Effect of Dietary Carbohydrate and Phenotype on Sucrase, Maltase, Lactase, and Alkaline Phosphatase Specific Activity in SHR/N-*cp* Rat (43544)

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Abstract. **The obese spontaneous hypertensive rat/NIH-corpulent (SHR/N-*cp*) rat exhibits some of the metabolic and pathologic alterations associated with non-insulin-dependent diabetes mellitus and hypertension. The current study was conducted to investigate the influence of phenotype (*ob* versus *ln*) and source of dietary carbohydrate (sucrose versus starch) on intestinal sucrase, maltase, lactase, and alkaline phosphatase activity in SHR/N-*cp* rats. For 3 months, lean and obese male SHR/N-*cp* rats were fed isocaloric diets containing as the sole source of carbohydrate either 54% cooked corn starch or sucrose.**

Serum and urine markers for diabetes were observed in obese rats. Wet weight and length of intestines were significantly increased in obese rats compared with lean littermates. Among the intestinal enzymes measured, statistical tests confirmed that sucrase activity was significantly increased ($P < 0.01$) by both phenotype (*ob* > *ln*) and feeding a sucrose diet. Diet alone (sucrose > starch) significantly increased ($P < 0.05$) maltase activity in obese rats, but had no effect on lean rats. Lactase activity was significantly higher ($P < 0.05$) in obese sucrose-fed rats compared with obese starch-fed and/or lean littermates.

Statistical tests revealed that intestinal alkaline phosphatase activity was significantly altered ($P < 0.05$) by both phenotype and diet. Intestinal alkaline phosphatase was higher in starch-fed lean rats compared with lean littermates fed sucrose and to starch or sucrose-fed obese rats. These results are not indicative of a simple, nonspecific increase in intestinal enzyme activity, since the effects observed in intestinal alkaline phosphatase contrast the effects observed in intestinal sucrase, maltase, and lactase activity.

These results indicate that both phenotype and diet alter structural and enzymatic intestinal activities of SHR/N-*cp* rats. Distinct variations in the observed intestinal enzymatic activities suggest that these enzymes are under the control of genetic, hormonal, and dietary factors. Rationale for these differences are discussed.

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Non-insulin-dependent diabetes mellitus ([NIDDM] Type II) is an increasingly prevalent disease in the United States (1). Furthermore, carbohydrates, especially simple sugars, have been reported to alter one of the metabolic risk factors for NIDDM, insulin response (2).

Changes in intestinal structure and function have been reported in insulin-dependent diabetes ([IDDM] Type I) in chemically or drug-induced diabetic rats (3, 4). Increases in intestinal length and mass, enhanced disaccharidase activity, and transport of monosaccharides have been reported in both rats and mice with drug-induced IDDM (4, 5). In nondiabetic as well as drug-induced diabetic rodents, both the amount and specific activity of intestinal disaccharidases are influ-

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enced by type and amount of carbohydrate consumed (3, 6–8).

The primary genetic rodent model used to study IDDM and NIDDM is the mouse (9–11). Relatively little is known about physical characteristics and intestinal mucosal enzyme activity of the brush border membrane in spontaneous IDDM or NIDDM diabetic rat models such as the spontaneous hypertensive rat/NIH-corpulent (SHR/N-*cp*) rat.

The corpulent, or *cp*, gene of the SHR/N-*cp* rat is an autosomal recessive mutation that arose spontaneously after several generations of inbreeding of a female SHR rat with a male, normotensive Sprague-Dawley rat. Rats that are homozygous (*cp/cp*) are obese and those that are heterozygous (*cp*/+) or homozygous-normal (+/+) are lean. Descriptions of this rat and other rodent models used to study obesity and diabetes have recently been published (12). The obese or corpulent SHR/N-*cp* rat is mildly hypertensive, hyperinsulinemic in the basal state, and, in response to an oral glucose challenge, both hyperinsulinemic and hyperglycemic. Obese SHR/N-*cp* rats also exhibit hyperlipidemia and glucosuria and develop proteinuria (13). Lean rats are more severely hypertensive than obese rats and develop some impairment of glucose tolerance much later in life. Decreased binding of both insulin and glucagon to liver plasma membranes has also been reported in obese rats compared with lean littermates (14). Pathologic changes associated with NIDDM observed in SHR/N-*cp* obese rats include, e.g., marked hyperplastic pancreatic β cells (15), fatty livers (16), and nephropathy (17). These changes are observed to a much lesser degree in lean SHR/N-*cp* rats. Pancreatic enzyme activities, including amylase, nonspecific lipase, chymotrypsinogen, and trypsinogen, are elevated in obese SHR/N-*cp* rats compared with lean littermates (18).

