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Morning Preprandial Plasma Ghrelin and Catecholamine Concentrations in Patients with Phenylketonuria and Normal Controls: Evidence for Catecholamine-Mediated Ghrelin Regulation

KLEOPATRA H. SCHULPIS, IOANNIS PAPASSOTIRIOU, MARIA VOUNATSOU, GEORGE A. KARIKAS, STYLIANOS TSAKIRIS, AND GEORGE P. CHROUSOS

Institute of Child Health (K.H.S.), 11527 Athens, Greece; Department of Clinical Biochemistry, Aghia Sophia Children's Hospital (I.P., M.V., G.A.K.), 11527 Athens, Greece; Blood Transfusion Service, Henri Dunant Hospital (M.V.), 11527 Athens, Greece; and Departments of Experimental Physiology (S.T.) and Pediatrics (G.P.C.), Athens University Medical School, 11527 Athens, Greece

Patients with phenylketonuria (PKU) have a diet-controlled deficiency in the conversion of phenylalanine (Phe) to tyrosine (Tyr), leading to decreased production of noradrenaline, adrenaline, and dopamine. Poor diet control results in high plasma Phe and low plasma Tyr and catecholamine concentrations. Ghrelin, a recently described gastrointestinal hormone that is elevated in the fasting state and low in the fed state, is considered a major appetite-stimulating hormone, possibly involved in the generation of obesity and insulin resistance. We evaluated morning preprandial plasma ghrelin levels in 14 diet-controlled and 15 poorly controlled PKU patients and 20 age- and body mass index (BMI)-matched healthy children (controls) and correlated its concentrations with those of Phe and catecholamines as well as with their BMI and 24-h nutrient intake. Plasma ghrelin levels were measured by RIA, plasma catecholamine concentrations were determined by HPLC with electrochemical detection, and Phe and Tyr levels were measured in an amino acid analyzer. The ghrelin concentration (744 ± 25 ng/liter) in diet-controlled patients did not differ from that in controls (802 ± 26 ng/liter; $P > 0.05$). On the contrary, the ghrelin concentration was significantly reduced in poorly controlled patients (353 ± 23 ng/liter; $P < 0.0001$). Ghrelin correlated negatively with Phe in all three groups, whereas it correlated positively with catecholamine levels and energy intake and negatively with BMI only in diet-controlled patients and controls. We conclude that ghrelin secretion may receive positive direct or indirect input from catecholamines. The absence of a correlation between ghrelin and catecholamines, energy intake, or BMI in PKU patients on an inadequate diet may be due to dysregulation of their neuroendocrine system and might be affected by high Phe levels in the stomach and/or central nervous system. (*J Clin Endocrinol Metab* 89: 3983–3987, 2004)

CLASSIC PHENYLKETONURIA (PKU) is an inborn error of metabolism in which the aromatic amino acid phenylalanine (Phe) cannot be converted to tyrosine (Tyr) (1, 2). PKU is successfully treated with a low Phe diet started as soon as possible, in the first days of life. Many PKU patients, however, do not adhere strictly to this diet, and this results in high plasma levels of Phe interfering with the conversion of Tyr to the catecholamine neurotransmitters noradrenaline (NA), adrenaline (A) and dopamine (DA) (3), and low plasma NA, A, and DA concentrations (4, 5). Poorly controlled patients with PKU have significantly elevated concentrations of plasma leptin, the adipose tissue hormone that plays a role in inhibiting food intake and stimulating the basal metabolic rate (6). Because the secretion of this adipokine is normally inhibited by NA and/or A via β-adrenergic receptors on fat cells, the decreased catecholamine levels of poorly controlled PKU patients appear to result in disinhibition of plasma leptin concentrations (6).

Ghrelin is the endogenous ligand for the GH secretagogue receptor, a G protein-coupled receptor expressed in the hypothalamus, pituitary, and pancreas (7). Ghrelin was recently isolated from the stomach, where its concentrations are quite high (8), although lower amounts were also found in hypothalamic arcuate nucleus neurons as well as in the pituitary, kidney, placenta, bowel, and pancreas (9, 10). Ghrelin concentrations are generally negatively correlated with the levels of leptin, and accordingly, this gastric hormone is, respectively, stimulated or inhibited by fasting and food intake. Furthermore, ghrelin diametrically opposes the actions of leptin, stimulating food intake, inhibiting metabolic rate, and increasing body weight in experimental animals (11).

