Handbook of Experimental Pharmacology 239

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Editor

Gastrointestinal Pharmacology

Springer

Handbook of Experimental Pharmacology

Volume 239

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ISSN 0171-2004 ISSN 1865-0325 (electronic)
Handbook of Experimental Pharmacology
ISBN 978-3-319-56359-6 ISBN 978-3-319-56360-2 (eBook)
DOI 10.1007/978-3-319-56360-2

Library of Congress Control Number: 2017937312

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

In 1982, two volumes of the *Handbook of Experimental Pharmacology* edited by Professor Giulio Bertaccini, M.D., addressing Mediators and Drugs in Gastrointestinal Motility I and II were published. In 1993, David R. Brown, Ph.D., edited a volume in the *Handbook of Experimental Pharmacology* on Gastrointestinal Regulatory Peptides. Over 20 years later this latest volume of the *Handbook of Experimental Pharmacology* aims to connect current ideas and concepts about gastrointestinal (GI) disorders with the search for novel therapeutics. Towards this goal, the following chapters will provide a timely state-of-the-art overview of the GI tract in health and disease, current treatment approaches and ongoing developments in drug discovery, and their potential for the better treatment of patients with GI disorders. GI disorders rank among the most prevalent disorders, with the most common including esophageal and swallowing disorders, gastric and peptic ulcer disease, gastroparesis or delayed gastric emptying, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). Some of these disorders are organic involving pathological damage to the GI tract as seen in IBD when the bowel becomes inflamed and damaged, leading to abdominal pain, diarrhea, and rectal bleeding. Other GI disorders such as IBS are termed "functional" disorders because they lack a structural or biochemically defined cause. Recent estimates suggest that one in four people suffer from a functional bowel disorder and they represent 40% of GI problems seen by physicians. The major symptoms of common GI disorders include recurrent abdominal pain and bloating, heartburn, indigestion/dyspepsia, nausea and vomiting, diarrhea, and constipation. Despite GI disorders placing a growing burden on today's healthcare system, many GI disorders are difficult to diagnose and the symptoms are not effectively managed. In addition, many patients with GI disorders do not benefit from the currently available therapeutics. Novel effective therapeutics are thus urgently needed. Currently, there are a limited number of medications available or approved to treat GI disorders due, in part, to a lack of knowledge of the exact mechanisms underlying GI motility, absorption, secretion, inflammation, and sensation. Although significant gaps in the understanding of GI disorders still exist, new therapies are likely to emerge from current research and development. The immune system in the gut is currently offering a wide variety of therapeutic targets to treat IBD, whereas concepts that have emerged to treat GI dysmotility, abdominal pain and IBS, include the

brain-gut axis linking the nervous system in the GI tract to the CNS. The gut microbiome is currently an area of active research. Moreover, our understanding of the gut microbiota remains in its infancy; however major advances linking the intestinal microbiome to the brain-gut axis are likely over the upcoming years and will offer new therapeutic targets for the development of novel drugs to treat GI disorders.

I am immensely grateful to James Barrett for inviting me to serve as the Editor of this volume on Gastrointestinal Pharmacology in the *Handbook of Experimental Pharmacology* book series. I would like to thank the editorial staff from Springer for all their support. Most importantly, the success of this volume on Gastrointestinal Pharmacology is due to each of my colleagues who generously contributed their expertise and time to preparing such outstanding chapters for this volume of the *Handbook of Experimental Pharmacology*. I am indebted to this team of highly distinguished leaders in the GI field. We hope that this volume of the handbook will serve as an essential reference to investigators and scholars involved in basic and clinical GI research as well as individuals treating patients with GI disorders.

