Histidine Intake May Negatively Correlate with Energy Intake in Human: A Cross-Sectional Study in Japanese Female Students Aged 18 Years

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Summary L-Histidine (histidine), a precursor of neuronal histamine, has recently been hypothesized to suppress food intake. The association between dietary histidine and energy intake was examined among 1,689 Japanese female students of dietetic courses aged 18 y. Nutrient intakes were assessed over a 1-mo period with a validated, self-administered, diet history questionnaire. Both intake of histidine and the ratio of histidine to protein (histidine/protein) statistically and positively correlated with energy intake. After adjustment for potential non-dietary confounding factors, including body height, body weight, physical activity level, and rate of eating, both the histidine intake and histidine/protein ratio statistically and positively correlated with energy intake (Pearson’s correlation coefficient, \( r = 0.62 \) and 0.12, respectively, \( p < 0.001 \)). Moreover, when protein or protein excluding histidine was additionally included into the covariates in order to minimize the effect of dietary factors and other amino acids, both histidine intake and histidine/protein ratio turned out to show a statistically negative correlation with energy intake (\( r = -0.22 \) and -0.23, respectively, \( p < 0.001 \)). Considering the influence of unavoidable various covariates, we found an inverse association between histidine/protein ratio and energy intake among the young female Japanese students.

Key Words dietary histidine, energy intake, young Japanese women, epidemiology

Hypothalamus neuronal histamine has been shown to regulate food intake through the histamine H1-receptor in the ventromedial hypothalamic nucleus and the paraventricular nucleus (1–3). Recently, it has been hypothesized that L-histidine (histidine), an essential amino acid, might also control food intake through its conversion into histamine (4–6). Histidine preloads delivered by intraperitoneal injection (IP) into rats reduced food intake (7; 8) and increased water intake (8, 9). Although histidine given by the intragastric route showed a low sensitivity to food intake suppression compared to IP, dietary histidine might also play a role in regulating food intake in the short-term, at least partially through the histaminergic pathway (8). However, its physiological importance has not been established.

On the other hand, in human studies, the effect of histidine on food intake was examined in respect to the alterations in zinc metabolism accompanied by anorexia in the 1970s (10–13). Administration of a large dose of histidine induced zinc deficiency, which led to functional losses of taste, smell, appetite, and food intake. Therefore, according to the previous points of view from human studies, feeding suppression has seemed to be caused by alteration of zinc metabolism rather than direct effects of histidine. However, pretreatment with alpha-fluoromethyl histidine (FMH), a specific suicide inhibitor of histamine-synthesizing histidine decarboxylase (HDC), attenuated histidine-induced feeding suppression in animal studies (5, 6). These results support the view that histidine-induced histamine rather than the histidine-induced zinc deficiency affects food intake. Although the available evidence in animal studies strongly suggests the effect of histidine on food intake, in human, only two small observational studies conducted in Japan examined this issue (14, 15).

To examine the association in more detail, we conducted a cross-sectional study using a large and homogenous sample consisting of 1,689 Japanese female dietetic students aged 18 y.

SUBJECTS AND METHODS

Subjects. The subjects were freshmen who entered dietetic courses at 22 colleges and technical schools in Japan in April 1997 (n=2,069). All the questionnaires were distributed between April 7 and 21, 1997. A total of 2,063 students (2,017 women and 46 men) returned the completed questionnaires within 1 wk (response rate, 99.7%). Faculty members of each school checked the submitted questionnaires. When missing replies and/or errors were found, the subjects were requested to answer the questions again. All question-
naires were checked at least once by the local staff and once by the staff of the study center. The entire survey was completed before the end of May.

Assessment of dietary habits. We used a self-administered diet history questionnaire (DHQ). The DHQ is a validated 16-page questionnaire assessing dietary habits in the previous 1 mo. Intakes of 147 food items, 16 nutrients, and total energy intake were calculated using an ad-hoc computer algorithm developed to analyze the questionnaire. The 147 foods from the DHQ were grouped into 17 food groups, mainly according to the food composition tables of Japanese foods, 5th revised edition (16). The DHQ has been validated by comparison to 3-d dietary records. The Pearson's correlation coefficients were 0.48-0.55 for the macronutrients used in the study and 0.48 for energy. Moreover, the mean reported intakes of energy and three macronutrients assessed by the DHQ were close to the reported intakes assessed by dietary records, i.e., within ±3% difference. A more detailed description of the questionnaire, the methods of calculating nutrients, and the validity are given elsewhere (17, 18). We estimated histidine intake using the DHQ attached with the amino acid food composition table (19) and supplemental food composition table of amino acid proposed by Todoriki et al. (20). We examined the validity of histidine intake from the DHQ by comparison with 16-d dietary records (16-d DRs) among Japanese men (n=92) and women (n=92) aged 30-78 y. The mean intake assessed by the DHQ was 2.192±774 mg/d for men and 2.144±628 mg/d for women. The mean intake assessed by 16-d DRs was 2.084±492 mg/d and 1,744±326 mg/d, respectively. Moreover, the Pearson's correlation coefficients were 0.37 and 0.32 for men and women, respectively.

