BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH
www.bjournal.com.br

ISSN 0100-879X
Volume 45 (7) 565-680 July 2012

CLINICAL INVESTIGATION

Braz J Med Biol Res, July 2012, Volume 45(7) 656-664

doi: 10.1590/S0100-879X2012007500062

Correlations of circulating peptide YY and ghrelin with body weight, rate of weight gain, and time required to achieve the recommended daily intake in preterm infants

XiaFang Chen, Xueliang Du, JianXing Zhu, LiJuan Xie,YongJun Zhang and ZhenJuan He

Brazilian Journal of Medical and Biological Research (2012) 45: 656-664
ISSN 0100-879X

Correlations of circulating peptide YY and ghrelin with body weight, rate of weight gain, and time required to achieve the recommended daily intake in preterm infants

XiaFang Chen, Xueliang Du, JianXing Zhu, LiJuan Xie, YongJun Zhang and ZhenJuan He

Department of Pediatrics, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Abstract

The objective was to elucidate the relationships between serum concentrations of the gut hormone peptide YY (PYY) and ghrelin and growth development in infants for potential application to the clinical observation index. Serum concentrations of PYY and ghrelin were measured using radioimmunoassay from samples collected at the clinic. For each patient, gestational age, birth weight, time required to return to birth weight, rate of weight gain, time required to achieve recommended daily intake (RDI) standards, time required for full-gastric feeding, duration of hospitalization, and time of administration of total parenteral nutrition were recorded. Serum PYY and ghrelin concentrations were significantly higher in the preterm group (N = 20) than in the full-term group (N = 20; $P < 0.01$). Within the preterm infant group, the serum concentrations of PYY and ghrelin on postnatal day (PND) 7 (ghrelin = 1485.38 ± 409.24; PYY = 812.37 ± 153.77 ng/L) were significantly higher than on PND 1 (ghrelin = 956.85 ± 223.09; PYY = 545.27 ± 204.51 ng/L) or PND 3 (ghrelin = 1108.44 ± 351.36; PYY = 628.96 ± 235.63 ng/L; $P < 0.01$). Both serum PYY and ghrelin concentrations were negatively correlated with body weight, and the degree of correlation varied with age. Serum ghrelin concentration correlated negatively with birth weight and positively with the time required to achieve RDI ($P < 0.05$). In conclusion, serum PYY and ghrelin concentrations reflect a negative energy balance, predict postnatal growth, and enable compensation. Further studies are required to elucidate the precise concentration and roles of PYY and ghrelin in newborns and to determine the usefulness of measuring these hormones in clinical practice.

Key words: Peptide YY; Ghrelin; Preterm infants; Recommended daily intake

Introduction

Peptide YY (PYY) and ghrelin are two gastrointestinal tract hormones that play opposite roles in food intake and energy balance in adults (1,2). PYY is a 36-amino acid polypeptide containing N- and C-terminal tyrosine residues. PYY is synthesized predominantly by L cells of the colon and rectum through internal and paracrine secretion. It is released into the circulation in response to a meal and participates in signaling in the hypothalamus at the end of the meal (3). Food consumption and calorie intake directly influence serum PYY concentration (4). Specifically, a high-protein diet has the strongest effect on serum PYY concentration. In obese subjects, the mean basal serum PYY concentration is lower than that in normal subjects (5). Animal experiments demonstrate that chronic administration of PYY inhibits food intake and weight gain, indicating that PYY is a satiety signal influencing food intake (6).

Ghrelin, a 28-amino acid polypeptide, is the only natural ligand of the growth hormone secretogogue receptor (GHSR). *In vivo*, ghrelin can cross the blood-brain barrier and is activated upon interaction with GHSR in the central nervous system (7). Ghrelin is predominantly secreted by X/A-like endocrine cells of the oxyntic glands in the stomach fundus. The primary function of ghrelin is to stimulate secretion of growth hormone and to regulate energy balance (8). Circulating ghrelin concentrations are highest during fasting and decrease within 1 h after a meal (9). One study reported that chronic ghrelin administration significantly increases cumulative food intake and body weight gain,

Correspondence: ZhenJuan He, Kong Jiang Road, 1665, Shanghai, China. Fax: +86-21-65795173. E-mail: hezhenjuan@sjtu.edu.cn

Received August 1, 2011. Accepted April 13, 2012. Available online April 27, 2012. Published July 2, 2012.

supporting the view that ghrelin is a hunger signal (10). Thus, the role of ghrelin in food intake and energy balance is opposite to that of PYY. Ghrelin stimulates the hypothalamus to increase the expression levels of neuropeptide Y (NPY) and agouti-related protein (AgRP), whereas PYY decreases them (11).

Several studies have measured circulating concentrations of PYY and ghrelin in healthy and sick adults (12-14). These studies have established the importance of PYY and ghrelin in food intake and energy balance in adults, but little attention has been paid to the concentrations of these hormones in infants. Notably, the energy balance is often negative among preterm infants hospitalized immediately after birth (15). Preterm infants need to achieve catch-up growth, or they will have lower anthropometric measurements and be regarded as extrauterine growth-restricted upon discharge (16). Poor postnatal growth in preterm infants is associated with growth disorders, lower bone mineral content, and limited neuropsychological development (17-19).

