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Control of jejunal sucrase and maltase activity by dietary sucrose of fructose in man: *A model for the study of enzyme regulation in man*

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Fructose feeding, in two subjects, gave results similar to sucrose when comparing fructose and glucose diets. One subject was fed lactose, galactose, and maltose. These sugars, compared to glucose, did not increase disaccharidase activity. Fructose appears to be the active principle in the sucrose molecule.

These results demonstrate that specific dietary sugars can alter enzyme activity in the small intestine of man in a specific fashion. Sucrose and fructose are able to regulate sucrase and maltase activity. Dietary alteration of intestinal enzymes may represent a suitable system for studying the regulation of enzyme activity in man.

Control of Jejunal Sucrase and Maltase Activity by Dietary Sucrose or Fructose in Man

A MODEL FOR THE STUDY OF ENZYME REGULATION IN MAN

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ABSTRACT The specific effect of dietary sugars on jejunal disaccharidase activity in seven normal nonfasted male volunteers was studied. The sugars tested were sucrose, maltose, lactose, glucose, fructose, and galactose. Comparisons were made of the effects of each sugar in an isocaloric liquid diet.

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These results demonstrate that specific dietary sugars can alter enzyme activity in the small intestine of man in a specific fashion. Sucrose and fructose are able to regulate sucrase and maltase activity. Dietary alteration of intestinal enzymes may represent a suitable system for studying the regulation of enzyme activity in man.

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INTRODUCTION

Jejunal disaccharidase activity plays a fundamental role in the digestion of dietary carbohydrates. This activity is responsible for the hydrolysis of poorly absorbable dietary disaccharides (lactose, sucrose, and maltose) to the readily absorbable monosaccharides (glucose, galactose, and fructose). In certain small bowel diseases (1–3) and isolated disaccharidase deficiencies (4–6), there is decreased disaccharidase activity often leading to clinically significant malabsorption and diarrhea.

Previous studies have demonstrated the adaptable nature of intestinal disaccharidase activity in rats (7, 8). In these studies, there was a marked increase in sucrase and maltase activity when fasted rats fed a high carbohydrate diet were compared to fasted rats fed a high casein, carbohydrate-free diet. This increase was produced by several dietary mono- and disaccharides.

In humans, the effect of diet on jejunal disaccharidase activity has not been clearly delineated. Galactosemic patients, maintained on lactose- and galactose-free diets for many years, showed no evidence of lactase deficiency as measured by lactose tolerance testing (9), although jejunal enzyme assays were not done. Lactase-deficient patients fed a high milk diet for several months remained milk and lactose intolerant (10). The only available datum on the role of diet on sucrase and maltase activities in man is an abstract stating that fasting obese patients for 14–28 days produced approximately a 40% decline in all disaccharidase activity (11). There was a return toward normal

after glucose was given orally or intravenously. Since these patients were fasted, it is difficult to distinguish between a nonspecific caloric replacement and specific carbohydrate effects.

In normal man, the factors controlling disaccharidase activity are unknown, but it appears that dietary factors play some part in this control. Whether the dietary role is a nonspecific caloric effect, a general carbohydrate effect, or a specific effect of a specific sugar is not known. In the present study, we have investigated the specific effect of dietary sugars on jejunal disaccharidase activity in normal nonfasted male volunteers. The effect of sucrose, lactose, and maltose and the

TABLE I

Dietary Content and Number of Biopsies in All Five Studies

Study	Subject	Diet*	Carbohydrate	Fat	Protein	Days on diet	Number of biopsies
			% cal	*% cal*	*% cal*		
I	1‡	Glucose	40	45	15	20	7
		Sucrose	40	45	15	10	3
	2	Glucose	75	10	15	8	3
		Sucrose	75	10	15	7	3
	3	Glucose	20	65	15	28	5
		Glucose	40	45	15	14	1
		Glucose	60	25	15	14	1
		Glucose	80	5	15	14	1
		Sucrose	40	45	15	7	3
		Sucrose	80	5	15	15	5
	4	Glucose	40	45	15	23	5
		Sucrose	40	45	15	15	9
II	5	Sucrose	60	15	25	7	1
		Glucose	60	15	25	7	3
	6	Sucrose	60	15	25	7	1
		Glucose	60	15	25	7	3
	7	Sucrose	60	15	25	7	1
		Glucose	60	15	25	7	3
III	3	Glucose	20	65	15	20	3
		Glucose	40	45	15	14	1
		Glucose	60	25	15	14	1
		Fructose	20	65	15	14	4
		Fructose	40	45	15	14	1
		Fructose§	60	25	15	3	1
	4	Glucose	40	45	15	8	4
		Fructose	40	45	15	8	3
		Sucrose	40	45	15	8	4
IV	1‡	Glucose	40	45	15	13	4
		Lactose‖	40	45	15	14	3
		Sucrose	40	45	15	10	3
V	1‡	Glucose	40	45	15	7	3
		Galactose	40	45	15	7	3
		Maltose	40	45	15	7	3

