Neuroendocrinology Letters Volume 39 No. 3 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Neuroendocrine aspects of anorexia nervosa and bulimia nervosa

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Submitted: 2018-05-30 Accepted: 2018-07-17 Published online: 2018-09-15

Key words: **eating disorders; energy homeostasis; hormonal dysfunction**

Neuroendocrinol Lett 2018; **39**(3):172–178 **PMID:** 30431742 NEL390318XR05

Abstract

Endocrine dysfunctions in eating disorders (anorexia nervosa, bulimia nervosa) result from disturbed regulation of hypothalamo-pituitary-gonadal, hypothalamo-pituitary-adrenal, hypothalamo-pituitary-thyroid and hypothalamo-pituitary-GH-IGF1 axes as well as of altered peripheral endocrine metabolism.
Some peptides of hypothalamic origin, as well as those secreted by the adipose tissue and gastrointestinal tract including pancreatic hormones, are involved in the control of appetite and satiety. These peptides play also an important role in the mechanism of hormonal secretion. Altered activity of these biologically active substances may lead to the disturbances in the regulation of energy and hormonal homeostasis.

Abbreaviations:

AgRP	- Agouti – Related Peptide
AN	- Anorexia Nervosa
AN-BP	- Anorexia Nervosa –Binge Purging
AN-R	- Anorexia Nervosa – Restricting
BDNF	- Brain-Derived Neurotrophic Factor
BN	- Bulimia Nervosa
CART	- Cocaine Amphetamine Related Peptide
CNS	- Central Nervous System
CRH	- Corticotrophin-Releasing Hormone
CSF	- Cerebrospinal Fluid
GLP1	- Glucagon-Like Peptide 1
HMW	- High Molecular Weight
LHA	- Lateral Hypothalamus
LMW	- Low Molecular Weight
MCH	- Melanin-Concentrating Hormone
MMW	- Middle Molecular Weight
NPV	- Periventricular Nucleus
NPY	- Neuropeptide Y
POMC	- Proopiomelanocortin
PP	- Pancreatic Peptide
PYY	- Peptide YY
TRH	- Thyrotropin Hormone
TRH	- Thyrotropin-Releasing Hormone
VIP	- Vasoactive Intestinal Peptide

INTRODUCTION

Anorexia nervosa and bulimia nervosa belong to a group of psychosomatic disorders characterized by abnormal eating behavior with multiple metabolic and neuroendocrine disturbances. Endocrine dysfunctions result from disturbed hypothalamo-pituitary regulation as well as from altered peripheral hormonal metabolism (Baranowska *et al.* 2003; Warren 2011).

The exact etiology of eating disorders is still unknown but some factors including genetic, neurobiological, and psychological aspects play a role in morbidity.

It has been known that neuropeptides, neurotransmitters, and peripheral peptides impact not only the control of appetite, energy homeostasis but influence the mechanism of hormonal secretion (Baranowska *et al.* 2003; Monteleone *et al.* 2008; Misra & Klibanski 2010; Warren 2011).

CONTROL OF APPETITE

1. Hypothalamic neuropeptides

Selected peptides of hypothalamic origin, as well as those secreted by the adipose tissue and the gastrointestinal tract including pancreatic hormones, are involved in the control of appetite and satiety (Tortorella *et al.* 2014). The peripheral signals derived from the adipose tissue, gastrointestinal tract and pancreatic beta cells become integrated in the arcuate nucleus in the hypothalamus by orexigenic system producing neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) and anorexigenic system secreting proopiomelanocortin (POMC) and Cocaine and Amphetamine-Regulated Transcript (CART) (Tortorella *et al.* 2014).

The endocannabinoid system is also involved in the regulation of the central and peripheral energy balance and acts through cannabinoid receptors, CB1 and CB2. Activation of endocannabinoid system is mediated by the CB1 receptors and leads to a stimulation of food intake (Monteleone *et al.* 2008). Endogenous opioids, β endorphin and dynorphin, stimulate NPY/AgRP system.