The end products of the sympathetic system, especially NA, play a major role in the regulation of appetite, energy expenditure, and the secretion of adipokines such as leptin. We hypothesized that the secretion of ghrelin might be regulated by catecholamines in a fashion opposite that of leptin, and that an inborn error of metabolism, such as in PKU, characterized by decreased catecholamine production might reveal such regulation. The aim of this study was to evaluate the secretion of ghrelin in PKU patients under excellent or

Abbreviations: A, Adrenaline; BMI, body mass index; CV, coefficient of variation; DA, dopamine; NA, noradrenaline; Phe, phenylalanine; PKU, phenylketonuria; Tyr, tyrosine.

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poor dietary control and to correlate its concentrations with those of Phe and the catecholamines as well as with the 24-h nutrient intake and body mass index (BMI) of these subjects.

Subjects and Methods

Patients and controls

The study population consisted of 29 PKU patients who were divided into two groups according to their mean annual morning preprandial plasma Phe (Phe mean) concentrations and 20 appropriately matched control children (Table 1): group A (n = 14) included patients who adhered strictly to their special diet (mean annual Phe, 127.0 ± 72.6 μmol/liter), whereas group B included 15 PKU patients who were on a "loose" diet and had grossly elevated mean annual Phe levels (1234.2 ± 157.3 μmol/liter). All patients were initially detected by neonatal screening and placed on a special diet after a tetrahydropterin (BH4) loading test and dihydropteridine reductase evaluation confirmed the diagnosis of PKU. Their daily protein intake was largely replaced by PKU_2 (Milupa AG, Milupa GmbH, Friedrichdorf, Germany), which is a Phe-free mixture of amino acids. Group C was comprised of 20 healthy children of similar age to the PKU patients. Both patients and controls were prepubertal. All PKU patients and control children were admitted to a day clinic for evaluation and blood sampling. The daily nutrient intake of each child was calculated by a 24-h dietary recall of the day preceding admission according to a coded list (12). These subjects and their plasma leptin concentrations were previously reported (6).

Samples

The study was approved by the Aghia Sophia Children's Hospital ethics committee, and written consent was obtained from the parents of the children who participated in this study. All blood samples (5.0 ml) were drawn from an antecubital vein at the same time of the day (~0900 h) after a 10-h overnight fasting and after a 1- to 2-h period in the day clinic area to allow acclimatization to the environment and staff.

Methods

Height (centimeters) was measured on a portable stadiometer, calibrated with a machine meter rod, and weight (kilograms) was evaluated with an electronic scale. Genital or breast development was graded according to Tanner, with testicular volume (milliliters) defined by comparison with a Prader orchidometer. BMI was calculated and expressed as kilograms per meter squared (13).

Plasma catecholamine (NA, A, and DA) levels were measured by reverse phase HPLC with electrochemical detection (14). The interassay coefficients of variation (CVs) for NA, A, and DA were 3.2%, 2.9%, and 3.4%, respectively.

Plasma ghrelin levels were measured using a commercial RIA kit (Phoenix Pharmaceuticals, Belmont CA) that uses ^{125}I-labeled bioactive ghrelin as a tracer molecule and a rabbit polyclonal antibody against full-length octanoylated human ghrelin. This assay recognizes both active and inactive forms of ghrelin. The sensitivity of the assay was 10 pmol/liter, the intraassay CV was 5.5%, and the interassay CV was 2.1% (15).

Quantitative analysis of serum amino acids, including Phe and Tyr, was carried out using an automatic amino acid analyzer (LC 5001, Biotronik, Berlin, Germany). Results were calculated using nor-leucine as an internal standard. The CVs for Tyr and Phe were 2.1% and 2.3%, respectively.

Data analyses

Data are expressed as the mean ± SD or the mean ± SEM as indicated. Data were analyzed by ANOVA, followed by Bonferroni-corrected *t* test or a *post hoc* test (Tukey's), as indicated. The correlation coefficient r between the parameters tested was computed using least squares regression analysis. The *P* values reported are two-tailed. All statistical procedures were performed using the STATGRAFICS PLUS version 5.1 for Windows (Graphic Software System; Manugistics Inc., Rockville, MD), whereas the regression plot and box plots were prepared using the Sigma-Plot software version 8.0 program.

Results

Age, height, weight, and BMI did not differ among the three groups studied (Table 1). Twenty-four-hour energy intake, total protein, and carbohydrates also did not differ among the three groups; however, saturated and polyunsaturated fat intake values were different (Table 2). Statistically significant differences in total fat, monounsaturated fat, and fiber intake were found between groups A and B as well as between groups A and C.