Conversely, low birth weight in conjunction with rapid catch-up growth during the early postnatal period has been associated with a higher fat mass to lean mass ratio, a greater central fat deposition, and insulin resistance. These factors lead to an increased risk of adverse outcomes, namely obesity, cardiovascular diseases, and type 2 diabetes (20,21). For this reason, the mechanisms that regulate food intake and growth in infants with rapid catch-up growth are of great interest. We compared circulating PYY and ghrelin concentrations in preterm infants to those of full-term infants of the same postnatal age. We then evaluated the relationships between these two hormones and clinical parameters such as gestational age, birth weight, time required to return to birth weight, rate of weight gain, time required to achieve recommended daily intake (RDI) standards, time required for full-gastric feeding, duration of hospitalization, and duration of total parenteral nutrition, in order to identify the role of both hormones in infant growth.

Subjects and Methods

Study population and protocol

Seventy-one preterm infants (gestational age 28-36 weeks; birth weight 1100-2660 g) and 20 full-term infants (gestational age 38-41 weeks; birth weight 2940-4500 g) were enrolled. Gestational ages were estimated from the mother's last menstrual periods and supported by fetal ultrasound measurements. The primary reasons for preterm delivery were pregnancy complications and premature rupture of membranes. Infants with congenital malformations or major morbidities, such as necrotizing enterocolitis, bronchopulmonary dysplasia, severe intraventricular hemorrhage, birth asphyxia, or serious infection were excluded from the study. All infants in the study were fed the same commercial formula (S-26; Wyeth Nutritionals, Ireland). Prior to feeding in the morning, 2 mL whole blood was obtained for routine testing and for measurement of serum PYY and ghrelin. Venous blood samples from 20 full-term, breastfed infants hospitalized for mild jaundice served as a reference group for PYY and ghrelin measurements; jaundice does not influence the concentrations of these two hormones (22). Specimen collection was approved by the Ethics Committee of Xinhua Hospital affiliated with the Shanghai Jaotong University School of Medicine and the parents of the infants gave written informed consent to participate. Infant body weights were determined daily for the two groups using a standard electronic scale. The time to regain birth weight, rate of daily weight gain after returning to birth weight, time to reach RDI standards (120 kcal·kg^{-1}·day^{-1}, 3 g protein·kg^{-1}·day^{-1}), time required for full-volume feeding (100 kcal·kg^{-1}·day^{-1}), number of intravenous nutrition days, and days of hospitalization were recorded for preterm infants.

Hormone assays

Serum PYY concentrations were assayed using a human PYY radioimmunoassay (RIA) kit (Linco Research, USA) with ^{125}I-labeled bioactive PYY as a tracer molecule and rabbit polyclonal antibody raised against the full 1-36-amino acid and truncated 3-36-amino acid forms of human PYY. Based on 10 replicates using human serum with a mean PYY concentration of 827 ng/L, the inter-assay coefficient of variation (CV) for this antibody was 9.4%, and the intra-assay CV was 8.5%. Serum ghrelin concentrations were measured using a commercial RIA kit (Linco Research) with ^{125}I-labeled bioactive ghrelin as a tracer molecule and rabbit polyclonal antibody raised against both acetylated and non-acetylated human ghrelin to measure total circulating ghrelin concentrations. Based on 6 replicates using human serum with a mean ghrelin concentration of 1000 ng/L, the intra- and inter-assay CVs for this antibody were 3.3 and 7.9%, respectively, in a range of 10.5-1350 ng/L for PYY and 96.1-6150 ng/L for ghrelin. Measurements were done in duplicate.

Statistical analyses

Data are reported as means ± SD. PYY and ghrelin measurements followed a Gaussian distribution, both overall and for preterm and full-term infants separately. Therefore, no transformation was necessary. Differences in quantitative variables between preterm and full-term infants were evaluated using the *t*-test, as appropriate. Pearson's correlations were used to analyze relationships among the variables of interest. Multiple regression analyses were also performed to evaluate whether several variables were correlated independently with PYY and ghrelin concentrations or whether they were confounding factors. The level of significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS 13.0 statistical package.

Results

Patient characteristics

Seventy-one preterm infants were enrolled in the ex-

perimental group (39 males, 32 females; gestational age = 235 ± 13.52 days; birth weight = 2007 ± 382.03 g). Blood samples from postnatal day (PND) 1, 3, and 7 were available for 20 of these infants (8 males, 12 females; gestational age = 243 ± 28.7 days; birth weight = 2180 ± 302.7 g). For the remaining 51 preterm infants, blood samples were only obtained on PND 1. The control group consisted of 20 full-term infants (11 males, 9 females; gestational age = 276 ± 4.8 days; birth weight = 3523.9 ± 462.7 g) from whom blood samples were collected on PND 7. No statistically significant differences were detected between males and females in these two groups (P > 0.05; *t*-test).

Correlations of PYY and ghrelin concentrations with body weight in preterm and full-term infants

PYY and ghrelin concentrations were significantly higher in preterm than in full-term infants on PND 7 (P < 0.01; Figure 1). In the study population, serum PYY and serum ghrelin concentrations did not differ significantly between males and females. Serum ghrelin concentrations correlated negatively with body weights of preterm and full-term infants on PND 7 (preterm: r = -0.530, P = 0.001; full-term: r = -0.446, P = 0.003; Figure 2A). Serum PYY concentrations correlated negatively with body weights of preterm infants on PND 7 (r = -0.777, P = 0.029; Figure 2B), whereas serum PYY concentrations did not correlate with body weights of full-term infants on PND 7. In preterm infants, serum PYY concentrations correlated negatively with body weight, whereas this correlation did not exist in full-term infants.