Assessment of lifestyle variables. Lifestyle variables were obtained from the 4-page questionnaire designed for this survey. It included the frequency of sports club activity and smoking habits. The physical activity level was assessed by the monthly frequency of sports club activity without inquiring into the types of sports, their intensity or duration. The subjects who engaged in sports club activity at least once per week in the previous month were defined as 'physically active' and the others as 'sedentary.' Smoking habits were divided into three categories: never-, past-, and current smokers. Current smokers were defined as subjects who reported smoking cigarettes on a regular basis, whereas past-smokers were defined as subjects who quit smoking. Data on birthday, self-reported body weight, height, and rate of eating were obtained from the DHQ. Rate of eating was self-reported according to one of five qualitative categories: 'very slow,' 'relatively slow,' 'medium,' 'relatively fast,' and 'very fast.' The validity of this rating was described in the previous paper (21). BMI was calculated as body weight (kg) divided by the square of body height (m²).

Statistical analysis. We included 1,689 subjects (83.3%) who satisfied the following two criteria in the analysis:

1) Women aged 18 y on the surveyed day (n=1,744);
2) Those with reported energy intake of more than or equal to half of the energy requirement of the lowest physical activity category and less than 1.5 times the energy requirement of the highest physical activity category (22), i.e., the subjects with reported energy intake of 3.0-14.4 MJ/d (n=1,980).

Macronutrient intakes were energy-adjusted using an energy density model, i.e., the percentage of energy intake (%E). Histidine was divided by the protein intake, i.e., histidine/protein (mg/g).

Differences in the means of energy intake between categories were tested by the Student's t test or ANOVA. Multiple regression analysis was performed to examine the effect of daily histidine intake on energy intake. Several confounding factors have been reported for energy intake, such as body height, body weight, physical activity level, and rate of eating (21, 23-25). In this analysis, these non-dietary variables were included in the models as covariates (Model 2). Furthermore, we additionally adjusted for dietary variables such as dietary fiber and protein as dietary confounding factors (Model 3). When histidine intake was used as an independent variable, protein excluding histidine (protein-histidine) was included as a dietary covariate to adjust for possible effects of other types of amino acids. We also computed the partial correlation coefficients between each independent variable and energy intake adjusting for other independent variables.

All statistical analyses were performed using version 8.2 of the SAS software package (SAS Institute, Inc., Cary, North Carolina, USA). A p-value of <0.05 was considered significant.

RESULTS

Table 1 shows the characteristics of the subjects and Pearson's correlation coefficients for each variable with energy intake. The mean BMI±SD for the subjects was 20.8±2.6 kg/m², and 95% of the subjects were classified into the non-obese group (25 kg/m² < BMI). In Pearson's correlation coefficient, a significant correlation with energy intake was observed for body height (p<0.001), sports club activity (p=0.04), and all nutrients described in Table 1, such as macronutrients, total dietary fiber, histidine, protein extracting histidine, and histidine/protein ratio (p<0.001 in all nutrients). As for categorical variables, the mean energy intake was significantly different between the two physical activity levels (p<0.001) and among the five categories of rate of eating (p<0.001).

Table 2 shows the results of multiple regression analysis with energy intake as a dependent variable. Histidine positively correlated with energy intake regardless of the adjustment of non-dietary factors (partial regression coefficient, β=0.002 in Model 1: β=0.002 in Model 2). However, after additional adjustment for dietary factors, such as total dietary fiber and protein excluding histidine, histidine intake turned out to show a negative correlation with energy intake (β=
### Table 1. Physiological characteristics, lifestyle variables, and nutrient intakes of the subjects, and Pearson’s correlation coefficients with energy intake.

