INTOLERANCE TO LACTOSE AND OTHER DIETARY SUGARS

DALLAS M. SWALLOW, MARK POULTER, AND EDWARD J. HOLLOX

Medical Research Council Human Biochemical Genetics Unit, Galton laboratory, Department of Biology, London, United Kingdom

This paper is available online at http://dmd.aspetjournals.org

ABSTRACT:
Intolerance of dietary carbohydrate and sugars can result from a variety of genetically determined enzyme and transporter deficiencies. This article reviews this topic and discusses in more detail the current state of our own research on lactase.

Dietary carbohydrates are of two kinds: polysaccharides, such as starches, and sugars, that is, di- and monosaccharides. Starches from plants make up three-quarters of dietary carbohydrates and are composed of two structurally different polysaccharides, amylose, which is a linear α 1-4-linked D-glucose polymer, and amylpectin, with additional α 1-6 linkages, which give it a branched structure. Digestion commences with salivary and pancreatic amylases (EC 3.2.1.1). Alpha-amylase produces linear maltose (glucose α 1-4-glucose) and isomaltose (glucose α 1-6-glucose) oligosaccharides as well as some larger oligomers. The final hydrolysis of these occurs in the small intestine where the brush-border membrane maltase-glucoamylase (EC 3.2.1.20, 3.2.1.3) and sucrase-isomaltase (EC 3.2.1.48, 3.2.1.10) convert them to glucose, which is taken into the absorptive cells by the sodium-dependent glucose transporter SGLT1. Sucrase-isomaltase digests all the sucrose and 80% of the dietary maltose, while maltase-glucoamylase digests the remaining maltose and alone digests the glucose oligomers.

Dietary disaccharides include lactose, the main carbohydrate in human and other mammalian milks, sucrose from sugar beet and sugar cane, and a rather rarer dietary component trehalose (glucose α 1-1-glucose), which is present in mushrooms, insects, and certain seaweeds. These are hydrolyzed by lactase, sucrase, and trehalase, respectively, before transport of the component monosaccharides by the brush-border sugar transporters. The bulk of the molecule of each of the hydrolases projects into the lumen of the intestine, although the mode of anchorage into the membrane differs. The transporters in contrast span the membrane.

Dietary monosaccharides are present principally in fruits and are transported directly by the brush-border membrane transporters. Fructose, which is also one of the products of sucrose digestion, is transported by GLUT5, whereas glucose and galactose are transported by SGLT1.

There are thus several molecules at the apical surface of the small intestinal absorptive cells, which are of critical importance to normal carbohydrate digestion (Tables 1 and 2) (Levin, 1994). Reduced function of any one of these leads to the passage of undigested carbohydrate into the bowel where it is fermented by bacterial flora to form short-chain fatty acids and gases. While fatty acid absorption increased by colonic fermentation is thought by some to be beneficial, excessive production of gases leads to flatulence, and the osmotic effect of di- and monosaccharides in the luminal contents leads to diarrhea.

Tables 1 and 2 list these hydrolases and transporters and the known genetic deficiencies relating to them. These genetic deficiencies vary dramatically in frequency. Congenital glucose/galactose malabsorption, due to deficiency of SGLT1, which transports both the glucose and galactose produced by lactose digestion, is certainly rare. Congenital alactasia is very rare indeed, although a cluster of cases has been reported in Finland, where this is one of the “Finnish recessive disorders”. Both are very severe conditions, which can be fatal if not diagnosed immediately, since there is onset of symptoms as soon as milk is first consumed. In contrast, adult lactase deficiency or lactase nonpersistence is more common than lactase persistence and represents a genetically determined polymorphism in human populations that involves developmental regulation. It is uncertain how frequently genetic deficiencies of sucrase-isomaltase, trehalase, and maltase-glucoamylase occur. In most cases half levels of the normal protein, as present in heterozygotes, are sufficient to deal with the dietary load, but there are several indications that this is not always the case.

In the first part of the article current information on the proteins involved in digestion and transport is summarized. In the second part current progress on lactase is reviewed since lactase deficiency is perhaps the best understood and is the subject of our own research.

Properties of the Enzymes and Transporters

Sucrase-Isomaltase. The human sucrase-isomaltase gene (SI) on chromosome 3 encodes an mRNA transcript of 5.48 kb and a 1827-amino acid peptide precursor (Chantret et al., 1992). Sucrase-isomaltase is a two-active site molecule, synthesized as a single polypeptide chain (pro sucrase-isomaltase), which is cleaved by a pancreatic protease to form the two subunits with different substrate specificity (Semenza et al., 2000). The two subunits remain associated, and only one subunit of the dimer is attached to the brush-border membrane by its N-terminal end. These heterodimers themselves dimerize to form a tetramer, which is the active catalytic unit localized in the brush-border membrane.

