Psychoneuroendocrinology (2005) **30**, 534–540

PNEC

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Hormonal and metabolic responses to acute ghrelin administration in patients with bulimia nervosa

S. Fassino[a,*], G. Abbate Daga[a], V. Mondelli[a], A. Pierò[a], F. Broglio[b], A. Picu[b], R. Giordano[b], M. Baldi[b], E. Arvat[b], E. Ghigo[b], L. Gianotti[b]

[a]*Division of Psychiatry, Department of Neuroscience, University of Turin, Via Cherasco 11, 10126 Turin, Italy*
[b]*Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, Italy*

Received 1 July 2004; received in revised form 19 December 2004; accepted 22 December 2004

KEYWORDS
Ghrelin;
Bulimia;
GH;
PRL;
ACTH;
Insulin

Summary Ghrelin is generally influenced by energy balance status and is inversely associated with body mass index (BMI), being reduced in simple obesity, notable exception being Prader Willi syndrome, and elevated in several conditions of undernutrition, including anorexia nervosa (AN). Interestingly, ghrelin levels have also been found elevated in patients with bulimia nervosa (BN) in spite of normal BMI. In humans, intravenous (iv) ghrelin administration induces endocrine (increase in GH, PRL, ACTH and cortisol) and metabolic (increase in glucose and decrease in insulin) effects as well as an increase in appetite and food intake. In AN, ghrelin administration surprisingly leads to a decreased GH response and absence of glycemic variations but normal PRL, ACTH and insulin response. This pattern would reflect a decrease in sensitivity to ghrelin or, alternatively, the metabolic status of AN. To further clarify the function of ghrelin in eating disorders, the endocrine and metabolic response to acute iv ghrelin (1.0 μg/kg) was studied in seven young women with purging BN (BW, BMI, mean ± SEM: 20.3 ± 0.5 kg/m^2). Circulating total ghrelin levels were also measured. The results in BW were compared to those recorded in a group of nine healthy women (HW; BMI 22.3 ± 2.5 kg/m^2). The GH response to ghrelin in BW overlapped with that in HW. Ghrelin administration also led to a similar increase in PRL, ACTH, cortisol and glucose levels in the two groups. Insulin levels were not significantly modified by ghrelin administration in either group. The overlapping endocrine and metabolic response to ghrelin in the two groups occurred with regard to circulating total ghrelin levels which were higher in BW than in HW. In conclusion, BN, a condition of ghrelin hypersecretion, is connoted by a normal endocrine and metabolic response to exogenous ghrelin administration.

* Corresponding author. Tel.: +39 011 6638070; fax: +39 011 6638070.
E-mail address: secondo.fassino@unito.it (S. Fassino).

0306-4530/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.psyneuen.2004.12.008

1. Introduction

Ghrelin, a 28-amino acid peptide predominantly produced by the stomach (Kojima et al., 1999; van der Lely et al., 2004), displays a strong GH-releasing activity mediated by the activation of the 1a type GH segretagogues (GHS)-receptor (GHS-R) (Smith et al., 1997; Arvat et al., 2000, 2001; Takaya et al., 2000; Kojima et al., 2001; Gnanapavan et al., 2002; Muccioli et al., 2002; van der Lely et al., 2004). GHS-Rs are concentrated in the hypothalamus-pituitary unit but also distributed in other central and peripheral tissues (Smith et al., 1997; Papotti et al., 2000; Kojima et al., 2001; Gnanapavan et al., 2002; Muccioli et al., 2002). Ghrelin exerts central and peripheral endocrine and non-endocrine actions. Particularly, it stimulates PRL, ACTH and cortisol secretion and influences the exocrine and endocrine pancreatic function as well as glucose metabolism (Broglio et al., 2001, 2003a,b; Adeghate and Ponery, 2002; Date et al., 2002; Egido et al., 2002; Lee et al., 2002; Volante et al., 2002). A strong orexant action of ghrelin coupled with a role in the control of energy expenditure and food intake has also been demonstrated in humans as well as in animals (Tschop et al., 2000; Horvath et al., 2001; Wren et al., 2001; Muccioli et al., 2002; Yoshihara et al., 2002). The effect of ghrelin on appetite and food intake are opposite to those of leptin and both are mediated by the modulation of the activity of NPY and AGRP-secreting neurons (Horvath et al., 2001; Yoshihara et al., 2002). Other central actions of ghrelin include influence on sleep, cognitive function and a CRH-mediated anxiogenic action that has been shown in animals (Asakawa et al., 2001; Carlini et al., 2002; Weikel et al., 2003).