|                          | Mean±SD (n=1,689) | Pearson’s correlation coefficient with energy intake | p-value | t-value<sup>a</sup> | p-value |
|--------------------------|-------------------|-----------------------------------------------------|---------|---------------------|---------|
| Body height (cm)         | 158.0±5.2         | 0.13                                                | <0.001  | —                   | —       |
| Body weight (kg)         | 51.8±7.3          | 0.03                                                | 0.22    | —                   | —       |
| Body mass index (kg/m²)  | 20.8±2.6          | -0.03                                               | 0.17    | —                   | —       |
| Sports club activity (d/mo) | 1.7±4.2      | 0.05<sup>c</sup>                                   | 0.04    | —                   | —       |
| Nutrient intake          |                   |                                                     |         |                     |         |
| Energy intake (MJ/d)     | 7.2±2.0           |                                                    |         | —                   | —       |
| Carbohydrate (g/d)       | 234.1±58.8        | 0.86                                                | <0.001  | —                   | —       |
| Fat (g/d)                | 58.0±24.1         | 0.88                                                | <0.001  | —                   | —       |
| Total protein (g/d)      | 63.3±21.0         | 0.86                                                | <0.001  | —                   | —       |
| Total dietary fiber (g/d)| 12.0±4.7          | 0.66                                                | <0.001  | —                   | —       |
| Histidine (mg/d)         | 2081±788          | 0.79                                                | <0.001  | —                   | —       |
| Protein excluding histidine (g/d) | 61.2±20.3     | 0.86                                                | <0.001  | —                   | —       |
| Histidine/protein ratio (mg/g) | 32.6±3.2      | 0.12                                                | <0.001  | —                   | —       |
| Percentage of subjects (%)|                 |                                                     |         |                     |         |
| Physical activity level   |                   |                                                     |         |                     |         |
| Sedentary                | 88                | —                                                   | 3.74    | <0.001              | —       |
| Physically active<sup>d</sup> | 12            | —                                                   | 6.65<sup>f</sup> | <0.001 | —       |
| Rate of eating           |                   |                                                     |         |                     |         |
| Very slow                | 5                 | —                                                   |         |                     |         |
| Relatively slow          | 23                | —                                                   |         |                     |         |
| Medium                   | 36                | —                                                   |         |                     |         |
| Relatively fast          | 32                | —                                                   |         |                     |         |
| Very fast                | 4                 | —                                                   |         |                     |         |
| Experience of dieting<sup>g</sup> |             |                                                     | -0.85   | 0.40                | —       |
| No                       | 40                | —                                                   |         |                     |         |
| Yes                      | 60                | —                                                   |         |                     |         |
| Smoking habits           |                   |                                                     |         |                     |         |
| Current                  | 3                 | —                                                   |         |                     |         |
| Past                     | 3                 | —                                                   |         |                     |         |
| Never                    | 94                | —                                                   |         |                     |         |
| Alcohol intake<sup>h</sup> |             |                                                     | 0.60    | 0.55                | —       |
| Non-drinker              | 81                | —                                                   |         |                     |         |
| Drinker                  | 19                | —                                                   |         |                     |         |

<sup>a</sup> Unless otherwise specified, values are expressed as mean±SD.

<sup>b</sup> Pearson’s correlation coefficient for numerical variable.

<sup>c</sup> Spearman’s correlation coefficient for numerical variable because of the very skewed distribution.

<sup>d</sup> The subjects who took part in sports club activity at least once per week were defined as physically active.

<sup>e</sup> t-value for difference in energy intake between categories (t-test).

<sup>f</sup> F-value for difference in energy intake between categories (ANOVA).

<sup>g</sup> Dieting by intentional reduction of body weight within 1 mo by more than 2 kg.

<sup>h</sup> The subjects who did not drink alcohol during the previous 1 mo were defined as non-drinkers and the others as drinkers.

The results were similar for histidine/protein ($\beta = -0.079$ in Model 3).

### DISCUSSION

In this cross-sectional study of young Japanese women aged 18 y, both crude histidine intake and the ratio of histidine to protein (histidine/protein) negatively and significantly correlated with energy intake, independent of the other dietary factors and the currently known covariates (Pearson’s correlation coefficient, $r=-0.22$, $p<0.001$ for histidine crude value: $r=-0.23$, $p<0.001$ for histidine/protein). One small-scale cross-sectional study with 26 male and 38 female students has also found a negative association between histidine/protein and energy intake, but it was statistically significant only in women ($r=-0.18$ in men and $r=-0.34$, $p<0.05$ in women) (14). Therefore, our findings on the basis of data from a large and homogenous sample suggested that dietary histidine might have a suppressive effect on energy intake in human.

