INVITED REVIEW

Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: Beyond the homeostatic control of food intake

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KEYWORDS
Anorexia nervosa; Bulimia nervosa; Appetite modulators; Energy balance; Reward

Summary A large body of literature documents the occurrence of alterations in the physiology of both central and peripheral modulators of appetite in acute patients with anorexia nervosa (AN) and bulimia nervosa (BN). Until more recently the role of most of the appetite modulators in the control of eating behavior was conceptualized solely in terms of their influence on homeostatic control of energy balance. However, it is becoming more and more evident that appetite modulators also affect the non-homeostatic cognitive, emotional and rewarding component of food intake as well as non food-related reward, and, recently, AN and BN have been pathophysiologically linked to dysfunctions of reward mechanisms. Therefore, the possibility exists that observed changes in appetite modulators in acute AN and BN may represent not only homeostatic adaptations to malnutrition, but also contribute to the development and/or the maintenance of aberrant non-homeostatic behaviors, such as self-starvation and binge eating. In the present review, the evidences supporting a role of leptin, ghrelin, brain-derived neurotrophic factor and endocannabinoids in the homeostatic and non-homeostatic dysregulations of patients with AN and BN will be presented. The reviewed literature is highly suggestive that changes in the physiology of these modulators may play a pivotal role in the pathophysiology of eating disorders by providing a possible link between motivated behaviors, reward processes, cognitive functions and energy balance.

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1. Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are eating disorders (EDs) of complex and still unknown etiology. While a biological basis is widely recognized, it is acknowledged that sociocultural and psychological factors likely influence their development, progression and outcome. Aberrant eating behaviors represent the most prominent aspect of EDs, therefore, a great deal of biological research has been done on neurotransmitters, neuromodulators, neuropeptides and peripheral peptides involved in the regulation of eating behavior and energy homeostasis. Derangements in the physiology of appetite modulators have been detected in the acute phase of AN and BN and, generally, have been shown to disappear after recovery. Therefore, at the moment, it is commonly believed, although not definitively proved, that most of the secretory alterations of feeding regulatory substances are the consequence of the nutritional changes occurring with the disorder. However, even if those alterations are secondary phenomena disappearing after the recovery from the ED, they may hypothetically contribute to the maintenance of both aberrant eating behaviors and/or other symptomatic features.

Eating is co-determined by metabolic (homeostatic) and non-metabolic (non-homeostatic) factors. Among the latter, cognitive and emotional factors as well as reward play a pivotal role. It is widely known that, in humans, the initiation of food ingestion can be driven not only by a state of energy depletion, but also by a purely cognitive/ executive decision from the cortex in the absence of any depletion signal, as it occurs when high palatable food is consumed just for pleasure even if the subject is satiated. Sophisticated physiological mechanisms have evolved to regulate eating, and animal data support the view that distinguishable although overlapping neural and peripheral pathways, involving several appetite regulating substances, drive homeostatic- and hedonically based eating (Finlayson et al., 2007; Lutter and Nestler, 2009).

Until more recently, the role of most of the appetite modulators in the control of eating behavior was conceptualized solely in terms of their influence on hypothalamic and brainstem homeostatic control of hunger and satiety. However, it is becoming more and more evident that appetite modulators also affect the non-homeostatic cognitive, emotional and rewarding component of food intake. Thus, the traditional view of brain circuits regulating energy homeostasis has been expanded to include brain processes of learning, memory, emotion and reward. It is beyond the scope of this review to discuss and illustrate the complex physiological regulation of homeostatic and non-homeostatic eating and the physiological aberrations of appetite modulators occurring in patients with EDs. To this purpose several excellent published articles are available (Schwartz et al., 2000; Murphy and Bloom, 2006; Monteleone et al., 2008a; Prince et al., 2009; Kowalska et al., 2011) and a synopsis of the most relevant alterations of peptidergic feeding regulatory substances in both acute and recovered AN and BN patients is provided in Tables 1 and 2. Although a lot of central and peripheral modulators of eating behavior have been investigated in EDs, the present review will focus on a selected few appetite regulating substances, such as leptin, ghrelin, brain-derived neurotrophic factor (BDNF) and endocannabinoids, which are particularly relevant in the modulation of both homeostatic and rewarding aspects of eating behavior. Moreover, in the last years, it has become clearer and clearer that some of the appetite modulators are implicated in mediating reward not only from food but also from non food-related substances and behaviors. Therefore, changes in central and peripheral regulators of energy balance occurring in AN and BN may represent not only homeostatic adaptations to malnutrition, but also contribute to the development and/or the maintenance of aberrant non-homeostatic behaviors of EDs, such as self-starvation and binge eating. Indeed, AN has been conceptualized as a starvation-dependent syndrome that develops because eating less food is perceived as rewarding initially, and is then maintained through conditioning to the situations providing reward (Bergh and Søndersten, 1996; Støving et al., 2009). In line with this hypothesis, positive experiences of starvation have been long recognized among chronically fasting AN individuals, whose almost exclusive aim and pleasure is to maintain their cachectic conditions (Laségue, 1873; Pearce, 2004). Similarly, in BN, the ingestion of large amount of food during binge episode has been argued to aim at reducing the patient’s negative emotions by increasing food-derived feelings of pleasure, and people with binge eating syndromes usually report strong urges to eat with a sense of loss of control over their consummatory behavior and a transient binge-induced reduction of negative emotional states. Furthermore, anhedonia, that is a reduced ability to experience reward, is a key symptom in the clinical presentation of EDs and brain imaging studies in symptomatic and recovered AN and BN patients have shown, although not consistently, neuroanatomical abnormalities and dysfunctional activation of brain areas modulating reward, so that an involvement of central reward mechanisms has been suggested in the pathophysiology of EDs (Kaye et al., 2009; Keating et al., 2012; Holsee et al., 2012). Therefore, in the following paragraphs, the evidences supporting a role of appetite modulators in the homeostatic and non-homeostatic dysregulations of patients with AN and BN will be presented and the possible links between energy balance, cognitive functions and reward will be critically discussed.