In this study, the activity of three intestinal brush border disaccharidases—sucrase-isomaltase (EC 3.2.1.48-100), maltase-glucoamylase (EC 3.2.1.20), and lactase-phlorizin hydrolase (EC 3.2.1.23-46)—as well as intestinal and serum alkaline phosphatase (EC 3.1.3.1) were measured in obese and lean SHR/N-*cp* rats. The cause(s) of hyperglycemia in obese SHR/N-*cp* rats is not fully understood (12). This study was conducted to determine whether intestinal dissacharidases or environmental factors, such as type of dietary carbohydrate consumed, may contribute to obesity-associated pathogenesis of hyperglycemia and hyperlipidemia expressed in the obese SHR/N-*cp* rat. Disaccharidase activities will be referred to as sucrase, maltase, and lactase.

Methods

Materials. Horseradish peroxidase (EC 1.11.1.7), Type II, 220 units/mg; *O*-dianisidine di HCl, glucose oxidase (EC 1.1.3.4), Type VIII-S, 125 units/mg; and *p*-nitrophenyl phosphate were all obtained from Sigma Chemical Co., St. Louis, MO. *p*-Nitrophenol and all other general chemicals were obtained from Fisher Scientific, Silver Spring, MD. The insulin radioimmunoassay kit used to quantitate serum insulin was purchased from Amersham, Arlington Heights, IL. The sources and preparation of dietary ingredients have been published previously (19, 20).

Animals. Obese (*cp/cp*) and lean (?/+) male SHR/N-*cp* rats (5–6 weeks old) were obtained from Dr. Carl Hansen of the Small Animal Section, Veterinary Resources Branch, National Institutes of Health, Bethesda, MD. The rats were housed individually in stainless steel cages in a laminar, negative air flow system at 20–24°C and at a relative humidity of 40–50%. A reversed 12:12-hr light:dark cycle (2200:1000 hr light) was maintained throughout the study.

Diets. Upon arrival, 10 obese and 10 lean rats were randomly assigned to diets containing 54% carbohydrate as either cooked corn starch or sucrose. The remainder of each diet consisted of 10% vitamin-free casein, 10% lactalbumin, 5.9% cellulose (Alphacel non-nutritive bulk), 4% corn oil; 4% beef tallow, 4% lard, 4% hydrogenated coconut oil, 3.1% AIN mineral mix (prepared without sucrose), and 1% vitamin fortification mix (20).

Analysis of Blood and Urine Samples. After 12 weeks of feeding, fasting levels of insulin and glucose were determined. For the 1-hr responses, glucose and insulin levels were determined after an oral glucose load of 250 mg/100 g body wt in the early period of the dark cycle. Urinary glucose was measured in nonfasted rats housed in metabolic cages, using urine collected for a 17-hr period beginning 6 hr into the dark cycle (20). Toluene was added to the urine as a preservative.

Intestinal Cell Isolation. Rats (18 weeks old) were fasted overnight before decapitation and exsanguination. The small intestine from the pylorus to the ileocecal junction was quickly removed and stripped of adherent fat and connective tissue, and the length and wet weight of the cleaned intestine were determined. The first 5 cm of intestine, from the pylorus to the ligament of Treitz, was discarded and the next 10 cm of jejunum was transected and used for the isolation of intestinal cells. This 10-cm gut segment was flushed with 30 ml of iced physiologic saline containing 1 m*M* dithiothreitol, 0.001% soybean trypsin inhibitor, 1 mg/ml of leupeptin and 10,000 kallikrein inactivator units/liter of Trasylol. The everted gut segment was blotted on tissue paper prior to immersion in cell isolation buffer. The cell isolation procedure utilized two sequential incubations in divalent chelating buffers, referred to here as Buffer A and Buffer B (21). Each segment was incubated first for 10 min in oxygenated Buffer A (1.5 m*M* KCl, 96 m*M* NaCl, 27 m*M* sodium citrate, 8

