating) factor (Mieda et al., 2002). Orexin A can rapidly cross the brain - blood barrier to reach the brain from the blood. Although no saturable transport system was found for orexin A, its fast rate of entry is probably explained by simple diffusion facilitated by a high degree of lipophilicity (Kastin et al., 1999).

1.4 Leptin (LEP)– the anorexigenic peptide

The main anorexigenic peptide is leptin, of which the primary source is adipose cells. Leptin regulates energy balance throughout the body by controlling processes involved in energy intake and utilization (Myers 2004 and Hebebrand et al., 2007). Underweight AN patients have consistently been found to have significantly lower plasma leptin concentrations compared to normal weight controls (Grinspoon et al., 1996; Casaneuva et al., 1997; Ferron et al. 1997; Lob et al., 2003). LEP is a protein product of a OB (obese) gene. LEP comes in two types: free and bound with plasma protein, each having its own function in the system. Free LEP controls fat tissue mass, while LEP bound with soluble receptor form controls energy expenditure. The leptin receptor (OB-R) is a product of the OB-R gene located on chromosome 1 (1p31).

2. Participants

Thirty females suffering from AN-R of the restrictive type (AN-R) were included in the study (M age: 17 ± 1.59; range 14 - 20 years; SD: 1,59). They were diagnosed as AN-R according to DSM IV and ICD 10 criteria (APA, 1994 and ICD-10, 1998). They had a ≥15% body weight loss and their body mass index (BMI) was below 17.5 kg/m^2. The mean duration of the disease before admission to the hospital, established by interviews with the patients and their families, was 11.5 ± 7 months. All the patients were hospitalized for up to 3 months in the Child and Adolescent Psychiatry and Psychotherapy Ward at the John Paul II Pediatric Center in Sosnowiec.

During hospitalization the patients received treatment including a normocaloric diet (2300 kcal/d: 98.4 kcal/d of protein, 75 kcal/d of fat, and 376 kcal/d of carbohydrates), supervised meal consumption (the meals were provided 5 times a day) and cognitive-behavioral psychotherapy (CBT). CBT was performed by a team of psychiatrist, psychologist and a nurse. It was based on the constant number and time of meals. An individual system of positive and negative reinforcements was introduced. A positive reinforcement was given for an increase and a negative reinforcement for a decrease in body weight. Those patients who reached a

BMI of 16.5 kg/m^2 were allowed to leave the hospital for weekends. Psychotherapy was performed for 45 minutes twice a week on an individual basis by one psychologist and 60 minutes twice a week in group mode by two psychologists. When a BMI of 17 kg/m^2 was reached the patient was discharged from the hospital and ambulatory treatment was started. The patients were examined once a month and their weight was checked by a nurse and psychiatrist. AN-R patients did not take medicaments, only occasionally they have taken anxiolytic drugs because they had single symptoms of anxiety and depressive syndrome but depression and obsessive compulsive disorder were excluded.

The control group consisted of 20 healthy schoolgirls from Silesian colleges (M age:18.5; range 18.0-19.0 years; SD = 0.3), a mean BMI of 21.4 (range 17.6-25.7, SD = 2.1). None were suffering from any psychiatric disorder, including eating disorders or receiving any drugs. Their daily intake of food over the past year had per day a mean of 2100-2300 kcal. This information was gained from each girl during a clinical interview which contained eating disorder symptoms and behaviors and during psychiatric, neurological and physical examinations. The protocol of the study was approved by the Local Bioethics Committee and written informed consent to participate in the study was obtained from all those participants and their parents.

3. Laboratory methods

Blood was collected by the method described by Baranowska et al (2005). Venous blood samples were collected in the fasting state (between 8-9 a.m.) into Vacutainer tubes containing EDTA (1mg/ml of blood). The blood samples were gently shaken and then transferred to centrifuge tubes containing aprotinin (0.6TIU/ml of blood). They were centrifuged at 1,600 x g for 15 minutes at 4°C. The plasma collected was immediately frozen and kept at -70°C. The orexin A plasma level was measured by commercial radioimmunoassay kits (Phoenix Pharmaceuticals. Mountain View, California). Buffer A, a 1% water solution of trifluoroacetic acid and buffer B, a 60% solution of acetonitrol in a 1% solution of trifluoroacetic acid were used, as well as chromatography columns, for the extraction (SEP-PAK C-18. Waters Associates). The leptin plasma level was measured by commercial enzymoimmunological assay (Leptin Sandwich ELISA, DRG Instruments GmbH Deutschland) using a ELISA counter (DRG Elisa MAT 2000). Plasma orexin A levels were determined by means of LKB Wallac Clini Gamma 1272 gamma counter. The minimal detectable quantity was 0.001 ng/ml. Procedures recommended by Phoenix Peptide for extraction were followed. Plasma ghrelin levels were determined by radioimmunoassay (RIA, Linco Research, Inc.) using the LKB Wallac Cinigamma 1272 gamma counter. The procedure was done according to the manufacturer's instructions. The minimal detectable quantity was 93 pg/ml The AN-R patients' blood was sampled four times: at admission and after 2, 3 and 6 months of therapy. The control participants have blood drawn only once.

