Gastrointestinal Physiology

—*the essentials*

Second Edition

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Preface to the Second Edition

Our goals in this second edition have addressed the following needs: 1) references for further reading, 2) updating of all material and 3) revision of subject matter that reviewers identified as problematic. The chapter on carbohydrate absorption has been rewritten entirely. A set of questions has been added to stimulate thought in the subject matter and to serve as the basis for discussion in conference situations. The section on further reading was added primarily for the benefit of the graduate student, although the medical and health professional student will find these references useful as introductions to gastrointestinal pathophysiology.

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Preface to the First Edition

This book is intended to serve as an introduction to gastrointestinal physiology for beginning medical and graduate students. Realizing that these students usually have but a week or so to devote to the subject, the authors have placed a premium on essentials and brevity. Physiological mechanisms have been stressed, while structural and biochemical details have been omitted. Wherever possible, the essential concepts have been highlighted by clear and simple illustrations. These essential concepts and key words have been recapitulated as brief summaries at the end of all chapters and as a comprehensive summary in the final chapter.

In recognition of the medical orientation of our readership, well-defined clinical examples of gastrointestinal pathophysiology have been added to all chapters.

The topics considered in this monograph include general gastrointestinal functions, secretion and absorption. Membrane transport and gastrointestinal circulation have been given special emphasis, because these subjects are basic to an understanding of gastrointestinal secretion and absorption.

Finally, the authors are grateful to the many individuals who helped in the technical preparation of this text. We especially appreciate the illustrations drawn by Molly G. Sernka. We also wish to recognize the critical advice of Dr. Michael Eade in the preparation of the chapter on the circulation.

THOMAS J. SERNKA
EUGENE D. JACOBSON

Contents

chapter 1

Introduction

the general functions of the gastrointestinal tract and the medical importance of this system

Gastrointestinal physiology is the study of the many normal functions of the organs that comprise the gastrointestinal tract. These include the esophagus, stomach, liver, pancreas, small intestine and colon. This portion of the body is ultimately responsible for the fate of swallowed food and involves a number of processes essential for the conversion of food into a form that can be utilized by the rest of the body and for the elimination of waste material. In order to carry out these functions it is critical that some swallowed substances be moved as much as 450 cm from mouth to anus. It is also essential that various glandular structures in the gastrointestinal tract secrete juices which are added to ingested food to permit decomposition of complex molecules into smaller forms. Still another vital function of the system takes place in the small intestine where transport of small molecules from the lumen of the gut into the circulation takes place.

The processes of motility, secretion, absorption and excretion are regulated by both external and internal factors. The external factors include the autonomic nervous system and hormones. The internal factors involve certain properties of cells including excitability, membrane transport, biosynthesis and packaging of new molecules and release of synthesized materials. Gastrointestinal functions are also

influenced by local tissue substances and nervous networks contained in the walls of hollow organs.

The gastrointestinal tract is an interface between the outside world and the body. Most materials from the environment which enter the body, whether food or toxins, do so by passing through the lining of the gastrointestinal tract. This system, therefore, serves as a protective barrier which excludes many items that have been swallowed into the hollow tubes of this system from gaining access to the rest of the body. Thus, for example, many bacteria are contained in the food that we swallow, yet these organisms are not permitted to reach the circulation as do digested food materials.

Other less well-understood functions of the gastrointestinal organs include their large contribution to the immunological defenses of the body, their active metabolism of many substances in the body and their contribution to the regulation of fluid and electrolyte balance. The gastrointestinal organs are also an important reservoir of blood when the individual is at rest.

More than any other organ system of the body the gastrointestinal tract consists of an heterogenous collection of dissimilar organs. The functions of the esophagus and the pancreas are as unlike one another as are the functions of the liver and the colon. This dissimilarity among the functions of the components of the system adds to our difficulty in understanding what gastrointestinal physiology is all about.

One may reasonably ask at this point: What is the medical importance of gastrointestinal physiology or even of the gastrointestinal tract itself? In the evolution of multicellular animals it became necessary to develop a specialized portion of the body to handle ingested food. The food had to be converted to a usable form and nonusable materials needed to be excreted. Thus, the economy of the body depends to a large extent on a smoothly functioning gastrointestinal system. Beyond the key physiological role of the gastrointestinal tract there is the medical significance of digestive diseases. In the United States the total economic cost of illness due to diseases of the gastrointestinal tract is exceeded only by the total cost of cardiovascular diseases and the cost of violent death and injury (accidents and crime). One-tenth of the total economic burden of all illness in this country is attributable to digestive diseases which account for one in seven admissions to general hospitals, one in four surgical operations, direct medical costs

in excess of $15 billion and a total economic loss (direct medical costs plus costs of disability) of $50 billion annually.