1.1. Homeostatic implications of leptin in eating disorders

Leptin primarily acts as an adipocyte-derived factor that informs the central nervous system on the amount of energy
<table>
<thead>
<tr>
<th></th>
<th>AN Acute Phase</th>
<th>AN Weight-Restored</th>
<th>BN Acute Phase</th>
<th>BN Recovered</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>α-Melanocyte Stimulating</strong></td>
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<tr>
<td>Hormone (α-MSH)</td>
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<tr>
<td>Plasma α-MSH</td>
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<td></td>
<td></td>
<td></td>
<td>Moriya et al. (2006)</td>
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<td><strong>Aguti-related</strong></td>
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<td>Peptide (AGRP)</td>
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<tr>
<td>Plasma AGRP</td>
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<td></td>
<td>Moriya et al. (2006), Merle et al. (2011)</td>
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<td><strong>Brain-Derived Neurotrophic Factor (BDNF)</strong></td>
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<tr>
<td>Serum BDNF</td>
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<td>↑</td>
<td>↓</td>
<td>Nakazato et al. (2003), Monteleone et al. (2004, 2005c), Nakazato et al. (2006), Mercader et al. (2007), Ehrlich et al. (2009), Brandys et al. (2011)</td>
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<td>Plasma BDNF</td>
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<td>CSF CRH</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Gerner and Gwirtsman (1981), Gwirtsman et al. (1983), Hotta et al. (1986), Kaye et al. (1987b)</td>
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<td>Plasma Galanin</td>
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<td><strong>Endocannabinoids</strong></td>
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<td>Plasma AEA</td>
<td>↑</td>
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<td>Monteleone et al. (2005d), Frielinger et al. (2009), Schroeder et al. (2012)</td>
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<td>Plasma 2-AG</td>
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<tr>
<td>Plasma CB1 mRNA</td>
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<td><strong>Neuropeptide Y (NPY)</strong></td>
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<td>CSF NPY</td>
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<td>Nemerooff et al. (1989), Pirke et al. (1993)</td>
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<td>CSF dynorphins</td>
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<td>Plasma β-endorphins</td>
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<tr>
<td>T-lymphocyte β-endorphins</td>
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<td>Orexin</td>
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<td>Bronsky et al. (2011), Janas-Kozik et al. (2011)</td>
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<td>Plasma orexin A</td>
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<tr>
<td>Oxytocin</td>
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<td>Demitrack et al. (1990), Chiodera et al. (1991), Frank et al. (2000), Lawson et al. (2011, 2012)</td>
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<tr>
<td>CSF oxytocin</td>
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<td>Plasma oxytocin</td>
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<td>(response to a test meal)</td>
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<td>Plasma oxytocin</td>
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<td>(response to hypoglicemia)</td>
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<td>Somatostatin (SRIF)</td>
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<td>Gerner and Yamada (1982), Kaye et al. (1988), Pirke et al. (1993), Gianotti et al. (1999), Baranowska et al. (2000)</td>
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<td>CSF SRIF</td>
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<td>Plasma SRIF</td>
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<td>Plasma SRIF</td>
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<td>(response to test meal)</td>
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<tr>
<td>Thyrotropin-Releasing</td>
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<td></td>
<td>Lesem et al. (1994), Devlin et al. (1990), Hillebrand et al. (2002)</td>
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<td>Hormone (TRH)</td>
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<td>CSF TRH</td>
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<tr>
<td>Vasopressin</td>
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<tr>
<td>CSF Vasopressin</td>
<td>⇒ ↑</td>
<td></td>
<td></td>
<td></td>
<td>Gold et al. (1983), Demitrack et al. (1992), Chiodera et al. (1993), Frank et al. (2000)</td>
</tr>
<tr>
<td>Plasma Vasopressin</td>
<td>⇒ ↑</td>
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<tr>
<td>Plasma vasopressin</td>
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<tr>
<td>(osmotic response)</td>
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</tbody>
</table>

⇒: not different from healthy controls; ↑: higher than healthy controls; ↓: lower than healthy controls.

CSF: cerebrospinal fluid; AEA: anandamide; 2-AG: 2-arachidonoylglycerol; CB1: cannabinoid 1 receptor.

Data concerning endocannabinoids have been included, although they are neurotransmitters and not neuropeptides.

Plasma levels of CB1 receptor mRNA were reduced in those patients with impulsive self-injurious behavior.