Correlations of PYY and ghrelin concentrations with preterm infant body weight on PND 1, 3, and 7

Serum PYY and ghrelin concentrations increased significantly with postnatal age in preterm infants on PND 1 (PYY = 545.27 ± 204.51; ghrelin = 956.85 ± 223.09 ng/L), PND 3 (PYY = 628.96 ± 235.63; ghrelin = 1108.44 ± 351.36 ng/L), and PND 7 (PYY = 812.37 ± 153.77; ghrelin = 1485.38 ± 409.24 ng/L; P < 0.01; Figure 3). Negative correlations (Pearson's correlation) were detected between ghrelin concentrations and body weight among preterm infants on PND 1, 3, and 7 (PND 1: r = -0.602, P = 0.021; PND 3: r = -0.428, P = 0.042; PND 7: r = -0.530, P = 0.003; Figure 4A). PYY concentrations corresponding to PND 1, 3, and 7 also correlated negatively with body weight among preterm infants (PND 1: r = -0.913, P = 0.001; PND 3: r = -0.768, P = 0.016; PND 7: r = -0.777, P = 0.029, respectively; Figure 4B).

Relationships between concentrations of PYY and ghrelin and clinical observation indices among preterm infants

The relationships between PYY and ghrelin on PND 1 and the following clinical parameters were evaluated for 71 preterm infants: gestational age, birth weight, time to return to birth weight, rate of daily weight gain after return to birth weight, time to reach RDI (120 kcal·kg^{-1}·day^{-1}; 3 g protein·kg^{-1}·day^{-1}), time to full-volume feeding (100 kcal·kg^{-1}·day^{-1}), and numbers of intravenous nutrition days and hospitalization days. Serum PYY concentrations correlated

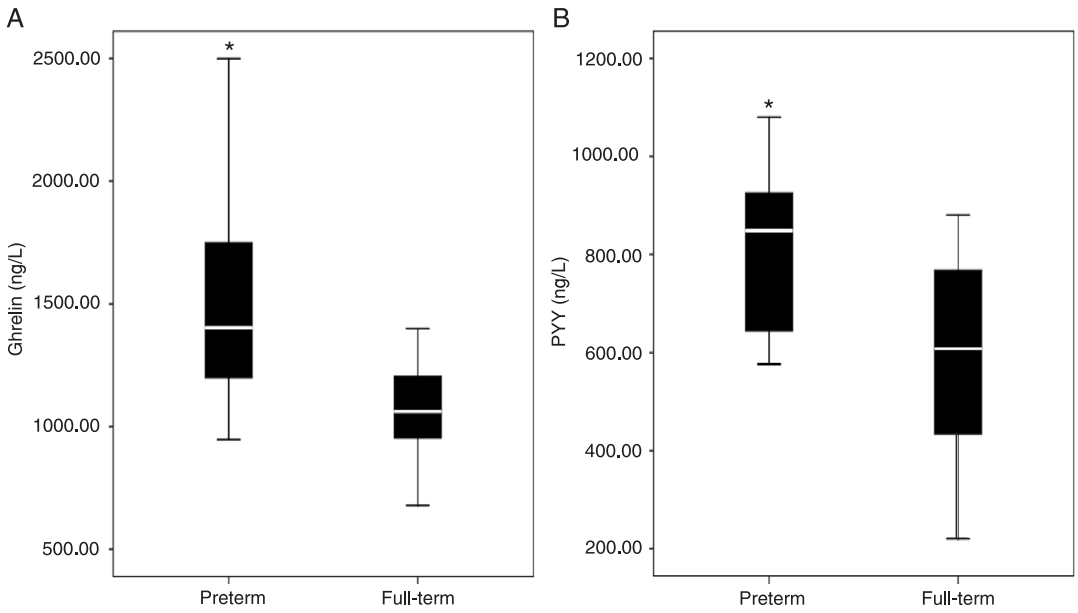

Figure 1. Serum ghrelin (*A*) and peptide YY (PYY) (*B*) concentrations in preterm and full-term infants. Boxes indicate interquartile ranges; white lines within boxes indicate median values; whiskers indicate the lowest and the highest observations. PYY and ghrelin concentrations were significantly higher among preterm infants than full-term infants on postnatal day 7 (*P < 0.01, *t*-test).