Plasma Phe was significantly different among the three groups, whereas Tyr levels were significantly reduced in group B compared with those in group A and controls (Table 3). On the contrary, plasma ghrelin (Fig. 1) as well as DA and NA did not differ between group A and controls, whereas the concentrations of these hormones were significantly differ-

TABLE 1. Clinical profile of PKU patients and controls

	Age (yr)	Sex	Height (cm)	Weight (kg)	BMI (kg/m^2)
Group A (n = 14)	6.2 ± 1.2	M, 7; F, 7	114.0 ± 3.5	18.5 ± 2.5	19.5 ± 6.5
Group B (n = 15)	6.8 ± 1.0	M, 7; F, 8	116.0 ± 4.0	20.0 ± 3.5	18.5 ± 7.0
Group C (n = 20)	7.0 ± 1.0	M, 11; F, 9	115.0 ± 4.0	19.8 ± 3.8	19.0 ± 7.0

Values are expressed as the mean ± SD.

TABLE 2. Estimated 24-h nutrient intake for PKU patients and controls

	Group A	Group B	Group C	Differences, *P* (A/C, B/C, and A/B)[a]
Energy intake (kcal)	2014 ± 463	2114 ± 487	2080 ± 417	NS
Total protein (g)	73.1 ± 12.0	70.2 ± 14.0	71.4 ± 12.0	NS
Natural protein (g)	7.3 ± 5.6	14.6 ± 5.0	71.4 ± 12.0	<0.0001
Phe-free formula (g)	66.8 ± 4.5	55.6 ± 4.2		NS, NS, <0.01
Carbohydrates (g)	260 ± 70	250 ± 74	255 ± 70	NS
Fiber (g)	31.0 ± 1.8	21.0 ± 1.9	24.0 ± 1.9	<0.01, NS, <0.01
Total fat (g)	70.5 ± 15.0	80.0 ± 10.0	85 ± 15	<0.0001, NS, <0.0001
Saturated fat (g)	22.5 ± 10.0	44.0 ± 10.0	53.0 ± 12.0	<0.0001, <0.001, <0.0001
Monounsaturated fat (g)	28.3 ± 1.0	18.0 ± 0.9	18.0 ± 1.0	<0.05, NS, <0.05
Polyunsaturated fat (g)	20.0 ± 1.9	18.0 ± 2.0	17.0 ± 1.9	<0.01, NS, <0.01
Poly/sat ratio	0.92 ± 0.20	0.26 ± 0.10	0.24 ± 0.10	<0.0001, NS, <0.0001

Values are expressed as the mean ± SD.
[a] By ANOVA followed by Tukey *post hoc* test. NS, Nonsignificant.

TABLE 3. Biochemical data in PKU patients and controls

	Group A	Group B	Group C	Differences, *P* (A/C, B/C, and A/B)[a]
Phe (μmol/liter)	156.6 ± 14.1	1260.3 ± 32.8	60.1 ± 1.7	<0.001
Tyr (μmol/liter)	80.0 ± 3.7	28.9 ± 2.0	86.1 ± 2.5	NS, <0.001, <0.001
DA (pmol/liter)	188.0 ± 10.3	33.0 ± 1.9	192.5 ± 6.2	NS, <0.001, <0.001
A (pmol/liter)	793.0 ± 29.6	144.7 ± 3.2	643.0 ± 80.9	NS, <0.001, <0.001
NA (nmol/liter)	2.6 ± 0.5	1.3 ± 0.02	2.7 ± 0.08	NS, <0.001, <0.001
Ghrelin (ng/liter)	744.0 ± 25.2	353.0 ± 23.5	802.0 ± 26.6	NS, <0.001, <0.001

Values are expressed as the mean ± SEM.
[a] By ANOVA followed by Tukey *post hoc* test. NS, Nonsignificant.