4. Statistical analysis

4.1 Ghrelin

All the values are presented as the mean ± SD. Statistical analysis was carried out by the Student's t-test. The Spearman's correlation was calculated using the Microsoft Excel 6.0 software. The $p < 0.05$ was accepted as the essential level of statistical significance.

4.2 Orexin A (OXA, hypocretine-1) and leptin (LEP)

Calculations were performed using the Statistica version 7.1 statistical package. The Shapiro-Wilk test was used to determine the normality of data distribution. The level of statistical significance was determined at $p < 0.05$. As the BMI results showed normal distribution, the ANOVA test for repeated measurements was used. To compare BMI parameters between periods of time, the LSD (least significant differences) – post hoc test was used. The non-paired t-test was used for comparison between patients and control participants. As the leptin and orexin A values did not show a normal distribution, the nonparametric Friedman test was performed in order to detect differences between multiple measurements. The mean range- post hoc test was used to compare leptin and orexin A parameters during the period of study. The non-parametric Mann-Whitney test was used for comparison between patients and control participants. The non-parametric Spearman's test was used to investigate any correlation between leptin or orexin A levels with BMI, or any reciprocal correlation between leptin and orexin A. When leptin levels were transformed into logarithmic values, as lg10, and the BMI was expressed as a BMI SDS (z-score), the Pearson test was used to assess the correlation between these parameters (Maliński, 2004 and Maliński et al., 1999).

5. Results

5.1 Ghrelin

5.1.1 Body mass index (BMI)

The BMI before the therapy calculated for all 30 AN-R patients was 15.1 kg/m^2 ± 1.4. After 3 months of treatment BMI increased to 17.2kg/m^2 ± 1.1 and a further increase was noted after 6 months of the therapy to 17.7 kg/m^2 ± 1.8. The BMI in the control group was 21.4 kg/m^2 ± 2.1. A statistically significant difference between BMI of AN-R patients and BMI of the control group was noted before the therapy, after 3 and 6 months of therapy compared with the control group ($p<0.001$, t-Student test).

5.1.2 The total ghrelin plasma level

The total ghrelin plasma level before therapy was 6652.1± 2152.7 pg/ml, after 3 months of treatment the total ghrelin plasma level decrease to 3858.5± 1331.8 pg/ml and after 6 months of treatment the total ghrelin plasma level decrease too and was 3187.4± 1348.2 pg/ml. The total ghrelin plasma level in the control group was 4855± 1421.4 pg/ml. A statistically significant difference between the total ghrelin plasma level of AN-R patients and the total ghrelin plasma level of the control group was noted before therapy, after 3 and 6 months of therapy compared with the control group, $p=0.002$; $p=0.015$ and $p<0.001$, respectively (t-Student test) .

5.1.3 Correlation between the BMI and the total ghrelin plasma level

There was no correlation between BMI and the total ghrelin plasma level in AN-R patients (n=30) before therapy (R= - 0,14, p=0,47, Spearman correlation). Also in the control group no correlation between BMI and the total ghrelin plasma level was observed (R=0,15; p=0,50).

5.1.4 Correlation between the total ghrelin plasma level change and BMI change in AN-R patients

A change of the BMI is understood as the difference between the BMI before and after 6 months of the therapy (BMI 6 - BMI 0). A change of the total ghrelin plasma level is the difference between the total ghrelin plasma level before and after 6 months of the therapy (Ghrelin 6 - Ghrelin 0). BMI change and the total ghrelin plasma level change before and after 3 months of the therapy did not show statistically significant correlation (R=-0.304; p=0.1011). BMI change and the total ghrelin plasma level change before and after 6 months of the therapy correlated in statistically significant relation (R = - 0.52; p=0.0054).