Among the very common diseases of the gastrointestinal system which confront most physicians are such entities as peptic ulcers, cirrhosis of the liver, hepatitis, gallstones, colitis, pancreatitis, diverticulitis, esophagitis, and cancers of the colon, pancreas, stomach, liver and esophagus.

Beside these serious and often life-threatening conditions there are a large number of symptoms referable to the gastrointestinal tract which cause people to seek the assistance of physicians. These include such common symptoms as indigestion, heartburn, vomiting, abdominal discomfort and pain, flatulence, constipation and diarrhea. In studies of otherwise healthy individuals in our society nearly one-half complain of the frequent occurrence of these symptoms. There is a flourishing over-the-counter business in American drugstores involving many remedies for these complaints.

Before one can hope to treat these symptoms or diseases in a rational manner it is essential that the normal functions of the gastrointestinal system be understood. At the present time there is a considerable body of information about gastrointestinal physiology and it is likely that the future will witness elucidation of many of the puzzling features of this complex set of organs.

chapter 2

Mucosal Metabolism

how gastrointestinal cells work and divide

Two major functions of the gastrointestinal mucosa are to secrete and to absorb. Both secretion and absorption require metabolic work by the epithelial cells lining the gastrointestinal tract. To perform this work gastrointestinal cells utilize their own energy stores and that of the blood bathing them. These cells age rapidly and are sloughed into the lumen of the gastrointestinal tract. Their work of secretion or absorption is taken up by younger cells that have recently divided.

Bioenergetics

The metabolic work of secretion is oxidative. Enzymes that form the secreted product receive energy from oxidations of the tricarboxylic acid cycle. Most energy derives from oxidation of substrates circulating in the mucosal blood. These include glucose and free fatty acids. The blood flow to the secreting mucosa also provides the oxygen for substrate oxidation. Epithelial cell pO_2 is about 15 mm Hg and decreases with ischemia. Other substrates for oxidation include glycogen and triglycerides stored within the gastrointestinal cells. Mitochondria in gastrointestinal cells contain the oxidative enzymes that metabolize all the substrates from pyruvate and fatty acids into carbon

dioxide. Other cytoplasmic enzymes metabolize stored glycogen and triglyceride into utilizable pyruvate and fatty acids.

Another oxidative pathway, the hexose monophosphate shunt, also forms pyruvate. In doing so, however, it synthesizes the NADPH essential to the formation of lipids. A bilayer of lipid is needed to form the unit membranes of gastrointestinal cells. Both plasma membranes and endoplasmic reticulum proliferate when secretion is stimulated. These membranes contain the transport enzymes for secretion.

The products of substrate oxidation in the gastrointestinal tract, as elsewhere, are reduced pyridine nucleotides, mainly NADH. These nucleotides, in turn, are oxidized within the mitochondria to yield the unit of chemical energy, ATP. The coupling of nucleotide oxidation to the phosphorylation of ADP provides the essential link between metabolism and secretion in the gastrointestinal tract.

A variety of substrate-specific ATPases in different gastrointestinal cells extract energy from the terminal phosphate bond of ATP to drive secretion. For example, $(H^+ + K^+)$-ATPase is thought to provide energy for H^+ secretion by oxyntic cells.

Figure 2.1 is a summary of the metabolic steps important to secretion by gastrointestinal cells: 1) glucose and fatty acids derived mainly from the blood are oxidized; 2) reduced pyridine nucleotides are used to synthesize ATP or membranes; and 3) substrate-specific ATPases utilize ATP to effect secretory transport into the lumen.

The metabolic work of absorption is also oxidative. Glucose and fatty acids are oxidized to form reduced pyridine nucleotides, and the latter are oxidized with coupled phosphorylation of ADP. The intestinal basolateral membranes contain $(Na^+ + K^+)$-ATPase to drive absorption of Na^+ and accompanying anions.

