Physiology of the Digestive Tract

An Introductory Text

HORACE W. DAVENPORT, Ph.D., D.Sc. (Oxon.)

FIFTH EDITION

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Preface

I HOPE THAT this fifth edition is what the title page of the first edition proclaimed it to be: an introductory text. From the beginning, the purpose of this book has been to make the basic facts of gastroenterological physiology readily available to the student or house officer beginning serious study of the digestive tract.

Since the first edition of this book was published in 1961, there has been an enormous increase in our knowledge of human gastroenterology; and man, well or ill, has become the chief subject of observation and experiment. As a result, this edition contains much information on the disordered physiology of the diseased digestive tract. Nevertheless, the experimental animal has continued to provide much important information. In many instances I have implied that knowledge derived from a dog, a rat, or an opossum applies to man; but I have not always warned the reader of my inference.

The plan of this book is to describe first the means by which the gastrointestinal tract is controlled: its neuromuscular apparatus and its chemical mediators. Then the reader is conducted on three journeys through the alimentary canal, the first two showing him how propulsion and secretion are accomplished and regulated. Finally, we repeat the trip, accompanying aliments in the process of being digested and absorbed, observing to the best of our ability how and to what extent the mechanisms of motility, secretion and their control are actually used. The usually relentlessly downward gradient of the digestive tract imposes tedious repetitiveness on this method of exposition, but I find the task of adding variety by beginning with an enema and ending with an eructation beyond my powers.

I cannot document with references the thousands of assertions of fact contained in this book. A fragment of the original literature has filtered through my understanding, and the casual student must trust me. The serious scholar can begin with the massive *Handbook of Physiology: The Alimentary Canal*, edited by Charles F. Code and published by the American Physiological Society. This contains references to most of the literature up to 1964–66, and it will remain the starting point for a search of the literature. The references I have added to each chapter include recent reviews whose text and references are useful. The papers I cite are usually the latest ones in an important series. The student can easily attain a view of a large field by working backward through the paper's references.

This is my last edition. I have lived through a glorious period of gastroenterological research; and in the successive editions of this book I have tried to summarize clearly, concisely, and correctly the rapidly expanding knowledge of the physiology and pathophysiology of the digestive tract. How well I have discharged that responsibility is for others to judge, but I must record that keeping up with the literature has been a pleasure as well as a burden.

I must thank the hundreds of persons I know only through their published work and whose accomplishments I admire. I thank the many friends who have given me advice, help, and access to unpublished work. In particular, I thank three preeminent physiologists, Charles F. Code, Morton I. Grossman, and Alan F. Hofmann, whose contributions to the physiology of the digestive tract and to this book overshadow all others.

HORACE W. DAVENPORT

Contents

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PART I

Mechanisms of Control

1

The Neuromuscular Apparatus of the Digestive Tract

EXCEPT AT ITS pharyngeal and anal ends, the motor function of the digestive tract is performed by smooth muscle. In order to understand the propulsion of food through the gut, it is necessary to know the structure, innervation, and physiological properties of intestinal muscle. Gastrointestinal smooth muscle structures are extremely diverse in form and function, and only the general properties of the neuromuscular apparatus will be considered here. Later, coordinated activity as expressed in peristalsis, spasm, and other movements will be discussed, together with special nervous and humoral factors influencing them.

Structure of Smooth Muscle Cells

At its greatest extension a living smooth muscle cell is less than 250 nm long and 6 nm thick. This is an order of magnitude smaller than a striated muscle cell, and, because it is so small, a smooth muscle cell has a very large surface-to-volume ratio. After death, intestinal smooth muscle cells greatly elongate, with the result that the length of the dead intestine is far greater than that of the living one.

An irregular array of collagen fibrils surrounds the cells and is attached to the membrane. The collagen fibrils form the tendon through which the muscle cells exert their force. The collagen is synthesized by fibroblasts, but intestinal smooth muscle cells may themselves be able to synthesize collagen in response to injury.