* Additional description of the diets is found under Methods in the text.

‡ Glucose and sucrose data for subject 1 in study I were taken from studies IV and V.

§ Produced diarrhea.

‖ 30% lactose, 10% glucose.

products of their hydrolysis, glucose, fructose, and galactose, were studied.

METHODS

Subjects. Seven normal male Caucasian volunteers, ranging in age from 19 to 25, with no history of disaccharide intolerance, were studied. All subjects were weighed daily after voiding before breakfast. All studies were conducted on a metabolic ward.

Diets. All diets for each subject are listed in Table I. Protein was in the form of sodium or calcium caseinate and fat as corn oil. Water, black coffee, and diet colas were allowed ad lib. One multivitamin tablet and constant NaCl and KCl supplements were given daily. In studies I, III, IV, and V, the subjects consumed a 3000 cal liquid diet, and in study II, a 2800 cal liquid diet. Diets were fed in three equal meals daily and the weights of the subjects remained constant on these diets.

Biopsies. Jejunal biopsies were obtained with the Crosby-Kugler capsule (12). The position of the capsule was verified radiographically before each biopsy. Specimens were immediately frozen and stored in small plastic containers at −85°C until assayed. Biopsies were weighed at the time of assay and all were subjected to an identical period of thaw. Tissue frozen at −85°C gave results similar to fresh tissue and tissue frozen at −20°C. In each subject a portion of the initial biopsy was examined histologically and was normal.

Disaccharidase assays. Disaccharidase assays were performed on homogenates of mucosa by the method of Dahlqvist (13). Substrates used were lactose, sucrose, and maltose made up in maleate buffer at pH 5.8. 1 unit of disaccharidase activity is equal to 1 μmole of substrate hydrolyzed/min per g wet weight of mucosa. In most instances, assays were run within 1 wk of biopsy.

In addition to expressing the results in units of absolute activity, sucrase to lactase (S/L) and maltase to lactase (M/L) ratios were computed for each biopsy. Standard error of the mean was calculated for absolute activities and ratios and Student's *t* test was used to determine significance (14).

Studies. The investigations were divided into five studies. In study I, the effects of glucose and sucrose diets in subjects 1–4 were compared. The data for subject 1 in study I were taken from the glucose and sucrose data of studies IV and V. In subject 1, two identical glucose diets were fed 5 months apart. Between the glucose diets, he ate a lactose diet for 14 days, a sucrose diet for 10 days, and an ad lib. diet for the remaining time. In subject 2, the diets were consecutive. For subject 3, glucose 20–80% and sucrose 40% were consecutive. Another sucrose diet, 80%, was fed 2 months later. Subject 4 ate two glucose and two sucrose diets, none of which were consecutive.

In study II, the effect of feeding glucose immediately after sucrose was studied.

In study III, glucose and fructose were fed. For subject 3, the diets of glucose, 20–60%, and fructose, 20–60%, were consecutive with a month of ad lib. diet between glucose and fructose. The diets for subject 4 were consecutive.

