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Peptide YY: A Gut Hormone Associated with Anorexia During Infectious Diarrhea In Children

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Abstract

Objective—To evaluate the effects of diarrhea on appetite among Peruvian children ages 12 to 71 months and to assess whether elevated plasma levels of peptide YY, TNF-α, and IL-1β contribute to anorexia in this population.

Study design—46 Peruvian children with diarrhea and 46 healthy controls underwent an observed feeding trial that was repeated when cases were healthy. Blood was taken from 30 cases

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and controls at the first trial and from 30 cases at the second trial and was assayed for peptide YY, TNF-α, and IL-1β.

Results—The mean consumption of cases when sick was less than when healthy. The mean plasma level of peptide YY was higher for cases than controls and higher for cases when sick compared with cases when healthy. TNF-α levels were higher in cases than controls at visit 1 and also higher in cases when sick than when healthy. There were no differences in IL-1β levels between cases and controls or between cases when sick and healthy. Peptide YY levels in children with diarrhea correlated with the likelihood of them eating less when sick compared with when healthy.

Conclusions—Elevated serum peptide YY may be a mechanism for anorexia among children with diarrhea.

Keywords

appetite; gastroenteritis; malnutrition; gut hormone

Diarrheal illness is a major cause of malnutrition among children in the developing world (1,2,3,4). Proposed mechanisms by which diarrhea may cause malnutrition include malabsorption of nutrients, increased metabolic demand and decreased intake from diarrhea-associated anorexia. The question of whether diarrhea leads to a decrease in appetite in children is particularly important to address because anorexia may thwart caregivers' attempts to ensure adequate caloric intake during diarrheal episodes.

Observational community studies of infants and toddlers in Nigeria and Peru found that solid food intake was significantly decreased during diarrhea while breast milk intake was unchanged (5,6). In a hospital based study in Bangladesh, children with diarrhea ate nearly 50% less than healthy controls, mostly as a result of decreased intake of non-breast milk sources (7). None of the existing studies on diarrhea and appetite attempted to determine the mechanism of anorexia.

Hormonal control of appetite has been a major topic of investigation in recent years leading to the discovery of molecules that both stimulate and suppress appetite. Peptide YY is a gut-derived hormone that induces satiety in humans by serving as a feedback signal to the hypothalamus (8,9,10). It has been shown to be elevated in adult patients with malabsorptive disorders including ulcerative colitis, celiac sprue, and infectious diarrhea (11). Thus, peptide YY is a potential candidate as a mechanism driving anorexia during diarrhea. Cytokines which are released in the acute phase response to an infection also cause anorexia (12). Of the cytokines released during the inflammatory response, IL-1β and TNF-α have been most consistently associated with anorexia (13,14).

Methods

We conducted a community based study to assess the affect of diarrhea on appetite among children ages 12 to 71 months living in an urban shantytown in Lima, Peru. Appetite was determined by an observed feeding trial administered to cases with diarrhea and healthy controls. The trial was repeated for cases and controls when cases were healthy. In addition,

we investigated the role of peptide YY, IL-1β and TNF-α as a mechanism for appetite suppression during diarrhea in this population.

Setting

This study was conducted in the community of Pampas de San Juan de Miraflores an urban shantytown in Lima, Peru. Most families immigrated from either the Peruvian Andes or coastal communities in the 1980s (15). Data collected by the non-profit organization AB PRISMA demonstrated that 97% of homes had electricity, 48% had toilets, and 64% had a household water connection (16). AB PRISMA has operated a field research site in Pampas since 1986.

Approval for this study was granted by the Institutional Review Boards of the Johns Hopkins University School of Public Health and the University of Connecticut Health Center. Approval was also granted by the ethics committee of both the Universidad Cayetano Heredia and AB PRISMA.

Study Design

A feeding trial was conducted with children ages 12 to 71 months with diarrhea and with healthy controls. Cases repeated the feeding trial when they were healthy as did controls. Being healthy was defined as not having any liquid or semi-liquid bowel movements in the previous three days or any other reported illnesses by the parent. Blood samples were taken from cases and controls before the first feeding trial and from cases before the second. Cases and controls were recruited from an ongoing diarrhea cohort study at the field site on exposure risk factors for enteric parasites. Participants were visited daily to determine diarrheal incidence. Cases and controls were enrolled from January through May of 2006. Informed written consent was obtained from the parent and assent was obtained from the child. Parents who did not want their child to have a blood draw were offered to have their child only participate in the feeding trial. Once a case was enrolled, a random list of age- and sex-matched children in the cohort was generated and parents of the children were contacted until a control was found.