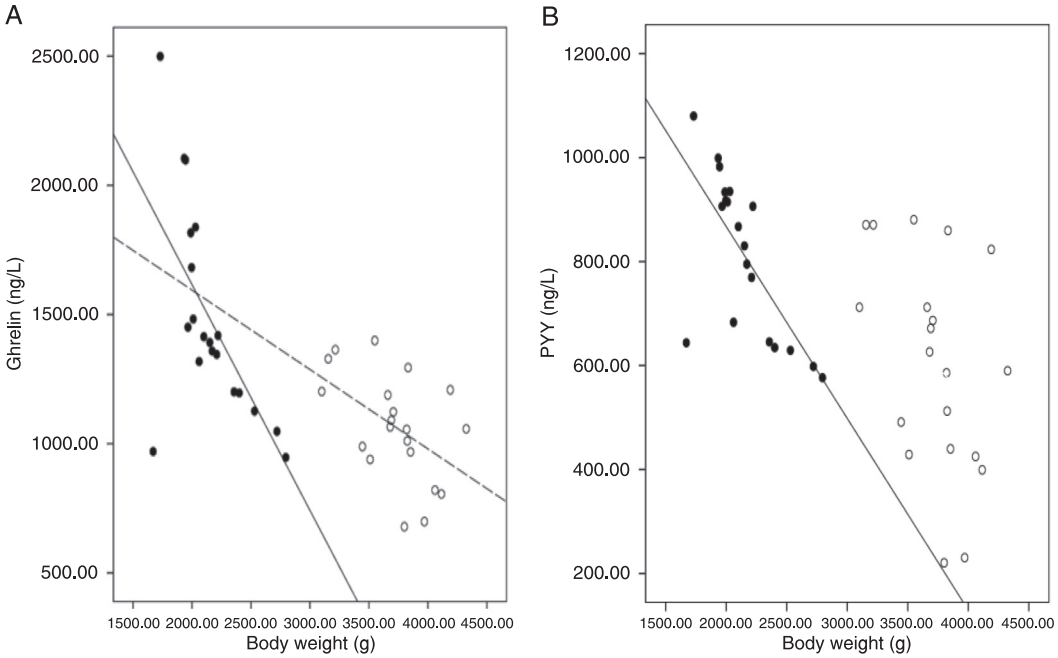

Figure 2. Correlations between serum ghrelin, peptide YY (PYY), and body weight of preterm infants and full-term infants on postnatal day (PND) 7. Filled circles indicate ghrelin (*A*) and PYY (*B*) concentrations for preterm infants; open circles indicate ghrelin (*A*) and PYY (*B*) concentrations for full-term infants. The lines indicate the regression slopes for preterm (smooth line; ghrelin: P = 0.001, PYY: P = 0.029) and full-term infants (dashed line; ghrelin: P = 0.003). Serum PYY and ghrelin concentrations correlated negatively with preterm infants' body weight on PND 7 (r = -0.777, P = 0.029; r = -0.530, P = 0.003, respectively; Pearson's correlation analysis). Serum ghrelin concentrations also correlated negatively with full-term infants' body weight on PND 7 (r = -0.446, P = 0.003; Pearson's correlation analysis).

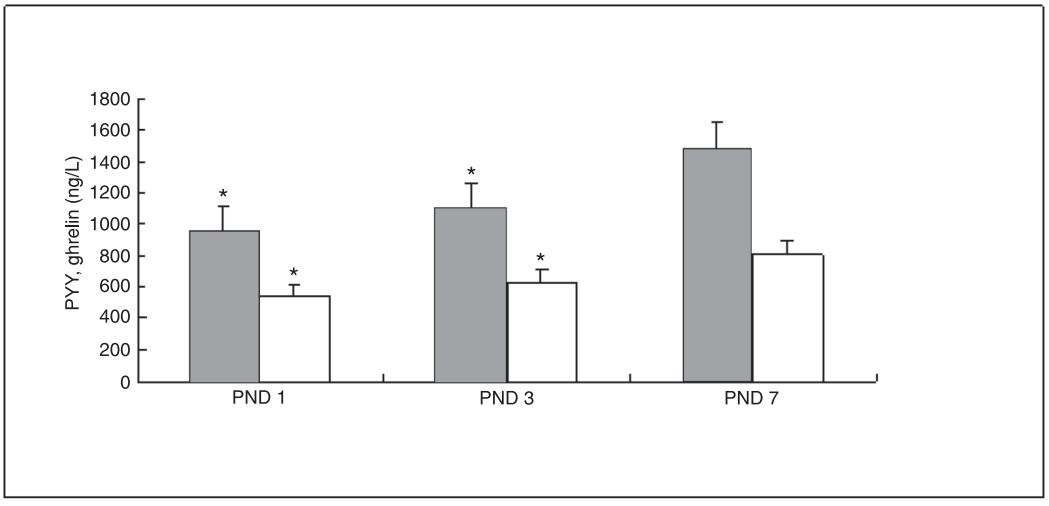

Figure 3. Serum peptide YY (PYY, open bars) and ghrelin (filled bars) concentrations in preterm infants on postnatal day (PND) 1, PND 3 and PND 7. Serum PYY and ghrelin concentrations increased with postnatal age. Hormone concentrations measured on PND 1 and PND 3 differed significantly from concentrations on PND 7 (*P < 0.01, *t*-test).