Short-term weight restored patients with persistent amenorrhea have been found to have significantly raised concentrations of CSF NPY.
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Summary of the most relevant changes of peripheral peptides regulating appetite in anorexia nervosa (AN) and bulimia nervosa (BN).</th>
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<tbody>
<tr>
<td></td>
<td>AN</td>
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<tr>
<td>Adiponectin</td>
<td>Acute Phase</td>
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<tr>
<td>Plasma adiponectin</td>
<td>⇒ ↑ ↓³⁵</td>
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<tr>
<td>CSF CCK</td>
<td>⇒ ↑</td>
</tr>
<tr>
<td>Plasma CCK</td>
<td>⇒ ↑</td>
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<tr>
<td>Lymphocyte CCK</td>
<td>↓</td>
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<tr>
<td>Plasma CCK (response to test meal or OGT)</td>
<td>⇒ ↑ ↓</td>
</tr>
<tr>
<td>Fibroblast Growth Factor (FGF)</td>
<td></td>
</tr>
<tr>
<td>Plasma FGF-21</td>
<td>↑ ↓</td>
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<tr>
<td>Plasma FGF-23</td>
<td>↑ ANBP</td>
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<tr>
<td>Gastrin</td>
<td></td>
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<tr>
<td>Plasma gastrin</td>
<td>↓↑</td>
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<tr>
<td>Plasma gastrin (response to test meal)</td>
<td>⇒</td>
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<tr>
<td>Ghrelin</td>
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<tr>
<td>Total plasma ghrelin</td>
<td>↑</td>
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<tr>
<td>Total plasma ghrelin (response to test meal or OGT)</td>
<td>↓ or time-delayed in ANPB</td>
</tr>
<tr>
<td>Total plasma ghrelin (response to sham-feeding)</td>
<td>↑</td>
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<tr>
<td><strong>Insulin</strong></td>
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<tr>
<td>Plasma insulin</td>
<td>$\Rightarrow \downarrow \uparrow$</td>
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<tr>
<td>Plasma insulin (response to test meal or OGT)</td>
<td>$\Rightarrow \downarrow$ or time-delayed</td>
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<tr>
<th><strong>Insulin Growth Factor-1 (IGF-1)</strong></th>
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<td>Plasma IGF-1</td>
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<tr>
<th><strong>Leptin</strong></th>
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<tbody>
<tr>
<td>CSF leptin</td>
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</tr>
<tr>
<td>Plasma leptin</td>
<td>$\downarrow$</td>
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<tr>
<td>Plasma leptin (response to test meal)</td>
<td>$\Rightarrow$</td>
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<tr>
<td>Plasma leptin (response to acute fasting)</td>
<td>$\downarrow$</td>
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<tr>
<th><strong>Macrophage Inhibitory Cytokine-1 (MIC-1)</strong></th>
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<tbody>
<tr>
<td>Plasma MIC-1</td>
<td>$\uparrow$</td>
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<tr>
<th><strong>Obestatin</strong></th>
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<tbody>
<tr>
<td>Plasma obestatin</td>
<td>$\uparrow$</td>
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<tr>
<td>Plasma ghrelin/obestatin ratio</td>
<td>$\uparrow \downarrow$</td>
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<tr>
<td>Plasma response to sham-feeding</td>
<td>$\uparrow$ drop</td>
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<tr>
<td>Plasma response to meal</td>
<td>$\Rightarrow$</td>
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<tr>
<th><strong>Pancreatic Polypeptide (PP)</strong></th>
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<tr>
<td>Plasma PP</td>
<td>$\Rightarrow$</td>
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<td>Plasma PP (response to test meal)</td>
<td>$\Rightarrow \uparrow \downarrow$</td>
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<tr>
<th><strong>Peptide YY3–36 (PYY3–36)</strong></th>
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<tr>
<td>CSF PYY3–36</td>
<td>$\Rightarrow$</td>
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<tr>
<td>Plasma PYY3–36</td>
<td>$\Rightarrow \uparrow$</td>
</tr>
<tr>
<td>Plasma PYY3–36 (response to test meal)</td>
<td>$\Rightarrow \uparrow$ or time-delayed</td>
</tr>
</tbody>
</table>


Misra et al. (2003), Stoving et al. (2007), Dostalova et al. (2008), Fazeli et al. (2010)

Hebebrand et al. (1997), Mantzoros et al. (1997), Balligand et al. (1998), Jimerson et al. (2000), Brewerton et al. (2000), Monteleone et al. (2000a,b, 2002a,b), Krizova et al. (2002), Holtkamp et al. (2003a,b, 2004), Lob et al. (2003), Djurovic et al. (2004), Misra et al. (2004a), Haas et al. (2005), Dostalova et al. (2005)

Dostálóvá et al. (2010)

Monteleone et al. (2008b,c), Harada et al. (2008), Nakahara et al. (2008), Germain et al. (2009), Sedláčková et al. (2011)

Uhe et al. (1992), Fujimoto et al. (1997), Tomask et al. (2005), Kinzig et al. (2007)

Monteleone et al. (2005b), Kojima et al. (2005), Stock et al. (2005), Misra et al. (2006), Nakahara et al. (2007), Otto et al. (2007)
Table 2 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>AN Acute Phase</th>
<th>Weight-Restored</th>
<th>BN Acute Phase</th>
<th>Recovered</th>
<th>References</th>
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<td>Resistin</td>
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<tr>
<td>Plasma resistin</td>
<td>⇒ ▼</td>
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<td>⇒</td>
<td></td>
<td>Housova et al. (2005), Dostalova et al. (2006a,b), Dolezalova et al. (2007), Ziora et al. (2011)</td>
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<td>Visfatin</td>
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<td>Plasma visfatin</td>
<td>⇒ ▼</td>
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<td>⇒</td>
<td></td>
<td>Dostalova et al. (2009), Ziora et al. (2012)</td>
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</tbody>
</table>

⇒ not different from healthy controls; ▼: higher than healthy controls; ▼: lower than healthy controls; ▼: different from; ANBP: anorexia nervosa binge-purging type; ANR: anorexia nervosa restricting type; OGT: oral glucose test.

a Most of the studies found increased adiponectin levels in malnourished AN patients.
b Both higher and lower values have been reported.
c The increase has been found in bulimics with high frequency bingeing.
d Not consistently found, since no significant difference has been also reported.
e Normal response to a high-carbohydrate meal.
f Improved, but not completely restored.