Cases were children in the cohort ages 12–71 months with diarrhea as defined by 3 or more liquid or semi-liquid stools in the 24-hour period preceding the feeding trial who were reported to be otherwise healthy by their parents. Cases were afebrile at the time of the feeding trial with no clinical evidence of dehydration. Controls were children ages 12–71 months with no diarrhea at the time of recruitment and no parental report of any other illness.

Study procedure

Parents of cases and controls were asked not to feed their child on the morning of the feeding trial. If the child was febrile or appeared dehydrated the study was not conducted and the child was referred to a local clinic. For those entered in the study who agreed to a blood draw, the nurse took 3 mL of blood via venipuncture into a specially prepared EDTA containing vacutainer (see below). Vials were transported in a cooler to a clinic where they

were centrifuged within 15 to 30 minutes of venipuncture. Plasma samples were stored in liquid nitrogen at the clinic and were later stored at −50° C in the laboratory.

Parents were asked whether the child breast-fed and if so how many times in 24 hours and the last time the child had eaten. Parents of cases were asked the number and type (solid, semi-liquid, liquid) of bowel movements in the previous 24 hours, and whether the child had fever, grossly blood stool or had vomited. After the interview, a health worker stayed in participants' homes to conduct a 2 hour observed feeding trial. Strawberry yogurt was selected as the test food based on taste testing with 20 children from the cohort. At the start of the feeding trial, the health worker offered yogurt to the child. When the child indicated that he was full the cap was replaced. After a five minute pause, the child was offered more yogurt. If the child accepted, he was allowed to eat ad libitum until another refusal. This process was repeated one and two hours after the initiation of the feeding trial. Health workers weighed each bottle when opened and when the child had finished.

Preparation of vacutainers for blood collection

An aprotinin (Roche Applied Science, Indiana) solution was added to the EDTA containing vacutainers prior to use to prevent destruction of peptide YY by proteases. A solution of 1.7 mg/mL of powdered aprotinin in distilled water (equivalent to 10 000 KIU/mL) was prepared and 0.06 mL of the solution was injected into each vacutainer for a desired concentration of 600 KIU/3mL of whole blood.

Assays for TNF-α and IL-1β

Plasma samples were assayed for IL-1β and TNF-α using Direct ELISA kits from Biosource (Carlsbad, California). The sensitivity of the TNF-α ELISA kit was 3 pg/mL (range 15–1500 pg/mL). The sensitivity of the IL-1β ELISA kit was 2 pg/mL (range 33–1400 pg/mL). Assays were performed by scientists blinded to clinical detail.

Assay for Peptide YY

Plasma from each sample was sent frozen to the Department of Metabolic Medicine at Imperial College London for peptide YY radioimmunoassay. As previously described, the antiserum (Y21) was produced in rabbits against synthetic porcine PYY coupled to bovine serum albumin by glutaraldehyde and used at a final dilution of 1:50,000 (17). This antibody cross-reacts fully with both PYY-(3–36)) and PYY-(1–36), but not with pancreatic polypeptide, neuropeptide Y, or other known gastrointestinal or pancreatic hormones. The 125-I PYY was prepared by the iodogen method and purified by high pressure liquid chromatography. The specific activity of the 125I PYY label was 54 Bq/fmol. The assay was performed in total volume of 0.7 ml of 0.06 M phosphate buffer PH 7.2 containing 0.3% bovine serum albumin. The assay was incubated for 3 days at 4°C before separation of free and antibody bound label by sheep anti-rabbit antibody. Detection limit of the assay was 2.5 pmol/l, with an intra-assay CV of 5.8 %. All samples were assayed in duplicate and in one run, thereby avoiding inter-assay variation. Assays were performed by scientists blinded to clinical details.

