REVIEW

Central and Peripheral Peptides Regulating Eating Behaviour and Energy Homeostasis in Anorexia Nervosa and Bulimia Nervosa: A Literature Review

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Abstract

A large body of literature suggests the occurrence of a dysregulation in both central and peripheral modulators of appetite in patients with anorexia nervosa (AN) and bulimia nervosa (BN), but at the moment, the state or trait-dependent nature of those changes is far from being clear. It has been proposed, although not definitively proved, that peptide alterations, even when secondary to malnutrition and/or to aberrant eating behaviours, might contribute to the genesis and the maintenance of some symptomatic aspects of AN and BN, thus affecting the course and the prognosis of these disorders. This review focuses on the most significant literature studies that explored the physiology of those central and peripheral peptides, which have prominent effects on eating behaviour, body weight and energy homeostasis in patients with AN and BN. The relevance of peptide dysfunctions for the pathophysiology of eating disorders is critically discussed.

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Keywords
anorexia nervosa; bulimia nervosa; eating disorders; neuroendocrinology; feeding regulators; central peptides; peripheral peptides

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Introduction

The two main disorders of eating behaviour, anorexia nervosa (AN) and bulimia nervosa (BN), are disorders of complex and still unknown aetiology whose development, progression and outcome are influenced by biological, sociocultural and psychological factors. In these disorders, the altered feeding component is probably only the visible part of a big iceberg whose underwater section represents the still unknown main psychopathological component leading to a secondary alteration of eating behaviour. However, alterations of eating behaviour are pathognomonic and paradigmatic for the nosographic definition of eating disorders (EDs). For this reason, a great deal of research has been performed on neurotransmitters, neuromodulators, neuropeptides and peripheral peptides involved in the regulation of eating behaviour, energy homeostasis and body weight (BW; Monteleone, 2011; Monteleone, Castaldo, & Maj, 2008; Monteleone & Maj, 2013). Although dysregulations of peripheral adipokines, gut-secreted peptides and central neurotransmitters involved in appetite modulation have been detected in patients with AN and BN, the significance of these derangements for the development, course and prognosis of EDs is still not clear. At present, there are no conclusive data as to whether alterations of feeding regulatory substances precede the appearance of an ED or are the consequence of the nutritional aberrations occurring in the disorder. It has been suggested, although not definitively proved, that those alterations, even when secondary to malnutrition and/or to aberrant eating behaviours, might contribute to the genesis and the maintenance of some symptomatic aspects of AN and BN, thus affecting the course and the prognosis of these disorders.

In this paper, we describe the most relevant changes of central and peripheral peptides regulating eating behaviour and energy homeostasis that have been reported in patients with AN and BN, and we discuss their possible involvement in the pathophysiology of EDs (Tables 1 and 2). A literature search was conducted using the electronic databases PubMed, Ovid and Embase and with additional hand searches through the reference lists obtained from the articles found. Journals were searched up to December 2013.

Central peptides modulating eating behaviour and energy homeostasis

Agouti-related peptide

The agouti-related peptide (AgRP) is a neuropeptide released with Neuropeptide Y (NPY) from specific neurons of the hypothalamic

Table 1 Summary of the most relevant changes of central peptides modulating eating behaviour and energy homeostasis in anorexia nervosa and bulimia nervosa

	AN	An	BN	BN	
	Acute phase	Weight restored	Acute phase	Recovered	References
Agouti-related peptide (AGRP)					
Plasma AGRP	↑	→			Moriya et al. (2006), Merle et al. (2011)
Brain-derived neurotrophic factor (BDNF)					Nakazato et al. (2003, 2006), Monteleone et al. (2004),
Serum BDNF	↓	↓	↓	↑	Monteleone, Fabrazzo, Martiadis, et al. (2005),
Plasma BDNF	↑		↑		Mercader et al. (2007), Ehrlich et al. (2009), Brandys et al. (2011), Yamada et al. (2012)
Corticotropin-releasing hormone (CRH)					Gwirtsman et al. (1983), Hotta et al. (1986),
CSF CRH	↑	↑	↑		Krahn and Gosnell (1989)
Galanin					Berrettini et al. (1988), Baranowska et al. (2001),
CSF Galanin	→	→[1]↓[2]			Frank et al. (2001)
Plasma Galanin	→		→		
α-melanocyte-stimulating hormone (α-MSH)					
Plasma α-MSH	→				Moriya et al. (2006)
Neuropeptide Y (NPY)					Kaye et al. (1990), Gendall et al. (1999), Nedvídková et al. (2000)
CSF NPY	↑	↑[3]→[4]			Baranowska et al. (2001), Sedlackova et al. (2011, 2012)
Plasma NPY	→↓↑		→↑	→	
Neurotensin					Nemeroff et al. (1989), Pirke et al. (1993)
Plasma neurotensin	→	→	→	→	
Oxytocin					
CSF oxytocin		→		↑	Demitrack et al. (1990), Chiodera et al. (1991), Frank et al. (2000),
Plasma oxytocin	↓				Lawson et al. (2011, 2012)
Plasma oxytocin (response to a test meal)	↑	↓			
Opioid peptides					
CSF β-endorphins	→↓	↓[1]→[2]	→↓		Kaye et al. (1982, 1987), Gerner et al. (1982), Waller et al. (1986)
CSF dynorphins	→	→	→		Fullerton et al. (1986), Baranowska (1990), Lesem et al. (1991),
Plasma β-endorphins	↑↓		↑↓		Brambilla et al. (1991), Brewerton et al. (1992)
Somatostatin (SRIF)					
CSF SRIF	↓		→	↑	Gerner and Yamada (1982), Kaye et al. (1988), Pirke et al. (1993),
Plasma SRIF	↓↑	→			Baranowska et al. (2000)
Plasma SRIF (response to test meal)	↑				
Thyrotropin-releasing hormone (TRH)					Devlin et al. (1990), Lesem et al. (1994)
CSF TRH	↓	↓	→		
Vasopressin					
CSF vasopressin	→↓	→↓		↑	Gold et al. (1983), Demitrack et al. (1992), Chiodera et al. (1993),
Plasma vasopressin	→↓	→↓	→↑	↑	Frank et al. (2000)
Plasma vasopressin (osmotic response)	↓	↓	↓	↑	

Note: AN, anorexia nervosa; BN, bulimia nervosa; CSF, cerebrospinal fluid.
→ not different from healthy controls; ↑ higher than healthy controls; ↓ lower than healthy controls.
[1]in patients weight-restored for more than 6 months but less than 1 year.
[2]in patients weight-restored for more than 1 year.
[3]after short-term weight restoration.
[4]after long-term weight restoration.

arcuate nucleus. It is one of the most potent and long-lasting appetite stimulator (Biebermann, Kühnen, Kleinau, & Krude, 2012).

