Physiology of the Gastrointestinal Tract

Volume 1

Editor-in-Chief
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Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data
Main entry under title:

Physiology of the gastrointestinal tract.

Includes bibliographies and index.
1. Gastrointestinal system. I. Johnson, Leonard R., 1942- [DNLM: 1. Gastrointestinal system—Physiology. WI 102 P578]
QP145.P492 612'.32 79-65145
ISBN 0-89004-440-6 AACR2

Preface

As with any publishing venture and especially one of this magnitude, one must first ask, "Why?" The Associate Editors and I were motivated primarily to collect in one set of volumes the most up-to-date and comprehensive knowledge in our field. Nothing comparable has been attempted in the area of gastrointestinal physiology during the past fourteen years. During this time, there has been a rapid expansion of knowledge and many new areas of investigation have been initiated.

More than fifty leading scientists—physiologists, clinical specialists, morphologists, pharmacologists, immunologists, and biochemists—have contributed chapters on their various areas of expertise for these volumes. Our original goal was to review the entire field of gastrointestinal physiology in one work. After examining all of the chapters, however, it was apparent that the final product encompassed more than physiology. The chapters reflect the backgrounds of the authors and the approaches of their different disciplines. As such, these volumes contain information for not only the investigator working in these fields but for the clinician or graduate student interested in the function of the gastrointestinal tract. Anyone involved in teaching gastrointestinal physiology or pathophysiology can readily find the latest and most pertinent information on any area in the discipline.

This work is divided into five sections. The first consists of topics, such as growth, the enteric nervous system and gastrointestinal peptides, each of which relates to all areas of the GI tract. The second section contains material describing smooth muscle physiology and gastrointestinal motility. The third section presents treatment of the functions of the stomach and pancreas. The fourth series of chapters treats the entire field of digestion and absorption. These chapters vary from basic electrophysiology and membrane transport to reviews of mechanisms leading to clinical conditions of malabsorption. The final section contains chapters on areas peripheral to physiology (such as immunology, parasitology, and prostaglandins) yet necessary for a comprehensive understanding of the subject.

No one person can presume to organize and edit a scientific work of this scope. I was fortunate to enlist the aid of four preeminent scientists whose expertises cover the entire field. James Christensen was primarily responsible for the chapters on smooth muscle and motility. Eugene D. Jacobson solicited and edited most of the chapters dealing with secretory mechanisms as well as those covering many of the general topics. Chapters relating to secretory regulation were primarily handled by Morton I. Grossman, and those covering aspects of digestion and absorption were organized and reviewed by Stanley G. Schultz. I am exceedingly grateful to these four men without whom this work would not have been possible.

L. R. J.

Acknowledgments

From the organizational stage to actual production Dr. Alan Edelson and his staff at Raven Press provided much help, many excellent suggestions, and a great deal of support. Their role has certainly been more than that of the usual publishing house, and I express my thanks to them. I am especially grateful to my own secretary, Ms. Barbara Suttle, who handled correspondence, kept track of chapters, contacted authors, and typed numerous chapters.

We as editors are especially grateful to the individual authors who took the time and effort to make their knowledge available. As such, almost all of the chapters are more than reviews of past contributions to a field; they synthesize, criticize, and point out those areas where voids exist in our knowledge. Many of the chapters are superb presentations of information in fields that never have been reviewed comprehensively before.

It is our expectation that in due course, a second edition will encompass what constraint of time has forced us to omit here as well as new advances in this rapidly progressing field.

L. R. J.

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Physiology of the Gastrointestinal Tract, edited by Leonard R. Johnson. Raven Press, New York © 1981

Chapter 1

Physiology of the Enteric Nervous System

J. D. Wood

Langley (104) introduced the term "enteric nervous system" to describe the neural elements that are distributed within the wall of the gastrointestinal tract. Langley coined the term because he believed that the enteric ganglia had unique structural and functional characteristics that distinguished them from autonomic ganglia outside the gut. The results of subsequent histoanatomical and electrophysiological studies have established this concept to the extent that the enteric ganglia are no longer considered to be simple-relay distribution centers where a multitude of parasympathetic postganglionic neurons relay excitatory signals from relatively few vagal or pelvic nerve fibers to the gastrointestinal effector systems. Current concepts regard the enteric nervous system as an independent integrative system with structural and functional properties analogous to the central nervous system. Command signals from the central nervous system are transmitted to the enteric nervous system along sympathetic and parasympathetic pathways; however, this represents only one kind of input to an integrative network that also contains circuitry for processing information supplied by various kinds of sensory receptors along the gut and synaptic circuitry that generates precise patterns of neural outflow.