Statistical Analysis

All data were analyzed with Intercooled Stata Version 8.2. All variables were tested for normality. For comparisons, the t-test was used for normal data and the non-parametric Mann-Whitney rank sum test was used for non normal data. Univariate and multivariate logistic regression was used to determine the relationship between characteristics of the diarrheal episodes and the change in intake of cases from visit 1(sick) to visit 2(healthy). In order to create a multivariate logistic model that included all cases, values for plasma peptide YY levels of cases who did not provide a blood sample were imputed (18,19). The imputation was performed using imputation by chained equations and then confirmed with best sub-set regression.

Results

The study enrolled 46 cases and 46 controls all of whom completed both feeding trials (Table I). Three children who served as controls when healthy went on to develop diarrhea later in the enrollment period. They were enrolled as cases and other controls were sought for them. Blood samples were taken from 30 cases and 30 controls. Cases who gave blood had higher weight-for-age Z-scores than those who did not ((WAZ 0.00 vs. −0.57 p=.05). The differences in height-for-age Z-score (HAZ), weight-for-height Z-score (WHZ), age and household income between cases who gave blood and cases who did not were not significant.

Anthropometric and socioeconomic values for the study participants were compared with that of all children ages 1–5 years in the larger cohort. There were no significant differences in mean HAZ, WAZ, WHZ and per person household income between children in the cohort who participated in the study and children who did not.

The median duration of the diarrheal episode was 2 days with a range of 1–13 days. All cases met the inclusion criteria with a median of 4.5 bowel movements in the 24 hours prior to the morning feeding trial. However, 20 out of 46 continued to have diarrhea in the 24 hours following the morning feeding trial. Among all cases, 12 children had fever, 12 children vomited, 6 children had both fever and vomiting and 7 children had blood in their stool. For the 16 children who did *not* give a blood sample, the median diarrheal duration was 3 days, the median number of bowel movements in the 24 hours preceding the feeding trial was 5. Five children had fever, 5 vomited, 2 had fever and vomiting and 1 had bloody stool.

The mean calorie consumption of children with diarrhea was less than healthy controls at visit, but this difference was not significant 1 (24.7 kcal/kg vs. 26.5 kcal/kg p=0.22; Table II). However, the mean consumption of cases at visit 1 (sick) was significantly less than consumption of cases at visit 2 (healthy) (24.7 kcal/kg vs. 29.5 kcal/kg p=.035). The mean consumption of healthy controls was not significantly less at visit 1 than visit 2.

The mean plasma levels of peptide YY were higher for cases than controls at visit 1 (p=. 0005; Table III). The cases' peptide YY levels were higher at visit 1 (sick) than visit 2 (healthy), although this difference was just below the level of statistical significance (p=.06).

Plasma TNF-α levels were higher in cases than controls at visit 1 (p=.0008) and also higher in cases when sick than when healthy (p=.0026). The mean IL-1β was slightly lower in cases than controls, but this difference was not significant.

Certain participant sub-groups had a much greater difference in caloric intake at visit 1 compared with visit 2 than others. For example, the mean intake of cases with fever was 17.1 kcal/kg at visit 1 versus 31 kcal/kg at visit 2. Cases whose episode of diarrhea lasted longer than three days had a mean intake of 19 kcal/kg at visit 1 versus 29 kcal/kg at visit 2. To examine the effect of a broad number of factors on the percent difference in intake among cases, this variable was dichotomized into those who ate more or less than 20% more at the second visit. The following variables were then analyzed in a univariate logistic regression to determine their relationship to the likelihood of a child with diarrhea eating greater than 20% more when healthy compared with when ill (suggesting anorexia during the illness): history of fever, history of vomiting, presence of blood in stool, duration of diarrhea, number of bowel movements 24 hours before the feeding trial, breastfeeding status, household income, age, sex, anthropometric values, plasma peptide YY at visit 1, plasma TNF-α at visit 1 and plasma IL-1β at visit 1. A history of fever, the duration of the diarrheal episode, whether the child had diarrhea in the 24 hours following the feeding trial and the plasma peptide YY level at visit 1 were all significant individual predictors of cases eating greater than 20% more when healthy than when sick. When the variable for peptide YY levels at visit 1 was dichotomized and analyzed in a univariate logistic regression, cases with a peptide YY level above the mean for all cases were 18 times more likely to eat greater than 20% more at visit 2 than cases with a peptide YY level less than the mean (p=<0.001).