In AN patients, plasma AgRP levels have been found to be significantly raised and not correlated to leptin concentration, although it has been suggested that AgRP secretion may be inhibited by leptin (Moriya, Takimoto, Yoshiuchi, Shimosawa, & Akabayashi, 2006). In a recent paper, Merle et al. (2011) reported that in weight-restored AN patients, plasma AgRP levels were similar to those of healthy controls, whereas in patients with symptomatic AN, they were increased. AgRP was inversely correlated with body mass index (BMI) and plasma leptin and progressively normalized during weight gain.

To the best of our knowledge, only the study of Lofrano-Prado et al. (2011) reported in adolescent patients with BN a negative

Table 2 Summary of the most relevant changes of peripheral peptides modulating eating behaviour and energy homeostasis in anorexia nervosa and bulimia nervosa

	AN	AN	BN	BN	References
	Acute phase	Weight restored	Acute phase	Recovered	
Apelin (APE)					
Plasma APE	↓				Ziora et al. (2010)
Adiponectin					Iwahashi et al. (2003), Monteleone, Fabrazzo, et al. (2003), Tagami et al. (2004), Housova et al. (2005), Dostálová et al. (2007), Dolezalova et al. (2007), Nogueira et al. (2010)
Plasma adiponectin	→↓↑	→	→↓↑		
Cholecystokinin (CCK)					Geracioti et al. (1992), Tamai et al. (1993), Lydiard et al. (1993), Brambilla, Brunetta, Peirone, et al. (1995), Brambilla, Brunetta, Draisci, et al. (1995), Fujimoto et al. (1997), Walsh (2002), Cuntz et al. (2013), Hannon-Engel et al. (2013)
CSF CCK	→↑	→	↓		
Plasma CCK	→↑	→	→↓		
Lymphocyte CCK	↓		↓		
Plasma CCK (response to test meal or OGT)	→↓↑	→	→↓		
Gastrin					Pirke et al. (1993), Baranowska et al. (2000)
Plasma gastrin	↓↑				
Plasma gastrin (response to test meal)	→				
Gastrin-releasing peptide (GRP)					Frank et al. (2001)
CSF GRP		→		↓	
Ghrelin					Nedvidkova et al. (2003), Tanaka, Naruo, et al. (2003), Tanaka, Tatebe, et al. (2003), Tanaka, Narau, et al. (2003), Nakai et al. (2003), Hotta et al. (2004), Misra et al. (2004), Troisi et al. (2005), Otto et al. (2005), Stock et al. (2005), Kojima et al. (2005), Harada et al. (2008), Monteleone, Fabrazzo, Tortorella, et al. (2005), Monteleone, Martiadis, et al. (2005), Monteleone, Castaldo, et al. (2008), Monteleone et al. (2008), Monteleone et al. (2009), Sedlackova et al. (2011)
Total plasma ghrelin	↑	→	↑→		
Total plasma ghrelin (response to test meal or OGT)	↑↓time-delayed AN-BP	↓	↓→		
Total plasma ghrelin (response to sham feeding)	↑		↑		
Plasma active ghrelin	↑↓				
Glucagon-like peptides (GLP)					Tomasik et al. (2002, 2004), Brambilla et al. (2009), Naessén et al. (2011)
Plasma GLP	↓		↑ (at 4:00 PM)		
Plasma GLP (response to test meal)			↓→		
Insulin					Tomasik et al. (2005), Kojima et al. (2005), Dostálová et al. (2007), Prince et al. (2009), Naessén et al. (2011), Misra and Klibanski (2009)
Plasma insulin	→↓↑	→	→		
Plasma insulin (response to test meal or OGT)	→↓or time delayed	→	↓		
Leptin					Gendall et al. (1999), Monteleone, Di Lieto, Tortorella, Longobardi, and Maj (2000), Monteleone, Bortolotti, et al. (2000), Monteleone, Fabrazzo, et al. (2002), Monteleone, Martiadis, et al. (2002), Djurovic et al. (2004), Haas et al. (2005)
CSF leptin	↓	→			
Plasma leptin	↓	→	→↓↑		
Plasma leptin (response to test meal)			→		
Plasma leptin (response to acute fasting)			↓		
Obestatin					Monteleone, Castaldo, et al. (2008), Monteleone, Serritella, et al. (2008), Nakahara et al. (2008), Germain et al. (2010), Harada et al. (2008), Uehara et al. (2011), Sedlackova et al. (2011)
Plasma obestatin	↓↑[1]		→↓↑		
Plasma ghrelin/obestatin ratio	↓↑		→↑		
Plasma (response to sham feeding)	↑drop				
Plasma (response to meal)	→		→		
Pancreatic polypeptide (PP)					Tomasik et al. (2005), Kinzig et al. (2007), Naessén et al. (2011)
Plasma PP	→↑	↑			
Plasma PP (response to test meal)	↓↑[2]→		↓		
Peptide YY_{3-36} (PYY_{3-36})					Kaye et al. (1990), Gendall et al. (1999), Kojima et al. (2005), Stock et al. (2005), Monteleone, Martiadis, et al. (2005), Misra et al. (2006), Nakahara et al. (2007), Germain et al. (2007, 2010)
CSF PYY_{3-36}			→	→	
Plasma PYY_{3-36}	→↑↓		→↓	→	
Plasma PYY_{3-36} (response to test meal)	↑ or time delayed	↑	↑↓		
Resistin (RES)					Housova et al. (2005), Dolezalova et al. (2007), Dostálová et al. (2007), Ziora et al. (2011a,), Terra et al. (2013)
Plasma RES	→↓				
Vasoactive intestinal peptide (VIP)					Harty et al. (1991), Baranowska et al. (2000)
Plasma VIP	↑→				
Plasma VIP (response to test meal)	→				
Visfatin					Dostálová et al. (2009), Ziora et al. (2012)
Plasma visfatin	→↓		→		

Note: AN, anorexia nervosa; BN, bulimia nervosa; CSF, cerebrospinal fluid; OGT, oral glucose test; AN-BP, anorexia nervosa bingeing–purging subtype; AN-R, anorexia nervosa restricting subtype after short-term weight restoration.
→ not different from healthy controls; ↑ higher than healthy controls; ↓ lower than healthy controls.
[1]in patients with AN-BP.
[2]in patients with AN-R.

correlation between circulating levels of AgRP and Binge Eating Scale, Binge Scale Questionnaire and Bulimic Investigation Test Edinburgh scores, suggesting a link between blood levels of AgRP and symptoms of bulimia and body image dissatisfaction.

Brain-derived neurotrophic factor

The brain-derived neurotrophic factor (BDNF) was originally characterized as a member of the neurotrophin family implicated in the processes of neuronal outgrowth and differentiation,

synaptic connectivity and neuronal repair. Subsequent research has unequivocally demonstrated that this neurotrophin has a role also in energy homeostasis, because it acts as an inhibitor of food intake.

