Dietary Stimulation of Sucrase in a Patient with Sucrase-Isomaltase Deficiency

HARRY L. GREENE, FRED B. STIFEL, AND ROBERT H. HERMAN

Metabolic Division, U. S. Army Medical Research and Nutrition Laboratory, Fitzsimons General Hospital, Denver, Colorado 80240

Received November 17, 1971

In 1961, Weijer et al. (1), Prader et al. (2) and Delaitre et al. (3) described several children with diarrhea caused by dietary sucrose. Soon afterward Auricchio et al. (4, 5) demonstrated the coexistence of isomaltose and sucrose intolerance. Although all the authors produced strong indirect evidence that the disaccharide intolerance was the result of a deficiency of sucrase and isomaltase, Anderson et al. (6) in 1963 was the first to provide direct confirmation of deficient sucrase–isomaltase activities in duodenal tissue obtained from siblings with sucrose intolerance. Recent reviews list references for approximately 60 similar patients in various parts of the world (7-9). In all the reported cases, the activities of both sucrase and isomaltase were deficient.

Symptoms usually begin in infancy with the introduction of sucrose into the diet, although recognition may be delayed until adulthood (10–12). Diarrhea is the principle symptom and occurs only with dietary sucrose or isomaltose. Secondary malabsorption of all foods ingested in conjunction with sucrose may occur, and is probably due to the rapid transit time. Because of the secondary malabsorption, the condition may be confused with other causes of malabsorption such as celiac disease, milk intolerance or pancreatic insufficiency. As the children mature, they are usually able to tolerate increasing amounts of sucrose and starch despite the fact that the specific activities of the enzymes remain low (12). Presumably this phenomenon is due to the normal growth and increasing absorptive area of the intestine.

Since many commercially available foods contain added sucrose it is often difficult for a child to be maintained on a diet free of sucrose and thereby avoid intermittent diarrheal episodes. Rosensweig and Herman (13) and Knudsen et al. (14) demonstrated that jejunal sucrase activity in normal humans could be significantly increased by certain dietary sugars, especially fructose (13). This suggested that if sucrase-deficient
patients were fed supplementary fructose, they might increase their intestinal sucrase activity to a level that would allow them to tolerate moderate amounts of oral sucrose without becoming symptomatic. Preliminary studies in one patient showed that despite the profound sucrase deficiency, fructose did increase intestinal sucrase activity (15).

On the basis of these preliminary data, these studies were extended in an effort to substantiate clinical as well as biochemical improvement. Multiple intestinal biopsy specimens were examined for sucrase activity. Sucrose tolerance tests including urinary and fecal measurements of sucrose concentrations were performed before and after treatment with dietary fructose. Certain of the jejunal glycolytic enzymes show adaptive increases in activity in response to dietary sugars (16) or to pharmacologic doses of folic acid (17). For this reason, the changes in pyruvate kinase (EC 2.7.1.40) and fructose diphosphate aldolase (EC 4.1.2.13) activities were also measured to determine the capability of the jejunum to respond to diet.

CASE REPORT

The patient was a Caucasian girl, studied at 7 years of age. Diarrheal episodes began at the time baby foods were first introduced into her diet (3–4 months of age). Despite repeated dietary manipulations she required hospitalization on two occasions during the first year of life for treatment and studies related to chronic malabsorption and poor weight gain. At 2 years of age, a milk-free, gluten-free diet was begun which caused some decrease in the number and severity of gastrointestinal symptoms. Linear growth and weight gain was maintained at a normal rate for the next 3 years. Toilet training was difficult but was achieved by 4 years of age.

At 6 years of age, she was hospitalized because of uncontrolled diarrhea and weight loss which had persisted for 4 weeks. Stool cultures for pathogenic bacteria and examinations for ova and parasites were negative. X-rays of the gastrointestinal tract were normal. Because the only abnormal absorption test was the 72-hour fecal fat, she was placed on a low fat diet in addition to the gluten-free, milk-free diet. However, despite these dietary restrictions she continued to have 4–6 semiliquid stools a day. At age 7 years she was referred to Fitzsimons General Hospital.

Physical examination showed her to be of normal development and in the 40th percentile for height and weight. Examination of duodenal secretions showed a pH of 6.5; neither parasites nor bacteria were found. The amylase, lipase and trypsin activities were normal. A jejunal biopsy specimen showed a normal histologic pattern. Jejunal disaccharidase measurements showed normal activity of lactase and maltase and a de-
ficiency of sucrase and isomaltase activities. These findings ruled out an acquired defect.