Longitudinal studies have shown that during refeeding treatments, leptin concentrations progressively increase with the regaining of BW and, in those cases with a too rapid weight restoration, they reach values disproportionately higher than normal (Hebrand et al., 1997; Hotchkiss et al., 2003; Labalaba et al., 2003; Mora et al., 2004b). The alterations of plasma and cerebrospinal fluid (CSF) leptin levels and changes in peripheral tissues, circulating levels of soluble OB-R and leptin receptors in serum, both normal leptin concentrations and the decrease in the subcutaneous fat, seem to be accompanied by an up-regulation of leptin levels in young patients. This normalization of the leptin level is accompanied by a normalization of body weight. The refeeding in patients with AN has also been associated with a decrease in body weight, although the improvement has not been accompanied by a decrease in leptin levels (Hebrand et al., 2003; Hotchkiss et al., 2003; Labalaba et al., 2003). In contrast, in patients with AN, plasma and cerebrospinal fluid leptin levels have been consistently reported to be significantly lower than normal and significantly correlated with body mass index and body fat mass (Hebrand et al., 2003; Hotchkiss et al., 2003; Labalaba et al., 2003). This homeostatic action is exerted mainly in the hypothalamus and pituitary gland, expressing pro-opiomelanocortin and inhibits orexinergic neurons expressing neuropeptide-Y and inhibits orexinergic neurons expressing neuropeptide-Y and regulates the hypothalamus-pituitary-adrenal axis. This homeostatic action is exerted mainly in the hypothalamus (Brodal et al., 1998). In anorexics, the reduction of leptin levels is accompanied by a reduction of body weight, and body weight is positively correlated with the increase in leptin levels. This strong positive correlation between body weight and leptin levels is consistent with the hypothesis that the up-regulation of leptin levels is a result of the normalization of body weight and body fat mass (Hebrand et al., 2003; Hotchkiss et al., 2003; Labalaba et al., 2003).
pertaining to AN patients who have gained weight (Djurovic et al., 2004). Therefore, the role of leptin in the process of BW recovery in AN needs to be further explored.

Since leptin exerts a stimulatory action on the gonadal axis, the reduced secretion of leptin may contribute to amenorrhea, which is a key symptom of AN. Evidence has been provided that, apparently, a serum leptin level of less than 1.85 μg/L predicts a lifetime history of amenorrhea and subnormal serum levels of luteinizing hormone in AN women (Ballauff et al., 1999; Chan and Mantzoros, 2005). However, persistence of amenorrhea is not rare in weight-restored AN women; in these cases leptin levels have been found to be still significantly lower than healthy controls (Brambilla et al., 2003). Leptin also stimulates the hypothalamic-pituitary-thyroid axis and inhibits the hypothalamic-pituitary-adrenal axis; therefore, low leptin of acute AN patients may contribute to their hypothyroidism and hypercortisolism. Limiting reproductive capacity, decreasing thyroid thermogenesis and increasing secretion of stress steroids are homeostatic adaptive responses with a survival significance during prolonged nutritional deprivation.

In normal weight subjects with BN, circulating leptin has been reported to be either decreased, normal or increased (Monteleone et al., 2000a,b, 2002a,b; Jimerson et al., 2000; Brewerton et al., 2000) possibly due to heterogeneity of patient samples. It has been reported that BN patients with a significantly longer duration of the illness and a significantly higher number of daily binge/vomiting episodes hyposcrete leptin in spite of no significant modifications in their BW (Monteleone et al., 2002b). Moreover, in BN women with hypoleptinemia, the fall of circulating leptin in response to acute fasting was almost completely blunted, whereas its response to short-term normal refeeding, although in percentage similar to that of normal controls, was not sufficient to restore normal blood levels of the hormone (Monteleone et al., 2000b). Therefore, it seems that, in BN, the role of leptin as a peripheral signal of the available energy stores is preserved, whereas, at least in those patients with anorexic-like leptin concentrations, its function as an index of acute changes in the energy balance is lost.

1.2. Non-homeostatic implications of leptin in eating disorders

Leptin regulates not only energy homeostasis but also hedonic and motivational components of reward. Mesolimbic dopaminergic pathways originating from the ventral tegmental area (VTA) and innervating the nucleus accumbens (NAC) have been unequivocally implicated in both food- and drug-related reward mechanisms. In particular, dopamine signaling in this system mediates the willingness to engage in rewarding behaviors (that is the “wanting”), while the pleasure associated with a specific reward (that is the “liking”) is attributed to mesolimbic opioid transmission (Berridge, 1996). VTA dopaminergic neurons are activated by orexin pathways coming from the lateral hypothalamus (LH), which have been shown to regulate both food- and drug-related reward (Narita et al., 2006; Zheng et al., 2007). Leptin receptors have been detected on both LH orexinergic neurons and VTA dopaminergic neurons and it is intriguing that leptin decreases the LH orexin tone and the firing of mesolimbic dopaminergic neurons as well as dopamine release and concentrations in the NAC (Krügel et al., 2003), thus negatively modulating reward-related behaviors (Davis et al., 2011). In support of this hypothesis, animal data unequivocally showed that dietary regimens increasing body weight and hence leptin levels decrease reward-related behaviors whereas caloric restriction or deprivation with decrease in leptin levels augments reward-related behaviors (Davis et al., 2010). Indeed, in experimental animals trained to self-administer high palatable food such as sucrose, intracerebroventricular administration of leptin was able to decrease responding for sucrose (Cowery et al., 2001). Similarly, laboratory animals trained to self-administer psychostimulant drugs increase the self-administer behavior after food deprivation whereas central administration of leptin decreases food deprivation-induced self-administration of heroin (Carroll et al., 1984; Shalev et al., 2001). In support of an inhibitory action of leptin on food-related reward mechanisms in humans, an fMRI study (Farooqi et al., 2007) showed that in satiated patients with congenital leptin deficiency the exposure to visual food stimuli resulted in an activation of NAC and caudate, which was associated with food wanting, although the subjects were in a condition of positive energy balance. This effect did not occur after 1 week of leptin treatment.

It is conceivable that reduced leptin levels of starved AN patients might facilitate the development and/or the maintenance of rewarding behaviors. In human beings, dieting with the consequent weight loss is generally experienced as rewarding, and in most cases AN starts with a diet. When weight loss set in, the positive experience of control on food intake results extremely rewarding for the patient and reinforces the dieting behavior. It is plausible that the decrease in leptin production occurring with the loss of adipose tissue (together with other starvation-induced biochemical changes) might consolidate dieting by reinforcing the activity of dopamine brain reward circuits. In support of this idea there is the observation that, in both animals and humans, obesity, an extreme weight condition opposite to AN and characterized by overeating and increased leptin production, has been found to be associated with decreases in dopamine release and dopamine D2 receptors (D2R) in striatal regions, which are part of the brain reward system (Wang et al., 2001; Geiger et al., 2009). This generated the reward-deficient hypothesis of obesity in which hypofunction of the dopamine reward system would generate overconsumption of food in the attempt to get an increase in mesolimbic dopamine signaling through an enhancement of food-induced dopamine release (Blum et al., 2011). In this line, it has been recently shown that in obese leptin-deficient ob/ob mice leptin administration increased the number of D2R in the NAC and caudate-putamen (Paffly et al., 2010), although this has been not confirmed in congenitally leptin-deficient humans (Ishibashi et al., 2012). Therefore, the modulatory role of leptin on dopamine reward pathways and the effects on eating behavior seems to differ in relation to type of dysregulation (chronic reduction of leptin secretion such as in AN or overproduction of leptin such as in dietary obesity or congenital deficiency of leptin such as in obese ob/ob mice and similar obese humans).