In emaciated AN patients, serum BDNF levels were found significantly reduced as compared with healthy controls (Ehrlich et al., 2009; Monteleone, Fabrazzo, Martiadis, et al., 2005; Monteleone et al., 2004), and this finding has been confirmed by a recent meta-analysis (Brandys, Kas, van Elburg, Campbell, & Adan, 2011). It was initially suggested that reduced circulating BDNF in AN patients might be related to concomitant depression and not to the ED, because serum BDNF levels negatively correlated with depressive symptoms (Nakazato et al., 2003). This likelihood was ruled out in subsequent studies, which found significant positive correlations of serum BDNF levels with the subjects' BW and BMI but not with the severity of depressive symptomatology (Monteleone, Fabrazzo, Martiadis, et al., 2005). Moreover, a positive correlation between BDNF levels and Eating Disorder Inventory scores was reported in AN and BN patients, suggesting a contributing role of the neurotrophin to the pathophysiology of EDs (Mercader et al., 2010). Finally, one study showed that BDNF levels did not change after partial weight recovery in patients with anorexia (Nakazato et al., 2006).

Serum BDNF levels were significantly reduced in BN subjects compared with healthy controls and were significantly higher after treatment (Yamada, Yoshimura, Nakajima, & Nagata, 2012). On the contrary, increased plasma BDNF levels were reported in both AN and BN by Mercader et al. (2007).

A non-homeostatic role for BDNF in EDs has been also supposed. It has been demonstrated that BDNF and its tyrosine kinase receptor are expressed also in dopaminergic neurons of the ventral tegmental area and BDNF is anterogradely transported to nucleus accumbens (Numan & Seroogy, 1999), which suggests a role for the neurotrophin in modulating either food-related and non-food-related reward behaviours (Monteleone & Maj, 2013)

Corticotropin-releasing hormone

The corticotropin-releasing hormone is a 41-amino-acid hypothalamic peptide regulating adrenocorticotropic hormone secretion and neuroendocrine and behavioural stress-related responses. It seems to play an important role also in feeding regulation, acting as a satiety stimulator (Bailer & Kaye, 2003).

Corticotropin-releasing hormone concentrations in the cerebrospinal fluid (CSF) of AN patients were higher than normal both during the active phase of the disease and after short-term weight recovery (Hotta et al., 1986).

Cerebrospinal fluid corticotropin-releasing hormone concentrations in patients with bulimia have been found to be normal by one research group (Gwirtsman, Roy-Byrne, Yager, & Gerner, 1983) and increased by another one (Krahn & Gosnell, 1989).

Galanin

Galanin is a neuropeptide widely expressed in the central and peripheral nervous system and in the endocrine system, which regulates several physiological processes including food intake by acting as hunger stimulator (Mitsukawa, Lu, & Bartfai, 2008).

Galanin concentrations in CSF and plasma were found to be normal in symptomatic patients with restricted AN and in those weight-restored for more than 6 months but less than 1 year but reduced in those weight-restored for more than 1 year (Baranowska, Wolinska-Witort, Wasilewska-Dziubinska, Roguski, & Chmielowska, 2001; Frank, Kaye, Sahu, Fernstrom, & McConaha, 2001).

No alterations in plasma galanin secretion have been reported in BN patients (Berrettini et al., 1988).

α-melanocyte-stimulating hormone

The anorexigenic neuropeptide α-melanocyte-stimulating hormone (α-MSH) is a 13-amino-acid-long peptide derived from sequential endoproteolytic cleavage and posttranslational modifications of the pro-opiomelanocortin hormone.

In AN patients, plasma α-MSH levels were found not different from those of normal controls (Moriya et al., 2006). Fetissov et al. (2002) demonstrated a significant increase of auto-antibodies to α-MSH in AN and in BN compared with controls. The same research group measured auto-antibodies to α-MSH, adrenocorticotropic hormone, oxytocin (OX) and vasopressin (VP) and showed a significant correlation between the Eating Disorder Inventory-2 score and the levels of auto-antibodies to α-MSH. The correlation was positive in AN but negative in BN (Fetissov et al., 2005). It remains to be established whether these auto-antibodies interfere with normal signal transduction in the brain melanocortin circuitry and in other central and peripheral sites relevant to food intake regulation.

Lofrano-Prado et al. (2011) evaluated 32 adolescent patients with BN or binge-ED and showed a negative correlation between α-MSH levels and Binge Eating Scale, Binge Scale Questionnaire and Bulimic Investigation Test Edinburgh scores, which suggests a relationship between bulimic and body image dissatisfaction symptoms and this anorexigenic factor.

Neuropeptide Y

Neuropeptide Y is one of the strongest orexigenic factors secreted in the hypothalamic arcuate nucleus of the hypothalamus, although it is reported to have also anxiolytic and antidepressant behaviour profiles (Hökfelt et al., 2008).

In the literature, there are conflicting data related to peripheral levels of NPY in patients with AN. Indeed, although some authors reported that plasma levels of NPY in AN patients did not differ from levels detected in healthy controls (Nedvídková, Papezová, Haluzík, & Schreiber, 2000), some others suggested that plasma levels of NPY were significantly lower in anorectic women than in control subjects (Baranowska et al., 2001). In a recent paper, Sedlackova et al. (2012) reported that fasting NPY plasma levels were significantly increased in AN and BN patients and did not change after a high-carbohydrate and high-protein breakfast.

In emaciated patients with anorexia, NPY concentrations in the CSF have been reported to be significantly elevated, and they do not normalize after short-term weight restoration but do so in long-term weight-restored patients (Gendall, Kaye, Altemus, McConaha, & La Via, 1999). Persistently elevated NPY levels in the central nervous system may contribute to several characteristic disturbances in AN, including menstrual dysregulation during and after recovery (Kaye, Berrettini, Gwirtsman, & George, 1990). Indeed, hypothalamic NPY is one of the essential messenger molecules serving as a communication bridge between the neural processes regulating reproduction and those maintaining energy homeostasis. For this reason, altered neuroregulation of NPY secretion may contribute to persistent

amenorrhea after weight gain in patients with anorexia with low initial BMI (Kalra & Kalra, 1996).

In symptomatic and remitted patients with bulimia, plasma levels of NPY were not found different from levels in age-matched and weight-matched controls (Gendall et al., 1999). However, significantly elevated plasma concentrations of NPY in patients with BN as compared with matched controls have been repeatedly reported by one research group (Sedlackova et al., 2011, 2012). CSF concentrations of NPY were found to be normal during both the symptomatic phase and after recovery from BN (Gendall et al., 1999).

Neurotensin

Neurotensin (NTS) is a 13-amino-acid neuropeptide expressed in the lateral hypothalamic area. Recent studies have suggested that NTS may be an endogenous satiety factor playing a role in short-term appetite regulation by a complex interaction with monoamines and neuropeptides, particularly norepinephrine and the kappa opioid agonist dynorphin (Kim & Mizuno, 2010).

In acutely ill AN patients and after refeeding, blood NTS levels were found normal (Pirke et al., 1993). Similarly, circulating NTS levels were normal in BN patients, in both the active phase of the disease and after recovery (Nemeroff et al., 1989).