m*M* KH_2PO_4, and 5.6 m*M* Na_2HPO_4 [pH 7.3]) at 37°C in a Dubnoff metabolic shaker. The segment was then incubated in oxygenated Buffer B (137 m*M* NaCl, 2.69 m*M* KCl, 8.1 m*M* Na_2HPO_4, 1.47 m*M* KH_2PO_4, 1.5 m*M* EDTA, and 0.5 m*M* dithiothreitol [pH 7.4]) for an additional 45 min. This technique released cells from villus tip to midvillus region (21). Dislodged cells were collected by centrifugation at 300*g*. Pelleted cells were then washed twice in Dulbecco's phosphate-buffered saline, resuspended in phosphate-buffered saline (20% w/v), and divided into small aliquots for storing at −80°C.

Cells were thawed only once. Preliminary studies suggested that repeated freezing and thawing decreased dissacharides 5% each thawing. Protein was determined by the Lowry method on isolated sonicated cells solubilized in 0.5 *N* NaOH, using bovine serum albumin as a standard (22).

Enzyme Assays. Sucrase-isomaltase (EC 3.2.1.48-10), maltase-glucoamylase (EC 3.2.1.20), and lactase-phlorizin hydrolase (EC 3.2.1.23-46) were measured by the method of Dahlqvist (23) using the following substrates: 0.03 *M* sucrose, 0.015 *M* maltose, and 0.06 *M* β-lactose in 0.1 *M* sodium maleate buffer (pH 6.0). The lactase assay contained *p*-hydroxymercuribenzoate to inhibit any residual lysosomal acid β-galactosidase activity (24). All enzyme assays were measured under conditions of linear activity. Assays were terminated by boiling 3 min. Controls, boiled at zero time, were otherwise treated in a manner identical to unknowns. Because maltose is degraded by both maltase and sucrase, maltase activity was corrected for contribution by sucrase as described by Morrill *et al.* (8). Enzyme activity is reported as specific activity. One unit of disaccharidase activity (sucrase and maltase) is defined as the amount of enzyme that hydrolyzes 1 μmol of substrate/10 min under assay conditions. Lactase activity is defined as nmol of substrate hydrolyzed/10 min.

Alkaline phosphatase (EC 3.1.3.1) activity was measured in both the intestinal homogenates (21) and the serum (19) by quantitating the release of *p*-nitrophenol from the substrate *p*-nitrophenylphosphate (18 m*M*) at 37°C, in a 50 m*M* glycine buffer (pH 9.7) containing 5 m*M* $MgCl_2$ and 1 m*M* $ZnSO_4$ using a recording Gilford spectrophotometer. A unit of intestinal alkaline phosphatase activity is defined as one μmol of substrate hydrolyzed/10 min. A unit of serum alkaline phosphatase activity was defined as one μmol of substrate hydrolyzed/hr. Disaccharidase and alkaline phosphatase activity are reported as specific activity (per mg cell protein).

Radioimmunoassay for Insulin. Serum insulin levels were determined by a radioimmunoassay method that used human insulin as a standard.

Statistical Analysis. Data were examined for homogeneity of variance and normality (25, 26). For those variables (fasting and response serum insulin and response serum glucose) where the assumption of homogeneity of variance was not met, a logarithmic transformation was successful and the analysis of variance was conducted on the transformed data. When the results of these analyses were reported, the antilog of the log mean (known as the geometric mean) was also reported to provide a mean value on the original scale of measurement (25, 26). The model included the main effects of phenotype (obese and lean) and diet (starch and sucrose) and the interaction effect in a 2 × 2 factorial analysis of variance. In this equally replicated, 2 × 2 factorial, the SE of the four treatment means, the main effects, and the interaction effect are identical. Therefore, in the Tables and Figures only one SE is given, since it applies to all means and effects for a given variable.