In order to do multivariate logistic regression analysis using all cases, values for plasma peptide YY levels of cases that did not provide a blood sample were first imputed by *best sub-set regression*. A multivariate logistic regression was run with the dichotomized outcome variable of a percent difference in intake from visit 1 to visit 2 of at least 20% and the following modifying variables: plasma peptide YY levels at visit 1 (including imputed values), a history of fever or not, the duration of the diarrheal episode and whether or not the child met the criteria for diarrhea in the 24 hours following the feeding trial (Table IV). In this model only the plasma peptide YY level remained significant (OR=1.06 p= .017).

The imputation of the missing peptide YY values was then repeated using imputation by chained equations. When the multivariate logistic regression was run using imputed values obtained by *imputation by chained equations*, peptide YY fell just short of significance as a predictor of cases eating more than 20% at the second visit (OR= 1.05 p= .055).

Discussion

This study evaluated the effects of community diarrhea on appetite using a case-control method and addressed possible molecular mechanisms for anorexia during diarrhea via measurement of peptide YY levels in children with community diarrhea. Our data showed a statistically significant difference in mean intake among cases when sick compared with cases when healthy (24.7 kcal/kg vs. 29.5 kcal/kg). Given that the mean intake of cases and controls was nearly identical at visit 2, this difference can be attributed to anorexia during

the diarrheal episode rather than increased appetite in the convalescent period. TNF-α levels were higher in cases than controls and also higher in cases when sick than when well, but TNF-α was not associated with a change in intake among cases. A key finding in this study was that peptide YY levels were significantly higher in cases than controls. In both univariate and multivariate logistic models, peptide YY levels were a significant predictor of the likelihood of cases eating at least 20% more when healthy as compared with when sick.

The severity of the diarrheal episode and associated symptoms were found to correlate with the degree of anorexia. In particular, a report of fever during the diarrheal episode was a significant predictor of cases eating less when sick than when well. The association between fever and anorexia in children has been documented by other researchers. In an observational study involving children ages 5 to 30 months in Bangladesh, Brown et al also found a decrease in dietary intake on days with fever (20). Rahman et al found that hospitalized Bangladeshi children with Shigella diarrhea and fever consumed less in the first 48 hours of hospitalization than children with Shigella diarrhea without fever (21).

We also found that the duration of the diarrheal episode was associated with decreased intake as was having diarrhea in the 24 hours following the feeding trial. Duration may be a marker of severity and the virulence of the pathogen involved, and children who continued to have diarrhea after the feeding trial were in a more acute phase of illness compared with those who were at the conclusion of an episode when the feeding trial took place.

Community diarrhea resulted in elevated plasma TNF-α in our population. The fact that TNF-α did not correlate with anorexia is somewhat surprising given that it is considered to be an appetite suppressant. It is possible that the elevations in TNF-α in our study population were too minor to affect appetite or that sample size was too small to detect a difference. Alternatively, peripheral TNF-α concentration may be a poor reflection of tissue levels. There were no significant differences in plasma IL-1β concentrations between cases and controls or between cases at visit 1 and visit 2 suggesting that IL-1β is not central in the inflammatory response to illness among children with community diarrhea in the population studied.

Peptide YY levels were significantly higher in cases than controls and that peptide YY levels for cases at visit 1 correlated with the increase in intake from visit 1 to visit 2. Peptide YY is a gut peptide produced by the L-cells of the gastrointestinal tract that acts on receptors of the arcuate nucleus of the hypothalamus to suppress appetite (22).

Peptide YY has mostly been studied in the context of obesity. However, in 1986 Adrian et al demonstrated that both basal and post-prandial levels of peptide YY are elevated in a number of malabsorptive disorders, including infectious diarrhea (11). In our study the cases' mean fasting peptide YY level was lower at visit 2 than visit 1, but still higher than that of controls. Thus, it appears that in some children the elevation in peptide YY persists even after the diarrheal episode is resolved. This data raises the possibility that children in developing countries who suffer from multiple diarrheal episodes over the course of a year may have persistent elevations in peptide YY with the potential for long term appetite suppression during crucial growth periods.