Oxytocin

Oxytocin is a nine-amino-acid peptide hormone that seems to be involved in the regulation of food intake by inhibiting reward-driven food intake.

In emaciated AN subjects, OX concentrations in the CSF were found to be reduced and its response to challenging stimuli to be impaired (Demitrack et al., 1990). Normal CSF OX concentrations, instead, have been reported in recovered AN patients (Chiodera et al., 1991). In two different recent papers, Lawson et al. (2011, 2012) showed that overnight secretion of OX in AN patients was decreased compared with healthy controls and that after a standardized mixed meal mean plasma OX levels were higher in AN than in healthy controls. Higher OX secretion in response to a meal was associated with higher levels of disordered eating psychopathology.

Mean CSF concentrations of OX were found to be normal in symptomatic BN women (Demitrack et al., 1990) but increased in recovered BN patients (Frank, Kaye, Altemus, & Greeno, 2000).

Opioid peptides

Opioid peptides are the main mediators of emotional responses to food selection and ingestion (Gosnell & Levine, 2009), which is responsible for reward-mediated food intake (Taha, 2010).

In emaciated AN patients opioid-like activity, which includes all the molecules expressing activity at the opioid μ receptor, was found to be increased in the CSF (Kaye, Pickar, Naber, & Ebert, 1982). However, when opioid peptides were examined separately, baseline CSF levels of β-endorphin (β-EP) were found to be either normal (Gerner, Sharp, & Catlin, 1982) or significantly lower than normal (Kaye, 1996). The reduced CSF β-EP concentrations persisted in short-term restored patients and normalized in long-term recovered ones (Kaye et al., 1987). Dynorphin concentrations in the CSF were detected to be normal in both emaciated and recovered AN patients (Kaye, 1996). In plasma, β-EP levels were reported to be higher (Brambilla et al., 1991) or lower than normal (Baranowska, 1990). Because endogenous opioids exert an inhibitory action on hypothalamic luteinizing hormone-releasing hormone, the increased central opioid-like activity of underweight patients with anorexia may contribute to dysfunctions in the hypothalamo–pituitary–gonadal axis and to the occurrence of amenorrhoea in these patients.

In BN patients, β-EP concentrations in the CSF have been reported to be not different from those of healthy controls (Lesem, Berrettini, Kaye, & Jimerson, 1991) or to be lower than normal (Brewerton, Lydiard, Laraia, Shook, & Ballenger, 1992), whereas dynorphin levels were in the normal range (Brewerton et al., 1992). In plasma, β-EP concentrations were found to be lower than normal in one study (Waller et al., 1986) but higher in another one (Fullerton, Swift, Getto, & Carlson, 1986).

The changes in both central and peripheral opioid substances observed in symptomatic ED individuals are consistent with the proposed dysregulation of reward processes in EDs (Kaye, Fudge, & Paulus, 2009; Monteleone & Maj, 2013).

Somatostatin

Somatostatin (SRIF) is a cyclic tetradecapeptide released by the hypothalamus to inhibit the release of growth hormone, somatotropin and thyroid-stimulating hormone from the anterior pituitary; it is also released by delta cells of the islets of Langerhans in the pancreas to inhibit the release of glucagon and insulin and by the similar D cells in the gastrointestinal tract. SRIF has been proposed as a satiety factor because of its ability to inhibit food intake (López, Nogueiras, Tena-Sempere, & Diéguez, 2010).

In AN patients, CSF levels of the peptide have been reported to be lower than normal (Gerner & Yamada, 1982), whereas plasma levels of the peptide have been reported to be either lower (Gerner & Yamada, 1982) or higher than normal (Pirke et al., 1993). After a standardized fat-rich and protein-rich fluid test meal, plasma SRIF levels were higher than normal in underweight patients with anorexia, and remained elevated for up to 100 min after the test meal (Pirke, Friess, Kellner, Krieg, & Fichter, 1994). In the acute phase of the disease, the sensitivity of somatotroph cells to exogenous SRIF was found to be preserved (Gianotti et al., 1999).

In BN patients, SRIF concentrations in the CSF have been shown to be normal in the symptomatic phase of the disease and to have increased after recovery (Kaye et al., 1988).

Thyrotropin-releasing hormone

The thyrotropin-releasing hormone (TRH) is produced in the neurons of the hypothalamic medial paraventricular nucleus and plays a major role in the regulation of the hypothalamus–pituitary–thyroid axis by stimulating the release of the thyroid-stimulating hormone. In addition, TRH inhibits food intake acting downstream of the leptin–melanocortin pathway (Mihaly et al., 2000).

In AN, TRH concentrations in the CSF were found to be decreased both in emaciated and in weight-recovered subjects (Lesem, Kaye, Bissette, Jimerson, & Nemeroff, 1994). Circulating TRH concentrations were found normal in BN subjects (Devlin et al., 1990).

Vasopressin

Several studies showed that the neuropeptide hormone VP is involved in eating behaviour, because it is able to reduce food intake (Kaye, 1996).

In symptomatic AN patients, VP concentrations in plasma and CSF have been reported to be not different from those of controls or to be abnormally high, and the osmoregulation of the peptide has been found to be impaired, with either a secretory deficiency or an erratic and osmotically uncontrolled release of the hormone, which does not return to normal for up to 6 months after recovery (Gold, Kaye, Robertson, & Ebert, 1983). Frank et al. (2000) reported that CSF VP levels were significantly increased in recovered AN patients.

In patients with bulimia, plasma VP concentrations have been found to be normal, whereas the responses of the peptide to hypertonic saline infusion and to insulin-induced hypoglycaemia were reduced (Chiodera et al., 1993). However, Demitrack et al. (1992) reported that in BN individuals, plasma VP levels were elevated both at admission and 1 month after nutritional rehabilitation. Elevated CSF levels of VP and an increased response to osmotic stimuli have been found in recovered BN patients (Frank et al., 2000)

Peripheral peptides modulating eating behaviour and energy homeostasis

Adiponectin

Adiponectin (AD) is an adipocyte-specific protein that modulates a number of metabolic processes, including glucose and lipid metabolism in insulin-sensitive tissues. Levels of the hormone are inversely correlated with body fat mass in adults.

With the exception of Iwahashi et al. (2003), who observed no difference in AD concentrations between AN patients and healthy women, and Tagami et al. (2004), who found even decreased AD levels in malnourished AN individuals with return to normal values after weight recovery, elevated levels of circulating AD were reported in underweight AN patients by most of the authors (Dolezalova et al., 2007; Dostálová, Smitka, Papezová, Kvasnicková, & Nedvídková, 2007; Housova et al., 2005). Moreover, it has been shown that less severely malnourished patients with AN binge–purge type (AN-BP) had a relatively modest increase in circulating AD, whereas a more prominent rise has been found in severely malnourished restrictive AN (AN-R) individuals (Housova et al., 2005; Nogueira et al., 2010). The physiologic relevance of high AD levels in AN is unclear. Two main hypotheses have been put forward. The first one suggests that, because intracerebroventricular administration of AD in mice decreased BW mainly by stimulating energy expenditure, hyperadiponectinemia could be a contributing etiopathogenetic factor to BW loss in AN (Qi et al., 2004). Alternatively, elevated circulating AD concentrations could represent a compensatory mechanism for the increased insulin sensitivity in AN patients, because a negative correlation between plasma AD and insulin was found in these patients (Dostálová et al., 2007).

