



Glucagon-like peptide-1 secretion in bulimia nervosa

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ABSTRACT

Blood concentrations of the satiety-inducing glucagon-like peptide-1 (GLP-1) were compared in 20 bulimic patients and 20 healthy controls to examine whether secretory impairment of the peptide could be involved in bulimia nervosa (BN). Basal GLP-1 concentrations were measured by means of an enzyme-linked immunosorbent assay (ELISA) in blood samples taken four times over a 12-h period (08.00h, 12.00h, 16.00h, 20.00h) and seven times over a 3-h period following administration of a test meal. Eating-related and non-eating related patients' psychopathological aspects were measured by the use of a battery of ad hoc rating scales (Eating Disorder Inventory-2 = EDI-2, Bulimic Investigation test-Edinburgh = B.I.T.E., Montgomery-Åsberg Depression Rating Scale = MADRS, Spielberger State-Trait Anxiety Inventory = STAI, Yale-Brown-Cornell Eating Disorder Scale = YBC-EDS). Basal GLP-1 values were higher in patients than in controls only in the blood samples taken at 16.00h, whereas no difference between patients and controls was observed in GLP-1 concentrations in response to the test meal stimulation. GLP-1 levels correlated positively with bingeing-vomiting frequency, with B.I.T.E. scores and the "bulimia" subitem scores of the EDI-2 scale, and negatively with the "ascetism" subitem score of the same scale.

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1. Introduction

Peripherally secreted hormones and peptides influence brain hunger-satiety regulating centers by crossing the blood-brain barrier via the area postrema and the subfornical organ, or by activating centripetal neuronal pathways. In experimental animals and human studies, the C-terminal 31-aminoacid glucagon-like peptide-1 (GLP-1), a glucose and fat dependent (insulinotropic) incretin, has been found to inhibit the feeling of hunger and to induce satiety, significantly reducing energy intake and prospective energy consumption. The peptide diminishes gastric emptying rate, gastrin secretion and gut motility. All these effects have been tentatively suggested, among other hypotheses, to underlie the increased feeling of satiety after feeding (Flint et al., 1998, 2001; Verdick et al., 2001; Vettor et al., 2002; De Graaf et al., 2004; Stanley et al., 2004; Meier and Nauck, 2005; Lopez et al., 2007). GLP-1 derives from preproglucagon, and is secreted by intestinal L-cells primarily in the ileum and by the pancreas. The peptide is also expressed in the central nervous system, specifically in the nucleus of the tractus solitarius whose neurons project into the hypothalamic nuclei, in particular into the arcuate and paraventricular nuclei (Stanley et al., 2004). GLP-1 acts on specific GLP-1 receptors (Lejeune et al.,

2006). The release of the peptide increases between 5 and 30 min after food ingestion, proportionally with meal calorie intake (Viltsboll et al., 2003; Frost et al., 2003).

Altered feelings of hunger and satiety have been reported to occur in patients with anorexia nervosa (AN) (Rolls et al., 1992). In these patients, basal GLP-1 secretion was found either significantly higher (Tomasik et al., 2005; Germain et al., 2007) or lower (D'Alessio et al., 1989) than normal, and highly correlated with glucose concentrations, whereas responses to a standard test meal and to an oral glucose tolerance test were lower than normal. These discordant results may be due to the patients' selection and to the different degrees of severity and duration of the disease, which could decrease (duration) or increase (severity) the secretion of the satiety-inducing peptide. To date, pertinent data about patients with bulimia nervosa (BN) are lacking. Since feelings of satiety have been repeatedly reported to be impaired in BN (Walsh et al., 1989; Rolls et al., 1992; Kissilef et al., 1996), we hypothesized that the secretion of GLP-1 could be impaired in BN patients. That is why in a group of bulimic patients, in an active phase of the disease, we have examined the secretion of GLP-1, in basal conditions four times over a 12-h period and then after a mixed test meal in a separate experiment. The aim of the study was to see whether or not the satiety-inducing GLP-1 secretion is impaired in bulimic patients in basal conditions and after food stimulation, such alterations possibly being responsible for the abnormal type of relationship with food, and whether the impairments may correlate with the patients' psychopathological aspects.

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2. Methods

2.1. Patients

The study sample comprised 20 female patients in an active phase of a bingeing/purging type of BN. All were enlisted at our Institute, and awaiting treatment for their disease. BN was diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994) by means of the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IP) (Spitzer, 1994). The controls were 20 women selected from hospital staff, matched for age with the BN patients, in good health according to physical and laboratory examinations and free of mental disorders according to the DSM IV and SCID criteria. After explanation of the study procedure, written informed consent was obtained from patients and controls. The study was approved by the local Ethics Committee.

Table 1 presents the demographic data of patients and controls, including age, duration of the disease (in patients), body mass index (BMI), and bingeing and vomiting frequency (in patients, monitored before the start of the experiments).

2.2. Procedures

Patients were carefully instructed not to binge or purge at home at least from 12.00h of the day before each of the two testings. They were under the control of relatives, and fully collaborated in this matter. GLP-1 concentrations were measured in plasma.

