Effects of Galanin on Growth Hormone and Prolactin Secretion in Anorexia Nervosa

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Galanin (GAL) elicits growth hormone (GH) release in normal subjects through interaction with hypothalamic somatostatin. GAL also stimulates GH-releasing hormone (GHRH) secretion in vitro. In rats, GAL is able to stimulate prolactin (PRL) release, but this effect is not clear in humans. We have thus investigated GAL effects on GH and PRL release in patients with anorexia nervosa (AN), known to have altered regulation of the GH–insulin-like growth factor axis and PRL dynamics, and compared the effects of GHRH and GAL on GH and PRL secretion in AN and normal healthy subjects. Eight women with AN (15 to 27 years; body mass index [BMI], 17 to 19.5 kg/m^2) were treated with (1) GHRH 50 μg intravenous (IV) injection, (2) porcine GAL 500 μg infusion from −10 to +30 minutes, and (3) 135-minutes saline infusion as a control, respectively. Both peptides induced a significant increase in plasma GH in AN patients (peak level, 27.41 ± 5.50 μg/L after GAL and 18.97 ± 2.67 μg/L after GHRH). When data for AN patients and the control group were compared, GH peak levels after GAL were significantly higher in AN patients (27.41 ± 5.50 *v* 13.64 ± 2.32 μg/L), while GH peak levels after GHRH were not different between the 2 groups (18.97 ± 2.67 *v* 15.98 ± 3.88μg/L). PRL levels significantly increased after both GHRH (peak, 11.70 ± 2.80 μg/L) and GAL (peak, 18.02 ± 5.10 μg/L) treatment in AN patients, but not in normal subjects. We conclude that GAL stimulates exaggerated GH release in AN patients as compared with normal controls, suggesting a dual hypothalamic interaction via both an increase in endogenous GHRH and a decrease in somatostatin secretion. Finally, GAL may act as a PRL secretagogue in AN patients.
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IT IS KNOWN that anorexia nervosa (AN) is characterized by various abnormalities in the dynamics of pituitary hormone secretion, pointing toward a hypothalamic derangement, which could be primary or secondary to malnutrition and body weight reduction. Among these abnormalities, a significant role is played by alterations in growth hormone (GH) secretion, which include elevated basal GH, an exaggerated response to GH-releasing hormone (GHRH), a lack of effect of cholinergic agents during the acute phase, abnormal responses to thyrotropin-releasing hormone and luteinizing hormone–releasing hormone, and lack of inhibition of GH secretion after a meal.[1-3]

Among the novel peptides capable of inducing GH secretion, interesting in vivo and in vitro data have been obtained with the use of galanin (GAL). GAL is a 29–amino acid peptide, initially isolated from porcine small intestine,[4] with little structural similarity to the other known peptides.[5] By means of molecular biological techniques, the structure of porcine, rat,[6] and, more recently, human GAL has been deduced.[7] GAL has been shown to elicit GH release in normal subjects.[8,9] It exerts a paradoxical inhibitory effect on GH secretion in acromegalic patients.[10]

Previous experimental studies have investigated whether the action of GAL is mediated by GHRH or by blocking somatostatin secretion. Data in favor of a GHRH-mediated action include the GAL-induced increase of GHRH release from median eminence fragments in vitro[11] and the abolishment of GAL effects by GHRH antiserum.[12] On the other hand, GAL action has somatostatin neurons as targets in animals,[13] fails to modify GH release after somatostatin antiserum,[14] and counteracts somatostatin-mediated negative GH-feedback mechanisms.[15] Moreover, β-adrenergic stimulation by salbutamol inhibits the potentiating GAL effect on GHRH-induced GH release.[16]

Some systemic and extrapituitary effects of the peptide are different among species.[17] In rats[18,19] and male humans,[20,21] GAL stimulates PRL secretion. On the contrary, it does not induce the same effect in normal females.[22]

Therefore, the aim of our study was to investigate the effects of this novel peptide on GH and PRL release in AN. The GH-releasing effects of GAL and of direct pituitary stimulation with GHRH were compared.