In BN patients, one study reported increased AD concentrations that resulted positively correlated with the severity of bingeing/purging behaviour (Monteleone, Fabrazzo, et al., 2003), whereas another study (Tagami et al., 2004) detected decreased circulating levels of the adipokine. Housova et al. (2005) found normal AD concentrations in symptomatic women with bulimia. Differences in the patient's samples, assay methods and time of the day of blood collection might be responsible for those discrepancies.

Apelin

Apelin (APE) is a recently discovered peptide that acts as the endogenous ligand of the human orphan receptor APJ (orphan G protein-coupled receptor). APE belongs to the adipokine group and is regulated by insulin and tumour necrosis factor-α (TNF-α) in the adipose tissue. Ziora et al. (2010) reported that serum APE concentrations in patients with AN-R or with ED not otherwise specified, were significantly lower than in the healthy controls.

Cholecystokinin

Cholecystokinin (CCK) is a member of the gut–brain family of peptide hormones that decreases hunger and feeding in humans (Degen, Matzinger, Drewe, & Beglinger, 2001).

In emaciated patients with AN, baseline levels of CCK in CSF and plasma were found to be normal (Geracioti, Liddle, Altemus, Demitrack, & Gold, 1992) or higher than normal but returning to normal after recovery (Cuntz et al., 2013). After a fat-reach meal, CCK was released more rapidly in AN-R than in normal controls, and its levels were higher than in controls. This response normalized in weight-recovered patients (Fujimoto et al., 1997). However, a normal postprandial rise in CCK has been reported also in emaciated AN subjects (Geracioti et al., 1992). In the acute phase of AN, the glucose load was followed by lower than normal CCK secretion, which returned to normal at recovery (Tamai et al., 1993). The concentrations of CCK measured in T-lymphocytes of AN patients were significantly lower than in normal volunteers (Brambilla, Brunetta, Peirone, et al., 1995).

In BN patients, circulating CCK levels have been reported to be similar to healthy controls (Hannon-Engel, Filin, & Wolfe, 2013) or lower than normal in plasma (Lydiard et al., 1993), in the CSF and in polymorphonucleate blood mononuclear cells (Brambilla et al., 1995). A normal or diminished CCK release after a test meal has been observed (Walsh, 2002). Decreased CCK values did not correlate to BMI or frequency of bingeing/vomiting episodes but were significantly related to anxiety, hostility, aggression and impairments of interpersonal sensitivity (Lydiard et al., 1993).

Gastrin

Gastrin is a peptide hormone secreted by the wall of the pyloric end of the stomach that stimulates secretion of gastric acid and promotes gastric motility. In AN patients, plasma gastrin levels were found lower than normal (Baranowska, Radzikowska, Wasilewska-Dziubinska, Roguski, & Boroviec, 2000) or relatively higher than in healthy controls (Pirke et al., 1993). After a test meal, plasma gastrin concentration did not differ between AN patients and controls (Pirke et al., 1993).

Gastrin-releasing peptide

The gastrin-releasing peptide (GRP) is a regulatory peptide that elicits gastrin release and regulates gastric acid secretion and enteric motor function. Frank et al. (2001) compared CSF GRP concentrations of patients who were long-term recovered from AN or BN with healthy control women. GRP concentrations were significantly lower in patients that recovered from BN compared with AN and healthy controls, suggesting that this alteration might be trait-related and contribute to episodic hyperphagia in BN.

Ghrelin

Ghrelin is a 28-amino-acid peptide mainly secreted by the oxyntic cells of the gastric mucosa with an acyl side chain attached to the serine residue at position 3, which is crucial for its orexigenic and gastric empting effects. Acylated ghrelin (active form) represents less than 10% of circulating ghrelin, which includes acylated and deacylated fragments (inactive forms). It has been shown that circulating ghrelin levels increase before meals and decrease after meals, returning progressively to baseline levels towards the late postprandial and interdigestive period, which suggests a role of hunger stimulator for this peptide.

In underweight AN patients, fasting circulating plasma levels of ghrelin have been reported to have raised (Monteleone, Castaldo, et al., 2008). Tanaka, Naruo, et al. (2003) reported that plasma ghrelin concentrations of women with AN-BP were significantly lower than those of women with AN-R, suggesting that bingeing–purging behaviour may have some influence on circulating ghrelin. However, Otto et al. (2005) found no significant difference in fasting plasma ghrelin concentrations between AN-R and AN-BP patients, whereas opposite results with higher plasma ghrelin levels in AN-R than in AN-BP subjects have also been reported (Troisi et al., 2005). The elevated plasma ghrelin concentrations in underweight patients with anorexia tend to normalize with recovery of BW, and the decline in circulating ghrelin seems to parallel the progressive increase in weight during restoration treatments (Misra et al., 2004; Otto et al., 2005). This supports the view that the elevated ghrelin secretion in symptomatic patients with anorexia is a state-dependent phenomenon that resolves with the restoration of normal eating habits.

In underweight patients with AN, the ghrelin secretion in the cephalic phase of food ingestion was found to have increased (Monteleone, Castaldo, et al., 2008), whereas Nedvidkova et al. (2003) reported that the food-induced suppression of circulating ghrelin was almost completely absent. Similarly, the suppressant effect of oral glucose administration on plasma ghrelin was significantly blunted in AN-R women but normal and delayed in those with AN-BP (Tanaka, Tatebe, et al., 2003). Otto et al. (2005), instead, found that postprandial ghrelin release in emaciated AN patients did not differ from that of healthy subjects; moreover, although morning ghrelin levels progressively declined with the recovery of weight, ghrelin response to food ingestion was not influenced by BW restoration. Two other studies, with different experimental designs, reported that in AN, elevated preprandial levels of ghrelin, although suppressed by food ingestion in percentages similar to those of normal subjects, remained significantly higher than in controls (Misra et al., 2004; Stock et al., 2005). Differences in the clinical characteristics of patients' samples, the type, composition and total calories of test meals and the timing of blood collection may partially explain the discrepancies between different studies.

A major technical issue in ghrelin studies is the rapid degradation of circulating ghrelin into inactive fragments. It is commonly accepted that concentrations of acylated ghrelin accounts for less than 10% of circulating ghrelin levels, which include acylated and deacylated fragments. Because most of the studies cited earlier measured total ghrelin concentrations without differentiating between active and inactive ghrelin, increases in total ghrelin plasma levels in AN could not be representative of increased active ghrelin production. When this aspect was taken into account, conflicting results emerged. In fact, Nakai et al. (2003) showed that in underweight AN patients, plasma active ghrelin was increased and normally suppressed after oral glucose administration. Hotta et al. (2004), instead, found that total ghrelin was elevated in underweight patients with anorexia and did not decrease after glucose infusion, whereas active ghrelin was reduced and showed normal glucose suppression.