The enteric nervous system functions like a "brain" that coordinates and programs gastrointestinal functions. An eminent neurophysiologist once responded to this statement with the frivolous question of what did I consider to be the "smartest" part of the gut. The reversal of the direction of peristaltic propulsion when the advancing bolus encounters an intestinal obstruction (16) immediately came to mind as "smart" behavior, because this involves mechanoreceptor detection of the halt in forward progress of the bolus, processing of the sensory information by internuncial circuitry, and finally neural outflow that coordinates contractile activity of the muscle layers to achieve retropulsion. Nevertheless, with more reflection on the question, it seemed that the stomach and esophagus of raptorial birds must certainly be the "smartest" part of all gastrointestinal tracts. After a great horned owl has ingested a mouse, the neural control system first programs for strong stomach contractions which crush, macerate, and mix the contents with gastric secretions. As digestion proceeds, information on the state of the lumen is furnished

by sensory detectors to the integrative networks that interpret the information and command a reduction from strong gastric contractions to gentle mixing waves. The stomach then empties the liquid content into the small bowel and forceful muscular contractions manipulate and compact the remaining bone and hair into a pellet. The final phase of the process is egestion of the pellet by coordinated movements and reverse peristalsis within the esophagus (100). Other gastrointestinal physiologists might justifiably argue for equally sophisticated neural control in specialized alimentary systems such as those of ruminant animals; however, the point is that the enteric nervous system is indeed "smart."

Although the enteric nervous system offers the most accessible source of neurons for biopsy to evaluate certain nervous disorders in humans, the system is deeply embedded within the gut wall and is not readily accessible for experimental purposes. It is apparent, in spite of this, that gastrointestinal function cannot be well understood without understanding the neurophysiology of the enteric nervous system. The most promising way to this understanding is to apply the same neurophysiological principles and techniques of study that are applied to the brain and spinal cord. During the past decade, many of the problems of inaccessibility of the system have been overcome and standard neurophysiological techniques have been utilized to study the functional properties of enteric ganglion cells. The results that have been obtained from electrophysiological studies of enteric neurons and the relevance of this information to gastrointestinal function constitute the remainder of this chapter.

HISTOANATOMY AND NEUROCHEMISTRY

The morphology of the enteric nervous system is described in another section of this volume. The purpose here is to point out that many histoanatomical and histochemical similarities exist between the enteric nervous system and the brain. This is emphasized because it is consistent with the view that information processing and integrative function are developed to a higher degree in enteric ganglia than in other autonomic ganglia.

The first in the series of similarities is the compact organization of neural and glial elements and paucity of extracellular space that are common characteristics of both enteric ganglia and the brain (52). The significance of this with respect to integrative function is unknown; however, there is evidence that close packing of glial and neural elements in the brain may be related to the glial functions of uptake and release of chemical transmitter substances and buffering of extracellular potassium concentration.

A dense synaptic neuropil exists within both enteric ganglia and central nervous systems. This is significant because in all integrative nervous systems, the bulk of information processing occurs in microcircuits within a synaptic neuropil (146). In invertebrate animals, most of the cell bodies of neurons in the central nervous system do not receive synaptic input and the information handling associated with behavior of the organism occurs within a synaptic neuropil. Axoaxonal and axodendritic synapses occur within the neuropil of enteric ganglia, and an ultrastructural study of this region within myenteric ganglia revealed at least eight morphologically distinct types of axon terminals based on the appearance of the synaptic vesicles (30). Synapses occur also on the somas of enteric neurons, and up to three morphologically distinct kinds of endings have been described at the neuronal soma (52).

Blood vessels do not enter the enteric ganglia, and a blood-ganglion barrier analogous to the blood-brain barrier has been demonstrated in the myenteric plexus (57). This blood-ganglion barrier to date has been demonstrated only for macromolecules. It appears to reside within the capillary endothelial layer and is unlike the blood-brain barrier in this respect. Nevertheless, it is characteristic of the distinction of the enteric nervous system and should be considered by investigators who feel that there is some advantage to close intra-arterial injection of neuroactive drugs in pharmacological experiments on the bowel.

The synaptic chemistry of the enteric nervous system bears a striking resemblance to the neurochemistry of the brain in that most putative neurotransmitters within the brain also have been implicated as enteric neurotransmitters. Below is a list of putative neurotransmitters or neuromodulators that are located in both the central nervous system and the enteric nervous system:

acetylcholine	somatostatin
norepinephrine	vasoactive intestinal peptide
5-hydroxytryptamine	enkephalin
purine nucleotides	substance P
dopamine	bombesin

This lengthy list, which is probably far from complete, suggests that chemical transfer of information in the enteric nervous system utilizes as diverse an array of messenger molecules for chemical transfer of information as the brain. Because chemical transmission is highly vulnerable to malfunction and to interference by exogenous substances, it suggests many sites for disease mechanisms to operate as well as numerous sites at which therapeutic drugs could be designed to operate.