5.1.5 Correlation between duration of disorder and the total ghrelin plasma level and BMI

There was no statistically significant correlation between the AN-R duration and either the total ghrelin plasma level (R = 0.10; p=0.58) or BMI change (R =-0.25; p=0.18) (Janas-Kozik et al, 2007).

5.2 Orexin A (OXA, hypocretine-1)

5.2.1 The orexin A (OXA) plasma level

The mean OXA plasma level before the therapy for all 30 AN-R patients was 0.04 ng/ml ± 0.05, significantly lower than in control group (0.08 ng/ml ± 0.10) (p= 0.039, Mann-Whitney test). After 2, 3, and 6 months of treatment the OXA plasma levels significantly decreased: 0.02 ng/ml ± 0.03, 0.01 ng/ml ± 0.01, 0.01 ng/ml ± 0.01, respectively ($p<0.001$, Friedman test). A significant decrease of OXA plasma level was observed after 3 and 6 months of therapy compared to baseline (NIR- post hoc test, $p<0.001$)

5.2.2 Body mass index (BMI) for orexin A (OXA) and leptin (LEP) plasma level

The mean BMI before the therapy for all 30 AN-R patients was 14.8 kg/m^2 ± 1.3. A statistically significant difference between BMI of AN-R patients and BMI of the control group was noted (non paired t-Student test, $p<0.001$). After 2 and 3 months of treatment BMI increased to 15.7 kg/m^2 ± 1.1 and 17.1 kg/m^2 ± 1.1, respectively. A further increase to 17.7 kg/m^2 ± 1.1 was noted after 6 months of the therapy. The increase of BMI in the described above periods of time, when measurements were done, i.e. after 2, 3 and 6 months of therapy was statistically significant, (ANOVA test F=29.51; $p< 0.001$). A statistically significant difference between BMI of AN-R patients and BMI of the control group was noted before the therapy, after 2, 3 and 6 months of therapy compared with the control group ($p<0.001$, non paired t-Student test).

5.2.3 Correlation between the change of BMI and the change of orexin A (OXA) plasma level

There was no correlation between BMI and OXA plasma level in AN-R patients before the therapy and after 2, 3 and 6 months of the therapy (R= 0.06, p=0.759; R=0.01, p=0.967;

R= 0.33, p=0.077; R= -0.01, p=0.98; respectively; the Spearman correlation). There was no correlation between BMI and OXA plasma level in control group (R=0.32, p= 0.171).

5.2.4 Correlation between a change of BMI and the orexin A (OXA) plasma level

Change of BMI and change of OXA plasma levels compared to baseline did not show statistically significant correlations (2 months: R = - 0.12, p = 0.514; 3 months: R = - 0.25, p = 0.177; 6 months: R = -0.25, p = 0.174, Spearman correlation).

5.3 The leptin (LEP)

5.3.1 The leptin (LEP) plasma level

The mean LEP plasma level before the therapy for all 30 AN-R patients was 1,00± 0.73 ng/ml while the LEP plasma level in the control group was 14.00 ± 11.99 ng/ml. After 2, 3 and 6 months of treatment LEP plasma levels in AN-R patients were 4.53 ± 4.74 ng/ml, 6.96 ± 5.58 ng/ml, 8.27 ± 6.94 ng/ml, respectively. Statistically significant increase of LEP plasma levels in investigated periods of time was observed ($p<0.001$, the Friedman test), although even after 6 months of therapy the LEP levels in patients made slightly more than a half of control participants values

5.3.2 Correlation between the BMI and the leptin (LEP) plasma level

There was no correlation between BMI and LEP plasma level in AN-R patients before the therapy and after 2 and 3 months of the therapy (R= 0.22; p=0.239; R=0.22; p=0.240; R=0.16, p=0.387, respectively; the Spearman correlation). There was, however a correlation between BMI and LEP plasma level in AN-R patients after 6 months of the therapy (R= 0.59; $p < 0.001$). There was no correlation between BMI and LEP plasma level in control group (R=0.20, p=0.402).

5.3.3 Correlation between the change change of BMI and the change of leptin (LEP) plasma level

A change of the BMI and LEP was expressed as a difference between the BMI and LEP values after 2, 3 and 6 months of the therapy compared to baseline. Change of BMI and LEP plasma levels showed statistically significant correlation (2 months: R = 0.54, p = 0.002; 3 months: R = 0.52, p = 0.003; 6 months R = 0.76, $p <0.001$; the Spearman correlation).