Cytokinetics

Digestion is the enzymatic hydrolysis of carbohydrate, protein and fat. The digestive work that precedes absorption can be and often is hypoxic or even anaerobic. Hypoxic conditions are largely a consequence of the villus structure. Because the arteriolar and venular branches of the villus capillaries run countercurrent and closely adjacent to one another, physically dissolved oxygen in the incoming blood can diffuse across the base of the villus rather than travel its length in the capillary. This physiological shunting of oxygen from arteriolar to venular blood of the villus makes the villus tip hypoxic. The cells at

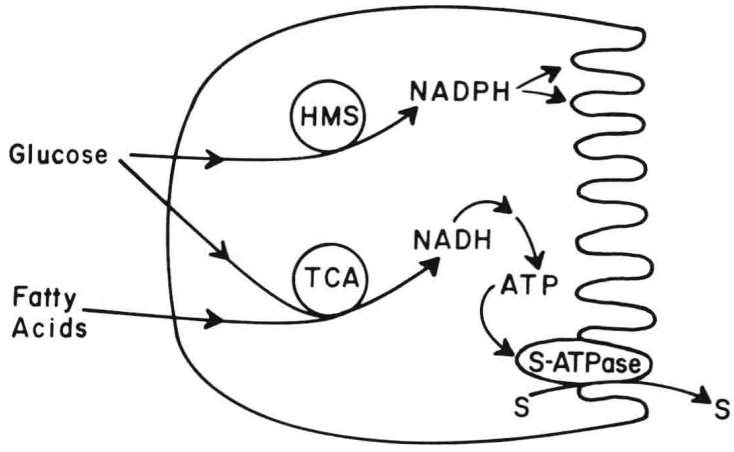

Figure 2.1. Basic metabolic mechanisms utilized in secretion of substance S by gastrointestinal cell. *TCA*, tricarboxylic acid cycle; *HMS*, hexose monophosphate shunt; *NAD(P)H*, reduced pyridine nucleotides; *S-ATPase*, substrate S-specific ATP phosphatase.

the villus tip can survive only a limited time in such a hypoxic environment. After a day or two these hypoxic cells are released from the epithelium into the lumen, a process called desquamation or sloughing.

Many of the digestive enzymes in the microvilli of such sloughed cells do not require oxygen. These include disaccharidases and dipeptidases that complete the breakdown of sugar and proteins. These enzymes continue to act long after they have been released into the gut lumen. They are essential to the final digestion and absorption of monosaccharides and amino acids in the intestine.

Cells that are being sloughed at the villus tip are constantly replaced by younger cells that migrate up the villus. The division of undifferentiated cells in the crypts between the villi is the source of this migration. As the cells emerge onto the villus base, they mature by acquiring digestive enzymes. In disease states such as sprue, the villi are denuded of their microvillar enzymes which contributes to malabsorption of nutrients.

Figure 2.2 is a summary of the metabolic steps important to absorption by intestinal cells: 1) immature crypt cells migrate and mature on the villus; 2) digestive enzymes in the microvilli or brush border region act either in intact or sloughed cells; and 3) countercurrent blood flow insures hypoxia of the tip of the villus and continual sloughing.

Regulation

Normally, secretory glands line the pits in the epithelium and do not become hypoxic. Their arteriolar and venular capillary blood flows are separated by the invaginated epithelium. However, after severe hemorrhage there is a reduced blood volume (hypovolemia) which causes generalized mucosal ischemia and even secretory cells become hypoxic. Reduction in blood flow to the stomach drastically lowers intracellular pO_2 and ATP production and inhibits active transport of ions. Prolonged hypoxia of the secretory cells of the stomach leads to a type of stress ulcer.

Constant sloughing and cell renewal is characteristic of both secretory and absorptive epithelia in the gastrointestinal tract. The stimulus for epithelial cell division is unknown, although regulatory factors have been identified. The rate of cell sloughing at the villus tip exerts