Sucrase-isomaltase deficiency is probably not uncommon. Deficiency of SI has been found in about 2% of diagnostic biopsies in London (A. D. Phillips, personal communication) and in the USA (Ringrose et al., 1979). In the Inuit from Greenland it was detected in...
10% of the population (McNair et al., 1972), where it was a significant clinical problem because of excessive feeding of sugar to babies; furthermore, there are reports of reduced SI in black South Africans, which suggests the possibility of activity polymorphism (Veitch et al., 1998). Studies on the protein suggest that various different mutations cause the deficiency, but so far only one exonic mutation has been identified, which results in substitution of proline by a glutamine at amino 1098 (Ouwendijk et al., 1996), but it is not known whether it is this mutation that occurs at high frequency. Severity of the condition depends directly on the dietary sucrose intake, and in the case of the Inuit the severity led to failure to thrive before this condition had been understood.

**Maltase-Glucoamylase.** Maltase-glucoamylase is encoded by a gene, MGAM, located on chromosome 7. The mRNA transcript is 6513 bp, and the calculated molecular weight of the protein (before glycosylation) is 209,702 (Nichols et al., 1998). This protein probably forms homodimers, and the complex is anchored to the brush-border membrane by a phosphatidylinositol anchor (Ruf et al., 1990). Trehalase deficiency is thought to be an autosomal recessive trait and has been reported at a frequency of 8% in Greenland (McNair et al., 1972), but has been reported in a parent and child and three other close relatives (Madzarovova-Nohejlova, 1973). Given the unusual distribution of the deficiency, deficiency has not been of any nutritional consequence until recently, but it may become a problem because of its introduction as a sweetener in foods.

**Sodium-Dependent Glucose Transporter (SGLT1).** SGLT1 is encoded by the gene SLC5A1 located on chromosome 22. It is a protein with 13 membrane spanning domains and is the major apical transporter of glucose and galactose. Deficiency of SGLT1 leads to congenital glucose/galactose malabsorption. Many different mutations have been found.

**Glucose Transporter GLUT5.** GLUT5 is an apical glucose transporter whose main role seems to be the transport of fructose (Levin, 1994). It also has many trans-membrane domains, and it is encoded by the gene SLC2A5.

**Glycosylation.** The brush-border hydrolases and transporters are all glycosylated, and in the case of lactase and sucrase-isomaltase there is not only evidence for both N- and O-glycosylation, but also person to person variation in terminal glycosylation since both proteins carry the ABH blood group antigens (Green et al., 1988).

**Hereditary Fructose Intolerance**

Intolerance of dietary fructose shows two quite different clinical presentations. Fructose malabsorption with the classical symptoms of diarrhea and flatulence was thought to be due to a transporter defect, but sequencing revealed no mutations in the coding sequence of GLUT5 (SLC2A5) (Wasserman et al., 1996). A somewhat more common condition manifests as recurrent hypoglycemia and vomiting, failure to thrive, and kidney and liver involvement. In this condition, deficiency of fructose phosphate aldolase (aldolase B) has been found. Aldolase catalyzes the conversion of fructose-1-phosphate to dihydroxyacetone phosphate and D-glyceraldehyde, and is thus essential for the metabolism of dietary fructose, which is transported to the liver from the enterocytes via the basolateral glucose transporter GLUT2. A number of different mutations leading to amino

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Di- and Polysaccharide</th>
<th>Enzyme</th>
<th>Gene Locus</th>
<th>Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Lactase</td>
<td>LCT</td>
<td>Congenital alactasia</td>
</tr>
<tr>
<td>Sucrose Maltose Isomaltose</td>
<td>Sacrose-isomaltase</td>
<td>SI</td>
<td>Congenital sucrase deficiency</td>
</tr>
<tr>
<td>Maltose</td>
<td>Maltase-glucoamylase</td>
<td>MGAM</td>
<td>Congenital maltase—glucoamylase deficiency</td>
</tr>
<tr>
<td>Terminal alpha 1-4 linkages on polysaccharides</td>
<td>Trehalase</td>
<td>TREH</td>
<td>Trehalase deficiency</td>
</tr>
</tbody>
</table>

*For official gene symbol see http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl for Online Mendelian Inheritance in Man (OMIM) and other literature and sequence links.

**TABLE 2**

<table>
<thead>
<tr>
<th>Monosaccharide</th>
<th>Transporter</th>
<th>Gene Locus</th>
<th>Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>SGLT1 sodium-dependent glucose transporter</td>
<td>SLC5A1</td>
<td>Glucose/galactose malabsorption</td>
</tr>
<tr>
<td>Galactose</td>
<td>GLUT5 glucose transporter 5</td>
<td>SLC2A5</td>
<td>? Hereditary Fructose malabsorption</td>
</tr>
</tbody>
</table>

*For official gene symbol see http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl for Online Mendelian Inheritance in Man (OMIM) and other literature and sequence links.
acid substitutions have been found, but a single mutation is found at a heterozygosity of more that 0.01 in the UK, for example (Ali et al., 1998). The high incidence of the deficiency alleles suggests that before the recent increase in intake of dietary fructose there was little selective disadvantage for this allele. The condition varies in its clinical severity according to the dietary intake of fructose, and removal of fructose from the diet prevents the disease. It is of interest to note that in patients who have consciously or unconsciously avoided fructose there is a remarkable absence of dental caries.

