Dietary regulation of small intestinal enzyme activity in man\textsuperscript{1,2,3}

Norton S. Rosensweig,\textsuperscript{4} M.D., Robert H. Herman,\textsuperscript{2} M.D., and Fred B. Stifel,\textsuperscript{6} Ph.D.

Much has been known about the normal digestive and absorptive action of the intestinal enzymes upon the dietary constituents, but until recently very little has been known about the effect of these dietary constituents on the enzyme activities in the normal and diseased human intestine.

In the last few years, studies carried out primarily in normal volunteers and obese patients at the United States Army Medical Research and Nutrition Laboratory in Denver, Colorado, have clearly established the adaptive response of human intestinal enzyme activities to a variety of dietary sugars, folic acid, hormones, and drugs. The enzyme systems that have been evaluated are predominantly disaccharidases and glycolytic enzymes.

Since it is relatively easy and safe to obtain human jejunal mucosal tissue by peroral intestinal biopsy, these studies have demonstrated that the adaptive response of jejunal enzyme activities to diet and other substances provides a convenient tool for studying the regulation of enzyme activities in the human intestine in both normal and disease states. As glycolytic enzymes are fundamental to all cells, this system also provides a model for the study of enzyme regulation in man. Studies in this area have provided some insights into the possible mechanisms of expression of the adaptive responses.

Effect of dietary sugars

The three common dietary disaccharides are lactose, sucrose, and maltose; they are poorly absorbed in the small intestine. To be absorbed, they must be hydrolyzed into their component monosaccharides by the disaccharidases, lactase, sucrase, and maltase. These disaccharidases are located in the brush border of the small intestinal epithelial cells, and their activities are highest in the jejunum.

To study the effect of dietary sugars on jejunal disaccharidase activities, normal male volunteers, with no history of disaccharide intolerance, were fed isocaloric liquid diets containing different dietary sugars (sucrose, maltose, lactose, glucose, fructose, and galactose) (1). Sucrose feeding, as compared with glucose feeding, significantly increased sucrase and maltase activities, but had no effect on lactase activity. This effect of sucrose was reproduced by fructose in two subjects. However, lactose, galactose, and maltose as compared with glucose did not increase sucrase and maltase activities in the same way as sucrose and fructose. It was concluded that normal human jejunal sucrase and maltase activities adapt to dietary sugar. Similar results had been obtained previously in rats (2, 3).

Other studies in humans have shown, also, that lactose or milk feeding did not increase lactase activity and lactose-free diets did not decrease lactase activity (4–7). On the other hand, recent studies in rats have shown that prolonged lactose feeding can increase lactase activity in some instances (8, 9).

When it was learned that fructose might be the active principle in the sucrose molecule,
it was postulated that fructose feeding might also produce adaptive increases in the activities of enzymes for which fructose is the primary substrate and not the end product as with sucrase. These enzymes are glycolytic enzymes and are located in the soluble fraction of the cell cytoplasm (Table 1). Studies in rats (10, 11) and in man (12) demonstrated that jejunal glycolytic enzyme activities adapt to dietary sugars. This is true for fructose, glucose, and galactose (13, 14). Fructose feeding produces the greatest increase in fructokinase and fructose-1-phosphate aldolase activities; glucose feeding gives the greatest increase in hexokinase; and galactose feeding produces the greatest increase in galactokinase, galactose-1-phosphate uridylyl transferase, and uridine diphosphate galactose-4-epimerase.

There are several degrees of specificity of dietary effects on the glycolytic enzymes. Noncarbohydrate calories will raise activities above that seen with fasting; carbohydrates, in general, will increase activities above that seen with isocaloric carbohydrate-free diets, and there is a gradient of responses among different carbohydrates.

More recent studies (15, 16) have extended this adaptive principle to include phosphofructokinase, pyruvate kinase, and the gluconeogenetic enzyme, fructosediphosphatase. In contrast with the glycolytic enzymes, fructosediphosphatase activity is highest with fasting and lowest with carbohydrate feeding.

**Effect of vitamins, hormones, and drugs**

Following the demonstration of the regulation of human jejunal disaccharidase and glycolytic enzyme activities by dietary sugars, investigations were expanded to include vitamins such as folic acid, hormones, and drugs.

Administration of folic acid orally to normal volunteers on a constant diet or to fasting obese patients produces a prompt rise in jejunal glycolytic enzyme activities but not in disaccharidase activities (17). This effect does not occur with intramuscular folic acid, oral vitamin B₁₂, or oral tetracycline. Similar results were obtained when folate-deficient germfree and pathogen-free rats were repleted with folate (18). Thus, folic acid is intimately involved in regulating the enzymes of carbohydrate metabolism even though it is neither a substrate nor a coenzyme of these enzymes.

In studies that were a direct outgrowth of the work with dietary sugars and folic acid, it has been shown that both dietary sugars and folic acid can regulate folate-metabolizing enzymes in the rat (19).

