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Ghrelin response to hedonic eating in underweight and short-term weight restored patients with anorexia nervosa

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ABSTRACT

Recently, anorexia nervosa (AN) has been conceptualized as a reward-related disorder, and alterations in brain reward processes have been documented in both acute and recovered AN patients. However, the role of endogenous biochemical mediators, such as ghrelin, in the modulation of reward processes has been poorly investigated in this eating disorder. Hedonic eating, that is the consumption of food exclusively for pleasure and not to maintain energy homeostasis, is a useful paradigm to investigate the physiology of food-related reward. Therefore, we assessed the response of peripheral ghrelin to hedonic eating in 7 underweight and 7 recently weight-restored AN patients and compared it to that of previously studied healthy controls. We found that in satiated underweight patients with AN plasma ghrelin levels progressively decreased after the exposure and the consumption of both the favorite and unfavorite food whereas in satiated weight-restored AN patients and satiated healthy controls plasma ghrelin concentrations significantly increased after the exposure to the favorite food and after eating it, but decreased after the unfavorite food. These results suggest a derangement in the ghrelin modulation of food-related pleasurable and rewarding feelings, which might sustain the reduced motivation toward food intake of acute AN patients.

1. Introduction

Peripheral enteroendocrine hormones not only act on hypothalamic and brainstem homeostatic centers to control energy balance, but they are involved also in the regulation of non-homeostatic rewarding component of food intake (Saper et al., 2002). In particular, ghrelin, a 28-aminoacid peptide primarily produced by endocrine cells in the stomach, behaves both as a hunger hormone stimulating appetite and promoting food intake in condition of negative energy balance, and enhancing non-homeostatic eating by intervening in the modulation of reward and motivated behaviors (Perello and Zigman, 2012). The ghrelin's unique specific receptor, the growth hormone secretagogue receptor type 1A, has been detected on dopaminergic neurons in the ventral tegmental area (VTA) of the brain (Abizaid et al., 2006). Moreover, both central VTA and peripheral administration of ghrelin in the rodents increase the dopamine release and turnover in the nucleus accumbens and the activity of the mesolimbic dopaminergic system, suggesting that both centrally and peripherally produced ghrelin is able to activate mesolimbic reward circuits (Abizaid et al., 2006; Jerlhag et al., 2007; Jerlhag, 2008). It has been also found that ghrelin drastically stimulates the consumption of palatable food in sated rats, just to obtain food-related reward (Perello et al., 2010; Skibicka et al., 2012), and its administration to humans increases the activation of reward-related brain centers in response to tempting food pictures (Malik et al., 2008). All the above data support its role in mediating the rewarding aspects of food intake.

Recently, aberrant reward processes have been suggested to play a role in the pathophysiology of anorexia nervosa (AN) (Walsh, 2013; Park et al., 2014) and brain imaging studies have shown functional and structural abnormalities in areas of the brain, which are involved in reward processing in general (Kaye et al., 2009, 2013) and, specifically, in food-related reward (Wagner et al., 2007, 2008; Holsen et al., 2012). These data suggest that the investigation of the physiological modulation of food-related reward in AN, in particular the assessment of the role of ghrelin, might help to further understand the pathophysiology of this severe and debilitating disorder of unknown etiology.

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In two previous studies (Monteleone et al., 2012, 2013), we observed that the consumption of food exclusively for pleasure and not to maintain energy homeostasis (that is hedonic eating) is followed by increases in peripheral levels of ghrelin in healthy subjects, suggesting a role for this peptide in the modulation of food-related reward. However, no data are yet available on subjects with AN.

The aim of the present study was to explore peripheral ghrelin response to hedonic eating in underweight and short-term weight restored AN patients, and compare it to those of previously studied healthy controls. We hypothesized that, if ghrelin is involved in the modulation of aberrant food-related reward mechanisms of AN, its response to hedonic eating should be deranged in patients with this disorder.