In studies IV and V, the other dietary saccharides, lactose, maltose, and galactose were fed. Glucose, lactose, and sucrose were fed consecutively followed by 2 months

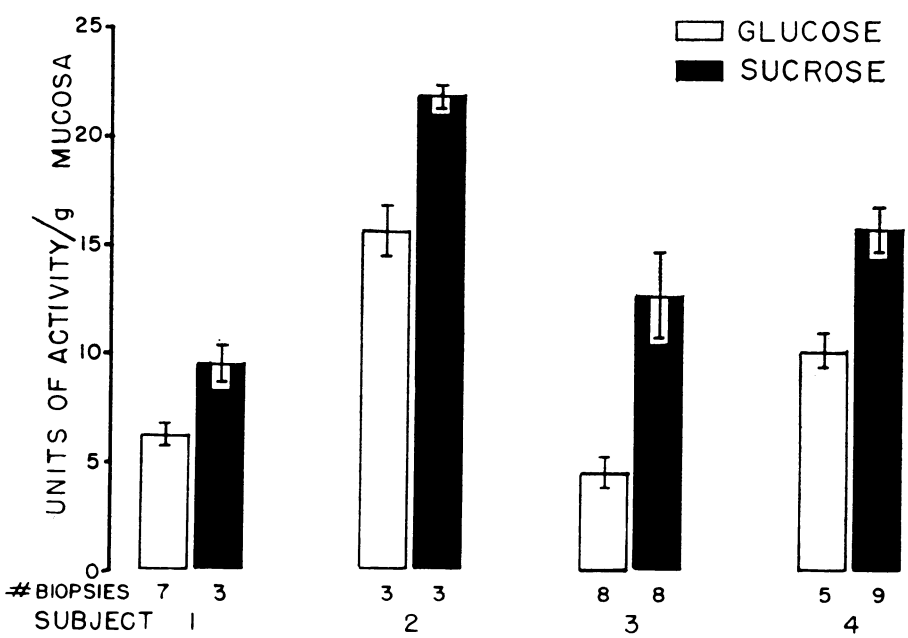

FIGURE 1 Mean sucrase activity in subjects 1–4 (study I) on glucose and sucrose diets. The standard error of the mean is in brackets.

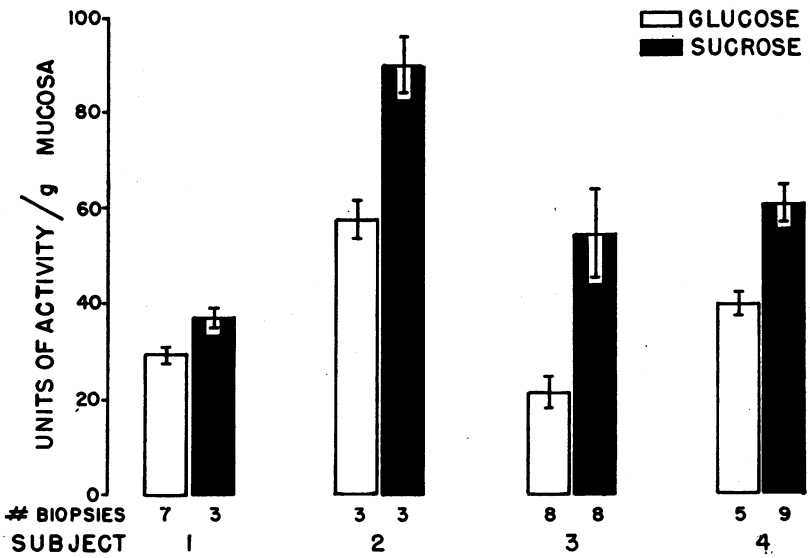

FIGURE 2 Mean maltase activity in subjects 1–4 (study I) on glucose and sucrose diets. The standard error of the mean is in brackets.

of ad lib. diet. After this, glucose, galactose, and maltose were fed consecutively.

In all studies, all biopsies were obtained after at least 2 days of the diet except for subject 3 who had one biopsy after 1 day of 80% sucrose and subject 4 who had biopsies after 1 day of 40% glucose and after 1 day of 40% sucrose.

RESULTS

A comparison of mean disaccharidase activities in all subjects on both glucose and sucrose diets (studies I and II) is presented in Figs. 1–5. For each subject in study I (Fig. 1) the mean sucrase activity was significantly higher on the sucrose diet than on the glucose diet ($P < 0.01$). Similar results are noted for maltase activity as shown in Fig. 2 (subjects 2 and 3, $P < 0.01$; 1 and 4, $P < 0.05$). In contrast with the increase in sucrase and maltase activities, lactase activity was unchanged on glucose and sucrose diets (Fig. 3).

Fig. 4 presents the mean S/L and M/L ratios for each subject on both glucose and sucrose diets. The ratios on the glucose and sucrose diets were significantly different at the 1% level.