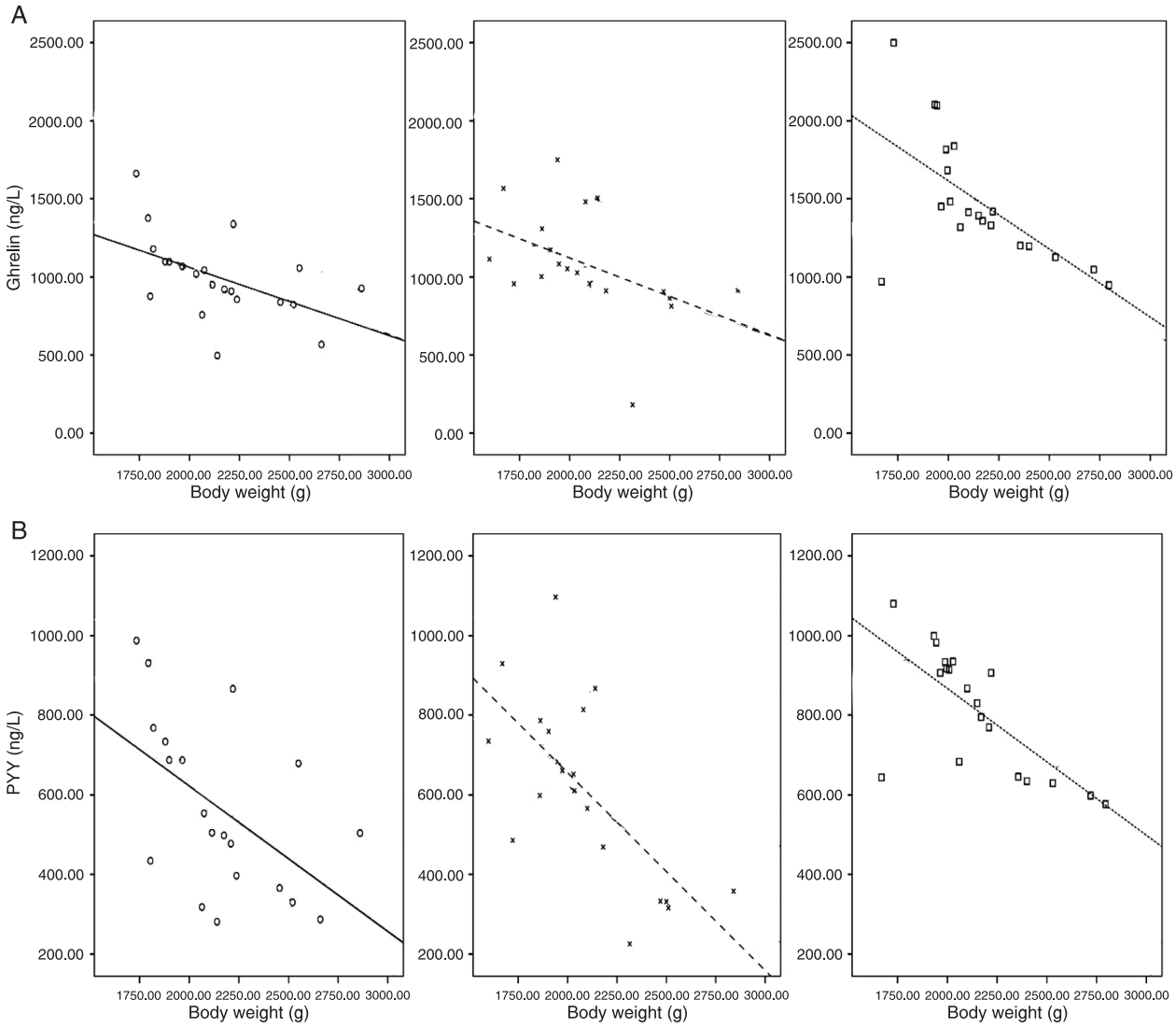

Figure 4. Correlations between serum ghrelin (*A*), PYY (*B*), and body weight of preterm infants on postnatal day (PND) 1, 3, and 7. *A*, Circles indicate serum ghrelin on PND 1; X's indicate serum ghrelin on PND 3; squares indicate serum ghrelin concentrations on PND 7. Smooth lines indicate regression slopes corresponding to PND 1 for ghrelin; dashed lines indicate regression slopes corresponding to PND 3 for ghrelin; dotted lines indicate regression slopes corresponding to PND 7 for ghrelin. Ghrelin concentrations correlated negatively with body weight on PND 1, 3 and 7 in the preterm group (PND 1: r = -0.602, P = 0.021; PND 3: r = -0.428, P = 0.042; PND 7: r = -0.530, P = 0.003; Pearson's correlation analysis). *B*, Circles indicate serum PYY concentrations on PND 1; X's indicate serum PYY concentrations on PND 3; squares indicate serum PYY concentrations on PND 7. Smooth lines indicate regression slopes corresponding to PND 1 for PYY; dashed lines indicate regression slopes corresponding to PND 3 for PYY; dotted lines indicate regression slopes corresponding to PND 7 for PYY. PYY concentrations also correlated negatively with body weights on PND 1, 3, and 7 in the preterm group (PND 1: r = -0.913, P = 0.001; PND 3: r = -0.768, P = 0.016; PND 7: r = -0.777, P = 0.029; Pearson's correlation analysis).

negatively with birth weights and rates of weight gain and correlated positively with ghrelin concentrations (PYY/birth weight: B = -0.176, β = -0.358, t = -3.527, P = 0.001, 95%CI = -0.276 to -0.077; PYY/gain rate: B = -3.254, β = -0.162, t = -2.136, P = 0.036, 95%CI = -6.296 to -0.213; PYY/ghrelin: B = 0.249, β = 0.465, t = 4.593, P = 0.000, 95%CI = 0.141 to 0.358; Table 1). Serum ghrelin concentrations correlated negatively with birth weights and positively with times to reach RDI (ghrelin/birth weight: B = -0.212, β = -0.230, t = -2.299, P = 0.025, 95%CI = -0.395 to -0.028; ghrelin/RDI: B = 17.009, β = 0.389, t = 4.209, P = 0.000, 95%CI = 8.943 to 25.075; Table 2).