After integration in the arcuate nucleus, the signals are transmitted to other nuclei of the central nervous system (CNS) and to the peripheral nervous system. Anorexigenic neuropeptides: TRH, CRH and oxytocin, are secreted from the periventricular nucleus (NPV). In turn, the lateral hypothalamus (LHA) is the place where orexigenic peptides: orexins and melanin-concentrating hormone (MCH) are produced. The secretion of these peptides is stimulated by NPY (Tortorella *et al.* 2014).

In addition, BDNF (brain-derived neurotrophic factor) exerts a modulatory action on the activity of NPY/AgRP and POMC/CART (Monteleone 2008). Moreover, some neurotransmitters may also participate in the regulation of appetite. Increased activity of dopaminergic, α adrenergic and GABA-ergic systems lead to stimulation of appetite (Sodersten *et al.* 2016, Lechin *et al.* 2010). On the contrary, increased β adrenergic, cholinergic and serotoninergic activity is connected with inhibition of appetite (Baranowska *et al.* 1990; Kaye *et al.* 2000; Jimerson *et al.* 2000; Baranowska *et al.* 2011).

It has been reported that concentrations of these neuropeptides and neurotransmitters in serum and in cerebrospinal fluid (CSF) are disturbed in subjects suffering from eating disorders (Tortorella *et al.* 2014). However, the controversial results concerning changes in neuropeptides and neurotransmitters secretion and activity have been found. Some authors observed that plasma NPY concentrations in anorexia nervosa were unchanged (Nedvidkova *et al.* 2000) or lower as compared with control group (Baranowska *et al.* 2001). However, in CSF NPY levels were elevated (Gendall *et al.* 1999). It has been observed that in bulimia nervosa (BN) plasma NPY did not differ from the controls (Gendall *et al.* 1999) or the levels of plasma NPY were increased in anorexia nervosa and bulimia nervosa (Sedlackova *et al.* 2011).

Plasma AgRP levels were found to be increased (Moriya *et al.* 2006). Furthermore, a negative correlation between AgRP and Binge Eating Scale was observed in bulimia nervosa (Lofrano-Prado *et al.* 2011).

When data concerning serum BDNF levels were evaluated, it has been reported by some authors that BDNF was decreased in both anorexia nervosa (Monteleone *et al.* 2005; Ehrlich *et al.* 2009) and bulimia nervosa (Yamada *et al.* 2012). However, other authors observed increased plasma BDNF concentrations in these eating disorders (Mercader *et al.* 2007).

Studies on β-endorphin assessment in CSF in anorexia nervosa revealed that β-endorphin was within normal values for the controls or even decreased (Gerner & Yamada 1982; Kaye 1996).

Furthermore, the results of β-endorphin concentrations in plasma of AN varies between the studies as they were reported to be higher (Brambilla *et al.* 1991) or lower (Baranowska 1990) in comparison to those of the controls. Similarly, controversial results have been also reported in bulimia nervosa (Lesem *et al.* 1991; Brewerton *et al.* 1992).

2. The role of Klotho protein

Klotho protein is a newly discovered peptide that is involved in the metabolic processes including glucose and lipid metabolism. It also participates in differentiation and maturation of adipocytes and possesses neuroprotective properties (Chihara *et al.* 2006; Razzaque 2012; Chen *et al.* 2013). Expression of Klotho protein was found in the adipose tissue, kidneys and central nervous system. Interestingly, Amitami *et al.* 2013 observed a decrease of serum Klotho in patients with anorexia nervosa.

3. Peptides of adipose tissue

Adipose tissue is able to produce the biologically active substance termed adipokines. Leptin, adiponectin, resistin, vaspin and visfatin are among these peptides. Adipokines may play a pivotal role in energy homeostasis (Dolezalova *et al.* 2007). Leptin is well-characterized adipokine as it was discovered in the nineties of the 20th century. This adipokine reveals its central activity through receptors located, among others, in the hypothalamic arcuate nucleus. It exerts anorectic effects.

Interestingly, in underweight anorectic patients serum and CSF levels of leptin were found to be decreased (Monteleone *et al.* 2000; Monteleone *et al.* 2000; Baranowska *et al.* 2001; Haas *et al.* 2005; Tor-

torella *et al.* 2014) while normalization of leptin was observed after weight restoration (Haas *et al.* 2005; Baranowska-Bik *et al.* 2017).