In experiment 1, the 20 patients and 20 controls fasted 12 h before arriving in the morning at our institute laboratory. EDTA-treated blood samples for the assays were taken at 08.00h, 12.00h, 16.00h, 20.00h, before eating breakfast, lunch and dinner. The 1600h specimen corresponded to the time when patients at home were usually having a snack or a binge episode. The timepoints were selected as far as possible from the previous meal and immediately before the next one, in order to have basal and not feeding-induced GLP-1 concentrations. Patients and controls received a standard breakfast of 840 KJ at 08.30h, and a lunch of 5460 KJ at 12.30h. All the meals, both breakfast and lunch, contained 55% carbohydrate, 15% proteins and 33% fat. No snacks were served, and dinner was taken after 20.30h at home. Patients and controls were asked to entirely finish their meals within 15 min, which they did, and patients were monitored to prevent self-induced vomiting.

In preparation for blood collection, an intravenous catheter left open by a saline infusion was inserted into an antecubital vein 30 min before blood drawing, during which patients rested supine. EDTA-treated blood samples were immediately centrifuged and plasma was stored at -25°C until assayed.

In experiment 2, which took place 48 h later, the same patients and controls arrived at our Clinic Research Unit at 08.00h, after a 12-h fast. At 11.45h, an i.v. catheter was inserted into an antecubital vein and connected to a saline solution slowly infused to keep the catheter open. At 12.00h, a lunch of 5460 KJ, consisting of 80 g bread and 235 g mascarpone cheese (with 15% of carbohydrate, 10% of proteins, 75% of fat) was served. Patients and controls were asked to finish their lunch

Table 1
Demographic and nutritional characteristics of bulimic patients and controls.

	Patients	Controls
Age (yrs)	26 ± 6	25 ± 5
Duration of the disease (yrs)	8 ± 7	
BMI	20.1 ± 3.1	21.4 ± 1.8
Binge frequency (week)	7.3 ± 6.6	
Vomiting frequency (week)	6.7 ± 5.5	

Values = means ± standard deviations.
BMI = Body Mass Index = kg/m^2 .

Table 2
GLP-1 stimulation by a test meal in bulimic patients and control.

	Patients	Controls
Basal GLP-1 values (ng/ml)	6.3 ± 3.7	8.1 ± 3.2
AUC	1267 ± 856	1274 ± 530

Means ± standard deviations.
AUC = area under the curve.

within 15 min, which they did, and were monitored to prevent self-induced vomiting. EDTA-treated-blood samples were drawn immediately before (T 0) and at 15, 30, 45, 60, 90, 120, 180 min after lunch. The samples were collected as mentioned above, and were assayed together with those of experiment 1, to avoid changes in reagents that could interfere with the results.

2.3. Biochemical assay

Plasma GLP-1 (7–36 and 7–37 amide) concentrations were measured by a commercially available enzyme-linked immunosorbent assay (ELISA) purchased from Pantec S.r.L (Turin, Italy). The sensitivity of the method was 2 pM (100 μl); intra-assay and interassay coefficients of variations were 6% and 7% at the concentrations of 12 pM.

2.4. Psychological ratings

At baseline assessment, the psychopathological aspects of the patients were investigated by means of the Eating-Disorders Inventory-2 (EDI-2) to assess the typical psychopathology of BN, and by the Bulimic Investigating Test, Edinburgh (B.I.T.E.) to measure frequency and severity of the bulimic symptomatology. The Montgomery-Åsberg scale for depression (MADRS), the Spielberger State-Trait Anxiety Inventory (STAI) for anxiety, and the Yale-Brown-Cornell for Eating Disorders Scale (YBC-EDS) for obsession-compulsion were also administered.

Controls were not investigated with the rating scales since they were defined as normal by DSM-IV criteria and SCID examination.

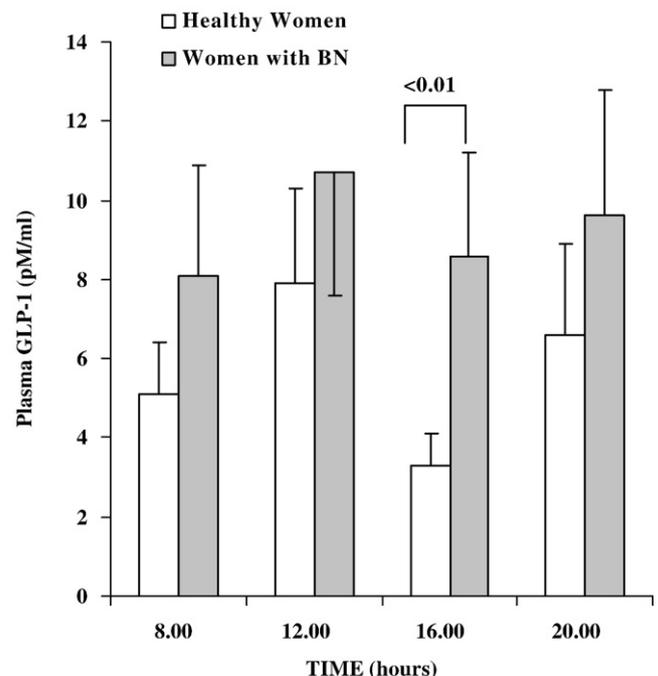


Fig. 1. Glucagon-like peptide-1 secretion at four points during the day in anorexic patients and in controls.

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