Table 1. Correlations between PYY concentrations and clinical observation indices of preterm infants.

Model	Unstandardized coefficients		Standardized coefficients	*t*-test	P	95%CI for B	
	B	SE	β			Lower limit	Upper limit
1							
(Constant)	53.863	65.887		0.818	0.416	-77.578	185.304
Ghrelin	0.386	0.045	0.722	8.657	0.000	0.297	0.476
2							
(Constant)	609.030	167.773		3.630	0.001	274.244	943.817
Ghrelin	0.254	0.056	0.474	4.567	0.000	0.143	0.365
Birth weight	-0.182	0.051	-0.369	-3.552	0.001	-0.284	-0.080
3							
(Constant)	687.571	167.626		4.102	0.000	352.989	1022.154
Ghrelin	0.249	0.054	0.465	4.593	0.000	0.141	0.358
Birth weight	-0.176	0.050	-0.358	-3.527	0.001	-0.276	-0.077
Rate of weight gain	-3.254	1.524	-0.162	-2.136	0.036	-6.296	-0.213

The relationships between PYY on postnatal day 1 and the following clinical parameters were evaluated for 71 preterm infants: gestational age, birth weight, time to return to birth weight, rate of daily weight gain after return to birth weight, time to reach recommended daily intake (120 kcal·kg^{-1}·day^{-1}; 3 g protein·kg^{-1}·day^{-1}), time to full-volume feeding (100 kcal·kg^{-1}·day^{-1}), and numbers of intravenous nutrition days and hospitalization days. Serum PYY concentrations correlated negatively with birth weights and rates of weight gain and correlated positively with ghrelin concentrations (Pearson's correlation). Dependent variable = peptide YY (PYY); SE = standard error of regression coefficient; CI = confidence interval of regression coefficient.

Table 2. Correlations between ghrelin concentrations and clinical observation indices of preterm infants.

Model	Unstandardized coefficients		Standardized coefficient	*t*-test	P	95%CI for B	
	B	SE	β			Lower limit	Upper limit
1							
(Constant)	614.825	99.006		6.210	0.000	417.312	812.337
PYY	1.347	0.156	0.722	8.657	0.000	1.037	1.658
2							
(Constant)	635.737	86.525		7.347	0.000	463.079	808.395
PYY	0.841	0.173	0.451	4.874	0.000	0.497	1.186
RDIS	19.225	4.046	0.439	4.752	0.000	11.151	27.299
3							
(Constant)	1237.391	274.822		4.503	0.000	688.844	1785.937
PYY	0.605	0.196	0.324	3.079	0.003	0.213	0.997
RDIS	17.009	4.041	0.389	4.209	0.000	8.943	25.075
Birth weight	-0.212	0.092	-0.230	-2.299	0.025	-0.395	-0.028

The relationships between ghrelin on postnatal day 1 and the following clinical parameters were evaluated for 71 preterm infants: gestational age, birth weight, time to return to birth weight, rate of daily weight gain after return to birth weight, time to reach recommended daily intake (120 kcal·kg^{-1}·day^{-1}; 3 g protein·kg^{-1}·day^{-1}), time to full-volume feeding (100 kcal·kg^{-1}·day^{-1}), and numbers of intravenous nutrition days and hospitalization days. Serum ghrelin concentrations correlated negatively with birth weights and positively with times to reach recommended daily intake (Pearson's correlation). Dependent variable = ghrelin; RDIS = recommended daily intake standards; SE = standard error of regression coefficient; CI = confidence interval of regression coefficient.

Discussion

In recent years, the incidence of premature delivery in China has exhibited an increasing trend. According to 2003-2004 survey data, the Chinese premature delivery rate is 7.8% (23). As survival rates of preterm infants increase globally, feeding problems and growth have emerged as primary concerns rather than merely ensuring survival. The complexities of growth issues contribute even greater challenges to the medical realm. Compared to full-term infants, preterm infants are more susceptible to malnutrition and extrauterine growth retardation early in life and are more likely to experience growth failure, skeletal mineral deficiencies, and neuropsychological development restrictions later in life (19,24). Furthermore, overfeeding and associated diseases, such as adolescent diabetes mellitus, present additional concerns. Thus, the energy balance and nutritional status are of vital importance in the early stages of preterm infancy. Clinical trials examining nutritional regimens should be designed to achieve specific patterns of postnatal growth. Clinical practice should include the systematic capture of neonatal nutritional intake (25). PYY and ghrelin concentrations correlate closely with energy metabolism and nutritional status. Consequently, studies evaluating PYY and ghrelin concentrations in preterm infants are meaningful and necessary.

We observed that PYY and ghrelin concentrations are significantly higher in preterm infants than in full-term infants. There are two possible explanations for this: preterm infants may exhibit an increase in their synthesis/secretion rate for these hormones and/or may exhibit a decrease in their clearance rate. The clearance mechanism of PYY is under investigation, whereas ghrelin has been more extensively studied (26-28). The kidney is regarded as the primary site of ghrelin clearance, with the liver playing a secondary role (29). It is possible that circulating ghrelin accumulates in preterm infants because the two main clearance sites of ghrelin are immature. However, circulating ghrelin concentrations have been reported to peak after the first postnatal month and up to the 24th month in healthy full-term infants (30), making the possibility of decreased clearance in our preterm infants unlikely. In addition, circulating concentrations of PYY have been reported to be increased on PND 12 versus PND 6 in healthy preterm infants (31). This supports the notion that the elevated ghrelin concentrations we observed in preterm infants probably resulted from increased synthesis and secretion of ghrelin. Another possibility is degradation in the serum.