Ghrelin secretion is mainly modulated by the nutritional status, being increased by fasting-as well as by energy restriction-and decreased by food intake (Ariyasu et al., 2001; Cummings et al., 2001; Tschop et al., 2001a). It is usually inversely associated to body mass index (BMI), being increased in anorexia nervosa (AN), malnutrition and cachexia (Ariyasu et al., 2001; Nagaya et al., 2001; Otto et al., 2001; Shiiya et al., 2002) and reduced in obesity (Tschop et al., 2001b; Cummings et al., 2002a,b; Shiiya et al., 2002). Notable exception is represented by Prader-Willi Syndrome, a well-known condition of obesity associated with hypogonadism, short stature and hyperfagia, where absolute or relative increased ghrelin levels have been found (Cummings et al., 2002a; Del Parigi et al., 2002).

Ghrelin levels are restored to normal range by recovery of ideal body weight both in AN and in obesity (Otto et al., 2001; Cummings et al., 2002b; Hansen et al., 2002). In fact, ghrelin is probably a hormone signaling to the central nervous system (CNS) the metabolic balance and likely managing the neuroendocrine and metabolic responses to short-term changes in the energy balance (Horvath et al., 2001; Altman, 2002; Yoshihara et al., 2002).

Ghrelin levels have been reported altered in different disordered eating conditions. In anorexia nervosa of both subtypes (restricter and binge-purging) ghrelin levels are typically elevated while in bulimia nervosa (BN) ghrelin levels have been reported elevated or normal (Tanaka et al., 2002; Monteleone et al., 2003, 2005). On the other hand, obese patients with binge-eating disorder (BED) have been recently reported to have reduced ghrelin levels similar to patients with simple obesity (Monteleone et al., 2005). Thus, the role of ghrelin in the pathogenesis of the eating behaviour is still puzzling.

Concerning the endocrine and metabolic effects of ghrelin in eating disorders, data in literature are scanty. It has been reported that in AN exogenous ghrelin surprisingly leads to decreased GH response and absence of glycemic variations but normal PRL, ACTH and insulin response (Broglio et al., 2004), likely reflecting a decrease in sensitivity to the endocrine activity of the peptide.

Thus, to further clarify the function of the ghrelin system in eating disorders, the endocrine and metabolic responses to acute iv ghrelin administration was studied in a group of young women with BN, in whom basal total ghrelin levels were also measured. The results in BN patients were compared with those recorded in a group of healthy women.

2. Subjects and methods

Seven women with purging BN (BW; age (mean $\pm$ SEM): 24.5 ± 2.1 year; body mass index (BMI): 20.3 ± 0.5 kg/m^2) and nine healthy young women in the early follicular phase (HW; age: 25.9 ± 2.2 year; BMI: 22.3 ± 2.5 kg/m^2) were studied. The diagnosis of BN was based on the criteria proposed by DSM IV-TR and none of the patients presented a previous diagnosis of anorexia nervosa (APA, 2000). In the control group, psychiatric disorders were excluded based on accurate clinical assessment, though a structured clinical interview was not performed. All the patients had major nutritional parameters and electrolytes in the normal range and had regular menstrual bleeding. Both BW and HW were studied in the early follicular phase.