The results show not only a statistically sig-

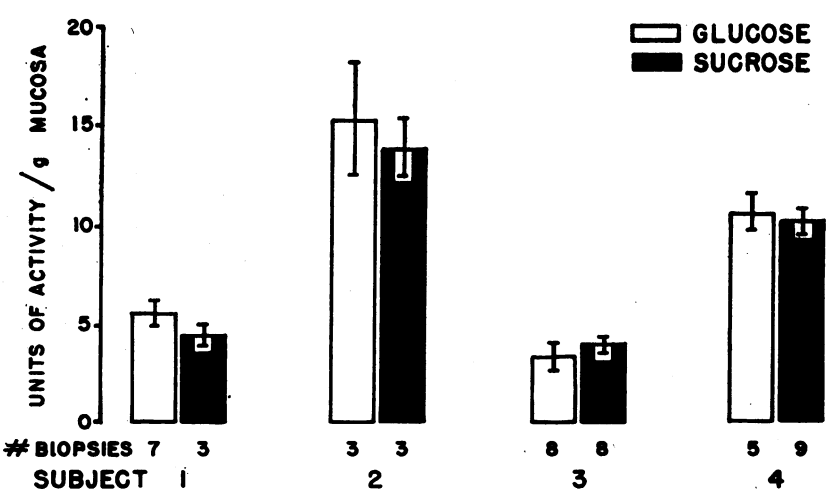

FIGURE 3 Mean lactase activity in subjects 1–4 (study I) on glucose and sucrose diets. The standard error of the mean is in brackets.

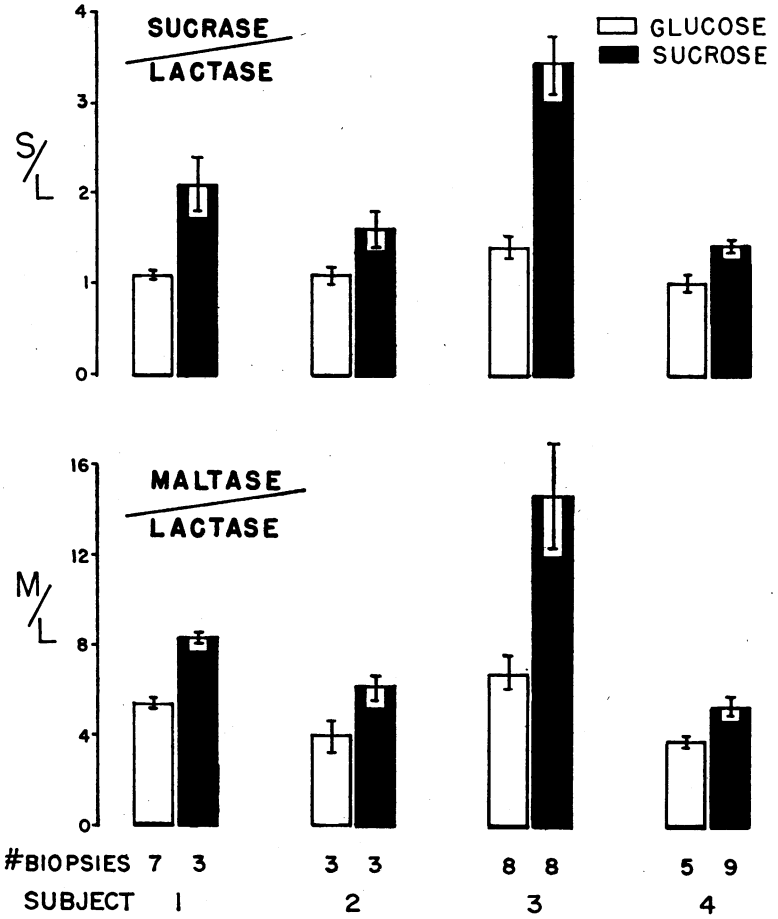

FIGURE 4 Mean sucrase to lactase (S/L) and maltase to lactase (M/L) ratios in subjects 1–4 (study I) on glucose and sucrose diets. The standard error of the mean is in brackets.

nificant absolute increase in sucrase and maltase activities on a sucrose diet, but also a significant increase in sucrase and maltase activities relative to lactase activity.