Regardless of the cause of increased PYY and ghrelin concentrations, these elevated hormones represent negative nitrogen balances and nutrition deficiencies. Such alterations in PYY and ghrelin are also detected in anorexia nervosa, angiocardiopathy, and cachexia caused by malignancy (32,33). In these cases, the increase in ghrelin concentrations is regarded as a compensational effect. Adequate concentrations of serum ghrelin are beneficial to stimulate the appetite of preterm infants, maintain an appropriate blood sugar level, and promote fat formation

PYY and ghrelin concentrations are closely related to body weight in adults. Any change in body weight can directly affect the level of these two hormones (34-36). In the present study, however, an increase in postnatal age was associated with a concomitant increase in PYY and ghrelin along with physiological weight loss. It might be that physiological weight loss is 1) characteristically no more than 8% of the birth weight, 2) mainly caused by meconium and urine output and the loss of water from the skin and lungs, 3) due to inadequate milk intake during the first few days following birth, and 4) not caused by consumption diseases. Therefore, the concentrations of these two hormones would not be affected in infants in the same way as they would in adults.

The correlations of PYY and ghrelin with time to reach RDI and with weight gain rate in preterm infants on PND 1 indicate that PYY and ghrelin may predict postnatal growth. The positive correlation between ghrelin concentrations and time to reach RDI in preterm infants suggests that preterm infants with elevated ghrelin concentrations on PND 1 will be delayed in reaching RDI. The definition of RDI is a daily calorie intake of 120 kcal/kg and a daily protein intake of 3 g/kg. Both enteral and parenteral nutrition, as long as they provide calories and key nutrients to meet the RDI, are recommended for preterm infants to reach the rate of intrauterine growth of infants of the same gestational age (37). High circulating ghrelin concentrations in preterm infants at birth represent a negative energy balance or malnutrition and involve a longer time to reach RDI.

The negative correlation between PYY concentration and rate of weight gain in preterm infants suggests that preterm infants who have higher PYY concentrations on PND 1 will exhibit a lower rate of weight gain later. Evidence supports an inhibitory role of PYY. Chronic administration of PYY inhibits food intake for more than 24 h in healthy volunteers (38). Preterm infants who have depressed PYY levels may have a better appetite or a stronger feeding ability, translating to a faster postnatal weight gain.

The positive correlation between PYY and ghrelin concentrations in preterm infants suggests that these gastrointestinal hormones may share regulatory mechanisms of synthesis and secretion. Alternatively, PYY and ghrelin may be involved in mutual regulation. These possibilities remain to be elucidated. However, it is interesting that PYY and ghrelin both act upon hypothalamic NPY/AgRP; ghrelin increases these factors, whereas PYY decreases them. These opposite effects suggest that the relationships between them and body weight should also be opposite as observed in many studies on adults (13,34,35). In animals, PYY concentrations in plasma as well as in the descending colon and rectal tissues were increased throughout pregnancy and lactation, and PYY did not inhibit the enhance-

ment of appetite during pregnancy (39). Gomez et al. (40) administered high doses of PYY to young nursing rats and adult mice and identified trophic effects in the gastrointestinal tract. On the basis of these findings, we believe that the roles of PYY and ghrelin may be different during the perinatal period as compared to adulthood. In neonates, these hormones may both reflect nutritional status and exert trophic effects to promote gastrointestinal maturation.