5.4 Correlation between leptin (LEP) and orexin A (OXA) plasma levels

Before the therapy a statistically significant negative correlation between OXA and LEP levels in patients with AN-R was observed (R= - 0.38, p=0.039; the Spearman correlation). There was no correlation between LEP and OXA after 2 and 3 and 6 months of the therapy (R= 0.24; p=0.203, R=0.33; p=0.076, R=0.07, p=0.699, respectively). There was no correlation between OXA plasma levels and LEP plasma levels in the control group (R=0.06, p=0.806). In patients suffering from AN-R, no statistically significant correlation between duration of the illness and LEP or OXA plasma levels was found (R= -0.03, p= 0.868, R=0.19, p=0.309, respectively, the Spearman correlation). (Janas-Kozik et al, 2011)

6. Discussion

6.1 The total ghrelin plasma level study in patients of suffering from anorexia nervosa

Ghrelin is the most sensitive determinant of the nutrition state. Secretion of ghrelin is strongly related to food intake. The hypothalamic-pituitary-suprarenal axis is activated when access to food is limited and during the stress. The secretion of ghrelin mobilizes mechanisms counteracting states of energy deficits, stimulates searching for food and influences memory of information connected with eating (Ziegman et al. 2003; Inui, 2001; Wu et al.,2004). The secretion of ghrelin increases during starvation and during expecting a meal (Murray et al., 2003). In ghrelin study before the therapy BMI was significantly lower in the restricting anorectic patients (AN-R) patients (15.1 kg/m^2 ± 1.4.) compared with the control group (21.4 kg/m^2 ± 2.1; $p<0.001$). After 3 and 6 months of cognitive-behavioral therapy, increase of BMI was observed in AN-R patients (17.2kg/m^2 ± 1.1 and 17.7 kg/m^2 ± 1.8., respectively) but during the therapy the BMI was always significantly lower in AN-R patients compared with the control group (21.4 kg/m^2 ± 2.1).

In ghrelin study before the therapy in patients suffering from AN-R the total ghrelin plasma level was significantly higher (6652.1± 2152.7 pg/ml) compared with the control group (4855± 1421.4 pg/ml; p=0.002). This observation has been confirmed by other scientists (Otto et al., 2001; Nedvikova et al., 2003; Tanaka et al., 2203; Toole et al., 2003). After 3 and 6 months of therapy the total ghrelin plasma level in AN-R patients was significantly lower compared with the control group (3858.5± 1331.8 pg/ml; p=0.015 and 3187.4± 1348.2 pg/ml; $p<0.001$, respectively).

We suggest that in AN-R patients before the therapy ghrelin plays a role of the orexigenic peptide and informs CNS (central nervous system) about deficit of energy when the BMI is low. We observe that after 3 months of therapy in AN-R patients ghrelin stops playing this role, because its level dramatically decreases compared with the control group (3858.5 ± 1331.8 pg/ml; 4855± 1421.4 pg/ml, respectively, p=0.002). After 3 months of the therapy the BMI is low (17.2kg/m^2 ± 1.1) and the total ghrelin plasma level decreases in AN-R patients (the total ghrelin plasma level before the therapy was 6652.1± 2152.7 pg/ml and the total ghrelin plasma level after 3 months the therapy was 3858.5± 1331.8 pg/ml). It is interesting that after 6 months of the observation BMI is still low (17.7 kg/m^2 ± 1.8.) and the total ghrelin plasma level is still decreasing in AN-R patients (3187.4± 1348.2 pg/ml) compared with the control group (4855± 1421.4 pg/ml). No correlation was observed between BMI and the total ghrelin plasma level both in AN-R patients before therapy (R= - 0,14, p=0,47) and in the control group (R=0,15; p=0,50) analyzed separately. However, there was a statistically significant negative correlation between the total ghrelin plasma level change and BMI change in AN-R patients after 6 months of therapy (R = - 0.52; p=0.0054). We suggest that in AN-R patients ghrelin does not send "correct" information to CNS about state of the organism feeding. We think that in AN-R patients ghrelin is rather responsible for model of eating behavior (for regularly and normocaloric diet), but is not responsible for stimulation of food intake. Our results show that 6 months of the therapy is sufficient to form a new habits connected with food intake. Before the therapy the higher total ghrelin plasma level (6652.1± 2152.7 pg/ml) is observed in AN-R patients comparing to the control group (4855± 1421.4 pg/ml) in our study (Janas-Kozik et al. 2007).