ELECTRICAL PROPERTIES OF ENTERIC GANGLION CELLS

Although reports on the electrophysiology of the enteric nervous system have appeared at an increasing rate

over the past decade, relatively few laboratories are involved with this research, and the only region of the gastrointestinal tract that has received extensive study is the small intestine. Studies of the large intestine have been limited to extracellular recording and no work on enteric neurons of the stomach, esophagus, or specialized regions such as sphincters and the cecum has been reported. Consequently, all of the following discussion directly relates only to the small bowel.

Electrophysiological Methods

Important information on properties and functions of enteric neurons has been obtained with both extracellular and intracellular methods of recording neuronal electrical activity. Several different kinds of metal microelectrodes (169,180) and suction electrodes (39,141) for extracellular recording from enteric neurons have yielded essentially similar results. With extracellular recording, the electrode tip may be designed to be small enough to detect the action potential discharge of portions of single neurons (single-unit recording) or the electrode tip may be sufficiently large to obtain "multiunit" recordings. Because the electrode tip is in the extraneuronal space, this kind of recording provides information only on the occurrence of action potentials within a particular time domain. The principal advantage of extracellular recording is that discharge patterns of single units can be studied over prolonged time spans and several units can be recorded simultaneously for analysis of neuronal interactions. Additional information is obtained by testing the effects of pharmacological agents on the neural activity and by comparing neural activity with behavior of the effector system.

Intracellular recording is technically more difficult than extracellular recording, but it yields a greater variety of information about the membrane properties of the neurons. Information on resting membrane potential, membrane constants, synaptic potentials, and changes in ionic conductances can be obtained only by intracellular recording. A significant advantage of intracellular recording is that the experimenter can control the membrane potential of a neuron by injecting electrical current into the cell through the recording microelectrode (Fig. 1). Depolarizing current can be injected to excite the cell or hyperpolarizing current can be used to move the membrane potential away from action potential threshold and to reduce excitability. The amount of injected current and the corresponding change in transmembrane voltage are measurable parameters with which the ohmic equation (R = V/I) can be used to compute the electrical resistance of the cell membrane. The resistance of a membrane is determined by its permeability to ions; consequently, changes in ionic conductance of the membrane produced by synaptic transmitter substances, sensory stimuli, drugs, etc.

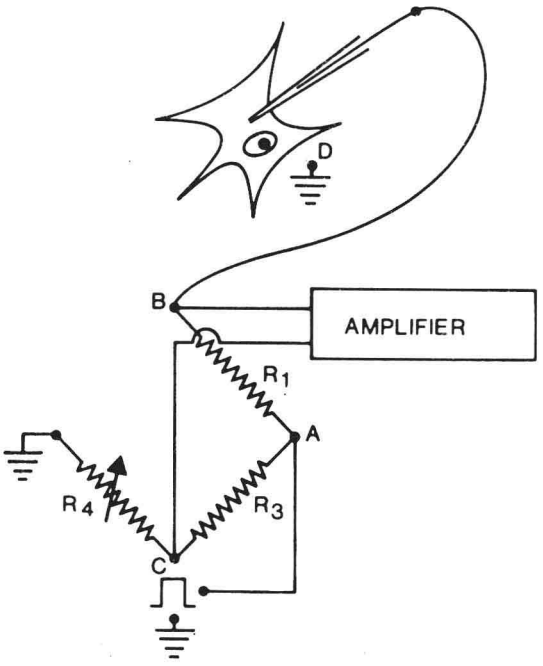

FIG. 1. Wheatstone bridge circuit used to pass electrical current across the membrane of neurons. A single microelectrode is used to inject current into the cell and to record the resulting electrotonic potential across the membrane. The current pulses are passed between points *A* and *D* (ground), and the bridge circuit functions to null out the voltage drop that occurs across the resistance of the microelectrode so that only the potential change across the membrane is recorded between points *B* and *C*. This is accomplished by adjusting R_4 until the current between *A* and *B* equals the current between point *B* and ground, and the current between *A* and *C* equals the current between *C* and ground. When this is done, the bridge is said to be balanced, and the current pulse between point *A* and ground does not change the potential between points *B* and *C*.

are reflected by changes in membrane resistance. The resistance measured by intracellular current injection is referred to as input resistance because it is not a precise measure of the specific resistance of any given patch of cell membrane. The input resistance is determined not only by the specific membrane resistance, but also by geometric variables such as size of the cell body, number of processes projecting from the cell body, and extent of branching of the processes—all of which are usually unmeasurable. Changes in the electrical characteristics of the microelectrode after impalement of the cell can also distort measurements of input resistance in unpredictable ways. Consequently, most measurements are estimates and only relative changes in input resistance produced by experimental manipulation are of consequence.

Dissection of the gastrointestinal wall is a prerequisite for electrical recording from neurons in the myenteric or submucous plexus (Fig. 2). Two methods are generally used to expose the myenteric plexus for electrical recording. The first method is to strip away the longitudinal muscle coat to expose the plexus on the underlying circular muscle. This preparation has the advan-