Oklahoma City, Oklahoma, USA Beverley Greenwood-Van Meerveld

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Gastrointestinal Physiology and Function

Beverley Greenwood-Van Meerveld, Anthony C. Johnson, and David Grundy

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Abstract

The gastrointestinal (GI) system is responsible for the digestion and absorption of ingested food and liquids. Due to the complexity of the GI tract and the

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B. Greenwood-Van Meerveld (ed.), *Gastrointestinal Pharmacology*,
Handbook of Experimental Pharmacology 239, DOI 10.1007/164_2016_118

substantial volume of material that could be covered under the scope of GI physiology, this chapter briefly reviews the overall function of the GI tract, and discusses the major factors affecting GI physiology and function, including the intestinal microbiota, chronic stress, inflammation, and aging with a focus on the neural regulation of the GI tract and an emphasis on basic brain-gut interactions that serve to modulate the GI tract. GI diseases refer to diseases of the esophagus, stomach, small intestine, colon, and rectum. The major symptoms of common GI disorders include recurrent abdominal pain and bloating, heartburn, indigestion/dyspepsia, nausea and vomiting, diarrhea, and constipation. GI disorders rank among the most prevalent disorders, with the most common including esophageal and swallowing disorders, gastric and peptic ulcer disease, gastroparesis or delayed gastric emptying, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD). Many GI disorders are difficult to diagnose and their symptoms are not effectively managed. Thus, basic research is required to drive the development of novel therapeutics which are urgently needed. One approach is to enhance our understanding of gut physiology and pathophysiology especially as it relates to gut-brain communications since they have clinical relevance to a number of GI complaints and represent a therapeutic target for the treatment of conditions including inflammatory diseases of the GI tract such as IBD and functional gut disorders such as IBS.

Keywords

Absorption • Barrier function • Central nervous system (CNS) • Colon • Constipation • Diarrhea • Digestion • Enteric nervous system (ENS) • Epithelial barrier • Gut microbiome • Inflammation • Inflammatory bowel disease (IBD) • Intestinal permeability • Irritable bowel syndrome (IBS) • Mucosa • Secretion • Small intestine • Smooth muscle • Stress • Visceral pain

1 Introduction

The overall function of the GI tract is to digest ingested nutrients through complex processes of digestive enzyme secretion and nutrient absorption. Luminal contents move along the GI tract via smooth muscle peristalsis, while smooth muscle segmentation ensures adequate contact time and exposure to the absorptive epithelial mucosal surface. The gut is capable of handling about 9 L of fluid per day, which is mainly absorbed by the small intestine. This fluid movement can occur through paracellular or transcellular routes. The former pathway involves water movements coupled to nutrient absorption via alterations in tight junction expression, while the transcellular route involves the passage of water through apical and basolateral membranes of epithelial cells by passive diffusion, cotransport with ions and nutrients, or through aquaporins. During intestinal absorption the epithelial barrier is specifically designed to protect against the movement of potentially

harmful antigenic, toxic, or infectious material across the GI mucosal surface (Camilleri et al. 2012).

To ensure effective digestion and proper GI tract health requires a complex series of coordinated neural events accomplished by the central nervous system (CNS), the nerve network within the gut itself known as the enteric nervous system (ENS), and a whole host of GI endocrine peptides that target specific cells and tissues that make up the GI tract. Specialized endoderm-derived epithelial cells termed enteroendocrine cells (EECs) form the largest endocrine organ in the body and are widely distributed throughout the GI tract. EECs play a key role in the control of GI function including secretion, motility, and regulation of food intake, postprandial glucose levels, and metabolism (Latorre et al. 2016). The gut also performs important immune functions and a vast array of inflammatory mediators can influence the recruitment of lymphocytes and other immune cells to the gut wall including mast cells, and at the same time modulate the activity of the gut neural networks (O'Malley 2015; Wouters et al. 2016). Additionally, the abundance of microbiota residing in the human intestine estimated at 10^{14} microorganisms plays a pivotal role in the development of the ENS, the overall health not only of the GI tract but also the entire human body via mechanisms that include activation of the immune system, and production of short-chain fatty acids (SCFAs) to promote colon cell health as well as brain-gut interactions (Patterson et al. 2014; Kabouridis and Pachnis 2015; Moloney et al. 2016; Obata and Pachnis 2016; Sandhu et al. 2016).

2 Basic Anatomy of the GI Tract

The human GI tract is composed of multiple different organs and can be divided into the upper and lower GI tract. The upper GI tract refers to the mouth, esophagus, stomach duodenum, jejunum, and ileum, while the colon, rectum, and anus make up the lower GI tract. The esophagus propels ingested food from the pharynx into the stomach via a wave of highly coordinated esophageal peristalsis. Once in the stomach, the food bolus is mixed with gastric acid and digestive enzymes and is broken down to allow digested material, now called chyme, to pass through the pyloric sphincter into the duodenum. Once in the small intestine (duodenum, jejunum, and finally ileum) the digestive process breaks down proteins, fats, and carbohydrates to smaller components to allow for nutrient absorption. Accessory organs that aid in the digestive process include the salivary glands, pancreas, liver, and gallbladder. Once the luminal contents reach the large intestine, the contents are now called feces, and are prepared for expulsion via the rectum and anal canal.