Nedvikowa (2003) and Toole (2003) suggest that such a significant increase of the total ghrelin plasma level in AN-R patients can be a result of compensating mechanisms in poor eating habits. According to Otto et al. (2001) ghrelin is a peripheral hormone related to appetite and food intake and informs CNS about a necessity of activating a metabolic variant which saves more energy. In AN-R patients there is no statistically significant correlation between BMI change and duration of AN-R (R =-0.25; p=0.18) and between the total ghrelin plasma level and duration of the disorder (R = 0.10; p=0.58). We suggest that the therapy is very important regardless of the duration of the Anorexia Nervosa (Janas-Kozik et al., 2007).

Two forms of ghrelin hav e been found, acylated ghrelin and desacyl ghrelin. Plasma desacyl ghrelin concentration accounts for more than 90% of total circulating ghrelin (Hosoda et al., 2000). Acylated ghrelin produces stimulatory effects on food intake. Physiological role of desacyl ghrelin is not well known. Some studies even showed that desacyl ghrelin decrease food intake and delay gastric empting in mice and rats (Asakawa et al., 2005 and Chen CY et al., 2005). Further study is required to determine whether desacyl ghrelin is biologically active and binds to an as-yet-unidentified receptor (hosoda et al., 2006). The role of acylated and desacyl ghrelin in anorexia has to be analyzed separately. It might give an explanation why total ghrelin level in anorexia decreased below the level of healthy participants after 3 and 6 months of therapy (Janas-Kozik et al., 2007).

6.2 Orexin A (OXA) plasma level in patients suffering from anorexia nervosa

In the present study, orexin A levels before treatment were significantly lower in the AN-R patients compared to control group, similarly as in our previous paper (Janas-Kozik et al., 2006). In the course of treatment and with subsequent weight gain, orexin A levels showed a further decline. A reduction of orexin A levels during AN realimentation was also found in a recent study of Bronsky et al (2010). However, their results differ with those of ours in that their baseline orexin A levels were higher than in healthy control participants. In our study baseline orexin A plasma levels was lower compared to control group (0.04 ng/ml ± 0.05; 0.08 ng/ml ± 0.10, respectively). Furthermore, we did not observe a statistically significant correlation between the BMI and orexin A plasma levels before the therapy or after 2, 3 and 6 months of treatment (R= 0.06, p=0.759; R=0.01, p=0.967; R= -0.33, p=0.077; R= -0.01, p=0.98; respectively; the Spearman correlation) and no correlation was also found between changes in orexin A plasma levels and changes in the BMI after 2, 3 and 6 months (2 months: R = -0.12, p = 0.514; 3 months: R = - 0.25, p = 0.177; 6 months: R = -0.25, p = 0.174, Spearman correlation). Generally, the pattern of orexin A levels during treatment of patients with AN-R was similar to that found in our previous paper for ghrelin (Janas-Kozik et al., 2006), however, the baseline orexin A levels were significantly lower compared to the control participants. A number of observations point to an increase in the orexin A level during fasting and weight loss, and a decrease during weight gain. Komaki et al. (2001) reported an increase in orexin A plasma levels in adult fasting, non-obese participants during 10 days of fasting which was followed by a reduction in orexin A plasma levels during subsequent re-feeding. Bronsky et al. (2007) observed a significant increase in orexin A plasma levels after a decrease of BMI from about 28 kg/m^2 to 26 kg/m^2 in fasting obese children. Also other studies of orexin A plasma levels showed a significant decrease of this peptide in obese, and morbidly obese participants (Adam et al., 2002). These results could be compatible with those obtained in our study with AN-R patients (Janas-Kozik et al., 2011).