Results

Body weight was significantly greater (+203 g) for obese than lean rats (Table I). Weight (+1.55 g) and

Table I. Body Weight and Weight and Length of Intestine of Male SHR/N-*cp* Rats Fed Sucrose or Starch

	Lean		Obese			Statistical comparison[b]		
	Starch	Sucrose	Starch	Sucrose	SE[a]	Phenotype (*ob-ln*)	Diet (sucrose-starch)	Phenotype × diet
Body wt (g)	431[c]	451	618	669	13	203***	36**	16
Intestine wt (g)	6.4	7.0	7.6	8.9	0.28	1.55***	0.95**	0.35
Intestine length (cm)	96	97	103	104	1.5	7.0**	1.0	0
Relative intestinal size (g/100 g body wt)	1.45	1.55	1.23	1.41	0.065	−0.175**	0.137*	0.04
Relative intestinal length (cm/100 g body wt)	21.9	21.5	16.8	15.5	0.50	−5.55***	−0.85	−0.45
Intestinal cell protein mg in 20% w/v homogenates	4.5	5.5	5.6	7.7	0.4	−1.60**	1.50**	0.60

[a] SE is also equal to SE of effects.
[b] Numbers represent arithmetic differences between the means. Effect significant at: *P <0.05, **P <0.01, ***P <0.001.
[c] Means for five rats/group.

Table II. Glucose, Insulin, and Intestinal Cell Protein Values from Male SHR/N-*cp* Rats Fed Sucrose or Starch

	Lean		Obese		SE	Statistical comparison[a]		
	Starch	Sucrose	Starch	Sucrose		Phenotype (*ob-ln*)	Diet (sucrose-starch)	Phenotype × diet
Serum glucose (mmol/liter)								
Fasting	5.8[b]	6.5	6.4	6.3	0.31[c]	0.20	0.30	−0.40
Response	0.91[d] (9)[f]	0.98 (9.4)	1.24 (17.15)	1.34 (21.6)	−1.23[e]	0.35***	0.09*	0.04
Serum insulin (pmol/liter)								
Fasting	2.45[d] (282)	2.54 (347)	3.29 (1932)	3.23 (1644)	0.93[e]	0.76***	0.02	−0.08
Response	2.72[d] (520)	2.86 (718)	3.54 (3467)	3.48 (2992)	0.89[e]	0.72***	0.04	−0.10**
Urine glucose (mg/17 hr)	1.02[b]	0.72	130	233	32.6[c]	181***	51	52

[a] Numbers represent arithmetic differences between the means. Effect significant at: *P <0.05, **P <0.01, ***P<0.001.
[b] Means for five rats/group.
[c] SE is also equal to SE of effects, since the above is a 2 × 2 factorial.
[d] Log mean.
[e] Log SE.
[f] The numbers in parentheses are geometric means.

Table III. Sucrase, Maltase, and Lactase Activity in Male SHR/N-*cp* Rats Fed Sucrose of Starch

	Lean		Obese		SE[a]	Statistical comparison[b]		
	Starch	Sucrose	Starch	Sucrose		Phenotype (*ob-ln*)	Diet (sucrose-starch)	Phenotype × diet
Sucrase[c]	0.31[d]	0.61	0.54	1.19	0.09	0.41*	0.48**	0.38**
Maltase[c]	2.4	2.5	2.2	3.0	0.19	0.15	0.45*	0.35*
Lactase[c]	152	130	136	300	40	77	71	93*

[a] SE is also equal to SE of effects, since the above is a 2 × 2 factorial.
[b] Numbers represent arithmetic differences between the means. Effect significant at: *P <0.05, **P <0.01, ***P <0.001.
[c] One unit of sucrase and maltase activity is defined as μmol/10/mg protein, and one unit of lactase is defined as one nmol/10 min/mg protein.
[d] Means for five rats/group.

length (+7.0 cm) of intestines were also significantly greater in obese than in lean rats. Sucrose-fed rats had significantly greater body weight (+35.5 g) and intestinal weight (+0.95 g) averages across phenotypes. Relative intestinal size (−0.175 g/100 g) and relative intestinal length (−5.55 cm/100 g) were significantly smaller in obese rats compared with lean rats. Intestinal cell protein (20% w/v homogenate of isolated cells) was significantly higher (+1.60 w/v) in obese rats compared with lean rats. Consumption of sucrose, regardless of phenotype, significantly increased intestinal cell protein (+1.50 w/v) concentration.