In other eating disorder, bulimia nervosa, plasma and CSF leptin concentrations were reported to be decreased, normal or increased (Monteleone *et al.* 2000).

It has commonly accepted that adiponectin possesses metabolic, antiatherogenic, anti-inflammatory and insulin-sensitizing properties. Adiponectin circulates in three forms: LMW -low molecular weight, MMW - middle molecular weight and HMW - high molecular weight adiponectin. HMW adiponectin is the most biologically active form. In contrast to other adipokines, adiponectin peripheral levels inversely correlate with the amount of body fat. In anorexia nervosa elevated levels of adiponectin were observed by the majority of authors (Tortorella *et al.* 2014) and the profile of adiponectin multimers was changed (Amitani *et al.* 2013). Amitani *et al.* observed that the percentage of HMW to total adiponectin was lower, however, LMW percentage to total adiponectin was higher than in the controls. These findings correlated with BMI and some psychopathological symptoms.

It is worth noting that in anorexia nervosa hyperadiponectinemia was associated with higher insulin sensitivity (Dostalova *et al.* 2007). However, the controversial results of adiponectin measurements in bulimia nervosa were reported (Tortorella *et al.* 2014).

Up to date, the biological role of others adipokines in the regulation of energy homeostasis in humans is poorly understood. Nevertheless, visfatin is produced by visceral adipose tissue. It has been speculated that it possesses insulin-mimetic properties and, in addition, that it may play a role in the process of adipocyte differentiation (Fukuhara *et al.* 2005). Contrary, the results of Skop *et al.* (2010) did not confirm insulin-sensitizing properties of visfatin in vivo. The controversial results of visfatin measurements were reported in patients with anorexia nervosa (Dostalova *et al.* 2009; Ziora *et al.* 2012; Baranowska-Bik *et al.* 2017).

Resistin is a peptide produced by adipocytes and immunocompetent cells. The discrepancy in the results of resistin in anorexia nervosa and bulimia nervosa was observed. The resistin assessment in subjects suffering from anorexia nervosa revealed similar levels or decreased values in comparison to the controls (Housova *et al.* 2005; Dostalova *et al.* 2006; Ziora *et al.* 2011; Baranowska-Bik *et al.* 2017).

4. Gastrointestinal and pancreatic peptides

Not only adipokines influence processes of appetite and satiety but also gastrointestinal peptides mainly ghrelin, cholecystokinin, gastrin, glucagon-like peptide 1 (GLP1) and peptide YY (PYY) may play an important role in maintaining nutritional status.

Under physiological conditions cholecystokinin inhibits appetite by binding to the CCK1, CCK2 receptors in the hypothalamus and in vagus nerve (Degen *et al.* 2001).

Data concerning cholecystokinin levels remain controversial. While in acute phase of anorexia nervosa plasma and CSF cholecystokinin levels were within normal range (Geracioti *et al.* 1992) or enhanced in comparison with healthy controls (Cuntz *et al.* 2013), in patients with bulimia nervosa plasma cholecystokinin concentrations were found to be unchanged or decreased (Lydiard *et al.* 1993; Hannon-Engel *et al.* 2013).

Glucagon-like peptide (GLP1) is synthesized by the jejunum, ileum colon and nucleus solitarius, and is involved in the mechanisms of satiety.

Results of plasma glucagon-like peptide (GLP1), which is promoting satiety peptide, are inconsistent in case of eating disorders. Assessed values of plasma GLP1 were reported to be low or high in anorectic patients (Tomasik *et al.* 2002; Tomasik *et al.* 2004; Brambilla *et al.* 2009). Furthermore, individuals with bulimia nervosa presented plasma GLP1 levels after test meal to be within normal range (Brambilla *et al.* 2009) or reduced (Naessen *et al.* 2011).

Interestingly, in patients suffering from bulimia nervosa decreased GLP-1 levels in response to a test meal may be responsible for bulimic behavior.

