The Influence of Various Carbohydrates on the Feeding Pattern of Rats Fed Zinc-Deficient Diets

Hirokazu KUBOTA, Tomoko OHYAMA, Yoko HORIKAWA, Koichi MATSUDA,
Shigeko FUJIMOTO-SAKATA and Nanaya TAMAKI*

Faculty of Nutrition and High Technology Research Center, Kobe Gakuin University,
Nishi-ku, Kobe 251–2180, Japan

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Summary When dextrin, maltose, sucrose, glucose, and fructose were used as a source of carbohydrate in a diet, the food intake of rats fed either a Zn-adequate or Zn-deficient diet was evaluated daily over 28 d. The average food intake of all groups of rats fed the Zn-deficient diet was significantly lower than that of the corresponding groups of Zn-adequate control rats. The food intake of the dextrin group was the highest under both Zn-deficient and Zn-adequate diets, and that of the fructose group was the lowest. All rats of the dextrin, maltose, sucrose, glucose, and fructose groups with the Zn-deficient status showed a characteristic cyclic variation in food intake and fitted well to a Cosinor curve. The values of the mesor, amplitude, and period of the food intake cycles showed significant differences among the groups. The higher intake of the glucose diet than the fructose diet of rats fed a Zn-deficient diet may be related to the different metabolisms of the carbohydrates used, from the comparison of the quantities consumed in the corresponding carbohydrates of Zn-adequate diets.

Key Words zinc deficiency, food intake, body weight change, carbohydrate

Zinc (Zn) deficiency has been claimed to be associated with anorexia, growth retardation, reproductive dysfunction, alopecia, dermatitis, slow wound healing, delayed sexual development and function, and reduced immunocompetence (1, 2). Rats fed a Zn-deficient diet show a characteristic cyclic variation in daily food intake, with a frequency of about 3.5 d (3–10). The cyclic variation of the food intake was analyzed with the four parameters of mesor (the rhythm-adjusted mean), amplitude (maximum and minimum value from the adjusted mean), period (length of one complete cycle), and acrophase (phase of the minimum value), using a personal computer (11–13).

The body-weight of rats fed a Zn-deficient diet also changed (7, 8) daily and was well synchronized with the cycle of the food intake (11–13). The values of mesor and, amplitude and the period of the food intake cycle showed a high correlation to the corresponding parameters of body-weight change (12). The values of amplitude for the food-intake cycle showed a positive correlation to their own day-to-day variations and to the correlation value of their own simulated cycles (13). The cyclic variation in the body-weight change of rats fed a Zn-deficient diet occurred similarly in pair-fed control rats (13). There were no significant differences in the mesors of the body-weight change cycles of Zn-deficient rats and pair-fed control rats (13).

The amplitude of the food-intake cycle decreased with increasing Zn-supplementation, while the mesor

increased (12–14). The requirement for normalizing the food intake of Zn from the diet in rats was about 120 µg/d, which is 8 mg/kg diet (13).

Reducing the protein content of the Zn-deficient diet from 20% to 5% weakened the cyclic pattern of food intake (6, 8, 15). The amplitude of the food-intake cycle of rats fed a Zn-deficient diet containing 5% protein increased twofold by supplementing the diet with L-threonine (15). However, we could not explain the mechanism of the appearance of the cyclical variation in the food intake cycle of rats fed a Zn-deficient diet. When Zn-deficient rats were allowed to freely select from simultaneously provided carbohydrate-, protein-, and fat-rich diets, carbohydrate intake decreased in parallel with the reduction in total intake (16). Several studies have proposed to link the trace metal Zn with changes in taste function (17–19).

The present study investigated the food intake of rats fed Zn-deficient and Zn-adequate diets containing dextrin, maltose, sucrose, glucose, or fructose. The qualitative differences among the various carbohydrates were studied in terms of food consumption and favorite food. We analyzed the food-intake cycle of rats fed a Zn-deficient diet, as the parameters of the cycle among the diets containing various carbohydrates as macronutrients.

MATERIALS AND METHODS

Animals. Male albino rats (Wistar ST strain, weighing 90–100 g) were purchased from Japan SLC Co. Ltd. (Hamamatsu, Japan) and housed in individual screen-bottomed cages in a room maintained at 23±1°C and

* To whom correspondence should be addressed.
E-mail: tamaki@nutr.kobegakuin.ac.jp

Table 1. Compositions of the diets (g/kg).