Obese and lean rats fed either starch or sucrose diets were normoglycemic in the fasted state (Table II). Obese rats were, however, hyperglycemic in response to a glucose challenge and had glucosuria. Serum glucose response levels were two times greater in obese than in lean rats. Fasting serum insulin levels were approximately six times greater ($P < 0.01$) in both starch- and sucrose-fed obese rats compared with lean littermates.

Disaccharidase activities were generally elevated in obese rats, especially when they consumed the sucrose diet. Differences in phenotype were clearly expressed by obese sucrose-fed rats in which sucrase-specific enzyme activity was approximately two times higher than that of lean sucrose-fed rats (Table III). Lean, starch-fed SHR/N-*cp* rats had significantly less sucrase activity when compared with lean sucrose-fed rats, but the difference between sucrose-fed and starch-fed lean rats was much smaller than the corresponding difference in obese rats. This difference between lean and obese animals in sucrase activity response to sucrose resulted in a significant interaction between diet and phenotype ($P < 0.01$).

Maltase-glucoamylase (maltase) activity was nearly three times higher than sucrase activity in obese rats (Table III). The interaction of phenotype by diet is seen

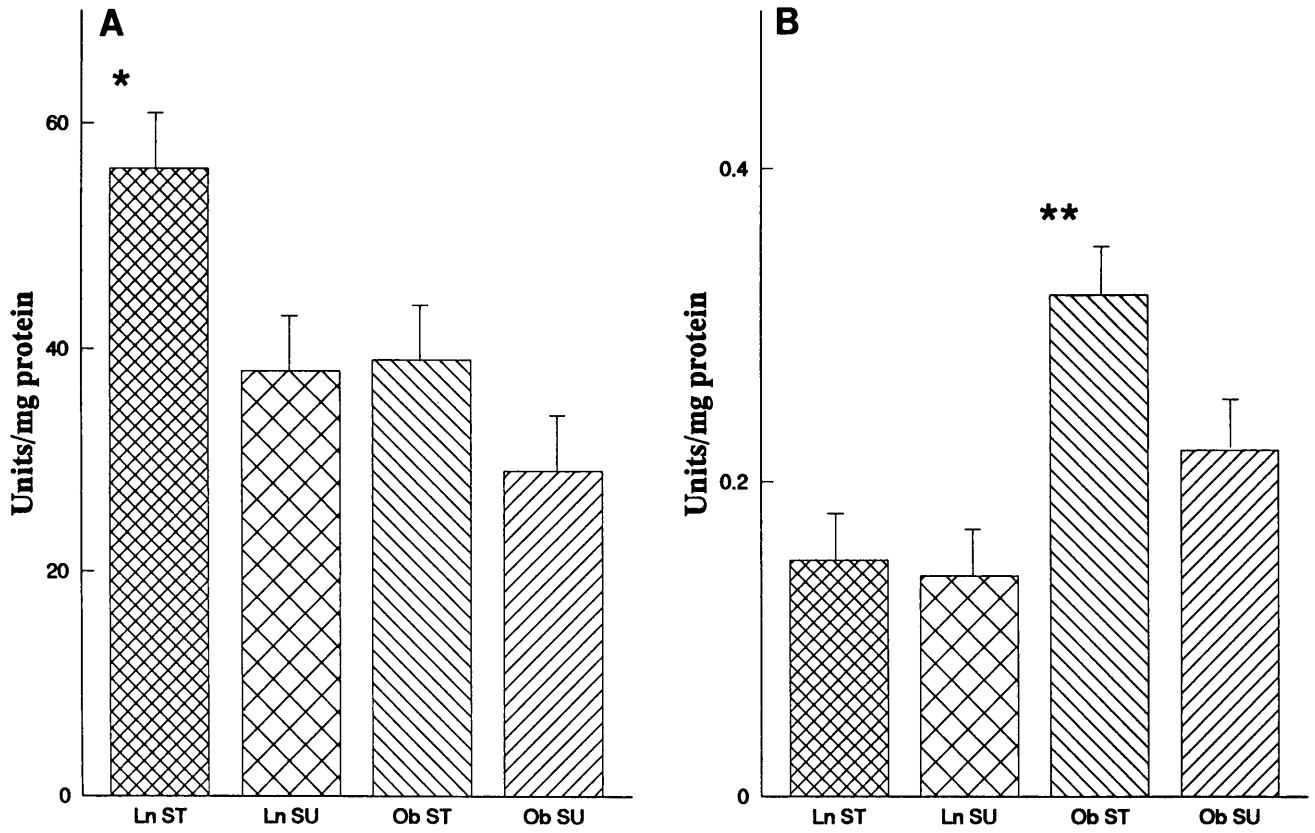

Figure 1. Effect of phenotype and diet on intestinal and serum alkaline phosphatase activity in male SHR/N-*cp* rats. (A) A unit of intestinal alkaline phosphatase is defined as μmol/10 min/mg of protein and represents the mean of five animals/group. Effects are significant at $^*P < 0.05$. 2 × 2 Factorial effects (numbers represent arithmetic differences between the means): phenotype (*ob-ln*), 13.0*; diet (SU-ST), 14.2*; phenotype × diet +4.0. (B) A unit of serum alkaline phosphatase is defined as μmol/hr/mg of protein and represents the mean of five animals/group. Effect is significant at $^{**}P < 0.01$. 2 × 2 Factorial effect (numbers represent arithmetic differences between the means): phenotype (*ob-ln*), 0.12**; diet (SU-ST) −0.05; phenotype × diet, 0.04.

as a greater diet difference in obese rats as compared with lean rats, with the largest response observed for sucrose-fed obese rats ($P < 0.05$).