During the succeeding 3-week period, she had no dietary restrictions except for sucrose. She gained 3 pounds and began having one or two formed stools a day. However, she would frequently indulge in candy or cookies offered by her friends and become ill for 1 or 2 days. Because of this, she was admitted to the metabolic ward on January 8, 1971, for the purpose of evaluating her jejunal sucrase response to dietary fructose in hopes that the jejunal sucrase activity could be increased sufficiently to allow her to eat small amounts of sucrose without becoming symptomatic.

METHODS

Disaccharidase Assays. The method of Dahlqvist (18) was used with the substrates lactose, sucrose, maltose and isomaltose made up in a maleate buffer at pH 5.8. One unit of disaccharidase activity is equal to 1 µmole of substrate hydrolyzed/minute/gram wet weight of mucosa. At the time of biopsy, all specimens were cut in two equal pieces, weighed, sealed in plastic containers and frozen immediately in acetone and dry ice. The specimens were stored at -85° and assayed simultaneously at the completion of the study to minimize variation in results. To further minimize variation in enzyme activity due to the depth of the biopsy, the results are also expressed as enzyme to lactase ratios since human lactase activity does not change with dietary manipulations (13, 14).

Sucrose Measurements. Sucrose concentrations in blood, urine and stool were assayed by enzyme hydrolysis of the sample with sucrase (Calbiochem Corp.) and by measuring the increase in amount of glucose and reducing sugars produced (19).

Glycolytic Enzyme Assays. Jejunal biopsy specimens were obtained and processed as described elsewhere (16). Enzyme activities were assayed as described previously (20). Activity is expressed as nanomoles of substrate metabolized per minute per milligram protein. Protein was measured by the method of Lowry et al. (21).

Diets. All the diets given were artificially prepared and the patient received between 1150 and 1230 calories per day throughout the study. The design of the diets was similar to that described earlier with added vitamins and minerals (13). Protein was in the form of calcium caseinate and fat as corn oil. The components of the diets are listed in Table 1 and are expressed as the percent of total calories.

Study Periods. The investigation was divided into four periods. The first period was the control period during which no dietary fructose was given. One jejunal biopsy specimen was obtained at the beginning and
another at the end of period I (Study Days 1–4). Two oral sucrose tolerance tests were performed on Days 2 and 4 of period I. During periods II–IV (Study Days 5–20), the diets were isocaloric and contained 40%, 50% or 60% of calories as fructose (Table 1). During period IV 15 mg/day of oral folic acid was given to test its effect on the jejunal glycolytic enzymes (Table 4). During each of these periods, jejunal biopsy specimens were obtained and oral sucrose tolerance tests were performed at the end of each study period. Prior to the beginning of the study, a glucose plus fructose tolerance test was performed using equimolar amounts of the monosaccharides, the total amount of carbohydrate being equal to the amount of sucrose used in the sucrose tolerance test (Fig. 2).

**Biopsies.** All biopsies were performed after an overnight fast using the Crosby–Kugler Pediatric capsule (22). The capsule was always localized under fluoroscopy and all specimens were taken from approximately the same area just distal to the ligament of Treitz. Biopsy specimens were taken from the patient’s parents and her two female siblings (ages 12 and 14 years) after an overnight fast and while eating an *ad libitum* diet.

**RESULTS**

Table 2 shows the values for jejunal disaccharidases in the patient, her parents and two siblings. Sucrase activity was normal in all members of the patient’s family. Interestingly, the father was lactase deficient, and gave a history of gastrointestinal symptoms when lactose-containing foods were eaten. Although the sisters of the patient had lactase activities below the control group, they frequently had milk and ice cream without a history of gastrointestinal complaints. These findings would support the concept that lactase deficiency is genetic in origin. The finding of lactase deficiency in the father and sucrase deficiency in the daughter has no proven relationship. The table also shows the values for jejunal disaccharidases in the patient during periods I and IV and the values after mixing the patient’s tissue with normal tissue.