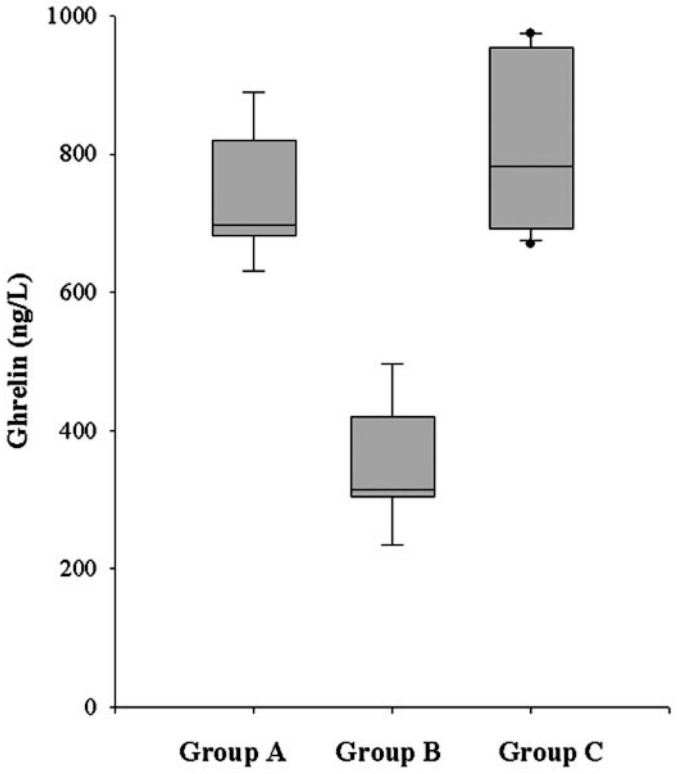

FIG. 1. Morning preprandial plasma ghrelin concentrations (median ± SD) in patients with PKU and matched normal controls. Group A, PKU patients well controlled on a strict diet; group B, PKU patients poorly controlled on a loose diet; group C, controls.

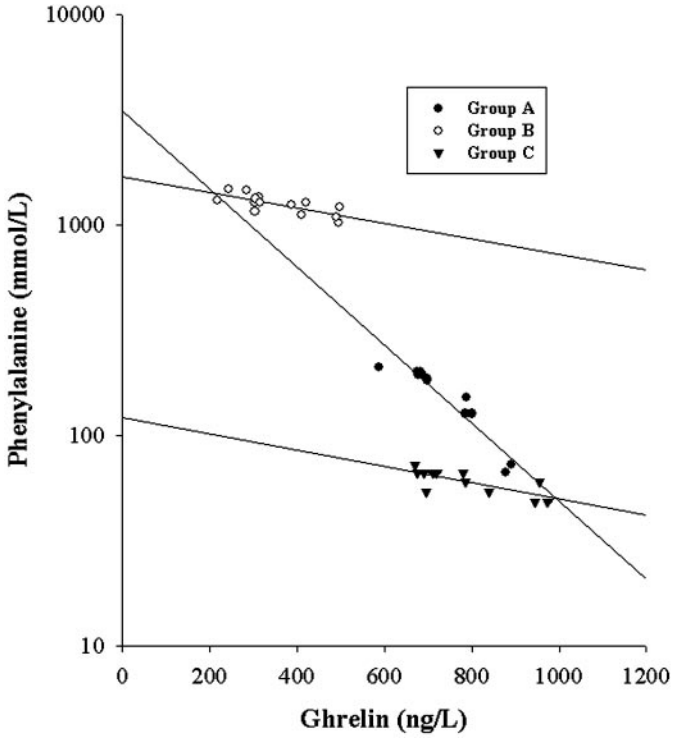

FIG. 2. Correlations between plasma Phe and ghrelin concentrations in patients with PKU and matched normal controls. Group A, PKU patients well controlled on a strict diet; group B, PKU patients poorly controlled on a loose diet; group C, controls.

ent between the two groups of PKU patients and between group B and controls. Plasma A levels were significantly higher in group A than in group B and slightly higher ($P = 0.04$) than those in controls.

Plasma ghrelin concentrations correlated negatively with Phe (Fig. 2) and BMI in all three groups. On the contrary, the hormone correlated positively with the 24-h energy intake, all three catecholamines, and Tyr only in group A and controls (Table 4). No correlation was found between plasma ghrelin concentrations and the above parameters in group B of patients who were poorly controlled by diet.

The plasma ghrelin levels correlated negatively with the leptin levels of the same patients measured and reported previously in group A and controls, but not in group C (6).

Discussion

Energy intake and body weight are tightly regulated at a remarkably consistent set-point by control systems in the hypothalamus and elsewhere in the central nervous system, receiving feedback from diverse peripheral signals (16). In addition, it is now recognized that there are many central and peripheral factors involved in energy homeostasis, and it is expected that the understanding of these mechanisms should lead to effective treatment for the control of body weight (17). Thus, all nutrients inhibit ghrelin secretion equally and can do this by administration via both the luminal and systemic routes (18). As expected, in this study, ghrelin levels positively correlated with energy intake and negatively with BMI in the diet-controlled patients of group A and controls, but not in the poorly controlled patients of group B. In our previous study (6), leptin, which signals the state of fat stores to the brain and inhibits food intake and further fat accumulation (19), correlated negatively with 24-h energy intake and BMI only in PKU patients who were well controlled on a strict diet. We suggested that the diminished concentrations of the catecholamines NA and A in these patients might have disinhibited leptin secretion and hence increased their