The modulator effect of leptin on reward-related behaviors has been implicated also in the development of
overexercise of AN patients. The most known animal model of AN is the activation-based anorexia (ABA), where rats are fed once per day (usually 1 h per day of food access) and have free access to a running wheel. In this condition, animals engage excessive wheel running, which incorporates antidepressant-like and rewarding properties (Marais et al., 2009), and undergo reduced body weight, amenorrhea and ultimately death. These features are similar to those of over-exercising patients with AN. It has been shown that the increase in running wheel activity parallels low plasma leptin levels (de Rijke et al., 2005) and that a continuous leptin infusion reduces the rat physical hyperactivity in the ABA model (Exner et al., 2000). Moreover, Verhagen et al. (2011) recently demonstrated that leptin injection into the VTA suppresses running wheel activity, which suggests that in the ABA model a reduced leptin signaling in the VTA increases mesolimbic dopaminergic activity leading to an enhancement of rewarding properties of running wheel activity. By translating these finding in EDs, it is known that a significant proportion of AN individuals display high levels of physical activity or overexercise likely because of the anxiolytic properties of this behavior, and an inverse correlation between the amount of food intake and physical activity has been detected in underweight AN individuals (Hebebrand et al., 2003; Holtkamp et al., 2003b, 2006). Moreover, low leptin levels have been shown to correlate with hyperactivity in starved anorexic women (Hebebrand et al., 2003). It has been pointed out that physical activity levels were lower in severely emaciated patients with almost non-detectable leptin levels than in patients who had somewhat higher levels, suggesting that the relationship between leptin and physical activity follows an inverted U (Holtkamp et al., 2006). This finding led to the hypothesis that the postulated effect of hypoleucinemia on activity levels declines when patients are close to starvation and thus critically ill as it occurs in rats in which ABA-induced hyperactivity ceases close to death (Hebebrand et al., 2003).

1.3. Homeostatic implications of ghrelin in eating disorders

Ghrelin, initially characterized as a ligand for the growth hormone secretagogue receptor (GHS-R), is primarily produced by endocrine cells in the stomach and behaves as a hunger hormone stimulating appetite and promoting gastric emptying. Indeed, circulating levels of ghrelin increase before meals, achieving concentrations sufficient to stimulate hunger and promote meal initiation, and decrease after food ingestion (Cummings et al., 2001). Ghrelin is a 28-aminoacid peptide with an acyl side chain attached to the serine residue at position 3 that is crucial for its orexigenic and gastric emptying effects. Acylated ghrelin (active form) represents less than 10% of circulating ghrelin, which includes acylated and desacylated fragments (inactive forms). Furthermore, ghrelin is synthesized from a precursor peptide of 117 residues, called preproghrelin, which undergoes stepwise processing to form ghrelin. Recently, it has been shown that preproghrelin undergoes additional proteolytic cleavage, generating a 23-amino acid peptide, which has been named obestatin (Zhang et al., 2005). In contrast to ghrelin, obestatin has anorexigenic effects, delays gastric emptying, inhibits jejunal contractions and suppresses BW gain in the animal (Zhang et al., 2005). Therefore, obestatin has been postulated to antagonize ghrelin actions on energy homeostasis and gastrointestinal functions, although this has been questioned by other authors (Seoane et al., 2006; Gourcerol et al., 2007) and controversies still exist on the definite effects of obestatin on food intake/energy balance as well as on the measurements of the hormone levels in the human blood (Garg, 2007). Moreover, initial findings showed that mice with a targeted disruption of ghrelin gene or GHS-R gene and fed with regular diet exhibited normal growth rates, energy balance, food intake and adiposity, questioning the crucial role for ghrelin in energy homeostasis (Sun et al., 2006; Zigman et al., 2005). However, mice with simultaneous ablation of both genes of the ghrelin system reported decreased BW, increased energy expenditure and enhanced motor activity, which suggests the putative existence of other endogenous components of the ghrelin system implicated in the modulation of energy homeostasis (Pfluger et al., 2008). In this line, it has been recently shown that, also in the absence of ghrelin, GHS-R allosterically modulate D2R modifying dopamine signaling in hypothalamic neurons coexpressing both receptors and this interaction is crucial for the anorexigenic effect of hypothalamic dopamine (Kern et al., 2012). Therefore, the role of the endogenous ghrelin system on energy homeostasis deserves further investigation.

Increased fasting plasma levels of total ghrelin (both acylated and non-acylated fragments) have been consistently reported in underweight patients with AN (Tanaka et al., 2003a,b; Misra et al., 2004; Soriano-Guillen et al., 2004; Troisi et al., 2005; Monteleone et al., 2008b; Sedličková et al., 2011). The enhanced ghrelin concentrations tend to normalize with the recovery of BW, and the reduction of circulating ghrelin seems to parallel the progressive increase in BW during weight restoration treatments (Soriano-Guillén et al., 2004; Tanaka et al., 2004; Otto et al., 2005; Janas-Kozik et al., 2007). Mixed results have emerged in studies assessing the dynamics of ghrelin secretion after energy intake. Indeed, Nedvidkova et al. (2003) found no suppression of circulating ghrelin after food ingestion in underweight AN patients, whereas, three subsequent studies reported that in symptomatic AN individuals enhanced preprandial levels of ghrelin, although suppressed by food ingestion in percentages similar to normal subjects, remained significantly higher than in controls (Misra et al., 2004b; Stock et al., 2005; Sedličková et al., 2011). The suppressant effect of oral glucose administration on plasma ghrelin has been found significantly blunted in women with restricting-type AN, and normal but delayed in patients with binge-purging type AN (Tanaka et al., 2003c). Differences in the clinical characteristics of patients’ samples, in the type, composition and total calories of test meals, and in the timing of blood collection may partially explain these discrepancies.