Ghrelin is secreted by cells of gastric mucosa and exerts orexigenic and gastric emptying properties. Acylated ghrelin is an active form. In physiological conditions, ghrelin levels increase before meals and decrease after meals. Ghrelin is also a strong stimulator of growth hormone (GH) release.

In a course of the acute phase of anorexia nervosa, an enhancement fasting plasma of ghrelin levels were observed (Monteleone *et al.* 2008).

The differences in plasma ghrelin concentrations were found between restrictive and binge-purging forms of anorexia nervosa (Tanaka *et al.* 2003). The controversial results of fasting plasma ghrelin and to food ingestion were found.

In subjects with bulimia nervosa the different plasma ghrelin levels and abnormal response to food ingestion were found (Monteleone *et al.* 2005; Monteleone *et al.* 2010).

Peptide YY (PYY) is secreted from L cells of ileum and colon. It is found in peripheral blood in two forms of PYY 1-36 and PYY 3-36. The controversial results of fasting plasma PYY as well as those in response to meal were observed in patients with anorexia nervosa and in bulimia nervosa, and negative correlation to ghrelin were found in bulimia nervosa (Kojima *et al.* 2005; Stock *et al.* 2005; Monteleone *et al.* 2005; Misra *et al.* 2006; Germain *et al.* 2007; Germain *et al.* 2010,).

The pancreatic polypeptide (PP) is a peptide released by the pancreas. It belongs to the satiety factors. Some authors observed that plasma PP levels did not differ in anorectic patients comparing to controls, but PP raises after a meal in the restrictive form of anorexia nervosa as reported by Tomasik and colleagues (2005).

A decrease in PP concentrations found in bulimia nervosa may suggest that PP peptide play a role in the mechanism of bulimia (Naessen *et al.* 2011).

Insulin is a key factor in maintaining carbohydrate homeostasis. However, insulin may also influence satiety mechanism. Data concerning plasma insulin levels in anorectic patients are equivocal (Tomasik *et al.* 2005; Misra *et al.* 2010).

An increase of insulin values after a meal was found in individuals with bulimia (Naessen *et al.* 2011).

Another peptide that may play a role in maintaining appetite/satiety is vasoactive intestinal peptide (VIP). It is secreted by the gut, pancreas and hypothalamic nuclei. It has been revealed that in anorexia nervosa plasma VIP levels were similar to those of the controls or enhanced (Harty *et al.* 1991; Baranowska *et al.* 2000).

Interestingly, the activity of both central and peripheral peptides involved in the mechanisms of eating behavior and energy homeostasis depends of the character of disease as the results differ between the restrictive and binge-purge form of anorexia nervosa as well as in bulimia nervosa (Tortorella *et al.* 2014).

It is worth to notice that a normalization of these peptides release was seen in anorectic patients after refeeding (Tortorella *et al.* 2014).

HORMONAL DISTURBANCES

1. Hypothalamo-pituitary regulation

Another point to be discussed is that endocrine disturbances in eating disorders result from functional dysfunction of hypothalamo-pituitary regulation. The involved axes consist of hypothalamo-pituitary-gonadal, hypothalamo-pituitary-thyroid, hypothalamo-pituitary-adrenal and hypothalamo-growth hormone-somatomedin axes (Warren 2011; Baranowska 2011; Nedvidkova *et al.* 2000).

The same neuropeptides and peripheral peptides that are involved in the regulation of eating behavior and energy homeostasis play also a pivotal role in the mechanism of hypothalamo-pituitary regulation. A disturbed neuroendocrine circuit in a course of eating disorders impacts on GnRH pulse generator. The lower secretion of GnRH leads to a decreased release of gonadotropins and, in consequence, estrogens and progesterone deficiency. Clinical manifestation of dysregulation of the hypothalamo-pituitary-gonadal axis is amenorrhea seen in women suffering from anorexia nervosa.

There is some evidence indicating the deficit of GnRH release such as the reduced circadian LH pulsatility, disturbed diurnal rhythm of LH, blunted response of LH to clomide administration, or decreased response of LH to small doses of 25ug LH-RH injection with normalization of LH response as a result of LH-RH injection in higher doses (Baranowska 2011).