To accomplish the digestive processes in a coordinated manner, the GI tract has a functional anatomy that in general terms is composed of a series of layers including the inner mucosal layer of the GI tract composed of absorptive and secretory epithelial cells. The remaining layers of the GI tract include the submucosal layer containing nerves, lymphatics, and connective tissue; the smooth muscle layer composed of longitudinal and circular smooth muscle; and the

outer serosal layer. Specialized ECCs that are diffusely scattered in the GI mucosa possess the capability of sensing the luminal content and in turn release signaling molecules that enter the circulation to act as classic hormones on distant targets, and act locally in a paracrine fashion on neighboring cells and on distinct neuronal pathways including enteric and extrinsic neurons. Each type of EEC has a characteristic distribution along the GI tract. Among the mediators released, cholecystokinin (CCK) and glucagon-like peptide (GLP-1) play important roles in reflex control of GI function and in regulating food intake. EECs are divided into "*open type*" with a bottleneck shape and an apical prolongation with microvilli facing towards the intestinal lumen or "*closed type*" that are located close to the basal membrane, do not reach the lumen of the gut, and lack microvilli. The open-type EECs directly detect luminal contents through the microvilli reaching the lumen, whereas the closed types are thought to be activated by luminal content indirectly either through neural or humoral pathways (Gribble and Reimann 2016; Latorre et al. 2016). This EEC-sensory neuron connection has thus opened a new exciting prospective on EECs and their role in the communication with ENS and CNS and sheds new light on our understanding of the complexity of the bidirectional communication between the brain and the gut. The therapeutic potential of compounds working via EEC function is high. In support a GLP-1R agonist is used to treat diabetes mellitus type 2, based on its ability to stimulate insulin secretion from pancreatic β-cells (van Raalte et al. 2016). Furthermore, in patients that have a gastric bypass the beneficial role of GLP-1 and $PYY_{3\text{-}36}$ secretion in the reduction of food intake may have additional therapeutic potential to treat obesity (Svane et al. 2016). Drugs acting to alter EEC functions may also participate in the control of depression, anxiety, and visceral hypersensitivity, which are key components of functional GI disorders.

2.1 Basic Functions of the GI Tract: GI Motility

The major functions of the GI tract are motility, secretion, and absorption. Smooth muscle tone and contractility are modulated by interstitial cells of Cajal (ICC), which serve as the pacemaker creating spontaneous electrical slow waves that spread from the ICC to the smooth muscle in the presence of a stimulus such as a neurotransmitter leading to contraction of the GI smooth muscle. The reader is referred to excellent reviews of the topic (Ward and Sanders 2001; Sanders et al. 2016). Small and large intestinal motility is under multiple levels of control including the ENS and CNS, as well as GI hormones and paracrine agents. In general, there are two distinct patterns of small intestinal motility (1) following a meal when the intestinal lumen contains chyme and (2) during the inter-digestive period. During the digestive phase the longitudinal and circular smooth muscle of the GI tract generates coordinated patterns of contractility termed peristalsis and segmentation. Peristalsis occurs in waves of contraction behind and relaxation ahead of the luminal bolus, and travels down the GI tract over short distances. Segmentation is a mixing pattern of contractility that is more irregular and allows

for luminal contents and digestive enzymes to have adequate contact with the absorbing epithelium. During the inter-digestive phase, a complex pattern of motility called the migrating motor complex (MMC) sweeps along the entire small intestine to clear the GI tract of any remaining luminal debris. Large intestinal motility patterns serve to impede aboral movement of luminal contents, which facilitates water absorption. Contractility patterns of the colon are predominantly non-peristaltic and mix the colonic contents back and forth to enhance contact with the absorbing mucosa. A less frequent pattern of colonic motility which occurs 6–8 times/day is the high-amplitude propagating contractions (HAPC) which sweep the colon and often trigger the urge to defecate.