When glucose was fed after sucrose in subjects 5, 6, and 7 (study II) sucrase and maltase activities fell in all three subjects while lactase activity remained unchanged (Fig. 5).

Effect of fructose. The specificity of the effect of dietary sucrose on jejunal sucrase was studied with dietary glucose and fructose (study III). Consecutive glucose, fructose, and sucrose diets were fed to subject 4 (Fig. 6*a*). Sucrase fell slightly during glucose feeding and then rose steadily on fructose feeding without any further significant rise when the diet was changed to sucrose. Changes in maltase were similar to that of sucrase. Lactase values were essentially unchanged on the three sugars. On day 24 in Fig. 6*a* the disaccharidase activity decreased. This de-

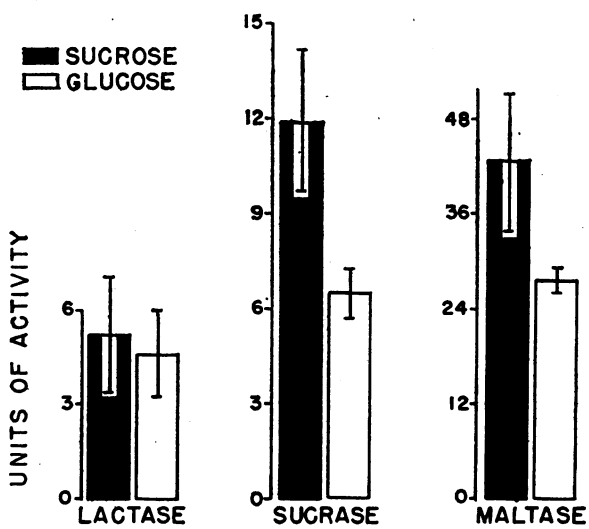

FIGURE 5 Mean disaccharidase activity in subjects 5–7 (study II) on sucrose and then glucose diets. Results given are the mean of the three subjects ± the SE. There was one biopsy on the sucrose diet and three on glucose.

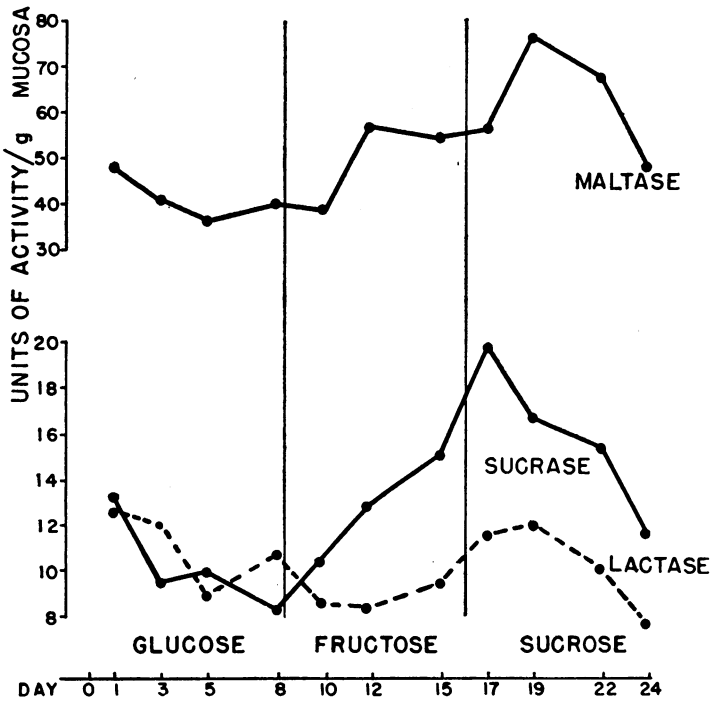

FIGURE 6a Disaccharidase activities in subject 4 (study III) on consecutive 40% carbohydrate diets.

