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Physiology of Intestinal Absorption and Secretion

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A B S T R A C T

Virtually all nutrients from the diet are absorbed into blood across the highly polarized epithelial cell layer forming the small and large intestinal mucosa. Anatomical, histological, and functional specializations along the gastrointestinal tract are responsible for the effective and regulated nutrient transport via both passive and active mechanisms. In this chapter, we summarize the current state of knowledge regarding the mechanism of intestinal absorption of key nutrients such as sodium, anions (chloride, sulfate, oxalate), carbohydrates, amino acids and peptides, lipids, lipid- and water-soluble vitamins, as well as the major minerals and micronutrients. This outline, including the molecular identity, specificity, and coordinated activities of key transport proteins and genes involved, serves as the background for the following chapters focused on the pathophysiology of acquired and congenital intestinal malabsorption, as well as clinical tools to test and treat malabsorptive symptoms.

Introduction

This chapter emphasizes the physiology of intestinal absorption. The transport protein responsible for absorptive function of the gastrointestinal tract resides in the apical side of the villous structure,

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which is involved in facilitating the transport of nutrients across the length of the small intestine. Recent advances in molecular cloning have led to further understanding of these transport proteins and how they are altered in the settings of health and disease states. The chapter will also discuss the intestinal transport of ions, short chain fatty acids, sulfate, oxalate; as well as major nutrients such as carbohydrates, proteins, and fats. The chapter concludes with a discussion of the absorption of water-soluble vitamins, fat-soluble vitamins, minerals, and micro-nutrients.

Functional anatomy of the GI tract

The GI tract evolved to facilitate the transport of nutrients throughout its length. The small intestine measures approximately 6 m in length and 2.5–3.0 cm in diameter. The colon measures approximately 1.5 m in length with a diameter of 6–7.5 cm. The surface area of the small intestine is significantly enhanced by the presence of villi and microvilli, which increase the intestinal surface area by 30–600 fold, respectively. Villi are approximately 0.5–1.6 mm in length and are covered with columnar epithelial cells at the tip. These are mostly absorptive cells, whereas crypt cells are generally regarded as secretory. Most of the nutrient transport occurs in the small intestine, whereas the colon is primarily responsible for water and electrolyte transport. The GI tract is responsible for handling approximately 8–10 L of fluid containing approximately 800 mmol of sodium (Na^+), 700 mmol of chloride (Cl^-), and 100 mmol of potassium (K^+) that passes through the intestinal lumen every day. The bulk of the transport of these fluids and electrolytes occurs through the small intestine, leaving approximately 1.5 L for the colon to absorb and leaving approximately 100 mL that is lost through the stools every day. The mechanisms responsible for the solute transport across the GI tract are secondary to several transport proteins located at the brush border membranes of the small and large intestine. The net fluid movement across the gastrointestinal epithelium is primarily the result of active transport of Na^+, Cl^-, and HCO_3^-, among others.

Intestinal Na^+ absorption

Three mechanisms contribute to the apical Na^+ transport in the small intestine: (*a*) nutrient-coupled Na^+ absorption mediated by several families of Na^+-dependent nutrient transporters such as sugar or amino acid transporters discussed separately in this chapter, (*b*) electroneutral NaCl absorption mediated primarily via the Na^+/H^+ exchange mechanism [1], and (*c*) colon-predominant electrogenic Na^+ absorption by the epithelial Na^+ channels (ENaC) [2]. Electroneutral NaCl absorption is attributed to members of the SLC9 family of Na^+/H^+ exchangers. Three NHE isoforms have been identified on the enterocyte apical membrane: NHE2, NHE3, and NHE8 [3–5]. Of the three, NHE3 contributes most significantly to the intestinal Na^+ and water absorption. Missense mutations in *SCL9A3* gene coding for NHE3 has been shown recently to be associated with congenital sodium diarrhea (CSD) [6]. Reduced expression and mistargeting of NHE3 protein in the enterocytes is also believed to be partially responsible for diarrhea in patients with microvillous inclusion disease, a rare genetic disorder associated with mutations in Myo5B or Syntaxin three. During intestinal inflammation, inhibition of NHE3-mediated Na^+/H^+ exchange has been postulated to lead to gut microbial dysbiosis, epithelial barrier defect, and exacerbated inflammatory response. There are scenarios, however, when NHE3 inhibition may be clinically beneficial. A recent study with a novel, poorly bioavailable, orally administered NHE3 inhibitor, tenapanor, showed that reduction of NHE3-mediated intestinal Na^+ absorption was beneficial in a rat model of chronic kidney disease, in which it reduced extracellular fluid volume, left ventricular hypertrophy, albuminuria, and blood pressure [7].

In the colon, particularly in the ascending segment, a substantial fraction of the net Na^+ absorption is also mediated by electroneutral NaCl transport. This process is a reflection of dual Na^+/H^+ - Cl^-/HCO_3^- exchanges [the latter mechanism mediated by PAT1 (*SLC26A6*) and downregulated in adenoma (DRA; *SLC26A3*)] operating in parallel in the apical membrane. The same three major Na^+/H^+ exchangers are expressed on the apical surface of colonocytes as in the small intestine. Electrogenic Na^+ absorption – predominant in the descending colon, sigmoid and rectum – is most commonly attributed to the activity of mineralocorticoid-regulated apical epithelial sodium channels (ENaC). This mechanism may have limited contribution to an ileal Na^+ transport, particularly as an adaptive