2. Methods

2.1. Subjects

Fourteen patients from those consecutively admitted to the eating disorder inpatient unit of Villa Garda Hospital were selected for the study, according to the following inclusion/exclusion criteria: (a) diagnosis of AN, either present or past, according to the Diagnostic and Statistical Manual for Mental Disorders-IV edition (DSM-IV) criteria; (b) age $\geq$ 18 yrs; (c) no history of psychosis, diabetes mellitus, psychoactive substance use or head trauma; (d) absence of severe physical disorders or comorbid psychiatric disorders; (e) no use of hormones or drugs in the past 2 months. Diagnoses were made by a trained psychiatrist using the Structured Clinical Interview for DSM-IV Axis I disorders-patient edition (First et al., 1995). Seven underweight patients (1 male, 6 females) were diagnosed with active AN (5 with restricting subtype and 2 with binge-eating/purging subtype) and 7 normal weight patients (2 males, 5 females) were diagnosed with past AN (5 with restricting subtype and 2 with binge-eating/purging subtype), since they had restored a normal body mass index (BMI), i.e., BMI $\geq$ 18.5 kg m^{-2}, with the inpatient treatment applied at Villa Garda Hospital. Underweight patients were tested within 2 weeks from their entry into the inpatient unit, before starting any specific weight-restoring program. Weight-restored patients were tested 2–14 weeks after reaching the normal BMI, when only minimal changes had occurred in their eating-related psychopathological aspects so they could be judged psychologically not adjusted. Clinical and demographic characteristics of patients are shown in Table 2.

Two healthy men and 5 healthy women, who had participated in our previous studies with identical methodological procedures (Monteleone et al., 2012, 2013) were used as control group.

All the subjects signed a written informed consent; the study was approved by the Ethics Committee of the University of Naples SUN; all the procedures were run in accordance with the Helsinki Declaration of 1975 as revised in 1983.

2.2. Procedure

Each participant underwent two experimental sessions, one week apart. The day before the first experimental session, the most favorite food of each participant was determined by asking the following question: “Which is your most favorite food that you would eat also when satiated, just for pleasure?”.

The test meal protocol is largely described elsewhere (Monteleone et al., 2012). Briefly, on the first session, 1 h after a breakfast of 300 kcal (including milk, bread and marmalade),

Table 1
List and total amount (Kcal.) of favorite and unfavorite foods eaten by each participant.

Subject	Favorite food		Unfavorite food	
	Food	Total amount (Kcal)	Food	Total amount (Kcal)
Healthy subjects				
S-1	*Delizia al limone* (typical Neapolitan sponge cake with custard lemon cream)	425	Bread + milk	389
S-2	Nutella	316	Bread + butter	319
S-3	*Babà* with Nutella (typical Neapolitan sponge cake soaked in a rum syrup and covered with Nutella)	373	Bread + butter	403
S-4	*Babà* with Nutella (typical Neapolitan sponge cake soaked in a rum syrup and covered with Nutella)	373	Bread + butter	403
S-5	*Cestino con fragoline* (typical Neapolitan pastefrolle cake covered with custard cream and strawberries)	460	Bread + butter	450
S-6	*Fiesta Ferrero* (sponge snack filled with cream and covered with chocolate)	489	Bread + butter	494
S-7	Dark chocolate	538	Bread + butter	567
Underweight patients with anorexia nervosa				
S-1	Chocolate muffin	450	Bread + butter	511
S-2	*Cioccolatini Raffaello* (white chocolates covered with grated coconut) and Bounty bar	497	Bread + butter	497
S-3	Chocolate-filled doughnut	390	Bread + butter	435
S-4	*Kinder Bueno* (chocolate and hazelnut cream bar) + *Kinder Cereali* (chocolate-coated cereal bar)	346	Bread + butter	345
S-5	Tiramisù	460	Bread + butter	475
S-6	Sliced white bread + Nutella	265	Bread + butter	257
S-7	Sliced white bread + Nutella	529	Bread + butter	539
Weight-restored patients with anorexia nervosa				
S-1	Tiramisù	835	Bread + butter	840
S-2	Sliced white bread + Nutella	585	Bread + butter	587
S-3	Ice-cream with nuts + cream	150	Bread + butter	190
S-4	Tiramisù	782	Bread + butter	738
S-5	Almond paste	371	Bread + butter	383
S-6	Chocolate and biscuit bar	360	Bread + butter	360
S-7	Tiramisù	506	Bread + butter	470