Ingredients	Zn-adequate	Zn-deficient
Egg Albumin	200	300
Carbohydrate ^a	637	637
Corn oil	100	100
Vitamin mixture ^b	11.7	11.7
Salt mixture (+Zn) ^c	31.3	—
Salt mixture (−Zn) ^d	—	31.3
Cellulose powder	20	20

^a Carbohydrates used were dextrin, maltose, sucrose, glucose, and fructose.

^b Vitamins (mg/kg of diet): retinyl acetate (2.01), cholecalciferol (0.03), α -tocopheryl acetate (58.5), menadi-one (60.8), thiamin hydrochloride (14.0), riboflavin (46.8), pyridoxine hydrochloride (9.4), cyanocobalamin (0.006), ascorbic acid (351), D-biotin (0.23), folic acid (2.34), calcium pantothenate (58.5), *p*-aminobenzoic acid (58.5), niacin (70.2), and choline chloride (2,340).

^c Minerals (+Zn) (g/kg of diet): $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (4.557), KH_2PO_4 (8.050), NaH_2PO_4 (2.927), NaCl (1.459), Ca-lactate (10.983), Fe-citrate (0.995), MgSO_4 (2.244), ZnCO_3 (0.034), $\text{MnSO}_4 \cdot 4\text{H}_2\text{O}$ (0.038), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.009), and KI (0.003).

^d Minerals (−Zn) (g/kg diet): ZnCO_3 was omitted from the above mixture.

50% humidity with controlled lighting conditions (lights on from 07:00 to 19:00). The animals were fed a commercial stock diet of Oriental MF (Oriental Yeast Ltd., Tokyo, Japan) and given tap water ad libitum for 1 wk before the experiment to allow acclimatization to the new environment. Acclimatized rats showing progressive weight gain were selected and separated into groups of 20 animals. Food intake and body weight were determined daily between 09:00 and 11:00. The rats were given the experimental diet for 4 wk, and sacrificed between 09:00 and 11:00 under anesthesia with diethyl ether. All procedures were performed in accordance with the Kobe Gakuin University Guide-lines for the Care and Use of Laboratory Animals.

Diet. The compositions of the Zn-deficient and Zn-adequate diets are shown in Table 1. The contents of Zn in the Zn-deficient dextrin, maltose, sucrose, glucose, and fructose diets from the mean values of three separate experiments were 0.95, 0.90, 1.20, 0.75, and 0.81 mg/kg diet, respectively.

Chemicals. All chemicals used were of analytical grade and were purchased from Nacalai Tesque (Kyoto, Japan) unless otherwise stated. Animal feed was obtained from Oriental Yeast Ltd. Maltose, sucrose, glucose, and fructose were from Nacalai Tesque. Glucose and fructose used as dietary ingredients were D-form.

Zn content. A 1-g portion of each test diet was heated for 48–72 h in a muffle oven at 450°C. After the sample cooled, 2 mL of 1 M HCl was added, and the digestates were heated and diluted with double-distilled deionized water. In the case of serum, it was diluted 1:4 with 0.83 M HCl and incubated for 30 min at about 4°C. After brief centrifugation (3,000 rpm for 10 min), the

supernatant was removed and used for Zn analysis. The stock Zn and sample solution were analyzed by atomic absorption spectroscopy with a Hitachi Z-5300 Polarized Zeema Atomic Absorption Spectrophotometer (Hitachi Ltd., Tokyo, Japan) at 213.8 nm.

Evaluation of food intake and body-weight changes. Food intake and body-weight change data from Zn-deficient rats were analyzed by the “Cosinor” method (11–13). Food intake (*F*) and body-weight change (ΔB) on day *t* were determined using the following equation:

$$F \text{ (or } \Delta B) = M + A \cos(2\pi t / \tau + \phi)$$

where *M*, *A*, τ , and ϕ represent the mesor (the rhythm-adjusted mean), amplitude (maximum and minimum value of the adjusted mean), period (length of one complete cycle), and acrophase (phase of minimum value), respectively. The experimental data were fitted to the above equation by the nonlinear least-squares method (20), and the four parameters, *M*, *A*, τ , and ϕ , were calculated using subroutine analysis (21).

