The reconstituted systems had the same characteristics as the original one. The observations available up to now restrict the choice of the possible mechanisms of the sucrase-dependent sugar-transport system to two. (i) If the hydrolysis is efficiently vectorial, a local hyperconcentration of glucose and fructose may arise which could provide a concentration ‘head’ for an apparently increased ‘passive’ diffusion across the lipid bilayer. (ii) The active site of sucrase may have access, either all the time or alternatively, to both sides of the lipid membrane (Semenza et al., 1975b).


---

**Clinical Studies of Carbohydrate Digestion and Absorption**

**HUGH B. McMICHAEL**  
*King Edward Memorial Hospital, London W13 9NU, U.K.*

Since stool water is essentially iso-osmotic (Wilson et al., 1968), the presence in the rectum of as little as 3 g of lactic acid derived from unabsorbed carbohydrate may cause diarrhoea
in man. Since the average daily intake of carbohydrate is about 300 g, the efficiency of its absorption should be at least 99%. The role of the colon in achieving this efficiency has not yet been evaluated, but clearly the efficiency of the small intestine must be very high, and be governed more by potential diarrhoea than by nutritional requirements.

Mechanisms of carbohydrate digestion and absorption are therefore of great interest to clinicians, who have utilized three main methods of study. First, human jejunal mucosal disaccharidase activities have been assayed in vitro; secondly, hydrolysis and absorption of sugars have been measured by steady-state perfusion of the intestinal lumen; and thirdly, naturally occurring deficiency states have been carefully documented. I will refer only briefly to the specific disaccharidase deficiencies.

Jejunal mucosal disaccharidase activity

Assay technique. Dahlqvist (1968) has developed the basic technique. It should now be considered essential to assay β-galactosidase (lactase) activity in the presence of p-chloromercuribenzoate, so that only the relevant brush-border enzyme is measured (Asp & Dahlqvist, 1972).

Analysis of results. Results of disaccharidase assays are scattered log-normally (McMichael et al., 1966). Failure to recognize this has led to many spurious statistical deductions, the commonest of which is the inclusion of zero activity within the range of the mean ± 2 standard deviations. A great benefit of expressing the results in logarithmic form is that the results of lactase assays (even in the absence of p-chloromercuribenzoate) are seen to fall clearly into two separate populations. Unfortunately, most authors have defined lactase deficiency on an arbitrary basis, and the arbitrary value chosen has varied considerably.

Effects of mucosal structural damage. The presence of minor degrees of structural damage of the mucosa greatly depresses mucosal disaccharidase activities. Lactase activity is depressed more than those of the other disaccharidases (Plotkin & Isselbacher, 1964; McMichael et al., 1966).

Functional interpretation of disaccharidase assays

Specific disaccharidase deficiencies. Disaccharidase deficiency in subjects with structurally normal mucosa is functionally significant and frequently associated with diarrhoea. In children, the stool often contains the affected sugar. The blood glucose fails to rise appropriately after ingestion of the relevant sugar (Weijers et al., 1961; McMichael, 1972). Steady-state intestinal-perfusion studies confirmed that the relevant disaccharide is poorly absorbed by the small intestine (McMichael et al., 1967).

Disaccharide hydrolysis and absorption related to disaccharidase activity in normal subjects. After excluding results from patients with structurally damaged mucosa and with statistically defined disaccharidase deficiency, steady-state perfusion studies show no correlation between the rates of absorption of lactose, sucrose or maltose and the relevant mucosal disaccharidase activity measured in vitro in a biopsy taken from the perfused region of gut in the same patient (McMichael et al., 1967; McMichael, 1971, 1972). Further, Fig. 1 shows that there is no correlation between mucosal maltase (α-glucosidase) activity and the rate of total maltose hydrolysis (i.e. the sum of the carbohydrate absorbed and the glucose found free in the lumen). These correlations were studied between 35 and 280 mM-disaccharide concentration, which includes the physiological concentration and the apparent $K_m$ of hydrolysis and absorption.

Lactose-tolerance tests and lactase activity. Gudmand-Hoyer & Jarnum (1968) suggested that there was a correlation between lactase activity and lactose absorption as measured by blood sugar rise after lactose ingestion in 13 normal subjects. We not only failed to find such a correlation (or trend) in a small number of perfusion studies but failed to find one between blood sugar rise after lactose and the measured lactase activity in 35 normal subjects (McMichael, 1972).

Effects of mucosal damage. Because of the commercial availability of milk-based protein, there has been great interest in the significance of the decreased lactase activity in
Maltase activity was measured \textit{in vitro} on peroral jejunal mucosal biopsy. Activity is expressed as $\mu$mol of maltose hydrolysed/min per g wet weight of tissue. Total hydrolysis was measured by steady-state jejunal lumenal perfusion \textit{in vivo}. Initial lumenal maltose concentration was 70mM.

the presence of mucosal damage, especially when this damage is due to protein malnutrition. Careful clinical studies measuring stool weight have shown clearly that lactose produces more diarrhoea than equivalent weights of glucose (Prinsloo \textit{et al.}, 1969). James (1968) showed by perfusion studies a decreased rate of lactose absorption compared with glucose which recovered after correction of the malnutrition.

Two special factors must be taken into account in interpreting these data. First, the subjects of both these studies were from ethnic groups with extremely high incidences of primary acquired lactase deficiency, as indeed is the case in most of the developing countries where malnutrition occurs (Simoons, 1969). Secondly, recent knowledge of the complexities of monosaccharide absorption indicate that absorption rates of glucose and galactose could be differentially affected by mucosal damage, so that impaired absorption of lactose is not necessarily due to depressed lactase activity.