The Molecular Basis of the Lactase Persistence/Nonpersistence Polymorphism

The expression of lactase is polymorphic in adult humans (Swallow and Hollox, 2000). This is an unusual genetically determined regulatory polymorphism with large differences in allele frequency in human populations. Lactase activity is necessary for obtaining full nutritional benefit from both human and animal milk because it is needed for digestion of the lactose, which is the major carbohydrate in milk. Lactase activity is thus vital in baby mammals. It shows tight control of developmental expression, being expressed at low levels in fetal life and increasing around birth, and it is only expressed in small-intestinal enterocytes (Wang et al., 1998). Lactase declines after weaning in most adults but persists into adult life in many others (Fig. 1). Lactase persistence tends to be the most frequent phenotype in populations where fresh milk forms a significant part of the adult diet; for example, Northern Europeans and pastoral nomadic tribes. Lactase-nonpersistent adults can usually consume only limited amounts of fresh milk without experiencing flatulence and diarrhea. The very high frequency of the lactase persistence allele in certain populations probably results from selection for milk drinking, due the nutritional value of milk.

We have shown that the lactase persistence/nonpersistence polymorphism is controlled by a cis-acting regulatory element (Fig. 2) and have provided direct evidence of down-regulation of one transcript in heterozygous children (Wang et al., 1995, 1998) by examining the level of expression of both transcripts in individuals heterozygous for exonic polymorphisms. Our hypothesis is that genetic differences in a sequence element, in the vicinity of the lactase gene, cause it to interact differentially with a developmentally regulated trans-acting protein(s).

We have studied 70-kb haplotypes across the lactase gene in different human populations (Hollox et al., 2001). The results show marked linkage disequilibrium across this region, although with population differences and much greater haplotype diversity in African populations. One particular haplotype, A, is associated with lactase persistence and is at very much higher frequency in Northern Europe than any other population (Harvey et al., 1998) (Fig. 3), suggesting a selective sweep by the linked alleles responsible for the phenotypic polymorphism. We have characterized a hypervariable region immediately upstream from the lactase gene and have shown evidence of variable binding to a possible trans-acting protein (Hollox et al., 1999), although this region does not correspond to the critical causative element.

Analysis of 12 kb of upstream sequence showed no polymorphism that associates exclusively with persistence (Boll et al., 1991; Lloyd et al., 1992; M. Poultier, E. J. Hollox, and D. M. Swallow, unpublished observations). Thus, to search the sequence responsible for this novel cis-acting mechanism, we have constructed a 700-kb contig (700-kb region covered by overlapping clones) centered on the lactase gene, and the sequences at the end of each clone or “sequence tag connectors” are being used to search for single nucleotide polymorphisms. These are being used to define the region of maximal association and subdivide the haplotypes, which will allow eventual identification of the causal element.

The locus responsible for Finnish congenital alactasia has also been genetically mapped 5’ of LCT (Jarvela et al., 1998). It is possible that this disorder involves disruption of the same element that controls the developmental down-regulation of lactase.

![Fig. 1. Diagrammatic representation of the level of lactase expression at different stages of development and in lactase persistent and nonpersistent adults.](image)

The levels of activity are mainly regulated at the RNA level.

![Fig. 2. Diagram showing the likely mechanism of the cis-acting polymorphism in determining lactase expression in persistent and nonpersistent adults.](image)

A developmentally regulated DNA binding protein may interact with a cis-element present on one allele and not the other (due to sequence differences within the elements).
The numbers represent the published lactase persistence allele frequencies (see Swallow and Hollox, 2000).

Conclusion

There are many examples of intolerance of dietary saccharides. These intolerances are not usually life threatening because symptoms can be avoided by removal of the offending sugar from the diet, although congenital lactase deficiency and glucose-galactose malabsorption can be fatal if not diagnosed quickly. The presence of some these deficiencies at relatively high frequencies in some populations is of evolutionary interest in relation to changes in human diet, and the significance of homozygosity or heterozygosity for deficiency alleles to human nutrition and health is an area that is relatively unexplored.

Acknowledgments. We thank M. Zvarik and V. Ferak (Bratislava); A. Krause and T. Jenkins (Witwatersrand, South Africa); A. Koslov (Moscow); and N. Saha, Singapore, for their contribution to the work on population samples, which will be published in detail elsewhere.

References


FIG. 3. Map of the world to show the distribution in the Old World of the lactase persistence allele (from published lactase tolerance studies) and the LCT haplotypes A, B, C, and U.

The Metabolic and Molecular Basis of Inherited Disease

Acknowledgments. We thank M. Zvarik and V. Ferak (Bratislava); A. Krause and T. Jenkins (Witwatersrand, South Africa); A. Koslov (Moscow); and N. Saha, Singapore, for their contribution to the work on population samples, which will be published in detail elsewhere.

References


The Metabolic and Molecular Basis of Inherited Disease

Acknowledgments. We thank M. Zvarik and V. Ferak (Bratislava); A. Krause and T. Jenkins (Witwatersrand, South Africa); A. Koslov (Moscow); and N. Saha, Singapore, for their contribution to the work on population samples, which will be published in detail elsewhere.