On the other hand, as the data from Zn-adequate rats were not fitted to the above equation, comparisons among groups were evaluated between the mean variation of daily food intake and body-weight change. The variation was calculated for each rat with the standard deviation of the estimate of the day-to-day variation in food intake and body-weight change for 28 d, and the group means presented.

Statistical analysis. Values for food intake and body-weight change are expressed as means $\pm$ SD. One-way analysis of variance (ANOVA) was used to compare the groups. When a significant difference ($p < 0.05$) was found between groups, the statistical significance of the difference between values was assessed using Duncan's multiple comparison test and considered significant at $p < 0.05$. When we made a comparison between groups, the statistical significance of differences between values was assessed by a Student's *t*-test.

RESULTS

Effect of carbohydrates on the food intake and body-weight change of rats fed either Zn-adequate or Zn-deficient diet

The carbohydrates used as macronutrients were dextrin, maltose, sucrose, glucose and fructose, and the food intake and body weight were estimated daily. The mean values and the day-to-day variations (variability) in food intake and body-weight change for 4 wk are summarized in Tables 2 and 3. The food intake and body-weight change of Zn-deficient rats were significantly less than those of the Zn-adequate control rats throughout the 4-wk study. However, the values of variability from mean food intake and body weight change in each group of Zn-deficient rats increased by about 2-fold compared to those in the Zn-adequate control groups (Tables 2 and 3). Among the Zn-adequate control groups throughout the 4 wk, the dextrin group showed the greatest appetite, while the fructose group showed the smallest appetite. The differences in food intake of Zn-deficient rats among carbohydrates follow those of Zn-adequate rats. In rats fed the Zn-adequate control diet, the dextrin group showed the most effec-

Table 2. Effect of carbohydrates on the food intake of rats fed either a Zn-adequate or Zn-deficient diet.

	Zn-adequate		Zn-deficient	
	Food intake (g/d)	Variation in food intake (g/d)	Food intake (g/d)	Variation in food intake (g/d)
Dextrin	15.6±1.7 ^c	2.2±0.5 ^c	10.5±1.5 ^{**d}	4.7±0.7 ^{**c}
Maltose	14.1±1.4 ^b	2.1±0.4 ^b	9.4±0.6 ^{**c}	4.1±0.6 ^{**b}
Sucrose	13.7±1.1 ^b	2.0±0.5 ^b	8.4±0.7 ^{**a,b}	3.9±0.4 ^{**b}
Glucose	13.7±1.0 ^b	1.7±0.4 ^a	8.5±0.9 ^{**b}	3.5±0.4 ^{**a}
Fructose	12.7±0.4 ^a	2.2±0.4 ^c	7.9±1.0 ^{**a}	3.4±0.7 ^{**a}

The values of food intake were from 20 rats for each group. The variations in food intake are given as standard deviations from the mean of 28 d of data for the groups. The values are shown as means with standard deviations. Values in each column not sharing a common superscript letter are significantly different (*p*<0.05).

** Mean value was significantly different from that of the control group, *p*<0.01.

Table 3. Effect of carbohydrates on the body-weight change of rats fed either a Zn-adequate or Zn-deficient diet.

	Zn-adequate		Zn-deficient	
	Weight change (g/d)	Variation in weight change (g/d)	Weight change (g/d)	Variation in weight change (g/d)
Dextrin	5.1±0.6 ^c	3.6±1.2 ^c	2.4±1.0 ^{**c}	8.1±1.6 ^{**c}
Maltose	4.0±1.1 ^b	2.7±0.4 ^a	1.0±0.3 ^{**b}	6.2±0.8 ^{**b}
Sucrose	4.0±0.7 ^b	3.0±0.7 ^{a,b}	0.5±0.5 ^{**a}	6.4±0.8 ^{**b}
Glucose	3.7±0.8 ^b	2.5±0.6 ^a	0.9±0.5 ^{**a,b}	5.4±0.7 ^{**a}
Fructose	3.2±0.4 ^a	3.3±0.7 ^{b,c}	0.5±0.5 ^{**a}	5.2±0.7 ^{**a}

The values of body-weight change were from 20 rats for each group. The variations in food intake are given as standard deviations from the mean of 28 d of data for the groups. The values are shown as means with standard deviations. Values in each column not sharing a common superscript letter are significantly different (*p*<0.05).