Other studies have shown that the sex hormones can regulate certain jejunal glycolytic enzyme activities in rat (20–22) and man (N. S. Rosensweig, R. H. Herman, E. Lufkin and F. B. Stifel, unpublished observations). Other hormones and certain drugs can also affect these enzyme systems (23–25).
Site of action

To gain further insight into the site or mechanism of action, or both, of these dietary substances on jejunal enzyme activities, time responses of the disaccharidase and glycolytic enzyme activities to these substances were carried out (26-29).

When normal volunteers were changed from a glucose to a sucrose diet, or from a sucrose to a carbohydrate-free diet, there was no change in disaccharidase activities after 1 day (26). The change in activity occurred in 2-5 days and there was no further change for 9 weeks thereafter. This time of 2-5 days is similar to the estimated time of intestinal epithelial cell turnover in man. Because of this similarity in the time response of disaccharidase activity and the intestinal epithelial cell turnover time, it was postulated that dietary sugars act primarily upon the crypt cell. As this crypt cell then migrates up the villus the increase in disaccharidase activity is manifested. This observation is consistent with the findings that most of the disaccharidase activity is found in the middle and upper villus cells with the crypts essentially devoid of activity (30, 31) and that near-maximal protein synthesis occurs in lower villus cells that appear to be responsible for disaccharidase synthesis (32).

It should be stressed that the human studies measured only a time response of enzyme activity to dietary sugars and did not in any direct way determine the mechanism of this change in activity. Therefore, the hypothesis that dietary sugars change disaccharidase activity through an action upon the crypt cell should be considered a working one until complete proof is obtained.

In contrast with the time response of disaccharidase activity, diet-induced changes in glycolytic enzyme activity occur in hours and are essentially complete in 1 day (27, 28). Since this response takes place so rapidly, it seems likely that the effect of the dietary sugars, in this instance, is directly at the villus epithelial cell level. Again, no specific proof of this hypothesis is available at this time, but the rapidity of the response makes it unlikely that the effect is mediated via epithelial cell turnover.

It is of interest that the 1-day time response of the glycolytic enzyme activities is quite similar whether the changes in activity are induced by dietary sugars (27, 28), folic acid (29), or hormones (23). This implies that these substances act in a similar manner at some stage of the mechanism that increases activity. However, when the earliest time responses are examined, there is a suggestion that the folate effect precedes the dietary sugar effect that precedes the sex hormone effect (23). This would imply a possible action of sugars and sex hormones via a folate-mediated pathway. However, since some of these studies were performed in rats and some in man, there are not enough data available at this time to make a definitive statement regarding this point.

There appear, therefore, to be at least two types of adaptive responses of human jejunal enzyme activities. There is a rapid (hours), direct, adaptive response of each epithelial cell and a slower (2-5 days) adaptive response that appears to act at the crypt cell level with appearance of the response as the cell migrates up the villus.

Recent studies in rats suggest that lactase activity adapts to 8 or 10 weeks of high lactose feeding (8). This would imply a third adaptive response, one which is very slow and has a long latent period before becoming manifest. There are no comparable studies in man. The mechanism of this very slow response is unknown, but it is almost certainly not at the epithelial cell level. This leaves the crypt or a nonepithelial cell as its site of action. If at the crypt cell, then it is not on a crypt cell that is about to migrate up the villus, but rather on a cell that is relatively static. By inference, then, the disaccharidase effect must be on a cell that is just about to leave the crypt or on a cell that is at the base of the villus, having just left the crypt.

The studies with folic acid strengthen further the identification of two types of adaptive responses. Folic acid increases glycolytic enzyme activity and does so within 1 day. On the other hand, it has no effect on disaccharidase activity even after 7 days of administration.

On the basis of data currently available, one is tempted to suggest that the 2-5-day
response of disaccharidases is characteristic of brush border enzymes and that the 1-day response of glycolytic enzymes is characteristic of soluble cytoplasmic enzymes. Again, more information must be obtained regarding other brush border enzymes, such as alkaline phosphatase and ATPase, before this question can be solved.

In summary, these recent studies on the regulation of jejunal disaccharidase and glycolytic enzyme activities have shed new light on the normal physiologic mechanisms of the human intestine. That intestinal enzyme activities adapt to dietary sugars, vitamins, hormones, and drugs is now established. This helps to call attention to the fact that the intestine as an organ has many capabilities other than the function of absorption. Its large size and the active turnover of its epithelium give it the capacity to perform a significant metabolic role in the body. In some studies in rats, the jejenum and liver have shown a similar enzyme response to dietary challenge (10, 15). This has suggested that the intestine might be used to reflect changes occurring in the liver and elsewhere in the body because of the ease and safety of obtaining intestinal tissue in man. Some caution in extrapolation to other tissues is indicated, however, since recent studies in alloxan-diabetic rats have shown differences between the jejenum and the liver (33). Nonetheless, measurement of the adaptive responses of intestinal enzymes should provide a valuable tool for a further understanding of intestinal physiology in health and disease.

References