MATERIALS AND METHODS

The study was approved by the ethics committees of our Institutions. We studied a group of 8 females with AN after provision of informed consent. They were aged 15 to 27 years, with a body mass index (BMI) of 17 to 19.5 kg/m^2. All had amenorrhea as established using DSM-IV criteria.[23] All were affected by restrictive-type AN, although 2 had previously shown vomiting features. They were not on any medication from at least 2 weeks before the study. They have not been treated with fluoxetine, depot neuroleptics, or other psychotropic medications for a long period.

Five normally menstruating females aged 18 to 28 years with a normal BMI (21.1 to 23.2 kg/m^2) were also studied as controls. They were tested during the follicular phase of the menstrual cycle, assessed by hormone values and the ultrasound pattern of the ovary.

The tests were performed in randomized order with an interval of at least 3 days in an outpatient setting. After an overnight fast, at 9:00 AM, all patients and controls underwent the following tests: (1) GHRH: an injection of human GHRH (1-29)NH_2 (GEREF; Serono, Rome, Italy) 50 μg as an intravenous (IV) bolus at time 0 (9:15 AM), with blood samples collected at −15, −10, 0, 15, 30, 60, 90, and 120 minutes; (2) GAL: a 40-min IV infusion with 500 μg porcine GAL (Inalco, Milan, Italy) from −10 to +30 minutes (from 9:05 to 9:45 AM), with blood samples collected at −15, −10, 0, 15, 30, 60, 90, and 120 minutes; and (3) saline: an IV infusion of normal saline for 135 minutes (from 9:00 to 11:15 AM), with blood samples collected at the same times reported for GHRH and GAL. The dose and modality of GAL administration was chosen, according to other studies in man, because it is currently the

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maximal dose of porcine or rat GAL infused in humans without relevant side effects and with a clear biological effect on GH secretion.[8]

Blood samples were centrifuged within 2 hours after collection, and separate plasma aliquots were stored at −20°C until assayed.

Plasma GH and prolactin (PRL) levels were measured by radioimmunoassay using commercial kits from Radim (Pomezia, Italy). The intraassay and interassay coefficients of variation were 2.5% and 5.8% for GH and 2.1% and 3.1% for PRL, respectively.

A "paradoxical" PRL response to GHRH is defined as an increase of at least 50% over basal levels.[2]

Statistics

All results are expressed as the mean ± SEM. GH plasma concentrations are also presented as the area under the curve (AUC) relative to 0 calculated by the trapezoidal rule. The incremental delta value is the difference between peak and basal values.

The distribution of the data was tested with the Kolmogorov-Smirnov test to verify whether the samples arise from a specified distribution. We found that the data were not normally distributed. The significance of differences was assessed by nonparametric tests: Wilcoxon rank-sum test (intragroup comparison) and Mann-Whitney *U* test (intergroup comparison, AN *v* control). The significance level was set at a *P* value less than .05. For statistical evaluation, we used the software package Statistica (Statsoft, Tulsa, OK; release 4.1, 1993) for Windows 3.1.

RESULTS

We report the effects of GHRH and GAL on GH secretion, comparing AN patients and control subjects. Then, we report the results concerning PRL secretion following these treatments.

GH Response

The GH response to GHRH in AN patients is shown in Fig 1. The GH-AUC peak level, and incremental delta value are reported in Table 1. No difference was found for AN patients compared with controls (Table 1).

Figure 1 also shows the GH response to GAL or saline infusion in AN patients. GH release was significantly higher after GAL versus saline infusion (mean peak level, 27.41 ± 5.50 *v* 2.85 ± 0.78 μg/L, $P < .01$). The GH-AUC and peak values after GAL are reported in Table 1.

GAL induced a significantly greater GH release in AN subjects versus controls (27.41 ± 5.50 *v* 13.64 ± 2.32 μg/L), while GH peak levels after GHRH were not different between the 2 groups (18.97 ± 2.67 *v* 15.98 ± 3.88 μg/L).

PRL Response

We observed a significant PRL response to GHRH in patients with AN (Fig 2). The mean peak value was 11.70 ± 2.80 μg/L after GHRH (*v* 6.48 ± 0.78 μg/L during saline, $P < .05$, and *v* 6.30 ± 2.71 μg/L in controls, $P < .05$). The mean PRL-AUC and incremental delta values are reported in Table 2.

