Pharmacological Management of Diarrhea

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KEYWORDS

• Diarrhea • Secretory diarrhea • Secretion
• Enkephalinase inhibitors • Vasoactive intestinal polypeptide
• 5-HT

According to the World Health Organization, there are approximately 2 billion annual cases of diarrhea worldwide. Diarrhea is the leading cause of death in children younger than 5 years and kills 1.5 million children each year. It is especially prevalent in the developing world, where mortality is related to dehydration, electrolyte disturbance, and the resultant acidosis, and in 2001 it accounted for 1.78 million deaths (3.7% of total deaths) in low- and middle-income countries.[1] However, diarrhea is also a common problem in the developed world, with 211 million to 375 million episodes of infectious diarrheal illnesses in the United States annually, resulting in 73 million physician consultations, 1.8 million hospitalizations, and 3100 deaths.[2] Furthermore, 4% to 5% of the Western population suffers from chronic diarrhea.[3] Given the high prevalence of diarrhea, research has been directed at learning more about the cellular mechanisms underlying diarrheal illnesses in order to develop new medications directed at novel cellular targets. These cellular mechanisms and targets are discussed in this article.

MECHANISMS OF DIARRHEA

Ingestion of fluids and secretion of salivary, gastrointestinal, and pancreatic juices result in up to 10 L of fluid passing through the small intestinal lumen daily. A maximum of 16 L/d and 5 L/d can be absorbed in to the small intestine and colon, respectively. Normally, secretion and absorption of fluids are tightly regulated. Diarrhea develops

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when the balance between secretion and absorption is disrupted, and in adults, diarrhea has been defined as a stool output of 200 mL or more per day. Patients typically complain of increased stool frequency, reduced stool consistency, and urgency. Diarrhea can be defined as secretory, osmotic, or due to disordered motility. Secretory diarrhea results from excessive secretion or reduced absorption of water and electrolytes by epithelial cells, usually with little structural damage. Secretory diarrhea is commonly caused by some microbial infections, gastrointestinal hormone–producing tumors, and inflammatory mediators (eg, prostaglandins). Osmotic diarrhea occurs when there is an excessive luminal osmotic load, causing retention of water in the intestinal lumen. Osmotic diarrhea typically occurs in 2 situations: ingestion of a poorly absorbed substrate (eg, laxative use, mannitol, sorbitol) or malabsorption (eg, lactase deficiency, celiac disease). Disordered motility can lead to accelerated transit, reducing the ability of the gastrointestinal tract to absorb water and nutrients. Hyperthyroidism and irritable bowel syndrome can cause diarrhea via this mechanism.

Ion Secretion

Epithelial cells form an impermeable and selective barrier, adjoined to each other by tight junctions that act as selective pores, thus determining the permeability of the membrane. Intestinal fluid secretion results predominantly from the active secretion of chloride and bicarbonate ions. Chloride secretion relies on 4 membrane transport complexes: the apical chloride channel, the basolateral potassium channel, the sodium-potassium pump (Na^+,K^+-ATPase), and the $Na^+/K^+/2Cl^-$ cotransporter (**Fig. 1**). The opening of the chloride channels results in the movement of chloride into the intestinal lumen down an electrochemical gradient. Chloride secretion is regulated by a coordinated intracellular and extracellular cascade, involving agonists or antagonists from the intestinal lumen or lamina propria. These agonists or antagonists bind to membrane-bound receptors, for example, vasoactive intestinal polypeptides

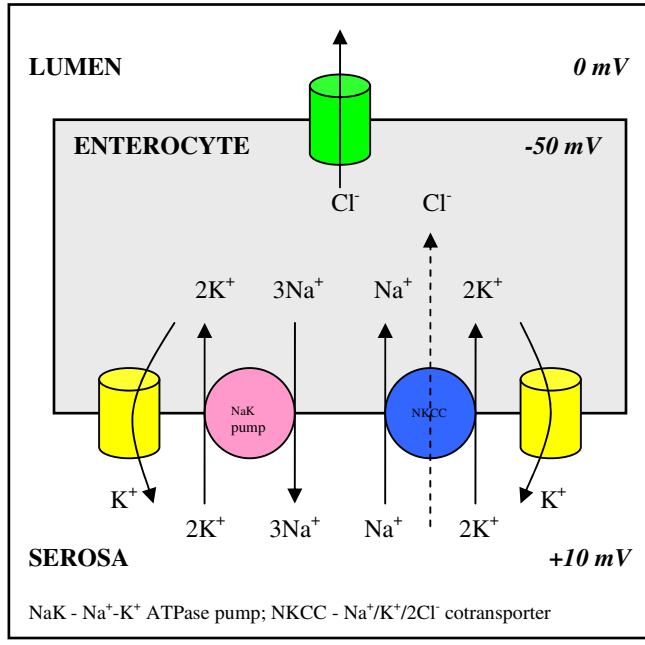

Fig. 1. Sodium and chloride secretion.