\textit{Conclusion.} These findings suggest that, in the normal subject, rates of hydrolysis and absorption are limited by factors other than the mucosal disaccharidase activity. The factor likely to be limiting absorption is the rate of membrane transport of the released monosaccharides. The rate of hydrolysis is probably limited by the accumulation of the hydrolysis products within a partially confined space around the disaccharidases (Hamilton & McMichael, 1968; McMichael, 1974). Rate-limiting factors in the presence of mucosal damage are, as yet, unknown.

\textit{Monosaccharide transport}

In the late 1960s, monosaccharide transport seemed to be largely understood (Crane, 1968). Since then, more and more unexplained facets have come to light, so that Semenza (1975) is now suggesting the existence of four systems which can be defined \textit{in vitro}. It is the purpose of this section to describe some experiments \textit{in vivo}, and observations which confirm that the situation is complex, particularly since they do not obviously fit in with the data \textit{in vitro}. My own work in this field has been done by using a steady-state luminal perfusion system in anaesthetized rats (Dawson & McMichael, 1968) and some of the results have been reported as an abstract (McMichael, 1973).

\textit{Jejunal and ileal kinetic studies.} It has been shown previously that the apparent $K_m$ of glucose absorption is lower in the ileum than the jejunum, for example in man (Schedl & Clifton, 1961) and in rats (Rider \textit{et al.}, 1967). Such kinetic differences have various possible interpretations and have been described for unrelated substances such as methionine

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{\textit{Total maltose hydrolysis related to jejunal mucosal maltase activity}}
\end{figure}

\begin{itemize}
\item Maltase activity was measured \textit{in vitro} on peroral jejunal mucosal biopsy. Activity is expressed as $\mu$mol of maltose hydrolysed/min per g wet weight of tissue. Total hydrolysis was measured by steady-state jejunal lumenal perfusion \textit{in vivo}. Initial lumenal maltose concentration was 70mM.
\end{itemize}
(Schedl et al., 1968), but we were unable to show a comparable difference in apparent $K_m$ for galactose. It may be noted that a low ileal $K_m$ is teleologically advantageous.

Glucose and galactose competition in vivo. Holdsworth & Dawson (1964) inhibited the absorption of galactose by glucose in man but found no inhibition of glucose absorption by galactose. We have confirmed these findings in rat jejunum but were able easily to inhibit glucose absorption by galactose in the ileum.

Uranyl nitrate and monosaccharide transport. Ponz & Lluch (1958) in vivo and Newey et al. (1966) in vitro have shown that absorption of glucose is more inhibited by uranyl nitrate than that of galactose. We have now shown that glucose transport in the ileum is more sensitive to uranyl nitrate than that in the jejunum (an effect which might be due to differential microclimate pH).

Phlorrhizin inhibition. By using very high phlorrhizin concentrations (up to 10 mm) we inhibited nearly all the absorption of glucose and galactose in vivo. The inhibition curves were monophasic for galactose but biphasic for glucose (Fig. 2).

Effects of Na+ on glucose transport in vivo. Observations by Olsen & Ingelfinger (1968) suggested that intraluminal Na+ ions were of some significance in man in vivo when glucose was being perfused against a concentration gradient. Even this minor effect is now being questioned (Saltzman et al., 1972). Our own observations in rats have failed to show any effect of intraluminal sodium on active glucose transport. The experimental technique, of course, cannot exclude the presence of Na+ ions in the microclimate adjacent to the absorbing membrane. The experimental emphasis on Na+ ions in vitro cannot be transferred to the situation in vivo.

---

Fig. 2. Inhibition by phlorrhizin of glucose and galactose transport (rat jejunum in vivo)

Absorption rate is expressed as a percentage of the absorption rate in each rat in the absence of phlorrhizin. Mean $\pm$ S.E.M., $n = 6$. ○, Galactose; ■, glucose. Glucose substrate concentration was 20 mm.
Glucose–galactose malabsorption. This rare genetically determined syndrome is at first sight difficult to correlate with any hypothesis that there is more than one mechanism for glucose transfer, but several explanations are possible. First, in subjects with this condition the absorption of galactose is undetectable but small amounts of glucose are still absorbed (Meeuwisse & Melin, 1969). Secondly, two systems may be determined by a single gene (as is sucrase–isomaltase deficiency). Thirdly, it is possible that one of two systems is frequently absent producing no or only mild symptoms and severe symptoms occur when both are absent simultaneously.

Conclusions. There is evidence in vivo that there are two (or more) systems for glucose transport, only one of which is shared with galactose. They are probably present in different ratios in the jejunum and ileum. The two mechanisms emerging from studies in vivo do not readily coincide with observations in vitro.

General summary and conclusions

In the normal subject, the rates of disaccharide digestion and absorption appear to be limited by the rate of monosaccharide transfer across the cell membrane. Selective disaccharidase deficiencies occur which inhibit hydrolysis and absorption.

More than one system of glucose transport probably exists, and a low-\(K_m\) system in the ileum may be of particular relevance in the prevention of diarrhoea in man.

McMichael, H. B. (1973) Gut 14, 428

Specific Disaccharidase Deficiency in Adults

ARNE DAHLQVIST and NILS-GEORG ASP

Department of Nutrition, Chemical Centre, P.O. Box 740, S-220 07 Lund 7, Sweden

Our concept of the biochemistry, physiology and clinical importance of the intestinal disaccharidases has become clearer during the last decade. Semenza (1975) has