References

1. Gardiner JV, Jayasena CN, Bloom SR. Gut hormones: a weight off your mind. *J Neuroendocrinol* 2008; 20: 834-841.
2. Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* 2009; 15: 1546-1558.
3. Karra E, Chandarana K, Batterham RL. The role of peptide YY in appetite regulation and obesity. *J Physiol* 2009; 587: 19-25.
4. Lemmens SG, Martens EA, Born JM, Martens MJ, Westerterp-Plantenga MS. Staggered meal consumption facilitates appetite control without affecting postprandial energy intake. *J Nutr* 2011; 141: 482-488.
5. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake. *Nutr Metab Cardiovasc Dis* 2008; 18: 158-168.
6. D'Alessio D. Intestinal hormones and regulation of satiety: the case for CCK, GLP-1, PYY, and Apo A-IV. *JPEN J Parenter Enteral Nutr* 2008; 32: 567-568.
7. Vergnano AM, Ferrini F, Salio C, Lossi L, Baratta M, Merighi A. The gastrointestinal hormone ghrelin modulates inhibitory neurotransmission in deep laminae of mouse spinal cord dorsal horn. *Endocrinology* 2008; 149: 2306-2312.
8. van der Lely AJ, Tschop M, Heiman ML, Ghigo E. Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. *Endocr Rev* 2004; 25: 426-457.
9. Camilleri M. Peripheral mechanisms in the control of appetite and related experimental therapies in obesity. *Regul Pept* 2009; 156: 24-27.
10. Vincent RP, le Roux CW. The satiety hormone peptide YY as a regulator of appetite. *J Clin Pathol* 2008; 61: 548-552.
11. Pfluger PT, Castaneda TR, Heppner KM, Strassburg S, Kruthaupt T, Chaudhary N, et al. Ghrelin, peptide YY and their hypothalamic targets differentially regulate spontaneous physical activity. *Physiol Behav* 2011; 105: 52-61.
12. Stengel A, Tache Y. Regulation of food intake: the gastric X/A-like endocrine cell in the spotlight. *Curr Gastroenterol Rep* 2009; 11: 448-454.
13. Neary MT, Batterham RL. Gut hormones: implications for the treatment of obesity. *Pharmacol Ther* 2009; 124: 44-56.
14. Karra E, Batterham RL. The role of gut hormones in the regulation of body weight and energy homeostasis. *Mol Cell Endocrinol* 2010; 316: 120-128.
15. Hulzebos CV, Sauer PJ. Energy requirements. *Semin Fetal Neonatal Med* 2007; 12: 2-10.
16. Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up? *Semin Perinatol* 2003; 27: 302-310.
17. Ahmad I, Nemet D, Eliakim A, Koeppel R, Grochow D, Coussens M, et al. Body composition and its components in preterm and term newborns: A cross-sectional, multimodal investigation. *Am J Hum Biol* 2010; 22: 69-75.
18. Hovi P, Andersson S, Jarvenpaa AL, Eriksson JG, Strang-Karlsson S, Kajantie E, et al. Decreased bone mineral density in adults born with very low birth weight: a cohort study. *PLoS Med* 2009; 6: e1000135.
19. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* 2009; 124: 717-728.
20. Sun SS, Liang R, Huang TT, Daniels SR, Arslanian S, Liu K, et al. Childhood obesity predicts adult metabolic syndrome: the Fels Longitudinal Study. *J Pediatr* 2008; 152: 191-200.
21. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. *BMJ* 2005; 331: 929.
22. Shen Zhen-yu, Du Min-lian, Su Zhe. Relationship between ghrelin level and growth axis of small for gestational age newborns. *J Clin Pediatr* 2007; 25: 999-1001.
23. Kelun Wei, Yujia Yang, Yu Yao, et al. An initial epidemiologic investigation of preterm infants in cities of China. *Chinese J Contemp Pediatrics* 2005; 7: 25-28.
24. Gibson A, Carney S, Wales JK. Growth and the premature baby. *Horm Res* 2006; 65 (Suppl 3): 75-81.
25. Vasu V, Modi N. Assessing the impact of preterm nutrition. *Early Hum Dev* 2007; 83: 813-818.
26. Lomenick JP, Melguizo MS, Mitchell SL, Summar ML, Anderson JW. Effects of meals high in carbohydrate, protein, and fat on ghrelin and peptide YY secretion in prepubertal children. *J Clin Endocrinol Metab* 2009; 94: 4463-4471.
27. Crespo MA, Gonzalez Matias LC, Lozano MG, Paz SF, Perez MR, Gago EV, et al. [Gastrointestinal hormones in food intake control]. *Endocrinol Nutr* 2009; 56: 317-330.
28. Ueno H, Yamaguchi H, Mizuta M, Nakazato M. The role of PYY in feeding regulation. *Regul Pept* 2008; 145: 12-16.
29. Hosoda H, Kojima M, Kangawa K. Biological, physiological, and pharmacological aspects of ghrelin. *J Pharmacol Sci* 2006; 100: 398-410.
30. Schubert ML. Gastric exocrine and endocrine secretion. *Curr Opin Gastroenterol* 2009; 25: 529-536.
31. Yin X, Li Y, Xu G, An W, Zhang W. Ghrelin fluctuation, what determines its production? *Acta Biochim Biophys Sin* 2009; 41: 188-197.
32. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, et al. Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. *Circulation* 2001; 104: 2034-2038.
33. Poitras P, Tomasetto C. The potential of ghrelin as a prokinetic. *Regul Pept* 2009; 155: 24-27.
34. Juvonen KR, Purhonen AK, Karhunen LJ, Herzig KH, Poutanen KS. [Regulation of food intake by gastrointestinal peptides]. *Duodecim* 2009; 125: 2067-2074.
35. Wu R, Zhou M, Cui X, Simms HH, Wang P. Ghrelin clearance is reduced at the late stage of polymicrobial sepsis. *Int J Mol Med* 2003; 12: 777-781.

36. Tomasik PJ, Sztefko K. The effect of enteral and parenteral feeding on secretion of orexigenic peptides in infants. *BMC Gastroenterol* 2009; 9: 92.
37. Soriano-Guillen L, Barrios V, Chowen JA, Sanchez I, Vila S, Quero J, et al. Ghrelin levels from fetal life through early adulthood: relationship with endocrine and metabolic and anthropometric measures. *J Pediatr* 2004; 144: 30-35.
38. Dietrich MO, Horvath TL. Feeding signals and brain circuitry. *Eur J Neurosci* 2009; 30: 1688-1696.
39. Taylor VJ, Patterson M, Ghatei MA, Bloom SR, Wilson CA. Ghrelin and peptide YY (PYY) profiles in gastrointestinal tissues and the circulation of the rat during pregnancy and lactation. *Peptides* 2009; 30: 2213-2220.
40. Gomez G, Zhang T, Rajaraman S. Intestinal peptide YY: ontogeny of gene expression in rat bowel and trophic actions on rat and mouse bowel. *Am J Physiol* 1995; 268: G71-G81.