6.3 Leptin (LEP) plasma level in patients suffering from anorexia nervosa

The results of our study corroborate those of other researchers showing a decrease of leptin levels in patients with AN-R, compared with those in control participants (1.00± 0.73 ng/ml in AN-R patients before the therapy and 14.00 ± 11.99 ng/ml in the control group) and its increase during increment in body weight (Casaneuva et al., 1997 and Hebebrandt et al., 2007). Leptin appears to play an important role in triggering an adaptive response to starvation and a low level of this peptide is connected with stimulating the increase of orexigenic peptides and subsequent weight gain. Holtkamp et al. (2004) suggested that high serum leptin levels at discharge from inpatient treatment may indicate a risk for renewed weight loss and an unfavorable 1 year outcome in AN patients. In our AN-R patients the leptin plasma levels increased significantly after 2, 3 and 6 months of treatment (4.53 ± 4.74 ng/ml, 6.96 ± 5.58 ng/ml, 8.27 ± 6.94 ng/ml, respectively)and there was a statistically significant correlation between the BMI and leptin plasma levels after 6 months of treatment ($R= 0.59$; $p < 0.001$). Changes in the BMI and leptin plasma levels also showed a statistically significant correlation during the 6-month observation period (2 months: $R = 0.54$, $p = 0.002$; 3 months: $R = 0.52$, $p = 0.003$; 6 months $R = 0.76$, $p <0.001$; the Spearman correlation). However, there was no correlation between the change in leptin level after 2 months and the change in BMI after 6 months, compared to baseline. Therefore, our results suggest that changes in leptin levels in the early phase of treatment may not predict body weight gain after 6 months of treatment. The lack of correlation between the BMI and leptin in our control participants may indicate that such a correlation may not hold for participants with a BMI within the normal range (Janas-Kozik et al., 2011).

6.4 Correlation between leptin (LEP) and orexin A (OXA) plasma levels

Before treatment, a significant negative correlation between leptin and orexin A plasma levels in our AN-R patients was observed ($R= - 0.38$, $p=0.039$; the Spearman correlation). This means that lower leptin levels were associated with relatively higher levels of orexin A, however, orexin A levels being still in a range lower than that of the control participants. A reciprocal relationship between leptin and orexin effects on hypothalamic neurons was found in a study of Muroya et al.(2004). Also recently, a bidirectional association between plasma concentration of leptin and orexin as regards nicotine craving was demonstrated (von der Goltz et al., 2010). Such inverse correlation between leptin and orexin plasma levels was also found both in obese and non-obese participants (Komaki et al., 2001 and Bronsky et al. 2007). However, in AN-R patients studied by us, such an association was observed only initially and has not hold during the course of treatment (Janas-Kozik et al., 2011). Also Bronsky et al.(2010) did not find such an association during an 8-week realimentation of AN patients. A limitation to our study may be that the participants in the control group had a narrower age range, which did not exactly match the AN-R patients for age. Furthermore, during treatment no records were taken of the symptoms of anorexia such as drive for thinness, strength of appetite or desire for eating as well as of the type of food consumed. Despite these limitations we believe that our study of anorexigenic and orexigenic peptides during treatment of participants with the restrictive type of anorexia nervosa produced some interesting outcomes. We confirmed the results of other studies on the specific pattern of leptin in AN patients, such as baseline low levels and increase during treatment. We also corroborated an effect described by Bronsky et al. (2010), such as a decrease of orexin A levels during anorexia treatment (Janas-Kozik et al, 2011).

7. Conclusions

7.1. The total ghrelin plasma level in the restrictive type of anorexia nervosa (AN-R) is connected with the pathological feeding behavior (Janas-Kozik et al., 2007).

7.2. It is not known, which proportion of orexin A in plasma comes from brain and which from gut, and whether or not plasma orexin A is orexigenic (Janas-Kozik et al., 2011).

7.3. In AN-R patients before treatment we found a significant reciprocal correlation between plasma levels of leptin and orexin which may suggest some relationship between these two peptides in AN-R patients (Janas-Kozik et al., 2011).

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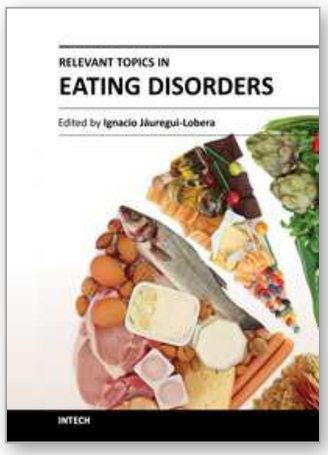

Relevant topics in Eating Disorders
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Eating disorders are common, frequently severe, and often devastating pathologies. Biological, psychological, and social factors are usually involved in these disorders in both the aetiopathogeny and the course of disease. The interaction among these factors might better explain the problem of the development of each particular eating disorder, its specific expression, and the course and outcome. This book includes different studies about the core concepts of eating disorders, from general topics to some different modalities of treatment. Epidemiology, the key variables in the development of eating disorders, the role of some psychosocial factors, as well as the role of some biological influences, some clinical and therapeutic issues from both psychosocial and biological points of view, and the nutritional evaluation and nutritional treatment, are clearly presented by the authors of the corresponding chapters. Professionals such as psychologists, nurses, doctors, and nutritionists, among others, may be interested in this book.

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