Of the three disaccharidases assayed, lactase-phlorizin hydrolase (lactase) had the lowest activity. There was, however, a significant interaction between diet and phenotype in lactase activity (Table III). Lactase activity was similar for lean rats regardless of diet, but in obese rats, lactase activity was significantly greater for sucrose-fed rats than for starch-fed rats ($P < 0.05$).

In contrast, alkaline phosphatase, another hydrolytic enzyme located within the brush border of intestinal cells, was significantly higher in lean rats compared with obese rats (Fig. 1A). Intestinal cell alkaline phosphatase activity was significantly reduced in sucrose-fed rats compared with starch-fed rats. These results, therefore, are opposite of the phenotypic and dietary effects observed with disaccharidase activities.

Unlike intestinal alkaline phosphatase, serum alkaline phosphatase activity was significantly higher ($P < 0.01$) in obese rats compared with lean littermates (Fig. 1B). There was no significant dietary carbohydrate effect on serum alkaline phosphatase activity in lean rats. Serum alkaline phosphatase activity in obese starch-fed rats was significantly higher than in obese sucrose-fed rats ($P < 0.01$).

Discussion

Obese SHR/N-*cp* rats fed *ad libitum* were both hyperglycemic and hyperinsulinemic in response to a glucose challenge. These rats exhibited significant increases in intestinal disaccharidase activity as well. The type of carbohydrate consumed (cooked corn starch or sucrose) and the phenotypic expression of obesity and/or diabetes, singly and/or in combination, affected various intestinal parameters and the activity of some, but not all, intestinal hydrolases. Compared with lean littermates, obese SHR/N-*cp* rats exhibited a significant increase in body weight, intestinal wet weight and length, and intestinal cell protein.

Changes observed in intestinal protein and physical structure may be due to the phenotype as well as to hyperphagia. The SHR/N-*cp* rat exhibits traits associated with both corpulent gene and hyperphagia (20). Obese SHR/N-*cp* rats consume similar amounts of food

per body weight as lean littermates; however, the total intake of food is greater (20).