Increases in plasma levels of total ghrelin in AN may not be representative of an increased production of active ghrelin, and when acylated ghrelin has been measured, conflicting results have emerged with both increased and reduced plasma values (Nakai et al., 2003; Hotta et al., 2004). Increased levels of total ghrelin but only slightly enhanced concentrations of acylated ghrelin have been reported in a mixed sample of symptomatic AN and BN patients (Uehara et al., 2005).
The ghrelin sibling peptide obestatin has been recently investigated in patients with EDs. Increased levels of obestatin with either enhanced or decreased ghrelin to obestatin ratio have been detected in underweight AN patients (Monteleone et al., 2008b, 2008c; Harada et al., 2008; Nakahara et al., 2008; Germain et al., 2009; Sedláčková et al., 2011). The secretion of ghrelin and obestatin in response to sham feeding (i.e., only smelling and chewing a meal without swallowing), which is a technique able to explore the cephalic phase of food ingestion, has been reported to be deranged in acute AN individuals, who showed an enhanced sham feeding-induced ghrelin secretion and a more robust obestatin drop as compared to healthy controls (Monteleone et al., 2008b). If one assumes that ghrelin and obestatin have opposite effects on food intake, then the increased baseline ghrelin to obestatin ratio and the enhanced opposite changes in obestatin and ghrelin secretion during the cephalic phase of food ingestion 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 (Sedláčková et al., 2011).

In BN it was initially reported that fasting ghrelin levels were increased in symptomatic patients especially in those with frequent binge-purging episodes (Tanaka et al., 2003b). However, this increase was not confirmed by several subsequent studies (Troisi et al., 2005; Nakazato et al., 2004; Monteleone et al., 2005a; Sedláčková et al., 2011). The ghrelin responses to a macronutrient balanced meal and to a fat rich meal have been reported to be blunted in symptomatic binge/purge BN women as compared to healthy controls (Monteleone et al., 2005b; Kojima et al., 2005) while the ghrelin response to a high carbohydrate meal has been found to be normal (Sedláčková et al., 2011). The ghrelin response to sham feeding in symptomatic BN women has been found to be increased (Monteleone et al., 2009a). No significant changes in plasma levels of obestatin or in the ghrelin to obestatin ratio have been detected in symptomatic BN women by our group (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 Sedláčková et al. (2011).

1.4. Non-homeostatic implications of ghrelin in eating disorders

Ghrelin not only acts as an orexigenic signal regulating homeostatic feeding driven by metabolic need, but also enhances non-homeostatic feeding by intervening in the modulation of reward and motivated behaviors as well as in the regulation of higher brain functions such as learning and memory. Ghrelin receptors are expressed on dopaminergic neurons of the VTA (Abizaid et al., 2006) and both central, VTA and peripheral administration of ghrelin in the rodents increases the locomotor activity of the animal, the dopamine release and turnover in the NAc and the activity of the mesolimbic dopaminergic system, which suggests that both centrally and peripherally produced ghrelin is able to activate mesolimbic reward circuits (Jerlhag et al., 2007; Jerlhag, 2008; Abizaid et al., 2006). Therefore, it has been proposed that the ghrelin-induced increase of locomotor activity likely enhances exploratory behavior, which in turn would facilitate food-seeking behavior, while the ghrelin-induced activation of the dopaminergic reward system, increases the incentive value of signals associated with motivated behavior of importance for survival such as feeding behavior (Jerlhag et al., 2007). In this line, it has been shown that ghrelin drastically increases food-motivated behaviors in satiated rats, leading to the consumption of food also in the absence of immediate energy need, just to obtain food-related reward (Perello et al., 2010; Skibicka et al., 2011). Similarly, Monteleone et al. (2012a) recently showed that in satiated healthy subjects circulating ghrelin levels before and during the consumption of a high-pleasurable food are higher than during the ingestion of a non-palatable meal.