** Mean value was significantly different from that of the control group, *p*<0.01.

tive growth and the fructose group the lowest (Table 3). The body-weight change of rats fed the Zn-deficient diet was retarded as compared to those of the corresponding carbohydrate groups fed the Zn-adequate diet. The variation in food intake and body-weight change of rats fed the Zn-deficient diet containing each carbohydrate increased about 2- to 4-fold more and followed a cyclic variation. Dextrin was the most favorable for the growth of rats fed either the Zn-adequate diet or the Zn-deficient diet. Fructose and sucrose showed a lower contribution to growth than maltose for Zn-deficient rats.

In rats fed the Zn-adequate diet, the food intake of all groups increased throughout the 4 wk, but that in the groups fed the Zn-deficient diet was not affected by age except for the maltose group (data not shown). The significant difference of variation in the food intake of rats fed the Zn-deficient diet and the control rats fed the Zn-adequate diet appeared in the 1st week and the values of variation in food intake increased with age except for the dextrin-group (data not shown).

The Zn level in the serum showed a significant decrease in the Zn-deficient diet groups (Fig. 1). However, none of the carbohydrates used in the Zn-deficient diets showed any significant differences among the groups.

Fig. 1. Zn concentration in serum. Carbohydrates administered to rats fed Zn-adequate (white column) and Zn-deficient (dotted column) diets. Values are means, with their standard errors indicated by the vertical bars. ** *p*<0.01 compared with the corresponding Zn-adequate control.

Table 4. Effect of dietary carbohydrates on the parameters of food intake and body-weight change cycles of rats fed the Zn-deficient diet.

	M (g/d)	A (g/d)	τ (d)	ϕ (radian)
Food intake				
Dextrin	10.4±1.5 ^c	5.3±1.1 ^c	3.5±0.3 ^a	-0.4±2.13
Maltose	9.4±0.5 ^b	4.5±0.9 ^a	3.8±0.2 ^b	0.1±2.2
Sucrose	8.3±0.7 ^a	4.4±0.7 ^b	3.8±0.2 ^b	0.8±2.5
Glucose	8.5±0.9 ^a	3.6±0.8 ^a	3.7±0.2 ^b	0.4±2.4
Fructose	7.9±1.0 ^a	4.0±0.7 ^{a,b}	4.0±0.3 ^c	-0.1±2.2
Body-weight change				
Dextrin	2.3±1.0 ^c	8.7±2.2 ^c	3.5±0.4 ^a	-0.4±2.2
Maltose	1.0±0.3 ^b	6.6±1.5 ^b	3.7±0.2 ^b	0.8±2.0
Sucrose	0.5±0.6 ^a	6.8±1.4 ^b	3.7±0.2 ^b	1.6±2.0
Glucose	0.8±0.5 ^{a,b}	5.6±1.3 ^a	3.6±0.2 ^{a,b}	0.2±2.4
Fructose	0.6±0.5 ^a	5.6±0.9 ^a	3.9±0.3 ^c	1.2±1.8

Each rat was fed the experimental diet for 28 d under the conditions described in Materials and Methods. Food intake (F) or body-weight change (ΔB) in the previous 24-h period at day t : F (or ΔB) = $M + A \cos(2\pi t/\tau \pm \phi)$. Each value is the mean $\pm$ SD. Values in each column not sharing a common superscript letter are significantly different ($p < 0.05$).

Comparison of cyclical food intake cycles of rats fed Zn-deficient diets containing dextrin, maltose, sucrose, glucose, or fructose

When dextrin, maltose, sucrose, glucose, or fructose were used as a source of carbohydrates in the Zn-deficient diet, rats fed all kinds of carbohydrates showed a characteristic cyclic variations in food intake. However, the food intake of rats fed the Zn-adequate diet did not show any signs of cyclic variation. The body-weight changes of the Zn-deficient rats also showed cyclic variations and were well synchronized with food intake.

The findings for food intake and body-weight change in the previous 24-h period for the Zn-deficient rats were analyzed. We evaluated the parameters of both cycles of rats fed the Zn-deficient diet containing dextrin, maltose, sucrose, glucose, and fructose as shown in Table 4. We found significant differences in the parameters among the groups. The mesor of the food intake and body-weight cycles was highest in the dextrin group, followed by the maltose group, and was lowest in the sucrose, glucose, and fructose groups. The amplitude of the food intake and body-weight change cycles was highest in the dextrin group, followed by the disaccharide groups. The periods for both groups were expanded in the fructose group. The acrophase of both cycles showed high individual variation and there were no significant differences among the groups, based on reflections of variations in the rate of initial onset of the deficiency (11, 12).