In BN, it was initially reported that fasting ghrelin was increased and that this increase was evident in patients with frequent binge–purge episodes but not in non-purging ones, supporting the idea that binge/purge cycles with vomiting as opposed to binge-eating episodes alone can influence fasting plasma ghrelin (Tanaka, Narau, et al., 2003). However, subsequent studies on relatively small patients' samples, detected no significant difference in plasma ghrelin concentrations between bingeing–purging patients with bulimia and healthy controls (Sedlackova et al., 2011). Monteleone, Fabrazzo, Tortorella, et al. (2005) measured fasting ghrelin concentrations in a relatively large sample of 56 subjects with binge–purge BN and 51 healthy controls, without detecting any significant difference in circulating ghrelin levels between the two groups. Moreover, no significant correlation was found between plasma ghrelin and severity of the bingeing/vomiting behaviour. The secretion of ghrelin in the cephalic phase of food ingestion has been found increased in symptomatic BN women (Monteleone, Serritella, Scognamiglio, & Maj, 2009), whilst ghrelin responses to a macronutrient balanced meal and a fat-rich meal have been reported to be blunted in symptomatic binge/purge patients with bulimia as compared with healthy controls (Kojima et al., 2005; Monteleone, Martiadis, et al., 2005). It is noteworthy that some but not all experimental human studies suggested diminished satiety responses to meals in BN patients (Kissileff et al., 1996), which could be mediated, at least in part, by their impaired food-induced responses of ghrelin.

Glucagon-like peptide

The glucagon-like peptides (GLP-1 and 2) are synthesized by the jejunum, ileum, colon and neurons of nucleus tractus solitarius; they are involved in nutrient assimilation and energy homeostasis, by promoting satiety.

Tomasik, Sztefko, and Malek (2002) and Tomasik, Sztefko, and Starzyk (2004) showed that after an overnight fast, mean plasma GLP-1 concentrations were significantly lower in AN patients than in healthy subjects. Blood GLP-1 concentrations, instead, were significantly higher in AN patients than in subjects (Germain et al., 2007) with a constitutional thinness.

In BN patients, plasma GLP-1 levels have been reported to be similar to healthy controls in response to a test meal (Brambilla, Monteleone, & Maj, 2009) but higher than normal at 4:00 PM.

In a recent paper, Naessén, Carlström, Holst, Hellström, and Hirschberg (2011) reported that women with BN secrete abnormally low amounts of GLP-1 in response to a test meal, which could play a role in the maintenance of bulimic behaviour.

Insulin

Insulin plays a key role in glucose metabolism and acts also as a satiety signal in the brain.

In AN patients, insulin secretion has been reported to be normal, increased or decreased during the active phase of the disease and to return to normal after recovery (Misra & Klibanski, 2009; Prince, Brooks, Stahl, & Treasure, 2009). In the oral glucose tolerance test, insulin output has been demonstrated to be lower in AN than in controls (Tomasik, Sztefko, Starzyk, Rogatko, & Szafran, 2005). These alterations resolve after refeeding and weight gain (Dostálová et al., 2007).

Patients with bulimia nervosa have been shown to exhibit elevated postprandial plasma insulin responses (Kojima et al., 2005). Recently, Naessén et al. (2011) reported significantly attenuated basal and peak insulin concentrations after a test meal in BN subjects.

Leptin

Leptin is a protein with hormone/cytokine activities released primarily by white adipose tissue in direct proportion to body fat mass. Leptin is a key regulator of energy balance as it acts in the brain to decrease food intake and increase energy expenditure.

It has been reported that plasma and CSF levels of leptin are considerably lower than normal in underweight patients with anorexia (Monteleone, Castaldo, et al., 2008). Leptin receptors, instead, were found to be increased in symptomatic AN patients (Dolezalova et al., 2007; Monteleone, Fabrazzo, Tortorella, Fuschino, & Maj, 2002). The circadian rhythm of leptin was reported to be disrupted in AN patients, with attenuation or abolition of the physiological nocturnal surge (Balligand, Brichard, Brichard, Desager, & Lambert, 1998). Alterations of leptin resolve with the recovery of BW (Haas et al., 2005), and in long-term recovered AN patients, both plasma and CSF levels of the hormone appear to be similar to those of healthy controls (Gendall et al., 1999). Moreover, longitudinal studies have shown that during refeeding treatments, leptin concentrations and secretion rate progressively increase as the weight is regained and in those cases with a too rapid weight restoration, they reach values disproportionately higher than normal (Lob et al., 2003). It has been argued that hyperleptinaemia in AN patients during refeeding may be a major factor in the patient's difficulty to reach or maintain target-weight and hyperleptinaemia was found to be associated with an elevated risk of renewed weight loss (Holtkamp et al., 2004). Because circulating levels of leptin receptors are drastically elevated in underweight anorectic women (Dolezalova et al., 2007; Monteleone, Fabrazzo, et al., 2002), a too rapid increase in circulating leptin in AN patients might theoretically result in a potentiation of leptin-induced appetite suppression and energy expenditure, thus counteracting the therapeutic process. However, it has been reported that in patients with anorexia, whose caloric intake during refeeding was adapted daily to keep circulating leptin within the reference range for the patient's current BW, the outcome was not improved (Lob et al., 2003). Therefore, the role of leptin in weight recovery in AN needs to be further explored. It should be pointed out that relative hyperleptinaemia is not a universal finding in studies on AN patients who regained weight (Djurovic et al., 2004). Because leptin exerts modulatory effects on some neuroendocrine functions, reduced secretion of leptin in AN patients has been considered responsible for a lifetime history of amenorrhea and subnormal serum levels of luteinizing hormone, being a necessary, even though not sufficient, factor for the resumption of menses (Brambilla et al., 2003). Low leptin secretion is also considered potentially responsible for low hypothalamus–pituitary–thyroid axis function, increased hypothalamo–pituitary–adrenal axis function and osteopenia in AN (Brambilla & Monteleone, 2003).

Excessive physical activity has been reported in 31–80% of AN patients. An inverse correlation between food intake and physical activity has been shown during the acute weight loss phase of AN suggesting a relationship between energy balance and activity levels (Hebebrand, Muller, Holtkamp, & Herpertz-Dahlmann, 2007). It has also been demonstrated that leptin concentrations in AN inpatients were inversely correlated with levels of physical exercise and predicted physical activity, supporting the idea that hypoleptinaemia may be an important factor to sustain an excessive physical activity in women with AN (Holtkamp et al., 2003). Consistent with this idea, an involvement of leptin has been demonstrated in the pathophysiology of the rodent model of activity-based anorexia (Hillebrand, Koeners, de Rijke, Kas, & Adan, 2005).