In our studies, there was significant phenotypic interaction observed in sucrase activity, a significant diet effect for sucrase and maltase, and a phenotype-diet interaction in sucrase, maltase, and lactase activity. This suggests different adaptive mechanisms for specific disaccharidases. The mechanism by which intestinal hydrolase activity was increased in obese rats is unknown. Elevated level of glucocorticoids or insulin may be responsible for an increase in the mass of the intestinal mucosa, an increase in enzyme activation, an increase in enzyme synthesis, or, conversely, a decrease in enzyme degradation.

Spontaneous diabetic mice and SHR/N-*cp* rats exhibit similar changes in intestinal disaccharidase activity and pathologic abnormalities (9–11, 14, 15). Disaccharidase activity, especially sucrase, in spontaneously diabetic mice (C-57 BLKsJ *db/db*) has been reported to be influenced by both phenotype and dietary carbohydrate consumed (10, 11).

The clinical importance of increased intestinal disaccharidase activity in the regulation of hyperglycemia is shown by studies that differentially inhibit disaccharidase function. For example, the potent α-glycosidase inhibitor acarbose, when consumed by spontaneously diabetic mice, was found to reduce intestinal sucrase and maltase, but not lactase specific activity (27, 28). In addition, in both the BLKsJ *db/db* mice and the SHR/N-*cp* rat, feeding acarbose improved glucose tolerance and reduced the insulin response to a glucose load (20, 28, 29). Therefore, increased sucrase and maltase activities may be one indicator for hyperglycemia and a decrease in their activities may be suggestive of possible treatments for obesity and glycemia associated with diabetes.

Intestinal alkaline phosphatase activity, on the other hand, was lower in sucrose-fed obese SHR/N-*cp* rats than in lean littermates. Nakabou *et al.* (30) reported similar differential induction of intestinal hydrolases: sucrase activity was increased in alloxan-diabetic rats, whereas alkaline phosphatase was not.

After a 12-h fast, serum alkaline phosphatase activity of obese SHR/N-*cp* rats was almost twice as high as that found in lean littermates. Fasting serum insulin levels in these obese rats were five times higher than those in lean littermates. Both fasting and insulin administration have been reported previously to reduce serum alkaline phosphatase in IDDM rats (19). Since, both obese and lean rats in this study were fasted, and the obese rats retained much higher insulin levels, this suggests differences in the mechanism of increase in alkaline phosphatase dependent on the type of diabetes, i.e., chemically induced diabetes versus spontaneous NIDDM. The source of increased levels of serum alkaline phosphatase activity is presently unknown. Tissues that may contribute to the observed changes in serum alkaline phosphatase are bone, liver (the liver of the obese SHR/N-*cp* is hyperplastic and has increased glycogenic and lipogenic enzyme activity), and intestine.

Glucocorticoids, such as corticosterone, are reported to increase intestinal protein and disaccharidase synthesis. Glucocorticoids are known to increase the postnatal rat intestinal enzymes sucrase, maltase, and alkaline phosphatase (31, 32). Glucocorticoids, on the other hand, have been reported to reduce lactase activity in nondiabetic, postnatal rats (33). Both adrenal production and plasma concentration of glucocorticoids are two times higher in obese SHR/N-*cp* rats when compared with lean littermates (34, 35). Sucrose feeding compared with starch feeding enhances the level of corticosterone, glucagon, and insulin levels in both the lean and obese rats (34). Elevated glucocorticoids could, therefore, be responsible for the induction of some intestinal hydrolases such as sucrase and maltase, but not others such as lactase and alkaline phosphatase.

The type of carbohydrate consumed (sucrose versus starch) can influence the specific enzymatic activity of intestinal brush border hydrolases in obese SHR/N-*cp* rats. Factors associated with phenotypic expression of obesity and/or diabetes may influence others. Specifically, integrated changes observed in this model for NIDDM, such as high levels of insulin and glucocorticoids, may jointly contribute to the increase in select intestinal disaccharidases and serum alkaline phosphatase and the decrease in intestinal alkaline phosphatase. The study suggests that increased intestinal disaccharidases, especially sucrase and maltase, are indicative of hyperglycemia associated with obesity and NIDDM in SHR/N-*cp* rats. Conversely, a decrease in the specific activity of these enzymes or interference with their function is indicative of a better metabolic control of glycemia.

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