The cell membrane is approximately 0.015 nm thick, and it contains a large number of flask-like invaginations, 168,000 in a single cell of taenia coli. These increase the cell surface by 30%. They are probably sites of calcium accumulation and are not pinocytotic vesicles. Mitochondria are less numerous than in striated muscle cells, and they are grouped near the periphery of the cell or in the perinuclear region. Thick myosin filaments lie parallel to the long axis of the cell, and they are surrounded by thin filaments of actin and tropomyosin. There is no troponin-like component. There are 15 actin filaments surrounding one myosin filament, and the bundles are arranged in an approximately 60–80 nm lattice. Longitudinally, there is no regular transverse alignment or cross-banding. An important physiological consequence is that the filaments may slide to an unlimited extent with respect to one another; this accounts for the great range of length over which tension can be exerted. Many, but not all, of the actin filaments are attached to the cell wall at dense bodies that are smooth muscle's equivalent of the Z disc. Contraction causes lateral indentations on the cell border, so that the cell seems to fold on itself like an accordion.

The sarcoplasmic reticulum is a closed tubular system that does not communicate directly with the extracellular space. It is the intracellular site of calcium accumulation and release. The cell's large surface-to-volume ratio allows calcium from the extracellular fluid to activate the contractile mechanism simply by diffusing into the cell at the time of the action potential, so there is no need for T tubules.

When smooth muscle is relaxed, intracellular concentration of ionized calcium is about 10^{-7} M. In that situation actin and myosin do not significantly interact with adenosine triphosphate (ATP). Activation occurs when intracellular calcium concentration rises, the additional calcium coming from extracellular fluid dur-

ing the action potential and from intracellular stores. At rest, smooth muscle has a low content of ATP and phosphocreatine, but ATP is simultaneously synthesized by mitochondria and hydrolyzed when actin and myosin are permitted to interact by calcium. Use of ATP by smooth muscle is very economical, and the rate of oxygen consumption is directly proportional to the level of maintained tension.

Connections of Smooth Muscle Cells

Groups of muscle cells are organized as bundles. In the circular muscle of the cat intestine, these bundles are 500 nm thick and contain about 7,000 cells in cross section. Cells may be connected with each other through gap junctions or nexuses, and gap junctions are particularly abundant in the circular layer. In the guinea pig ileal circular muscle there are approximately 244 gap junctions connecting one cell with its neighbors. Electrical resistance between cells through gap junctions is less than resistance of the cell membrane, and therefore gap junctions permit electrical coupling between cells in a bundle. However, gap junctions are absent in the longitudinal layer of the dog intestine and infrequent in the longitudinal muscle of the dog stomach. Nevertheless, cells in these muscle layers are electrically coupled.

Bundles are attached to adjacent bundles by connective tissue. Larger units, made up of many bundles, form the circular layer on the mucosal side and the surrounding longitudinal layer on the serosal side. In some tissues, thin muscle strands connect the circular and longitudinal layers and are responsible for interaction between the layers.

The details of organization of bundles into layers are disputed. Some anatomists believe the circular layer is wound in a helix, whose direction is counterclockwise (viewed from the oral end), and that the longitudinal layer consists of bundles twisting in a more open, elongated helix. Others think that the circular layer is formed by closed rings and the longitudinal layer by bands, whose axes are parallel with that of the gut. The muscularis mucosae, lying beneath the glandular mucosa, consists of both circular and longitudinal layers of muscle fibers. The layers vary greatly in thickness in different species and parts of the tract, and they are especially thick in the pig's esophagus and in the human stomach. Smooth muscle cells pass from the circular layer of the muscularis mucosae into the mucosa.

The submucosa is composed of interlacing collagenous fibers, which, when the intestine is relaxed, form helical coils at an approximately 45-degree angle with the axis, half clockwise and half counterclockwise. In the dog, this braided sheet is 18–24 layers thick.

Sympathetic Innervation

The autonomic innervation of intestinal smooth muscle is summarized in Table 1–1 and Figure 1–1. Efferent sympathetic fibers go to the stomach from the celiac plexus, to the small intestine from the celiac and superior mesenteric plexuses, and to the cecum, appendix, ascending colon, and transverse colon from the superior mesenteric plexus. The remainder of the colon receives sympathetic fibers from the superior and inferior hypogastric plexuses. Most sympathetic fibers to the intestine are postganglionic, and their cell bodies are in the ganglia named. Some sympathetic fibers entering the gut may be preganglionic ones, and their postganglionic fibers would be those of the cell bodies of the intramural plexuses upon which the preganglionic fibers terminate.