Brain imaging and neuroeconomics studies support a role of ghrelin in food-related reward in humans also. A functional magnetic resonance imaging study (Malik et al., 2008) showed that intravenous ghrelin administration in healthy subjects increased the neural response to food pictures in brain areas implicated in reward processing and appetitive behavior such as the amygdala, ventral striatum, anterior insula and orbitofrontal cortex. Moreover, ghrelin administration in humans has been found to enhance the perceived value of food and increase the amount of money subjects were willing to spend on food while decreasing their willingness to pay for non-food objects (Tang et al., 2011). It has been suggested that ghrelin may interact also with the learning process and learned cues for reward (Wise, 2002). Diano et al. (2006) detected ghrelin receptors on mouse hippocampal neurons and showed that ghrelin knockout animals had a reduced number of hippocampal spine synapses and performed worse than their wild-type littermates in memory spatial learning tests. Peripheral administration of ghrelin rapidly restored those deficits as well as promoted the formation of new spine synapses and generation of long-term potentiation in wild-type animals. These ghrelin-induced synaptic changes were paralleled by enhanced spatial learning and memory. This fits with the observation that, in the above mentioned study of Malik et al. (2008), food pictures shown in the ghrelin condition were more easily recalled than those shown in the placebo condition. Therefore, it could be speculated that the raised ghrelin levels of chronically fasting AN patients enhance their cognitive performances related to spatial learning and unfocused attention in order to potentiate their ability to identify and locate energy source, an effort that generally does not lead to food intake, because of their rigid control over food ingestion. This is consistent with the demonstration that ED patients were more accurate than healthy controls on spatial executive tasks (Galderseri et al., 2003). Furthermore, since in primates mesolimbic dopaminergic neurons have been shown to be easily conditioned to stimuli predicting reward (Schultz et al., 1997), it could be that in the presence of starvation-associated cues, enhanced ghrelin levels may stimulate the dopamine reward system in the ventral striatum and this may provide a mechanism through which the patient’s control over the food ingestion is perceived as rewarding. This would contribute to the above mentioned starvation-dependent syndrome that has been proposed as a main pathophysiological mechanism in the development and/or the maintenance of EDs (Støving et al., 2009).
It has been suggested that ghrelin may have a role in the pathophysiology of binge eating not only through the activation of homeostatic mechanisms, namely increasing hunger sensation in condition of energy deprivation as in starved patients, but also by promoting food ingestion in order to increase food-related reward. Indeed, the affect regulation theory of binge eating posits that many individuals binge in response to stress or negative mood states in attempt to reduce their anxiety and/or negative emotions by increasing feelings of pleasure derived by the ingestion of food (Johnson and Larson, 1982; Heatherton and Baumeister, 1991). A stress-induced rise in either gastric ghrelin mRNA or plasma total ghrelin was reported in rodents (Asakawa et al., 2001; Kristensson et al., 2006), and a significant increase of circulating ghrelin after the Trier Social Stress Test (TSST) was detected in both normal weight healthy subjects and obese persons with or without binge eating, who displayed a concomitant TSST-induced increase in plasma cortisol (Rouach et al., 2007). We recently reported that in symptomatic BN patients the ghrelin secretion in response to TSST was amplified, so we speculated that when BN patients are in conditions of negative mood states, the psychological distress may induce an exaggerated ghrelin secretion, which could prompt binge eating in order to reduce the patients’ anxiety and/or negative emotions by increasing food-related feelings of pleasure (Monteleone et al., 2012b).

2. Homeostatic and non-homeostatic implications of brain-derived neurotrophic factor in eating disorders

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. Indeed, heterozygous mice with one functional Bdnf allele and mice in which the Bdnf gene has been deleted in excitatory brain neurons display hyperphagia and develop an age-dependent obesity (Kerme et al., 2000). Moreover, both central and peripheral administration of BDNF decreases food intake, increases energy expenditure, reduces BW and ameliorates hyperinsulinemia and hyperglycemia in diabetic db/db mice (Nakagawa et al., 2000; Tschida et al., 2001). Finally, BDNF and its tyrosine kinase receptor (TRK) are highly expressed in the hypothalamus and the dorsal vagal complex, the two major autonomic centers implicated in the homeostatic regulation of eating behavior and energy balance (Nakagawa et al., 2000).

Reduced serum BDNF levels in women with AN or BN have been consistently found by independent research groups (Nakazato et al., 2003; Monteleone et al., 2004, 2005c; Nakazato et al., 2006; Ehrlich et al., 2009), and a recent meta-analysis of these studies have confirmed such a reduction (Brandys et al., 2011). It was initially suggested that reduced circulating BDNF in ED patients might be related to concomitant depression and not to the ED, since serum BDNF levels negatively correlated with depressive symptoms (Nakazato et al., 2003). This likelihood was ruled out in subsequent studies, which found a significant positive correlation between serum BDNF levels and the subjects’ BW and body mass index but not with the severity of depressive symptomatology (Monteleone et al., 2004, 2005c). Increased plasma BDNF levels in both AN and BN were reported by Mercader et al. (2007), who showed also a significant association between some haplotypes of the Bdnf gene, increased plasma levels of the neurotrophin and BN. The discrepancy with the previous studies could be partially explained by the fact that plasma and not serum BDNF was assayed. Finally, one small study showed that decreased circulating BDNF levels in emaciated AN patients were not restored after partial weight recovery (Nakazato et al., 2006), whereas a larger investigation found a normalization or even an elevation of serum BDNF in weight-recovered patients with AN (Ehrlich et al., 2009).

As for the pathophysiological significance of decreased circulating BDNF in ED patients, one explanation could be that, since BDNF has anorexic effect, its decline may represent an homeostatic adaptive phenomenon aiming to promote food intake in condition of chronic starvation.

A non-homeostatic role for BDNF in EDs can also be supposed. It has been demonstrated that BDNF and its TRK receptor are expressed also in VTA dopaminergic neurons and BDNF is anterogradely transported to NAc (Numan and Seroogy, 1999), which suggest a role for the neurotrophin in modulating reward. Cordeira et al. (2010) recently found that mutant mice depleted of central BDNF exhibited marked decrease in evoked release of dopamine in NAc and dorsal striatum. Notably, VTA-specific deletion of Bdnf gene resulted in increased ingestion of a palatable high fat diet not but of a standard diet. These results suggest that BDNF modulates positively hedonic eating by increasing mesolimbic dopaminergic activity.

In animal models, BDNF has been demonstrated to be involved in motivational and anticipatory aspects of eating behavior. Food anticipatory activity, that is the increase in locomotor activity prior to feeding in rodents undergoing restricted feeding paradigm, is considered an expression of the motivation to eat while the presence of wheel motor activity when food is available is believed to be an expression of the lack of motivation to eat. It has been recently shown that food anticipatory activity in mice was accompanied by a strong increase in BDNF expression levels in the hippocampus, whereas an increase of wheel activity in food-restricted mice when exposed to food was found in parallel with reduced hippocampal BDNF expression (Gelegen et al., 2008). Moreover, mice of the A/J strain, undergoing reduced brain BDNF expression in response to a restricted feeding schedule, have been shown to be highly susceptible to the ABA model whereas the mouse C57B/L6 strain, developing increased brain BDNF expression after food restriction, was not (Gelegen et al., 2008). Therefore, an impaired BDNF transmission in AN might sustain the physical hyperactivity of underweight AN patients through modulation of central reward pathways.