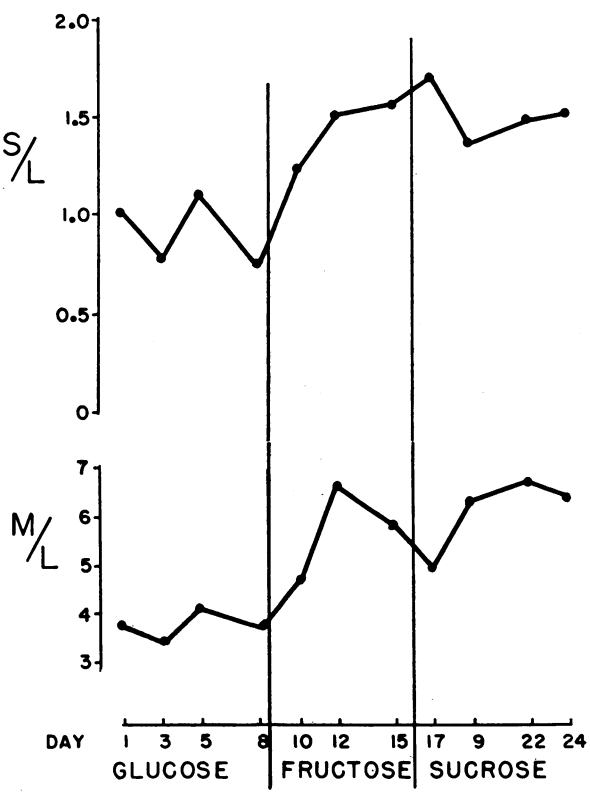

FIGURE 6b Disaccharidase ratios (S/L and M/L) in subject 4 (study III) on consecutive 40% carbohydrate diets.

crease appears to be an example of the variability to be found when studying absolute values. By contrast, the S/L and M/L ratios, which also rose on the fructose diet and remained at this level when fructose was changed to sucrose, did not fall on day 24 (Fig. 6*b*). Additional studies, not reported here, in which three subjects were fed sucrose for 10 wk did not reveal any late rise or decline in disaccharidase values or S/L and M/L ratios.

When glucose and fructose diets were compared in subject 3 (Fig. 7), the results with fructose were again similar to those with sucrose.

Effect of lactose, galactose, and maltose. In study IV, the effects of glucose, lactose, and sucrose diets were compared and in study V, the effects of glucose, galactose, and maltose were compared (Table II). All disaccharidase values on glucose and lactose were quite similar, while on sucrose, sucrase and maltase activities rose significantly while lactase activity fell slightly. The ratios, S/L and M/L, rose significantly on sucrose, but on lactose were similar to glucose. In the galactose and maltose studies, all three disaccharidase activities fell on galactose with no significant change when the diet was changed to maltose. In contrast to sucrose, the S/L ratio

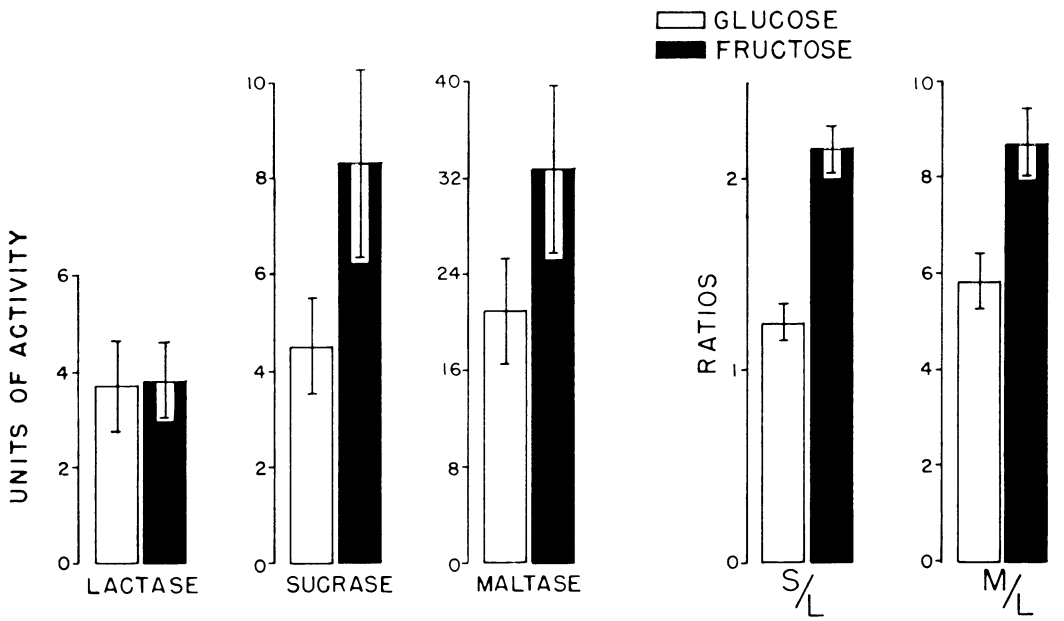

FIGURE 7 Mean disaccharidase activities and ratios in subject 3 (study III) on glucose and fructose diets. The standard error of the mean is in brackets.

remained the same and the M/L ratio fell when galactose and maltose were compared to glucose.