Sympathetic fibers innervating the intestine end in one of four places: (1) Some sympathetic fibers enter glandular tissue where they appear to innervate some secretory cells. (2) Some sympathetic fibers innervate smooth muscle cells of blood vessels, causing vasoconstriction, and smooth muscle cells of the muscularis mucosae, causing contraction. (3) Most sympathetic fibers terminate in contact with neuronal cell bodies of the intramural plexuses and with presynaptic fibers surrounding the cell bodies. They inhibit ganglionic activity, possibly by presynaptic inhibition. (4) Postganglionic adrenergic fibers directly innervate smooth muscle cells of the longitudinal and circular layers, but the extent to which this occurs is disputed. Such innervation is said to be rare in the longitudinal muscle layer of the guinea pig ileum but to be by no means rare in the circular layer. The muscle of the aganglionic segment of the colon of a patient with megacolon is rich in adrenergic innervation.

Sphincters of the gastrointestinal tract are adrenergically innervated, and the density of innervation is often greater than in adjacent muscle. Although there

TABLE 1–1. FUNCTIONAL CLASSIFICATION OF NERVES AFFECTING THE LOWER DIGESTIVE TRACT

Systems Mediating Extrinsic Sympathetic Innervation (see Fig 1–1,*A*):
Preganglionic cholinergic fibers pass
  from cell bodies in lateral columns of thoracolumbar region of cord, via white rami communicantes, to (chiefly) the prevertebral ganglia, where they synapse with
Postganglionic adrenergic (and cholinergic?) fibers, which pass
  from cell bodies in prevertebral ganglia, via thoracic splanchnic nerves, to endings on the following effectors:
    smooth muscle cells of blood vessels, constrictor (and dilator?)
    smooth muscle cells of muscularis mucosae, excitatory (and inhibitory?)
  cell bodies of neurons within the myenteric plexuses whose activity they modulate, inhibitory
    gland cells of salivary glands, excitatory
    gland cells of pancreas, small intestine and colon (inhibitory and excitatory?)
    smooth muscle cells of some circular layers, inhibitory
    smooth muscle cells of some sphincters, excitatory
Systems Mediating Extrinsic Parasympathetic Innervation (see Fig 1–1,*B*):
Preganglionic cholinergic, purinergic, and peptidergic fibers pass
  from cell bodies in the cranial division of neuraxis, via vagus nerves and from sacral region of the cord, via pelvic and splanchnic nerves to the digestive tract, where they synapse with
Postganglionic cholinergic, purinergic, and peptidergic fibers, which pass
  from cell bodies in ganglia of nerve plexuses to synapse with
  other ganglion cells in the same ganglion or in the same plexus or other plexuses and to the following effectors:
  smooth muscle cells in all muscle layers, chiefly excitatory, gland cells in the gastric antrum (and elsewhere?) that liberate
  hormones of the digestive tract, excitatory and inhibitory
  gland cells that liberate external secretions (but not directly to blood vessels)
Postganglionic fibers in the lower esophagus and stomach (and other sphincters?), inhibitory, nonadrenergic, noncholinergic
Systems Mediating Reflexes of Peripheral Location (see Fig 1–1,*C*):
Afferent limb, consisting of
  nerve terminals from which impulses originate
    in the mucosal epithelium
    in the muscle layers and plexuses
  cell bodies in the submucous (and myenteric?) plexus
    potentially effective stimuli of which are:
      stretch or distention
      pH of contents of viscus
      specific chemical constituents, such as amino acids, peptides, fats
  axons synapsing with
Efferent limb, consisting of
  cell bodies in myenteric and submucous plexuses
  second-order effector neurons and
  other (identical?) effector neurons of myenteric and submucous plexuses, which pass to
  endings that innervate the following effectors:
    smooth muscle cells of the digestive tract
    gland cells of internal secretion in gastric antrum (and elsewhere?) that liberate hormones of the digestive tract
    gland cells that liberate external secretions
    (smooth muscle cells of blood vessels?)
Systems Mediating Reflexes through Celiac Plexus (see Fig 1–1,*D*):
Afferent limb, consisting of
  nerve terminals from which impulses originate in epithelium of duodenal and other mucosa
  cell bodies in intrinsic plexuses
    potentially effective stimuli of which are:
      chemical composition of gastrointestinal contents, pH, osmotic pressure, digestion products of protein and fat
  axons synapsing in celiac plexus with
Efferent limb, consisting of
  cell bodies in celiac plexus
  postganglionic sympathetic fibers, which pass to endings on neuronal cell bodies within the intrinsic plexuses of stomach, inhibitory