TABLE 4. Correlation coefficients between ghrelin and plasma amino acids or catecholamines and 24-h nutrient intake or BMI in PKU patients and controls

Groups	Ghrelin
Phe	
A	−0.90[a]
B	−0.69[a]
C	−0.96[a]
Tyr	
A	0.49[b]
B	0.61[a]
C	0.50[b]
DA	
A	0.66[c]
B	0.10
C	0.66[c]
A	
A	0.66[c]
B	0.46
C	0.66[c]
NA	
A	0.93[a]
B	0.43
C	0.93[a]
Energy intake	
A	0.52[c]
B	0.10
C	0.49[b]
BMI	
A	−0.51[c]
B	0.12
C	−0.54[c]

[a] $P < 0.0001$.
[b] $P < 0.05$.
[c] $P < 0.01$.

plasma leptin concentrations. The same rationale could be applied for ghrelin to explain the diametrically opposite relations of this hormone with the catecholamines; only in this instance these hormones appear stimulatory.

Increased Phe concentrations, as we found in the poorly controlled PKU patients in group B, decrease the availability of the catecholamine precursor Tyr for catecholamine biosynthesis, which was indeed low in these patients, and might be the primary cause of their catecholamine depletion in the central nervous system and periphery (13, 20). Because the hypothalamus and brainstem lie inside the blood-brain barrier, movement of large neutral amino acids, including Phe and Tyr, across this barrier is mediated by a common high affinity transport system (21). In group B patients, the large excess of Phe may saturate this carrier system and thus block other amino acids, such as Tyr, from entering the brain and be available for the synthesis of catecholamines, leading to major brain dysfunction and decreased peripheral secretion of NA by the systemic sympathetic system (21, 22). Also, it is likely that the decreased Tyr concentrations in the plasma of PKU patients (group B) result in decreased uptake by chromaffin cells of the adrenal medulla, leading to low production of A, as found in the blood of these patients.

We know very little about the neural and hormonal regulation of ghrelin secretion by the stomach. Because food intake and energy expenditure are both regulated by the catecholamines NA and A, it is obvious that these biogenic amines might also affect the production of ghrelin (9, 22, 23). This suggestion is supported by the positive correlations found between ghrelin and catecholamines in patients on a strict diet (group A) and in healthy children (controls) and by the general decrease in ghrelin secretion in poorly controlled PKU children. Additionally, high levels of Phe may directly affect the arcuate hypothalamic nucleus, pituitary, and/or stomach (7, 9, 14, 22), resulting in an inhibition of ghrelin production, as shown by the significant negative correlations between ghrelin and Phe in all three groups. With regard to the healthy group of children, the small number of participants used suggests that further investigations are warranted.

Phe significantly decreases rat brain acetylcholinesterase activity *in vitro*, potentially resulting in increased cholinergic activity (24). Similarly, erythrocyte membrane acetylcholinesterase activity in poorly controlled PKU patients is markedly inhibited (25). Moreover, an increase in the Phe concentration appears to stimulate the production of GTP-cyclohydrolase-stimulating protein, which increases *de novo* the synthesis of tetrahydrobiopterin, a natural cofactor of Phe hydroxylase, which has direct acetylcholine-releasing action in the rat brain *in vivo* (26). The stomach is the major source of circulating ghrelin in humans (27), and high Phe-induced dysregulation of the gastric cholinergic system in poorly controlled PKU patients may result in decreased secretion of ghrelin (24–26). The latter hypothesis could be tested by measuring plasma ghrelin levels pre- and postloading with Phe (L-Phe, 100 mg/kg, orally) in healthy and gastrectomized patients (27).

These and previously reported data (6) in children with PKU show marked dysregulation in two major hormones regulating appetite, energy expenditure, and body weight, namely ghrelin and leptin, in poorly controlled patients. Yet, despite the gross change in the ratio of the concentrations of these hormones, poorly controlled PKU patients retain the ability to maintain a stable body weight regulatory set-point. This is in contradistinction with data from experimental animals, in which this set-point can be easily reset by administration of ghrelin or leptin and in concert with data from human adults. These findings together suggest that the regulation of body weight stability in humans contains many redundancies that are difficult to overcome with disturbance of one single hormone.

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Address all correspondence and requests for reprints to: Dr. I. Papassotiriou, Department of Clinical Biochemistry, Aghia Sophia Children's Hospital, 11527 Athens, Greece. E-mail: biochem@paidon-agiasofia.gr.

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