Figure 2 shows the PRL response to GAL infusion in AN patients. We observed a significant increase of PRL with GAL in comparison to saline infusion as single time points. The mean peak value (18.02 ± 5.10 *v* 6.48 ± 0.78 μg/L, $P < .01$) and mean PRL-AUC were significantly greater after GAL versus saline infusion (Table 2).

PRL levels after GAL in normal subjects are shown in Fig 2 and Table 2 (AUC, peak level, and incremental delta). The GAL infusion induced no significant PRL release.

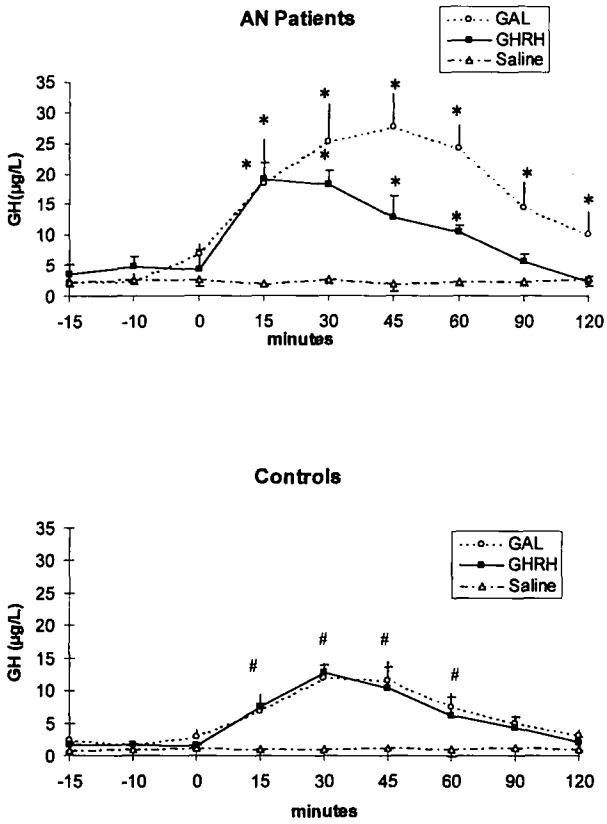

Fig 1. GH plasma values (mean ± SEM) after GAL, after GHRH, and during saline infusion in 8 AN patients and normal controls. *$P <$ .05 *v* saline; #$P < .05$, GHRH and GAL *v* saline.

DISCUSSION

Although no differences in GAL plasma levels were reported in obese women versus normal-weight women,[24] GAL is believed to have a role in the regulation of eating behavior, since

Table 1. GH-AUC (μg/L/120 min) and Peak Values (μg/L) in Eight AN Patients and Five Normal Females After GAL (500 μg in a 40-minute infusion), After GHRH (50 μg IV bolus), and During Saline

Condition	AN Patients	Controls
After GAL		
AUC	1565 ± 408*†	838 ± 206*
Peak	27.41 ± 5.50*‡	13.64 ± 2.32*
Delta	24.99 ± 7.03*‡§	10.43 ± 1.94*
After GHRH		
AUC	1118 ± 159*	793 ± 248*
Peak	18.97 ± 2.67*	15.98 ± 3.88*
Delta	12.76 ± 3.63*	14.40 ± 3.95*
During saline		
AUC	275 ± 76†	127 ± 14
Peak	2.85 ± 0.78†	1.34 ± 0.23

*$P <$ .01 *v* saline.
†$P <$ .05 *v* controls.
‡$P <$ .01 *v* controls.
§P = .03 *v* GHRH.