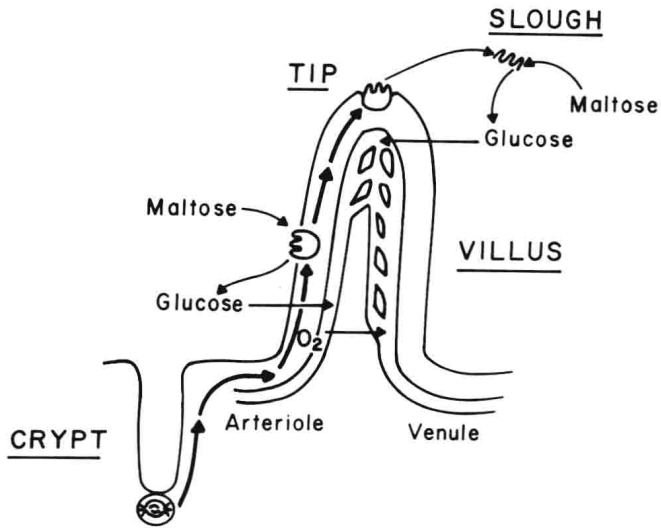

Figure 2.2. Metabolic aspects of absorption by gastrointestinal cells. Maltose is disaccharide of glucose.

feedback control over the rate of cell division in the crypts. Thus, in sprue, where villus cells are attacked and destroyed at high rates, crypt cells multiply at correspondingly high rates to replace them. Another regulatory factor for epithelial cell growth appears to be the hormone, gastrin, which is synthesized by the so-called "G cells" of the gastric antrum. The trophic effect of this hormone is the proliferation of the gastrointestinal mucosa. Deprivation from food, as during total parenteral nutrition, leads to reduced production of gastrin and mucosal atrophy. Gastrin acts by sequentially stimulating DNA, messenger RNA and protein synthesis of sensitive cells. It has also been found that resection of the proximal intestine stimulates proliferation of the distal small intestinal mucosa. The thickness of a given length of distal small intestine greatly increases after proximal resection. The number of cells per villus and the rates of migration and desquamation in the distal small intestine also increase after proximal resection, reflecting the heightened cell turnover.

Secretory cells of the stomach respond to the three basic stimuli: gastrin, acetylcholine and histamine. Much of the stimulation by all three agents is metabolic in that oxygen and substrates for oxidation are consumed. For example, acetoacetate alone does not stimulate gastric secretory cells but acetoacetate plus acetylcholine does. Apparently, gastric secretory cells have receptors on their basolateral membranes for gastrin, acetylcholine and histamine. When these receptors are occupied by the appropriate stimulants, the metabolism of the cell is affected.

Intracellular cyclic nucleotides, such as cyclic AMP and cyclic GMP, have been identified as key mediators of cellular responses to external agents, such as hormones. The hormone activates a membrane-bound enzyme, adenylate cyclase, which catalyzes the synthesis of cyclic AMP from intracellular ATP. The cyclic nucleotide then triggers a chain of reactions beginning with activation of a protein kinase, phosphorylation of an enzyme, calcium uptake and binding, activation of an ATPase and release of energy for secretion of solutes by mucosal cells. In intestinal diseases characterized by diarrhea due to secretion of fluid by the mucosa of the small intestine, for example, asiatic cholera, the preceding intracellular events occur. The stimulus for adenylate cyclase is an exotoxin of the bacteria which cause cholera. Other known stimuli include many of the prostaglandins, which are naturally occurring and which also cause diarrhea. The end result of stimulating the membrane-bound enzyme and causing accumulation of cyclic

AMP inside intestinal mucosal cells is the active secretion of chloride from the tissue into the lumen of the gut. As solute is secreted, water is attracted osmotically and this hypersecretion of large volumes of fluid prompts diarrhea.

Summary

The metabolic energy for secretion and absorption in gastrointestinal mucosa comes from oxidation of glucose and fatty acids. NADPH is manufactured for lipid membrane synthesis and NADH for ATP synthesis. Dephosphorylation of ATP drives secretion of substances from the mucosal cell into the lumen by means of specific ATPases.

Mucosal cells are constantly being sloughed and replaced. In the intestine the tips of the villi are made hypoxic and prone to sloughing by diffusion of oxygen across the base of the villus. Digestive enzymes in the microvilli of epithelial cells remain active even after sloughing. Newly divided and undifferentiated cells migrate from the deep to the superficial mucosa to replace sloughed cells.

Cell growth and division in the gut is regulated by the rate of sloughing, the amount of functional mucosa and the trophic hormone gastrin. Gastric secretion is regulated by acetylcholine, histamine and gastrin, and diarrheal intestinal secretion is mediated by cyclic AMP.