DISCUSSION

These results show that specific dietary sugars have specific effects upon jejunal disaccharidase activity in man. In seven normal human subjects, sucrose feeding, as compared to glucose feeding, significantly increased jejunal sucrase and maltase activities, but not lactase activity. The S/L and M/L ratios also were significantly increased. When glucose was fed after sucrose, sucrase and maltase activities fell. This demonstrates, therefore, that the human jejunum is capable of adaptive responses to dietary changes. These adaptive changes occur in a specific fashion, suggesting that the type of dietary sugar may serve as a specific stimulus for regulating disaccharidase activity.

The ability to increase maltase activity with sucrose feeding is consistent with reports that there are several maltase isoenzymes in man, two of which have sucrase activity (15, 16). There are also two sucrases which have maltase activity. Most likely maltases 3 and 4 and sucrases 1 and 2 are identical. We would postulate then, that only maltases 3 and 4 are increased by the sucrose feeding. If this is true, the effect of diet, if any, on the other maltases would remain to be determined.

The fact that fructose reproduces the sucrose

TABLE II

Disaccharidase Values in Subject 1, Studies IV and V

Study	Diet*	Lactase‡	Sucrase	Maltase	S/L	M/L
IV	a. Glucose	5.5 ± 0.4	6.2 ± 0.8	29.6 ± 3.7	1.1 ± 0.1	5.4 ± 0.4
	b. Lactose	5.6 ± 0.2	6.3 ± 0.5	29.2 ± 0.3	1.1 ± 0.03	5.2 ± 0.1
	c. Sucrose	4.5 ± 0.3	9.5 ± 0.8	37.2 ± 1.8	2.1 ± 0.3	8.3 ± 0.3
V	d. Glucose	5.6 ± 0.7	7.5 ± 0.8	36.2 ± 4.1	1.3 ± 0.1	6.5 ± 0.2
	e. Galactose	3.6 ± 0.5	4.9 ± 0.5	19.0 ± 1.8	1.4 ± 0.1	5.3 ± 0.3
	f. Maltose	4.8 ± 1.4	5.6 ± 1.3	22.9 ± 6.5	1.2 ± 0.1	4.8 ± 0.2

* Diets a-c and d-f were fed consecutively.

‡ Mean values given in units/g wet wt of mucosa ± SEM.

effect suggests that fructose is the active principle in the sucrose molecule. This demonstrates that the change in enzyme activity is not necessarily controlled by the enzyme substrate. These findings are consistent with other studies (7, 17) which show that substrates for enzymes need not have any regulatory effect on the enzyme and that substances with a regulatory effect need not be substrates.

Our results with lactose feeding are consistent with the findings that diets high in lactose do not increase lactase activity in lactase-deficient patients nor do diets free of lactose for prolonged periods produce lactase deficiency (9, 10). In fasting human subjects there is a fall in all disaccharidase activity including lactase (11). This decreased activity returns toward normal by refeeding glucose. In the present studies, diets in which glucose was the sole source of carbohydrate were employed as a control diet from which to compare the effects of other dietary sugars.

Although galactose feeding increased sucrase activity in the rat (7), this was not seen in the human subject. Galactose feeding, as compared to glucose feeding, actually lowered all disaccharidase activity with no change in the S/L ratio and a fall in the M/L ratio. The mechanism of the galactose effect is not clear.

When maltose was fed to one subject after galactose feeding, there were only small changes in disaccharidase activities; absolute activities increased slightly and the ratios decreased slightly. The effect of maltose feeding appears to be essentially similar to that of glucose feeding. Maltose yields two molecules of glucose when hydrolyzed, and this may explain the failure of maltose, as compared to sucrose, to cause an increase in disaccharidase activity, since fructose appears to be the regulatory sugar.