The mechanisms of functional GnRH impairment might be of different origin. Firstly, it may be caused by the changed activity of some peptides involved in the regulation of energy homeostasis. Furthermore, an increase of opioid activity may inhibit GnRH release. Study on anorectic females showed that an administration of opioid blocker, naloxone, caused an enhancement of LH, and this result was observed in the majority of AN subjects (Baranowska *et al.* 1984). Additionally, kisspeptin activates GnRH release and lower levels of kisspeptin in amenorrhoeic anorectic women may suggest that kisspeptin may participate in abnormal secretion of GnRH (Skorupskaite *et al.* 2014).

Finally, increased release of ghrelin and decreased release of leptin may also play a role in the inhibition of GnRH.

The dysregulation of the hypothalamic-GH-somatomedin axis leads to enhancement of GH secretion. Several changes are seen in anorexia nervosa including an enhancement of basal values of GH and secretory pulses and increased release of GH after GHRH or TRH administration. Of note, increased ghrelin and a decrease of somatostatin and leptin may influence on GH increase. It has been suggested that decreased IGF1 secretion may indicate resistance to GH (Stoving *et al.* 1999; Misra *et al.* 2003).

It has been reported that ghrelin is involved in the mechanism of persistent starvation, binge eating, rewarding feelings impulsivity and hyperactivity in patients with eating disorders (Steinglass *et al.* 2016, Anderberg *et al.* 2016, Monteleone *et al.* 2016, Monteleone *et al.* 2018).

Altered secretion of gut-brain-adipose peptides as well as neutralizing autoantibodies of these peptides may play a role in the mechanism of neuroendocrine disturbances in eating disorders (Smitka *et al.* 2013).

Elevated serum cortisol levels and corticotropin-releasing factor (CRH) found in cerebral spinal fluid (CSF) (Hotta *et al.* 1986; Misra *et al.* 2004) suggest abnormal hypothalamo-pituitary-adrenal regulation in anorexia nervosa but disturbed peripheral metabolism of cortisol may also be considered.

2. Peripheral metabolism

Thyroid homeostasis abnormalities are reported in AN. Alterations of conversion from thyroxin to triiodothyronine (T4→T3) were observed. Serum T3 and T4 were low whereas reverse T3 (rT3) concentration was elevated in underweight patients with anorexia nervosa. These changes are the result of impaired peripheral metabolism of thyroid hormones (Croxson & Ibbertson 1977; Lawson & Klibanski 2008).

However, delayed response of TSH to thyrotropin-releasing hormone (TRH) may indicate dysregulation of hypothalamo-pituitary-thyroid axis (Croxson & Ibbertson 1977; Lawson & Klibanski 2008).

Neuroendocrine abnormalities in a course of bulimia nervosa are also found but they are less pronounced than in anorexic individuals (Warren 2011). Low levels of gonadotropins, LH and FSH, were observed in nor-

mal-weight women with bulimia nervosa (Pirke *et al.* 1988).

Decreased T3 levels and delayed peak formation with a blunted response of TSH after TRH administration were reported but other authors observed the normal response of TSH in TRH test (Spalter *et al.* 1993). When considering the HPA, normal or increased cortisol levels were found in bulimia nervosa (Birketvedt *et al.* 2006).

Serum GH concentrations are unchanged when the results of subjects with bulimia were correlated with those of the controls. The normal response of GH to ghrelin administration was also observed (Fassino *et al.* 2005).

The novel hypothalamic neuropeptides such as nesfatin-1, phoenixin, spexin and kisspeptin not only affect energy homeostasis and eating behavior but also they may be considered as modulators of the stress response. Moreover, these peptides may be involved in the pathogenesis of anxiety-related in eating disorders (Skorupskaite *et al.* 2014; Pałasz *et al.* 2018).

SUMMARY

Endocrine abnormalities observed in eating disorders (anorexia nervosa and bulimia nervosa) result from complex processes of disturbed hypothalamo-pituitary-gonadal, -adrenal, -thyroid, -GH-somatomedin regulations as well as of altered peripheral hormonal secretion and metabolism.

Neuropeptides and peripheral peptides regulating energy homeostasis may play an important role in the mechanism of abnormal hormonal secretion seen in eating disorders.

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