Intestinal absorption of water-soluble vitamins
Focus on “Molecular mechanism of the intestinal biotin transport process”

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THE WATER-SOLUBLE VITAMINS represent a structurally and functionally distinct set of organic compounds that are essential for human health. It has long been recognized that they play a vital role in intermediary metabolism, energy production, and cell differentiation and proliferation (1, 4). Mammals, including humans, have lost their ability to synthesize these compounds and, therefore, must obtain them from diet and other exogenous sources (1, 4). Biotin deficiency in humans is associated with a range of clinical abnormalities, including neurological disorders, growth retardation, and skin abnormalities (1, 4). The cellular assimilation and function of vitamins are to a large extent dependent on their absorption via the gastrointestinal tract, making the studies of their intestinal absorption mechanisms and regulation extremely important. Although originally assumed to be absorbed by passive diffusion processes, intestinal absorption of these micronutrients has been shown to occur by specialized transport mechanisms (6–8). The current article in focus by Chatterjee et al. (Ref. 3, see page C605 in this issue) represents a significant contribution from a group of researchers who for many years have been carrying out studies of mechanisms and regulation of intestinal transport of a number of water-soluble vitamins at the tissue, cellular, membrane, and molecular levels. The study in focus describes the molecular characterization of the intestinal absorption process of one of the water-soluble vitamins, namely, biotin.

Biotin, also known as vitamin H and coenzyme R, acts as an essential coenzyme for four carboxylases that catalyze the incorporation of cellular bicarbonate into metabolically important organic compounds (1, 4). For example, the enzyme acetyl carboxylase catalyzes the formation of malonyl-CoA, which serves an important function as a substrate for fatty acid synthesis. The other biotin-requiring carboxylases are involved in gluconeogenesis and fatty acid and branched-chain amino acid metabolism. The mammalian intestine is exposed to biotin derived from the diet and from synthesis by normal colonic microflora. Similar to studies of intestinal transport of a number of nutrients, the chronology for biotin has evolved from an initial belief that the transport process is nonspecific and occurs by a simple diffusion process, to identification of a carrier-mediated system and its physiological and biochemical characterization using tissue slices and membrane vesicles, and finally to the current cloning of the transport protein involved (8). In the last decade, independent studies by Brown and Rosenberg (2) and Said and Redha (14), using intact small intestinal tissue preparations, have shown the involvement of a Na⁺-dependent, carrier-mediated mechanism for biotin transport in the rat small intestine. Subsequent studies from the laboratory of Said, using purified intestinal apical and basolateral membrane preparations, have demonstrated that the Na⁺-dependent, carrier-mediated process is localized in the apical domain of enterocytes (9, 13, 17). It was also shown that an outwardly directed Na⁺ gradient energized the transport of biotin across the apical membrane. The transport process was found to be electroneutral with a biotin/Na⁺ stoichiometric coupling ratio of 1:1. Recently, exciting and unexpected results regarding the function of the human colon in biotin transport revealed the presence of a similar transport process in human colonic apical membranes (12). These findings are very significant, because the transport process can be expected to fully utilize the biotin synthesized in the colonic lumen by bacteria. Regarding the efflux mechanism for biotin that is important for tissues other than the intestine, transport of biotin across the basolateral membrane domain was shown to occur by a Na⁺-independent, carrier-mediated process (16). Regional differences in transport characteristics for biotin have been shown, with the duodenum showing higher transport rates than the ileum (11, 14). The higher transport rates were shown to be related to an increase in maximal velocity rather than the Michaelis-Menten constant, indicating a higher number of carriers or increased turnover in the proximal part of the small intestine. Various studies of regulation of biotin transport have also shown ontogenic effects as well as regulation by extracellular substrate levels and protein kinase-mediated pathways (8, 10, 12, 15). A very interesting recent development in this area was the demonstration that the biotin transport system could be shared by an unrelated water-soluble vitamin, pantothentic acid (8, 12). However, the physiological and nutritional implications of such a vitamin-vitamin inter-
action at the transporter level are not currently understood. Future studies should focus on this important question, in view of the presence of >200-fold higher levels of pantothenic acid compared with biotin in the diet and the importance of both vitamins for vital metabolic functions.

The current article in focus describes the molecular characterization of an intestinal biotin transporter (3). These investigators have isolated three variants of the recently described placental transporter. It is noteworthy that the isolation of the placental transporter cDNA was purely serendipitous, in that those investigators initiated their search for a cationic transporter that ended up in the discovery of an anionic transporter (5). The three variants described in the investigations of Chatterjee et al. (3) are significant, in that they have the same open reading frame as the placental variant but differ in the 5’ untranslated end. Furthermore, the placental variant was not found in the small intestine. These results clearly point to the potential for future studies to investigate the transcriptional regulation of this transporter, to understand the tissue-specific expression and other regulatory mechanisms in its expression. The authors have transfected the cDNA into COS-7 cells and have confirmed that the transporter characteristics of the cloned transporter are similar to what they have observed in native intestinal membranes regarding substrate specificity, kinetics, and inhibitor profiles. It is clear that the molecular characterization of the intestinal biotin transport process described in this report will greatly assist in future investigations aimed at an understanding of the molecular regulation of the transport process of this essential micronutrient, not only in the intestine but also in other tissues that are involved in regulating biotin homeostasis.

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