2.2 Basic Functions of the GI Tract: GI Secretion and Absorption

The GI tract secretes up to 9 L of fluid/day containing digestive enzymes, bile, ions, water, and mucus. Important for secretion and absorption of fluids, electrolytes, and solutes are the epithelial cells which differ in structure and function depending on their location in the GI tract. The stomach is a glandular organ. Gastric parietal cells in glands within the gastric body are important for the secretion of gastric acid and intrinsic factor, pepsinogen is secreted by the chief cells also within the gastric body, while hormones (gastrin, histamine, serotonin, and somatostatin) are released from EEC throughout the stomach. Most of the digestive process and intestinal absorption of food and electrolytes occur in the duodenum, jejunum, and ileum. Proteins, fats, and carbohydrates are broken down via the action of digestive enzymes into smaller units in preparation for absorption into the network of capillaries and lymphatic vessels (lacteals) by the small intestinal epithelial cells located on the small intestinal villi. Any remaining material that is not absorbed by the small intestine passes though the ileocecal valve into the colon. The large intestinal mucosa is responsible for the absorption of water, solidification of the colonic contents into feces, and then storage of the feces prior to expulsion.

2.3 Basic Functions of the GI Tract: GI Barrier Function

Solute and particulate matter moves across the intestinal epithelium in a regulated manner either between epithelial cells or across the apical membrane of epithelial cells. Routes of transport across the epithelium include passive permeability (relevant for the passage of larger hydrophilic compounds), transcellular transport of lipophilic and small hydrophilic compounds, transcellular route via aqueous pores of small hydrophilic compounds, and active carrier-mediated absorption of nutrients and electrolytes, and endocytosis, followed by transcytosis and exocytosis of larger peptides, proteins, and particles. Transport between epithelial cells occurs via the tight junction region. Far from being static, tight junctions are continually being monitored and regulated by both intra- and extracellular signals. Several types of proteins contribute to the development of tight junctions including

the claudin family of proteins that form the actual paracellular pore within the tight junction and are associated with other transmembrane proteins called occludins. Zonula occludens (ZO)-1 and other cytoplasmic proteins, such as ZO-2 and ZO-3, attach and serve as junctional complex proteins. Also relevant to the barrier properties are adherens, junctions that are defined as a cell junction where the cytoplasmic face is linked to the actin cytoskeleton. At the basal pole of the intercellular space, desmosomes are formed by interactions between desmoglein, desmocollin, desmoplakin, and keratin filaments (Camilleri et al. 2012; Volynets et al. 2016). An important function of the gut epithelium is its protective role, functioning as a barrier between the external environment and the internal milieu. Several components form the multilayered intestinal barrier that is region specific; in the upper GI tract, gastric acid, pancreatic juice, and production of antimicrobial substances serve as a first line of defense. Next, the microenvironment close to the epithelium consists of the unstirred water layer, glycocalyx, and mucus layer, and below are epithelial cells separated by tight junctions. Under pathophysiological conditions, increases in epithelial permeability allow products to translocate the epithelial barrier including luminal antigens, toxins, and microbial fermentation. These products are capable of activating afferent nerve endings leading to visceral afferent sensitization, which is important since several different human diseases, including IBD, celiac disease (CD), and IBS, have been associated with increases in gut permeability and abnormal barrier function (Camilleri et al. 2012; Ohman et al. 2015).

3 Neural Control of the GI Tract

The neural innervation of the GI tract allows for the movement of contents along the GI tract, secretion of digestive enzymes, and absorption of luminal contents and makes certain that information from GI tract is carefully integrated and that the appropriate reflex responses are generated to ensure that all parts of the digestive system function in concert.

3.1 Enteric Nervous System

Contained within the gut wall is the ENS that is a subdivision of the autonomic nervous system (ANS) and is capable of autonomous activity. The ENS contains many of the transmitters and neuromodulators found in the CNS and is organized into specific circuits that control smooth muscle and mucosal function. These circuits within the ENS allow for the routine mechanisms of digestion to proceed without the involvement of the CNS. The ENS contains sensory neurons, motor neurons, and a complex number of interneurons that enable the information from the GI tract to be carefully integrated. Within the ENS, intrinsic primary afferent neurons are synaptically connected to interneurons that control the activity of