ADVANCES IN HUMAN GENETICS 16

Edited by

Harry Harris

and

Kurt Hirschhorn

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Chapter 1

Genetics of Lactose Digestion in Humans

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INTRODUCTION

Lactose is a biologically unique sugar. In contrast to the other nutritionally important disaccharides, the α-glycosides maltose and sucrose, lactose is a β-glycoside. Lactose occurs in large amounts and as a free molecule only in milk. It is thus a biochemical and nutritional characteristic of mammals and is not present in other classes of animals. Sugars more common than lactose and more ancient in evolutionary terms would presumably suffice for the supply of energy to the young mammal. The development of the intricate mechanisms of lactase synthesis in the mammary gland and of lactose digestion in the intestinal tract would therefore run counter to evolutionary economy if lactose did not convey a special selective advantage during the suckling period. Evidence of such an advantage is not available at present. Adult mammals usually do not have access to milk in their natural environment, and their lactose digestion capacity declines after weaning. The human species is no general exception to this rule: in the majority of humans there is a gradual decline of lactase activity during early childhood. Adults with persistent lactase activity and correspondingly high lactose digestion capacity are common in only a few populations. The causes and distribution of this dimorphism of lactase activity in human adults will be the main subjects of this review.

Scientific interest in lactose digestion dates back to the work of Pautz

and Vogel (1895), who reasoned that there must be a mechanism promoting the digestion of lactose in the intestinal tract of infants. By incubating in a lactose solution crude intestinal homogenates taken from a child they showed that lactose is effectively hydrolyzed in the small intestine, but not in the stomach or in the colon. In the same year Röhmann and Lappe (1895) demonstrated the hydrolysis of lactose in the small intestine of calves and puppies; in contrast, similar preparations from cows and adult dogs showed little or no lactase activity. The small intestine was firmly established as the location of disaccharide absorption in 1903, when Röhmann and Nagano (1903) narrowed the most active site of lactose hydrolysis to the jejunum. Mendel and Mitchell (1907) extended these experiments and confirmed the considerable difference in jejunal lactase activity between young and adult mammals, while Plimmer (1906) examined the question of whether lactose is an inducible enzyme. He found that dietary lactose given to adult rabbits and rats does not result in an increase in small-intestinal lactose digestion capacity. Had Plimmer's work not been forgotten, the heated controversy in the late 1960s regarding whether lactase activity was adaptively or genetically determined would have been resolved sooner.

Lactose-induced adaptation of lactase activity seemed very plausible. Since adult subhuman mammals do not feed on milk, it was assumed that their lactase activity is low due to lack of substrate-specific induction. Conditions were different in humans: in countries where medical research was active in the earlier part of this century, adults were found to consume copious amounts of milk and other lactose-containing foods. Consequently, their tolerance to milk and lactose was attributed to an adaptive maintenance of high lactase activity levels. This view was later strengthened by the discovery of substrate-induced enzyme synthesis in bacteria. The classical paradigm of this mechanism, stimulation of genetically controlled β-galactosidase synthesis by lactose in *Escherichia coli*, was readily—and as we know now, inappropriately—applied to human lactase. Tolerance to large amounts of milk and lactose was considered "normal" and "healthy." In retrospect, it is surprising that lactose intolerance in healthy adults with low lactase activity was not recognized before the 1960s. "Fermentative dyspepsia" as a result of incomplete absorption of carbohydrates had been recognized at the beginning of the century (Schmidt and Strasburger, 1901) and an enzymatic defect of lactose digestion had been suspected by Howland (1921).

Research with regard to nutritional adaptation to lactose was resumed