DISCUSSION

The findings reported here provide characteristic evidence that qualitative differences in dietary carbohydrates in rats could be found in the food intake and body-weight change between groups fed Zn-deficient diet and Zn-adequate diets. Here, we found that, in the fructose group, the food intake of rats fed the Zn-adequate diet was lower than that of the glucose group as

reported previously (22, 23). In the case of rats fed the Zn-deficient diet, the food intake in the fructose group was also lower than that in the glucose group (Table 2). The body-weight changes in the fructose group of both the Zn-adequate control rats and the Zn-deficient rats showed significant differences compared with those of the glucose group. The molecular formula of fructose is the same as glucose. The osmotic pressure in digestive tracts after feeding the diets may not have shown any significant difference between the fructose- and glucose-diet groups. Fructose can be phosphorylated by either hexokinase (EC 2.7.1.1) or ketohexokinase (EC 2.7.1.3) and is then catabolized via the glycolytic pathway. Comparisons of K_m values and V_{max} of hexokinase and ketohexokinase suggested that ketohexokinase has a more important role for the catabolism of fructose (24). The different catabolic pathway between glucose and fructose may affect the food intake of rats under Zn-deficient conditions in addition to Zn-adequate conditions.

The daily food intake and body-weight change of the dextrin group of rats under Zn-deficient conditions as well as those under Zn-adequate conditions showed higher values than those of the maltose-, sucrose-, glucose-, and fructose-groups. These results suggest that dextrin may weaken the osmotic stress in the small intestine more than disaccharides and monosaccharides under both Zn-deficient and Zn-adequate conditions, and that the dextrin diet may be favorable to be an energy source.

All values on the day-to-day variation of food intake of rats fed dextrin-, maltose-, sucrose-, glucose-, and fructose-Zn-deficient diets were higher than the corresponding variation in the Zn-adequate carbohydrate diet groups, and larger variations followed the appearance of the cyclic phenomena of food intake and body-weight change. Cyclical food intake appeared not to be caused by excess food consumption, but rather by a periodic reduction in the rat's appetite (13). When the

Zn-deficient rats were fed a glucose or fructose diet at the top of the food intake cycle, they ate these monosaccharides in smaller amounts than the disaccharides of maltose and sucrose.

The periods of food intake and body-weight change cycles of the rats fed the Zn-deficient fructose diet were expanded. Harper et al. (25), Cohen and Teitelbaum (26), and Chalvarjian and Stephens (27) suggested that the livers of animals fed a diet containing either sucrose or fructose contain more lipids than those of animals fed a diet containing starch, dextrin or glucose. Aoyama et al. (28, 29) proposed that feeding a protein-repletion diet containing fructose to protein-depleted rats results in marked lipid accumulation in the liver. Fructose degrades to dihydroxy acetone phosphate and D-glyceraldehyde via D-fructose 1-phosphate, and is further metabolized through glycolysis. Therefore, the expansion of the food-intake cycle period may depend on the glycolytic pathway of fructose. A retardation of the fructose diet was found under Zn-deficient conditions as well as Zn-adequate conditions.

The NaCl preference in rats fed the Zn-deficient diet was significantly greater than in pair-fed controls or in rats fed the Zn-supplemented diet ad libitum (30). Mc Connell and Henkin (30) proposed that the NaCl preference was related to the amount of dextrin in the diet. The carbohydrate preference in rats fed Zn-deficient diets is not well established. In the present study, we found that the food intake of the fructose-supplemented diet in rats fed the Zn-deficient diet was significantly less than that of the glucose, maltose, or sucrose diet. However, the daily food intake of the fructose diet in rats fed the Zn-adequate control diets was also significantly less than that of the other saccharide diets. These results suggest that the lower intake of the fructose-diet rats fed the Zn-deficient diet may not depend on retardation of appetite and altered taste perception. The plasma Zn concentration in rats falls by approximately 40% after 1 d on a Zn-deficient diet (31). Therefore, the decreased level of plasma Zn in rats fed the Zn-deficient diet may significantly increase the variability of food intake at an early stage and show signs of periodical retardation of food intake.

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