Previous investigators have shown that lactase activity does not change significantly with short-term dietary manipulation. To minimize variation
TREATMENT OF SUCRASE DEFICIENCY

TABLE 2
JEJUNAL DISACCHARIDASE VALUES IN THE PATIENT AND HER FAMILY

<table>
<thead>
<tr>
<th>Source of tissue</th>
<th>Lactase</th>
<th>Sucrase</th>
<th>Isomaltase</th>
<th>Maltase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>15.43a</td>
<td>10.01</td>
<td>19.31</td>
<td>51.26</td>
</tr>
<tr>
<td>Father</td>
<td>0.93</td>
<td>9.25</td>
<td>14.16</td>
<td>28.17</td>
</tr>
<tr>
<td>Sister 14 years old</td>
<td>4.05</td>
<td>7.53</td>
<td>11.62</td>
<td>51.08</td>
</tr>
<tr>
<td>Sister 12 years old</td>
<td>6.83</td>
<td>9.61</td>
<td>12.63</td>
<td>38.46</td>
</tr>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I (no fructose)</td>
<td>7.91</td>
<td>.38</td>
<td>3.41</td>
<td>33.53</td>
</tr>
<tr>
<td>Period IV (with fructose)</td>
<td>8.31</td>
<td>1.67</td>
<td>6.30</td>
<td>58.61</td>
</tr>
<tr>
<td>Mixture of tissue from patient + normalb</td>
<td>16.10 (15.10)</td>
<td>9.40 (9.11)</td>
<td>21.11 (20.25)</td>
<td>83.74 (88.51)</td>
</tr>
<tr>
<td>Normal rangeb</td>
<td>9–15</td>
<td>8–18</td>
<td>10–20</td>
<td>27–60</td>
</tr>
</tbody>
</table>

a Activity expressed as micromoles of substrate hydrolyzed/minute/gm wet weight mucosa.
b Represents values from 40 biopsy specimens from 10 normal Caucasian male subjects age 17–24 years on various diets. Tissue specimens from these controls were always assayed simultaneously with those of the patient and her family.
c Expected values in parentheses.

in the results due to differences in the depth of the biopsy specimens the changes in sucrase, maltase and isomaltase are expressed in terms of the enzyme to lactase ratios.

Figure 1 shows that by increasing the fructose portion of the diet there

---

**Fig. 1.** The changes in the ratio of disaccharidases to lactase activity before (no fructose) and after treatment (with fructose) with isocaloric diets. The numbers above each of the bars represent the amount of fructose in each of the diets. S/L = sucrase/lactase, I/L = isomaltase/lactase, M/L = maltase/lactase.
TABLE 3
SUCROSE TOLERANCE TESTS

<table>
<thead>
<tr>
<th>Time minutes</th>
<th>Blood glucose mg/100 ml</th>
<th>Blood sugar mg/100 ml</th>
<th>Before fructose</th>
<th>After fructose</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>85</td>
<td>87</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>0</td>
<td>87</td>
<td>88</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>82</td>
<td>97</td>
<td>105</td>
</tr>
<tr>
<td>20</td>
<td>81</td>
<td>83</td>
<td>118</td>
<td>130</td>
</tr>
<tr>
<td>30</td>
<td>81</td>
<td>81</td>
<td>115</td>
<td>125</td>
</tr>
<tr>
<td>45</td>
<td>83</td>
<td>85</td>
<td>105</td>
<td>110</td>
</tr>
<tr>
<td>60</td>
<td>86</td>
<td>86</td>
<td>100</td>
<td>102</td>
</tr>
<tr>
<td>90</td>
<td>85</td>
<td>86</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>120</td>
<td>87</td>
<td>88</td>
<td>84</td>
<td>84</td>
</tr>
</tbody>
</table>

was a concomitant increase in jejunal disaccharidase/lactase ratios. Similar changes occurred in the absolute activities of each of the enzymes except lactase as shown in Table 2.

Table 3 demonstrates that when sucrose was given there was no rise in either reducing sugar or in glucose before fructose treatment. Each value represents the mean from two separate sucrose tolerance tests. Following the 40% and 60% fructose diets (periods II and IV), there was a

---

**Fig. 2.** The effect of dietary fructose on urinary and fecal sucrose excretion after an oral sucrose load.
TABLE 4

<table>
<thead>
<tr>
<th>Diet</th>
<th>Pyruvate kinase</th>
<th>Fructose diphosphate aldolase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad libitum diet</td>
<td>172.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55.5</td>
</tr>
<tr>
<td>50% glucose</td>
<td>199.8</td>
<td>55.2</td>
</tr>
<tr>
<td>40% fructose</td>
<td>231.5</td>
<td>94.7</td>
</tr>
<tr>
<td>60% fructose + oral folate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>468.9</td>
<td>158.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Activities expressed as millimicromoles of substrate metabolized/minute/mg protein.
<sup>b</sup> 10 mg/day.

small rise in both the blood reducing sugars and glucose. Each of these values represents the mean from the two sucrose tolerance tests done during the 40% and 60% diets. An oral tolerance of the two monosaccharides contained in sucrose (glucose and fructose) showed a normal rise in both blood glucose and total reducing sugars.