TABLE 1–1.—*Continued*

Systems Mediating Reflexes Through Central Neuraxis (see Fig 1–1,*E*):
Afferent limb, consisting of
nerve terminals from which impulses originate
in epithelium
in plexuses
in smooth muscle, potentially effective stimuli of which are distention or chemical composition of content of viscus
fibers that pass centrally,
via thoracic, lumbar, or pelvic splanchnic nerves and dorsal roots, to cord, and having cell bodies in dorsal root ganglia or
via vagus nerves to brain stem,
mediating the following:
vasodilatation via axon reflexes
pain and other visceral sensations
vomiting reflex
defecation reflex
gallbladder reflex
response to obstruction, and
initiating specific action on
digestive tract reflexes, facilitating and inhibiting
somatic reflexes
cardiovascular reflexes and
centripetal fibers from cell bodies within intrinsic plexuses

is considerable species difference, in most species examined the effect of sympathetic innervation is to excite the lower esophageal sphincter, the choledochoduodenal sphincter, and the internal anal sphincter. Excitation is mediated by the action of norepinephrine upon alpha receptors of the smooth muscle cells.

Adrenergic nerve terminals avidly take up norepinephrine, thereby reducing the effectiveness of circulating norepinephrine.

Parasympathetic Innervation

Efferent parasympathetic innervation to the stomach, small intestine, cecum, appendix, ascending colon, and transverse colon is by way of the vagus, whose fibers follow blood vessels to end in the myenteric plexus. The rest of the colon receives parasympathetic innervation from the pelvic nerves via the hypogastric plexuses, and these, too, end in the myenteric plexus. The fibers are all preganglionic, and most are cholinergic and excitatory.

Current research shows that chemical mediation in the parasympathetic nervous system is not so straightforward as is implied in the old dicta that all pre- and postganglionic fibers are cholinergic and that the action of acetylcholine upon glands and muscles of the gut is excitatory. The vagus nerves contain fibers to the lower esophageal sphincter and to the stomach which are inhibitory, and those fibers are noncholinergic and nonadrenergic. Dopamine, 5-hydroxytryptamine, and purines are thought to be transmitters in such fibers. Many nerves have been shown to contain, and probably to release, peptide transmitters. For example, the human vagus nerve has been shown by immunochemical methods to contain substance P, vasoactive intestinal peptide (VIP), and enkaphalin-like compounds. VIP released from nerve endings mediates relaxation of the lower esophageal, pyloric, and internal anal sphincters. A peptide similar to cholecystokinin is synthesized in nerve cell bodies in the nodose ganglion and is transported centrally in the axoplasm of vagal afferent fibers. On the other hand, gastrin is carried peripherally in the axonal stream. Research in this area is developing so rapidly that few dogmatic statements can be made.

Plexuses

Five nerve plexuses are distinguished: subserous, myenteric, deep muscular, internal, and submucous. The deep muscular and the internal plexuses are probably formed by terminal fibers of the myenteric and submucous plexuses. Postganglionic sympathetic and preganglionic parasympathetic fibers make up a large

fraction of the plexuses and disappear after extrinsic denervation. The myenteric plexus in the interspaces between longitudinal and circular muscle layers consists of a mesh of fibers, with ganglion cells at the nodal points, all ensheathed by the cytoplasm and membranes of a connective tissue syncytium comparable with the neurilemma of myelinated fibers. The plexuses themselves are composed of individually distinct cells, not of a syncytial network. Nerve fibers extend within the plexus for several centimeters, and from the plexus arises the reticulum of fine fibers passing to muscle cells of the two layers.

Branches of the preganglionic parasympathetic fibers synapse with the ganglion cells, some with the first cell encountered after they enter the plexus and others with more remote cells. Still other preganglionic fibers pass through the myenteric plexus to the submucous plexus. In turn, fibers go from the reticulum of ganglion cells and from fibers forming the submucous plexus to the muscularis mucosae, to the gland cells of the mucosa, to unidentified endocrine cells and to muscular tissue within the mucosa. In addition, axonal processes from one ganglion cell synapse with cells in the same node or in neighboring ganglia. Nerve impulses initiated in one ganglion cell spread through multiple pathways, chiefly in the longitudinal direction, and experience synaptic transmission at conduction distances no longer than 4 mm. The result is that when extrinsic fibers have degenerated after denervation, ganglion cells are still functionally connected and are capable of mediating local reflexes. Afferent limbs of the reflex arcs are provided by cells in the submucous plexus whose dendrites are receptor organs in the mucosa and in the muscle layers and whose axons project to synapses formed with cells of either the submucous or the myenteric plexus.