A limitation to this study was that the feeding trial was carried out once during the illness; thus it may not have reflected the child's appetite throughout the illness. In addition, even though children liked the yogurt and were familiar with it, it is not the typical breakfast of most participants. Although we chose to focus on peptide YY because it is known to be elevated in infectious diarrhea, for future work on this topic, it would also be useful to measure other hormones involved in appetite regulation such as leptin and ghrelin. In future studies, it would also be useful to determine the etiology of the diarrhea to determine whether different pathogens have variable effects on appetite.

This study demonstrated that children ate significantly less when they had diarrhea than when they were healthy. Peptide YY levels are elevated in children with diarrhea and correlate with a difference in calorie intake when sick with diarrhea compared with when healthy. These results suggest that an elevation in peptide YY may be a key mechanism for anorexia in children with infectious diarrhea.

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Table 1

Demographic, socioeconomic, and nutritional characteristics of cases and controls who participated in a study of the effects of diarrhea on appetite. Cases are Peruvian children ages 12 to 71 months with diarrhea. Controls are age-matched healthy children from the same peri-urban community.

	Cases	Controls
N	46	46
# male	25	25
Age range (months)	12.8 to 68.8	12.7 to 70.5
Mean age (months)	39.4 ± 14.9	40.6 ± 14.2
Mean WAZ	−0.1	−0.37
Mean HAZ	−0.92	−1.09
Mean WHZ	0.64	0.41
# breastfeeding	8	4
Mean per person monthly income ($US)	40	45
Percentage with sewage connection	71	82
Percentage with indoor running water	63	71

[1]None of the differences in mean values were significant.

Table 2

Average intake of yogurt in kcal/kg of cases and controls at visit 1 and visit 2. Cases are Peruvian children ages 12 to 71 months who had diarrhea at visit 1 and were healthy at visit 2. Controls are age-matched healthy children from the same peri-urban communithy who were healthy at both visits.

	N	mean cal/kg visit 1	mean cal/kg visit 2
All cases	46	24.7 (± 11.1)	29.5[a] (± 10.5)
All controls	46	26.5 (± 9.3)	29.1 (± 9.8)

[1] Visit 2 was 10 days or more after visit 1.

[a] Significantly different from mean intake of cases at visit 1 (p=.035)

[b] Not significantly different from consumption of cases.

[c] Not significantly different from consumption of controls at visit 1

Table 3

Plasma levels of peptide YY, TNF-α and IL-1β of cases at visit 1, cases at visit 2 and controls. Cases are Peruvian children ages 12 to 71 months who had diarrhea at visit 1 and were healthy at visit 2. Cases are healthy age-matched children from the same peri-urban community.

	Peptide YY (pg/mL)	TNF-α (pg/mL)	IL-1β (pg/mL)
Cases Visit 1	53.5[a] (± 30.7)	69.8[c] (± 43.1)	12.2 (± 13.1)
Cases Visit 2	38.8[b] (± 14.0)	58.0[d] (± 54.1)	14.3 (± 11.0)
Controls	33.5 (± 16.4)	46.8 (± 17.5)	15.3 (± 31.0)

[1] Visit 2 was 10 days or more after visit 1.

[a] Significantly different from mean peptide YY of controls (p=.0005)

[b] Difference from mean peptide YY of cases at visit 1 of borderline significance (p=.06)

[c] Significantly different from mean TNF-α of controls (p=.0008)

[d] Significantly different from mean TNF-α of cases at visit 1 (p=.0026)

Table 4

Results of a multivariate logistic regression with the outcome variable of a 20% or greater increase in intake when healthy compared to when sick with diarrhea among Peruvian children ages 12 to 71 months and the following modifying variables: peptide YY level when sick with diarrhea, duration of the diarrheal episodes, history of fever, and diarrhea in the 24 hours following the first feeding trial.

	Odds Ratio	Std. Err.	Z	P>|z|	95% Conf. Interval
Peptide YY level visit 1 (sick)	1.058	0.024	2.38	0.017	1.010 – 1.170
Duration of diarrheal episode	1.038	0.279	0.14	0.889	.613 –1.759
History of fever	2.39	2.456	0.85	0.397	.319 –17.915
Diarrhea in 24 hrs. following first feeding trial	3.857	3.708	1.40	0.160	.586 –25.387