In normal-weight subjects with BN, CSF and plasma levels of leptin have been reported to be either decreased, normal or increased (Monteleone, Castaldo, et al., 2008), perhaps owing to clinical heterogeneity of patients' samples, because women with bulimia have been shown to exhibit plasma leptin levels ranging from anorexic-like to normal values depending on the severity and length of their illness (Monteleone, Martiadis, Colurcio, & Maj, 2002). Moreover, in patients with bulimia with hypoleptinaemia, the fall in circulating leptin in response to acute fasting is almost completely absent, whereas its response to short-term normal refeeding, although similar in percentage to that of controls, is not sufficient to restore normal blood levels of the hormone (Monteleone, Bortolotti, et al., 2000). Therefore, it seems that, at least in those BN patients with anorexic-like leptin concentrations, the function of leptin as an index of acute changes in energy balance is lost. This may have important pathogenic implications. In fact, because leptin behaves as a hunger-suppressant signal (Blundell, Goodson, & Halford, 2001), lower leptin values after eating together with alterations in other key modulators of hunger and satiety occurring in people with BN, such as the impaired meal-induced ghrelin suppression (Monteleone, Martiadis, Fabrazzo, Serritella, & Maj, 2003; Monteleone, Martiadis, et al., 2005) and the blunted postprandial CCK rise (Geracioti et al., 1992), could contribute to the binge-eating behaviour of BN patients.

Obestatin

Obestatin, a 23-amino-acid peptide released from the stomach after the proteolytic cleavage of the pro-hormone preproghrelin, appears to function as part of an anorexic gut–brain network that decreases food intake and reduces BW (Zhang et al., 2005). Obestatin has been postulated to antagonize ghrelin actions on energy homeostasis and gastrointestinal functions, although this has been questioned by some authors (Gourcerol & Taché, 2007) and controversies still exist on its specific effects on food intake/energy balance as well as on the measurements of the hormone levels in human blood (Garg, 2007).

In underweight AN patients, enhanced levels of obestatin with either enhanced or decreased ghrelin-to-obestatin ratio have been detected (Harada et al., 2008; Monteleone, Serritella, Martiadis, Scognamiglio, & Maj, 2008; Nakahara et al., 2008; Sedlackova et al., 2011). Moreover, Germain et al. (2010) reported that the circadian secretion of obestatin was increased in AN-R patients

but decreased in AN-BP ones. As compared with healthy controls, a more robust drop of circulating obestatin after sham feeding has been reported in symptomatic AN patients (Monteleone, Serritella, et al., 2008). This finding together with the enhanced sham-feeding-induced ghrelin secretion could result in an amplification of the peripheral hunger signal likely aiming to oppose the rigid control that AN patients exert over their food intake. The secretion of obestatin after food ingestion in underweight AN patients has been found to be normal although occurring at levels higher than in healthy controls (Sedlackova et al., 2011).

No significant changes in plasma levels of obestatin or in the ghrelin-to-obestatin ratio have been detected in symptomatic women with BN by Monteleone et al. (2008c), whereas increased levels of obestatin with normal suppression after food ingestion and increased ghrelin-to-obestatin ratio have been reported by Sedlackova et al. (2011). Germain et al. (2010), instead, found a lower than normal circadian secretion of obestatin in symptomatic BN patients.

Pancreatic polypeptide

The pancreatic polypeptide (PP), a hormone released by the pancreas after eating, acts as a circulating satiety factor.

In AN-R and AN-BP patients plasma PP levels were found not different from those of controls; however, after a fat-rich meal, plasma PP concentrations were higher than normal in patients with AN-R but not in those with AN-BP (Tomasik et al., 2005). Kinzig, Coughlin, Redgrave, Moran, and Guarda (2007) showed that plasma PP levels were increased in AN relative to controls and that short-term refeeding did not correct plasma PP levels.

Women with BN were found to secrete abnormally low amounts of PP after a test meal, which could play a role in the maintenance of bulimic behaviour (Naessén et al., 2011).

Peptide YY

The short-term appetite-regulator peptide YY (PYY), belonging to the NPY family, is a 36-amino-acid peptide released from the endocrine L cells of the distal ileum and colon in response to feeding (Adrian et al., 1985). PYY in the circulation exists in two major forms: $PYY_{1–36}$ and $PYY_{3–36}$.

In AN women, baseline plasma $PYY_{3–36}$ levels were reported to be normal (Stock et al., 2005), increased (Misra et al., 2006) or reduced (Germain et al., 2007, 2010), whereas plasma $PYY_{3–36}$ response to energy intake was reported to be time delayed (Stock et al., 2005) or increased and not completely restored after weight gain (Nakahara et al., 2007).

Initial studies in BN reported normal CSF and plasma levels of PYY in both symptomatic and 1-year recovered patients with bulimia (Gendall et al., 1999). Moreover, Kaye et al. (1990) measured plasma concentrations of PYY in five women with bulimia during episodes of bingeing/vomiting and in six healthy women, who experimentally binged without vomiting. In the latter, plasma PYY concentrations significantly rose after meals and remained elevated for the subsequent 2 h; in the former, circulating PYY increased after the first binge and remained elevated for the duration of bingeing and vomiting. Patients with bulimia exhibited a slightly higher postprandial peak value of PYY than did healthy volunteers. More recently, two independent research groups found a blunted $PYY_{3–36}$ response to food ingestion in symptomatic women with bulimia together with a decreased response of ghrelin (Kojima et al., 2005; Monteleone, Martiadis, et al., 2005). Moreover, both studies showed a negative correlation between meal-induced $PYY_{3–36}$ increase and ghrelin decrease, suggesting a negative interaction between $PYY_{3–36}$ and ghrelin. Suppression of circulating ghrelin and increase of plasma $PYY_{3–36}$ after food ingestion in healthy humans likely represent the activation of peripheral signals promoting the termination of food ingestion. Hence, in symptomatic patients with bulimia, the blunted responses of circulating ghrelin and $PYY_{3–36}$ to a test meal would denote the occurrence in these subjects of an impaired suppression of the drive to eat following a meal, which might play a role in their increased food consumption and binge eating. Recently, a lower than normal circadian secretion of $PYY_{3–36}$ has been reported in symptomatic BN women (Germain et al., 2010).

Resistin

Resistin (RES) is member of a class of cysteine-rich proteins collectively termed RES-like molecules initially described in adipose tissue and acting as a fuel homeostasis regulator (Jamaluddin, Weakley, Yao, & Chen, 2012).