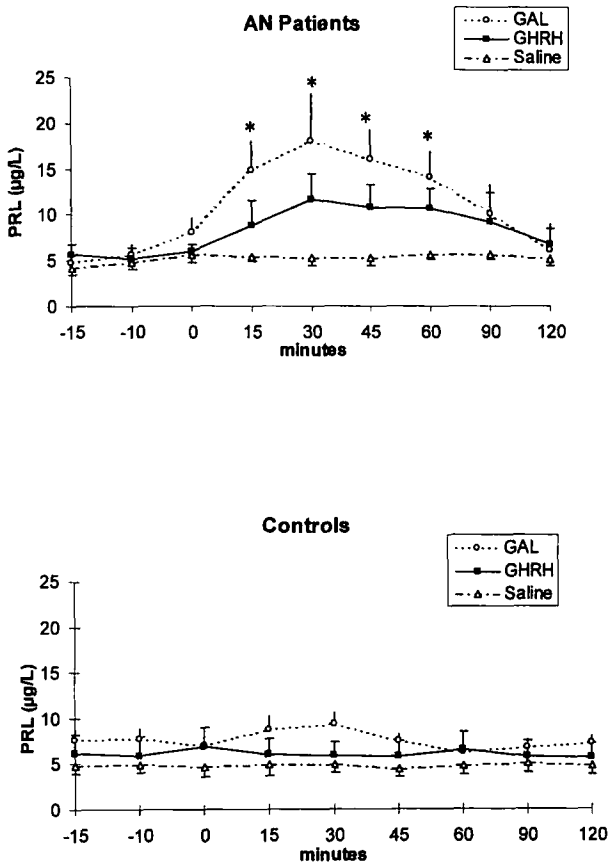

Fig 2. PRL plasma values (mean ± SEM) after GAL, after GHRH, and during saline infusion in 8 AN patients and normal controls. *$P <$ .05 *v* saline.

variations of the peptide in discrete brain areas may not be detectable in the general circulation. Although the pattern of secretion of GAL is not known, basal concentrations of GAL, together with neuropeptide Y (NPY) and leptin, have been determined in obesity and shown to be inappropriate when compared with a control group and AN patients.[25]

Table 2. PRL-AUC (µg/L/120 min) and Peak Values (µg/L) in Eight AN Patients and Five Normal Females After GAL (500 µg in a 40-minute infusion), After GHRH (50 µg IV bolus), and During Saline

Condition	AN Patients	Controls
After GAL		
AUC	1,227 ± 384*†	893 ± 148
Peak	18.02 ± 5.10*‡	7.98 ± 2.98
Delta	9.44 ± 8.84	3.64 ± 2.07
After GHRH		
AUC	796 ± 145§	723 ± 213
Peak	11.70 ± 2.80§	6.30 ± 2.71
Delta	5.47 ± 1.51	3.32 ± 1.19
During saline		
AUC	518 ± 72	581 ± 119
Peak	6.48 ± 0.78	5.79 ± 1.95

*$P <$ .01 *v* saline.
†$P <$ .05 *v* controls.
‡$P <$ .01 *v* controls.
§$P <$ .05 *v* saline.

Another way to investigate the role of GAL in eating disorders is to evaluate its effects on pituitary secretion: our data show that GAL stimulates GH release in patients with AN. Therefore, we hypothesize that in AN patients, GAL plays an important role in the secretion of GH.

Previously, GAL has been shown to elicit GH release in normal subjects.[8,9] The effects should be prevalently indirect, since in cultured anterior pituitary cells GAL has been shown to have only a modest GH-releasing effect.[10] Recently, GAL receptors have been characterized in normal human hypothalamus.[26] Concerning pituitary tissues, GAL receptors have been found in the GH3 pituitary cell line[27] and human GH-secreting pituitary tumors.[28]

It has been suggested that the GH-releasing action of GAL involves an action on somatostatin secretion.[13] It has been shown that GAL may increase the GH response to a maximal GHRH dose in normal humans.[20] However, other data suggest a role of GHRH also. GAL has been shown to increase GHRH release from median eminence fragments in vitro[11]; in rats, the GH-releasing effect of GAL is abolished by the GHRH antiserum.[29] Moreover, GAL has been shown to increase the GH response to the functional somatostatin antagonist in normal subjects.[30]

In patients with AN, several experiments have shown an altered somatostatin control of GH secretion, including abnormal responses to cholinergic agents,[31] abnormal effects of pyridostigmine,[32] diminished somatostatin levels in cerebrospinal fluid during the acute stage,[33] and diminished somatostatin levels in hypophyseal portal blood in animals during restricted feeding.[34] Very recently, an enhanced somatotrope sensitivity to exogenous somatostatin administration has been demonstrated. In fact, maximal GH inhibition is obtained with somatostatin doses that are ineffective in controls.[35] In previous studies,[36] we reported that an infusion of naloxone exerts differential effects on the postprandial GH response to GHRH in patients with AN. The opioid blockade was not able to inhibit GHRH-induced GH release in either the fasting state of the postprandial state in AN patients, suggesting an altered somatostatinergic tone in AN subjects. These data were further supported by evidence linking the somatostatinergic tone to circadian variations and food intake.[36]

The fact that GAL exerts its GH-releasing effect in the presence of an already reduced somatostatin tone points toward a GHRH-releasing effect of GAL.