Figure 2 shows that treatment with dietary fructose caused a decrease in urine and fecal sucrose excretion after the sucrose tolerance tests. The figure also shows a decrease in the number of stools after the high fructose diet, as indicated by the number of points on the graph.

Table 4 shows that the patient had a normal adaptive response of pyruvate kinase and fructose-1,6-diphosphate aldolase to dietary fructose and folic acid.

DISCUSSION

These studies have shown that dietary fructose can cause an adaptive response in jejunal sucrase activity in a sucrase-deficient patient which is qualitatively similar to that seen in normal individuals (13, 23, 24). Although the highest sucrase activity achieved was only 15% of that seen in normal individuals, this increased activity was enough to cause a rise in blood glucose and reducing sugar, as well as a decrease in the amount of sucrose excreted in the urine and stool after oral sucrose. After dietary treatment with fructose there was also a decrease in the total number of stools and gastrointestinal symptoms after the sucrose load. Subsequently, the patient was placed on a sucrose-free ad libitum diet supplemented with approximately 20% of the calories as fructose. Despite the fact that she occasionally ate sucrose-containing foods, she remained completely symptom-free for 6 months.

Burgess et al. (25) and Kerry et al. (26) found intestinal sucrase activities which were consistent with the carrier state in the parents of pa-
patients with sucrase–isomaltase deficiency. The findings in the family of our patient do not show that they are obvious heterozygotes. However, the control specimens were taken from normal individuals eating various types of diets whereas the family of the patient was eating a fructose-supplemented diet. Since dietary fructose may cause two- to threefold increases in activity (23), the heterozygotes might have sucrase activities in the low normal range. When this is taken into account, the findings in the family are consistent with a carrier state in both the patient’s parents as well as her two siblings.

The adaptive mechanism for the sucrase enzyme in this patient appears to be normal. It is possible that the sucrase enzyme may be an abnormal protein perhaps due to an amino acid substitution and is only partially enzymatically active. By causing an increase in the total amount of the abnormal protein then there would also be an increase in the amount that would be enzymatically active. Another possible mechanism is that the primary sucrase enzyme protein is absent and dietary fructose caused an adaptive response in one of the isoenzymes of sucrase (27) which is normally present in very small amounts. At any rate this small increase in enzyme activity would appear to be enough to allow some sucrose to be tolerated without the development of symptoms.

It should be emphasized that patients with disaccharidase deficiency may also have malabsorption of other foods when the offending disaccharide is taken in conjunction with the other foods. For this reason one may occasionally find an abnormal fecal fat excretion or the physical features of celiac disease as was seen in this patient. Since several causes of malabsorption may be confused on both clinical grounds and absorptive studies, a jejunal biopsy with histology and disaccharidase assays should be strongly considered in any patient with a malabsorptive syndrome since specific therapy may be instituted in many cases.

**SUMMARY**

A 7-year-old girl with a 6-year history of chronic diarrhea and poor weight gain was found to have jejunal sucrase–isomaltase deficiency. Dietary fructose was used as a form of therapy to increase the sucrase activity to a level that would allow her to ingest small amounts of sucrose without becoming symptomatic. Treatment with isocaloric diets containing fructose caused a concomitant increase in jejunal sucrase activity. The maximal sucrase activity was approximately four times that seen on a fructose free diet (from 0.38 to 1.67 µmoles substrate hydrolyzed/minute/gm mucosa). There was also an improvement in sucrose tolerance tests as measured by a rise in blood sugar and a decrease in urinary and fecal excretion of sucrose. She was subsequently treated with a sucrose-re-
TREATMENT OF SUCRASE DEFICIENCY

restricted diet which contained approximately 20% of the calories as fructose and has remained asymptomatic for 6 months despite occasional sucrose ingestion.

ACKNOWLEDGMENTS

The authors express their appreciation to Dr. James H. Skala for the sucrose determinations in urine, stool and plasma, Mrs. Valerie Evans for technical assistance, Major Clara Miller and staff for preparation of diets, Major Irene Haupert and staff for nursing care and Mrs. Marie L. Carlson for secretarial assistance.

REFERENCES