It should be noted that the studies with lactose, galactose, and maltose were done in only one subject. Therefore, we cannot say for certain that galactose, lactose, and maltose will have similar effects in all individuals. However, since this one subject was also fed sucrose, to which he responded, it does appear that glucose, galactose, lactose, and maltose do not increase disaccharidase activity in the same way as do fructose and sucrose.

This demonstration of an adaptive response to dietary sugars by the human jejunum is similar to studies reported in rats (7, 8). The effect appears to be more specific in the human since only sucrose or fructose are regulatory sugars, whereas in the rat, several mono- and disaccharides produced this same effect. Whether or not this is a real species difference is difficult to state at this time because in the human studies glucose diets were employed for base line comparison, while in the rat, carbohydrate-free, casein diets were the base line.

It is known that some variability of disaccharidase levels is characteristic of peroral biopsy specimens in humans. This may be explained partly by the variations in the depth of the biopsy and the varying proportions of epithelial cells included in the entire mucosal specimen (18). In addition, time of storage before assay may change activity (19). Since disaccharidase activity is located in the brush border of the epithelial cells (20), one would expect that any variation in activity due to the depth of the biopsy would have a similar effect on all three disaccharidases. On the other hand, a significant dietary effect on one disaccharidase should produce disproportionate changes relative to the activity of the other disaccharidases.

We have found that lactase activity does not change significantly on the various diets. To minimize variability from depth of biopsy, we chose lactase activity as a common denominator or reference point with which to compare the changes in sucrase and maltase activities.

Therefore, in addition to absolute values of activity, sucrase to lactase (S/L) and maltase to lactase (M/L) ratios were employed to characterize the changes seen with the different diets. Both the absolute activities and the ratios changed in similar fashion thereby supporting each other.

It should be noted that values for absolute activities and ratios are not completely analogous and not necessarily interchangeable. Absolute activity defines changes in enzyme activity in relation to the amount of tissue present. In comparing two diets or two enzymes, the reference point (or denominator) is a third variable, namely tissue weight. On the other hand, use of the ratios defines the changes in the absolute activities of two enzymes in relation to each other. It is possible,

then, to conceive of situations where either ratios or absolute activities, but not both, would change. With small changes in opposite directions in the numerator and denominator use of ratios may make it possible to define relative changes that would not be discernible by comparing absolute activity alone.

Although the present studies clearly demonstrate that dietary sucrose, as compared to glucose, will increase jejunal sucrase and maltase activities, these data do not allow us to draw any conclusions regarding the mechanism of this increase. At present, we tentatively propose that sucrose induces synthesis of sucrase de novo, but other explanations are certainly possible.

If this effect is true induction, one would expect that the changes seen should occur within the life cycle of a jejunal epithelial cell. In the few studies available, human intestinal cell turnover has been estimated at 2–5 days (21–24). Although sugars were fed in our present studies for 7 or more days, we have recently reported that the time response of human jejunal sucrase to a high sucrose diet is, indeed, 2–5 days.[1] This finding coincides with the human intestinal cell turnover time and suggests that the effect of sucrose and fructose is primarily at the crypt cell level, but the expression of disaccharidase activity does not occur until the affected crypt cells migrate up the villus. This is consistent with, but not proof of, an inductive effect.

Whether or not the increase in activity is due to the induction of new enzyme, these studies demonstrate that dietary sucrose (or fructose) is able to regulate human intestinal sucrase and maltase activity. This demonstration suggests that the jejunum can serve as a convenient model for studying the regulation of enzyme activity in man.

This model has certain advantages when compared with other tissues such as liver. First of all, jejunal biopsy is a painless and relatively safe procedure with only minimal discomfort to the patient. Secondly, with feeding by mouth or through a duodenal tube it is possible to place the substrate or substance being evaluated in direct contact with the enzyme site because the disaccharidases are located in the brush border. Furthermore, techniques are now being developed which enable the separation of the brush border from the rest of the intestinal mucosa (25, 26). Thus, one might be able ultimately to isolate and purify these enzymes in man. This, then, may represent a suitable system for investigating the regulation of enzyme activity in man.

[1] Rosensweig, N. S., and R. H. Herman. Time response of jejunal sucrase activity to a high sucrose diet. Presented to the Gastroenterology Research Forum, American Gastroenterology Association, 16 May 1968, Philadelphia, Pa.

ACKNOWLEDGMENTS

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