Among previous animal studies, a number of approaches have been tried to clarify the roles of the histamine signaling pathway in the regulation of food intake (5, 6, 26–28). However, the routes of histidine
Several dietary and non-dietary variables have been reported to show an association with energy intake (23-25). However, the previous epidemiologic studies have not taken into consideration the confounding factors that are unavoidable in epidemiologic studies. Therefore, it was nearly impossible to accept the observed negative correlation between histidine and energy intake. On the other hand, we considered the confounding factors in this study (Models 2 and 3 in Table 2). After adjustment for non-dietary factors, both histidine and histidine/protein ratio positively correlated with energy intake ($r=0.62$ and $0.12$, respectively, $p<0.001$). Since physical activity is known to be associated with energy intake, we also conducted the same analyses dividing the subjects into two groups by physical activity level, i.e., sedentary or physically active. However, the results did not materially change (data not shown). As for dietary factors, because both histidine and protein highly correlated with energy intake ($r=0.79$ and $0.86$, respectively), we entered protein intake as a covariate into the multiple regression analyses in order to avoid multicollinearity as much as possible. Moreover, we adjusted for protein excluding dietary histidine in order to minimize a possible effect of other amino acids. Dietary histidine negatively correlated with energy intake after adjustment for dietary and non-dietary confounding factors in our study. These findings provide a new insight into a role of dietary histidine in energy intake in human, although it is not enough. However, we do not know whether this model was fully appropriate for examining the association between dietary histidine and energy intake.

It is most important to understand that self-reported dietary intakes are not entirely free from reporting errors such as underreporting of energy and food intakes (29, 30). In this population, when we examined the validity of energy intake to basal metabolic rate (EI/BMR) (31, 32), 37% of subjects tended to underreport energy intake because their EI/BMR level was below the minimum survival value of 1.27 (33). Few studies have examined the bias in reporting nutrients and types of foods consumed (34, 35). Inconsistent with our results (data not shown), Livingstone and Black revealed that energy from protein tended to be significantly higher in low energy reporters (29). Moreover, the low energy reporters tended to report a higher consumption of "socially desirable" foods such as meat, fish, and vegetables (29). Therefore, the results should be cautiously interpreted in respect to underreporting of energy intake.

Our data are limited by the possibility of error with respect to the measurement of diet and the calculation of dietary histidine intake because of the lack of a comprehensive food composition table of amino acids (19). Therefore, when histidine content of a particular food was unavailable, we used the reported value for a similar food, as proposed by Todoriki et al. (20). This procedure was used for the development of the food composition table of amino acids (19). However, this procedure was far below the quality required for the study. Moreover, the validity of this procedure used for amino acids has not been reported. In addition, the food composition table of amino acid substitution used in this procedure is not available to the public. Nonetheless, we considered this method as the best available at the present time in Japan. The results should be interpreted very cautiously.

Some limitations of our study should be considered in interpreting the results. First, the subjects were not a
randomly sampled general Japanese population but selected female dietetic students aged 18–20 y. Because they were freshmen who entered the dietetic course, the participants in this study might be highly health-conscious. In order to minimize the influence of nutritional education, we finished the survey within almost 1 mo after entrance into the course. Secondly, our findings came from a cross-sectional study. Therefore, it was impossible to evaluate causal association between histidine and energy intake. Moreover, epidemiologic studies cannot clarify the mechanism of the effect of histidine intake on energy intake. Thirdly, the lists of food items in the DHQ, especially those of fishes, were made based on the conventional nutrients such as fats rather than histidine. The histidine intakes obtained by the DHQ in this study might have been less accurate than a direct observation by dietary record. Fourthly, the effective time, duration, and quantity of dietary histidine for regulating energy intake were not strictly clear in this study. In the case of animal studies, histidine was shown to be a regulator of short-term food intake, and the time interval for observation was designed within 24 h (6,8). We might have misunderstood the relationship between histidine and energy intake observed in this study because habitual histidine intake for the previous 1 mo was assessed in our study. Fifthly, although we adjusted for possible confounding variables, unmeasured or unknown confounding dietary factors cannot be excluded.

In conclusion, we found an inverse association between histidine/protein ratio and energy intake among young female Japanese students. Although the central roles of mechanisms for regulation of energy intake have already been established in animal and in vitro studies, the contribution of daily histidine intake is not yet fully understood in humans. Future epidemiologic studies with better study designs are warranted to examine the role of dietary histidine in energy intake in human.

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