3. Homeostatic and non-homeostatic implications of endocannabinoids in eating disorders

Overwhelming evidence has demonstrated the role of the endocannabinoid system in the modulation of eating behavior and reward processing (Cota et al., 2003a). In the brain,
the endogenous cannabinoids anandamide (arachidonoyl-
lactanamide, AEA) and 2-arachidonoylglycerol (2-AG) mod-
ulate feeding at two levels. First, they are released “on
demand” in the hypothalamus after short-term food de-
privation and then transiently regulate the levels and/or action
of other orexigenic and anorectic mediators such as leptin,
ghrelin and melanocortins (Cota et al., 2003b). Second, they
tonically reinforce the motivation to find and consume food
with a high incentive value, by interacting with the meso-
limbic dopaminergic pathway. Cannabinoid CB1 receptors are
particularly abundant in brain areas connected with reward
mechanisms and endocannabinoids progressively increase in
the limbic system following food deprivation (Kirkham et al.,
2002). The fasting-induced increase of endogenous cannabi-
noids may drive the motivation to eat (“wanting”) as well as
the enjoyment of food during ingestion (“liking”). Evidence has
been provided that the cannabinoid-induced food seeking and
liking are mediated by release of dopamine in the NAc
(Solinas et al., 2006) and can be attenuated by opioid
antagonists (Williams and Kirkham, 2002), suggesting the
existence of functional relationships between dopamine,
endocannabinoids and the endogenous opioid system in the
reward-related aspects of eating behavior.

Plasma levels of AEA were found significantly enhanced in
patients with AN or with binge eating disorder, but not in
women with BN (Monteleone et al., 2005d) while circulating
levels of 2-AG did not significantly differ between patients
and healthy controls. An inverse correlation between plasma
AEA levels and leptin concentrations was also detected,
suggesting a possible involvement of the decreased leptin
signaling of underweight AN patients in the enhancement of
AEA levels, since a negative modulation of leptin on endo-
cannabinoid production has been demonstrated (Di Marzo
et al., 2001). Frieling et al. (2009) reported higher blood
levels of CB1 receptor mRNA in AN and BN patients as
compared to healthy controls; however, patients with a
disturbed impulse regulation exhibited lower CB1 receptor
expression. This last finding was substantiated by a subse-
quent study of the same group showing that peripheral levels
of CB1 receptor mRNA were reduced in a mixed sample of AN
and BN patients with self-injurious behavior as compared to
those without self-injurious behavior and healthy controls
(Schroeder et al., 2012). Recently, a PET study demonstrated
an increased number of CB1 receptors in the insula and
inferior frontal and temporal cortex of underweight AN
patients as well as in the insula of symptomatic BN subjects
(Gérard et al., 2011). Moreover, significant associations have
been reported between AN and BN and single nucleotide
polymorphisms of genes coding the CB1 receptor and the
fatty acid amide hydrolase, the enzyme degrading AEA and 2-
AG (Monteleone et al., 2009b), although these results were
not consistent with a family trios study (Müller et al., 2008).

The dysregulated endocannabinoid tone of AN and BN
patients may represent an adaptive response with the
homeostatic aim of preserving energy balance by increasing
hunger and hence food ingestion. Moreover, the altered
endocannabinoid system may facilitate the rewarding prop-
erties of the aberrant eating behaviors occurring in ED
patients. In this line, a recent animal study showed that
Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive
ingredient in cannabis, attenuates the weight loss associated
with the development of the ABA model by either increasing
high-palatable food intake and moderately decreasing run-
ning wheel activity (Verty et al., 2011). Although an effect of
Δ9-THC on thermogenesis and lipolysis also occurred, the
authors speculated that the effectiveness of the exogenous
 cannabinoid in the ABA model was due to an increasing of
the endogenous cannabinoid tone. This points to a possible ther-
apuetic effect of cannabinoids in AN. However, two small
trials exploring the effects of Δ9-THC in underweight AN
patients found no significant effect of the cannabinoid on BW,
but an amelioration of depressive symptoms and perfection-
ism (Gross et al., 1983; Berry, 2006).

4. Conclusions

Although is still debated whether changes in both central and
peripheral appetite modulators come first or after the aber-
rant eating behaviors of ED patients, it seems likely that
these changes have both homeostatic and non-homeostatic
implications in the pathophysiology of AN and BN. A growing
body of evidence support the view that EDs might be linked to
reward-related processes. In this vein, functional brain ima-
ging studies specifically assessing the processing of food-
related stimuli, such as watching images of highly rewarding
foods, demonstrated, although not consistently, hypoactiva-
tion of brain areas that are part of the mesolimbic reward
system (Holsen et al., 2012). Instead, hyperactivation of
reward-related brain regions was documented in under-
weight AN patients upon processing of starvation-linked
stimuli, such as reading positive valued “thin” words (Red-
grave et al., 2008) or watching female body images with
underweight features (Fladung et al., 2010). These findings
are consistent with the hypothesis that an altered evaluation
of reward stimuli in AN individuals, represented by reduced
responsiveness toward food-related stimuli (especially foods
with high caloric content and reward value) and enhanced
reaction toward starvation-specific cues might enable AN
patients to avoid particularly “dangerous” foods, adopt
highly rigid eating patterns and experience a rewarding sense
of power over eating.

The literature reviewed above provides the evidence that
feeding regulatory substances such as leptin, ghrelin, BDNF
and endocannabinoids are involved also in the modulation of
reward processes, motivated behaviors and cognitive perfor-
mances. Therefore, changes in the physiology of appetite
modulators occurring in the acute phase of an ED may play a
pivotal role in the pathophysiology of the disorder by provid-
ing a possible link between motivated behaviors, reward
processes, cognitive functions and energy balance. It is likely
that increasing our knowledge in these putative pathophy-
siological mechanisms of AN and BN may help to develop new
and more effective interventions for the treatment and/or
prevention of EDs.

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