In patients with AN, GAL is able to elicit a greater GH response to GHRH than in normal subjects. Since GAL is hypothesized to elicit GH release via both an activation of endogenous GHRH release and a reduction in the somatostatin tone, it may be suggested that AN patients are more sensitive than normal subjects to the functional inhibition of the hypothalamic somatostatin tone exerted by GAL.

The exaggerated GH response to GAL is strengthened when considering the role of estrogen in modulating the GAL effect on pituitary hormones. Different experimental data indicate that estrogens enhance the responsiveness of GH to GAL, with it being significantly greater in young women versus age-matched men and the magnitude of the response correlating with estradiol and progesterone levels. The GH response to GAL is also significantly decreased by age only in female subjects.[37]

Since there is a low degree of estrogenization in AN patients, one should expect a lower, not an exaggerated, response to GAL in AN patients. Thus, it can be hypothesized that GAL also may have estrogen-independent actions on GH secretion in females.

On the other hand, a modulation of GH dynamics by glucocorticoids can be hypothesized, since in AN patients activation of the corticotropin-releasing factor (CRF)-corticotropin (ACTH)-cortisol axis has been demonstrated[38] and acute glucocorticoid administration has a net stimulatory effect on GH release both in vitro[39] and in vivo in normal[40] and pathological[41] states.

Our data also show a slight but significant release of PRL during GAL infusion in AN. The role of GAL in the control of PRL secretion is not entirely known. Although GAL seems to stimulate PRL secretion in rodents, the human data are conflicting. It has been reported that intracerebroventricular injection of GAL may increase plasma PRL levels in both anesthetized and conscious rats.[18,19] In humans, neither porcine nor rat GAL are able to influence baseline TSH or PRL secretion.[20] Similarly, other studies have not confirmed a clear stimulatory effect on PRL in men.[42-44] The discrepancies between rat and human data are not simply linked to the use of a non–species-specific GAL in humans. In fact, tests performed with human GAL failed to show an increase in PRL levels.[45]

An elevation in PRL levels was observed only after injection of human GAL at high doses in men.[46] Conversely, there are data showing a modest PRL-releasing effect of GAL in normal females.[22] Moreover, a marked increase in PRL has been observed in patients with Cushing's disease despite the fact that the PRL response to other secretagogues was blunted.[21] The exact mechanism of such a response is unclear, but suggests that GAL is oversecreted together with ACTH by the corticotropes and possibly augments the sensitivity of these cells to exogenous GAL via an increased expression of its own receptor. This model is interesting since, similar to Cushing's disease, in AN patients an activation of the CRF-ACTH-cortisol axis has been demonstrated.[38]

AN is another condition in which a weak but significant PRL response to GAL is present. Different hypothalamic alterations could allow the unmasking of this response, including activation of the CRF-ACTH-cortisol axis, a dopaminergic alteration, and/or a reaction to stressful situations. However, since PRL shows other paradoxical responses to nonspecific stimuli such as GnRH[47] and GHRH[48] (which is in part opioid-dependent), a more generalized dysfunction in PRL regulation is present in such a condition. We cannot explain whether GAL is active per se or via activation of other secretagogues or paracrine mechanisms operating in such a disease. The possible action via activation of GHRH release and/or activity could explain the PRL response occurring without other interference from neurotransmitters or neuropeptides.

The pathophysiological meaning of these data requires further investigation; in particular, we cannot establish if the observed abnormalities may induce AN or are secondary to malnutrition. However, different studies emphasize the role of GAL in feeding behavior. In female rats, both GAL and NPY in the medial preoptic area may contribute to overeating and increased weight gain during a fat-rich diet[49]; and feeding induced by decreased fatty acid oxidation relies on galanergic terminals in the hindbrain.[50]

In conclusion, GAL exerts a stimulatory effect on both GH and PRL release in patients with AN. Our findings suggest a prevalent estrogen-independent action via GHRH and could also explain the similar PRL response as compared with GHRH in these subjects.

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