Different research groups reported that plasma RES levels in patients with AN were not significantly different from those in healthy controls or in BN patients and showed no significant relation with BMI or body fat content (Dolezalova et al., 2007; Housova et al., 2005; Terra et al., 2013). On the contrary, significantly decreased plasma RES levels were detected in AN patients by Dostálová et al. (2007), who suggested that low plasma RES levels in AN were probably related to a defective mononuclear-macrophage number and/or function, because RES is expressed also in this cell line. Interestingly, an *in vivo* microdialysis experiment detected increased levels of RES in the subcutaneous adipose tissue of undernourished AN patients (Dostálová, Kunesova, Duskova, Papezová, & Nedvídková, 2006). Two subsequent papers (Ziora et al., 2011a, b) showed that mean serum RES concentration in AN were significantly lower than in healthy controls but after correction for BMI, RES values in AN resulted similarly to those of healthy subjects.

Vasoactive intestinal peptide

The vasoactive intestinal peptide (VIP), a peptide produced in many tissues including the gut, pancreas and suprachiasmatic nuclei of the hypothalamus, regulates smooth muscle activity, epithelial cell secretion and blood flow in the gastrointestinal tract. Harty, Pearson, Solomon, and McGuigan (1991) evaluated fasting and postprandial levels of VIP in AN patients and in healthy controls. Results of these studies indicate that plasma VIP levels were normal in both controls and AN patients after a liquid mixed meal. Different results have been detected by Baranowska et al. (2000) who reported baseline plasma values of VIP higher than normal in AN patients.

Visfatin

Visfatin (VISF) is an adipocytokine produced mainly in the adipose tissue, whose circulating levels are enhanced in metabolic disorders, such as type 2 diabetes mellitus and obesity. Two recent papers evaluated the role of VISF in ED patients. Dostálová, Sedlácková, Papezová, Nedvídková, and Haluzík (2009) showed that circulating VISF levels were not affected by the presence of

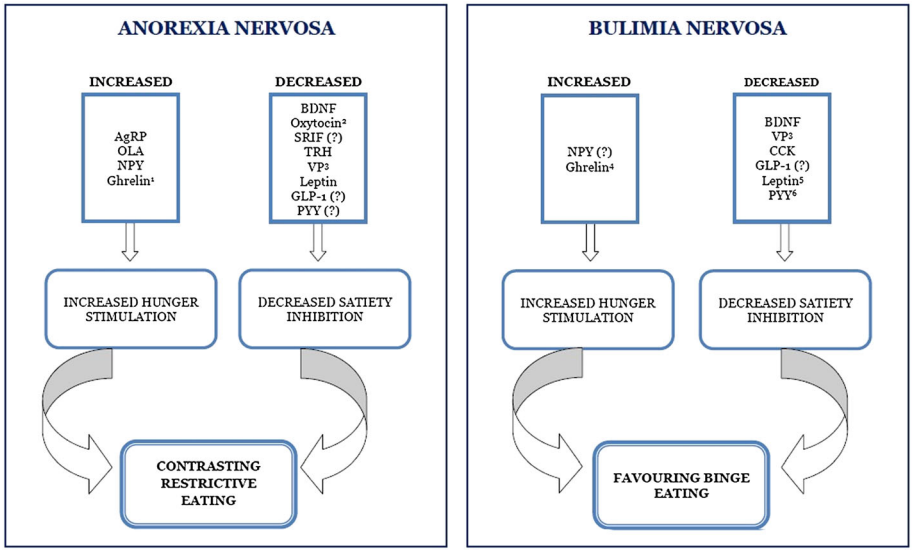

Figure 1. Possible pathophysiological significance of the most consistent peptide changes in patients with active anorexia nervosa and bulimia nervosa

both chronic malnutrition in AN or bingeing/purging behaviour in BN. Instead, Ziora et al. (2012) reported that when compared with healthy controls, serum VISF concentrations were decreased in AN patients.

Conclusions

The aim of this selective review was to describe the changes in both central and peripheral peptides regulating eating behaviour and energy homeostasis that have been detected in patients with AN and BN. The data reported here are not exhaustive of the literature on this topic, because other endogenous substances involved in the modulation of feeding and not included in this review, such as central monoamines, indolamines and endocannabinoids, have been shown to be deranged in EDs.

The aforementioned reviewed literature on peptidergic modulators of eating behaviour and energy homeostasis demonstrated that often, findings are non consistent amongst different studies. This can be explained by the relative small sizes of study samples, the clinical heterogeneity of the recruited patients and the differences in the study methodologies. Moreover, some studies are outdated and have never been replicated. Nevertheless, literature data unequivocally suggest that disturbances in both central and peripheral peptidergic eating behaviour modulators occur in EDs, although it is still debated which comes first: peptide alterations being a pathogenetic cause of EDs or the ED psychopathology leading to impaired nutrition and subsequent peptide damages. Even if this last hypothesis is currently believed to be the most probable, it has been demonstrated that alterations of some peptides persist or appear long after recovery from an ED. The persistence or the occurrence of a peptide derangement long after recovery from an ED suggests that such alterations might be trait rather than state-dependent phenomena, so they may precede the onset of the diseases as one of their causal factors or constitute a vulnerable biological background predisposing the patient to future relapses. Even so, it cannot be ruled out that the persistence or occurrence of peptide impairments long after recovery may be the expression of alterations occurring during the disease that are severe enough to induce a permanent damage or that they might depend on still not well defined persistent interfering factors.

As mentioned in the Introduction, deranged eating is the most evident disturbed behaviour of AN and BN patients, so peptide changes detected in the acute phase of both disorders have been interpreted to explain the pathophysiology of the aberrant restrictive behaviour of AN-R patients and binge eating of AN-BP and BN individuals. Indeed, an increase of peptidergic hunger stimulators and a decrease of satiety inhibitors have been interpreted as mechanisms aiming to oppose the extreme control on food intake in the acute phase of AN and to sustain binge eating in individuals with bulimia. The most consistent and relevant peptide findings likely contributing to such mechanisms are summarized in Figure 1.

Moreover, central and peripheral peptide alterations may be relevant not only for the genesis and/or the maintenance of aberrant eating behaviours but also for the development of specific psychopathological aspects of EDs. Indeed, it has been demonstrated that most of the peptidergic appetite modulators might also modulate anxiety, mood, aggressiveness and cognitive processes, particularly learning and memory, which are frequently deranged in subjects with EDs. Moreover, evidence has been provided that leptin, ghrelin, BDNF and opioids also modulate reward mechanisms being possibly involved in the pathophysiology of both food-related and non-food-related aberrant rewarding behaviours of AN and BN patients (Monteleone & Maj, 2013). This would suggest that peptide alterations may underlie some of the psychopathological aspects of EDs, although these connections have not been sufficiently studied yet and both their pathogenetic mechanisms and their relevance for the onset, course and therapeutic approach to EDs need to be more deeply investigated.

The research on feeding modulators in EDs needs to stretch beyond being merely descriptive and should elaborate, where

possible, pathogenetic theories able to explain potential causal connection between peptidergic determinants and both eating-related and non-eating-related psychopathological aspects of EDs. This would certainly contribute to a more comprehensive understanding of the etiopathogenesis of AN and BN, which could provide new knowledge to plan more effective preventive interventions and treatment programmes for these disorders.

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