Function of Sympathetic Innervation

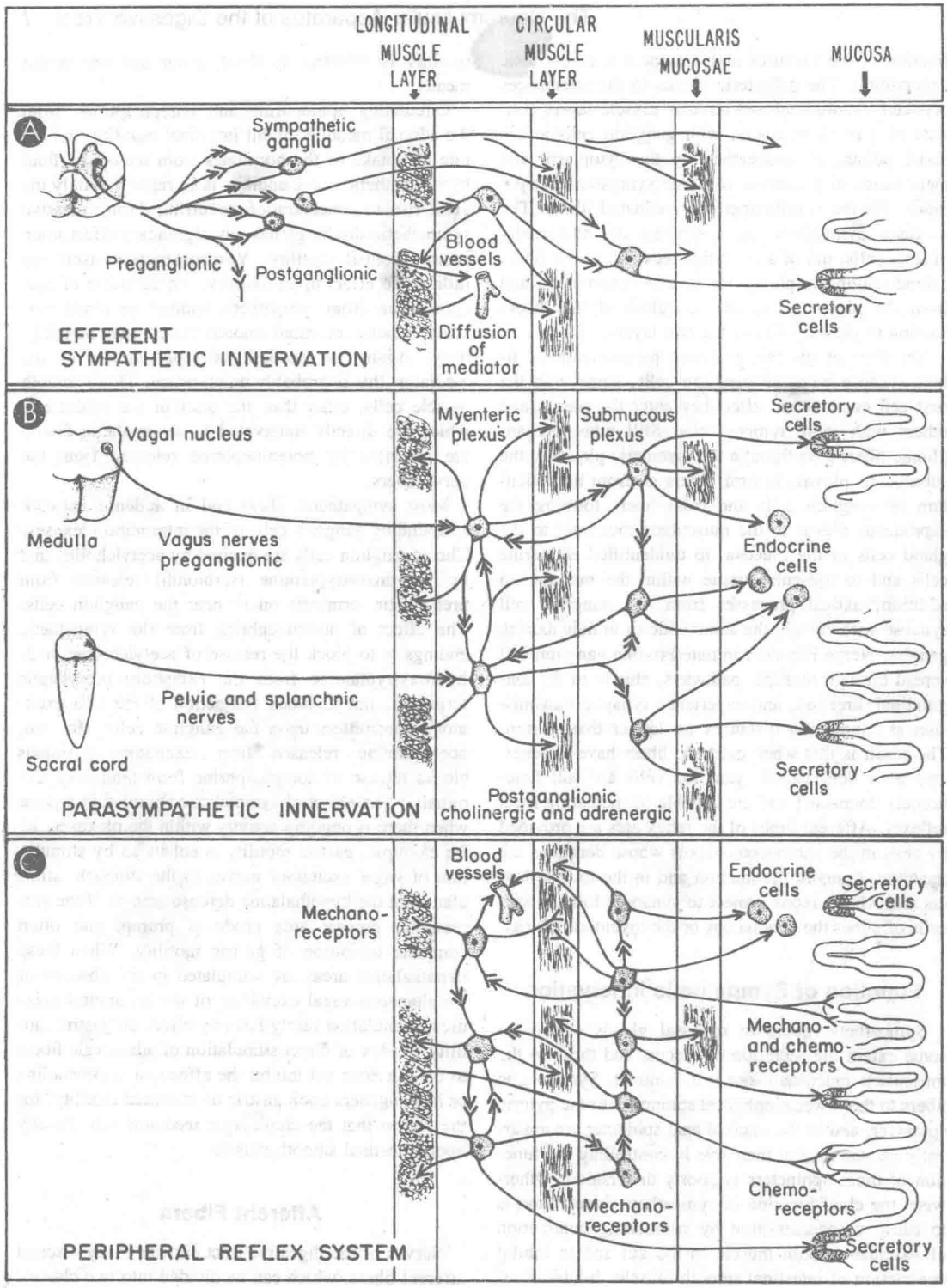
Sympathetic fibers to mucosal glands control to some extent the secretion of mucus, and those to the muscularis mucosae cause it to contract. Sympathetic fibers to the lower esophageal sphincter, to the pyloric sphincter, and to the internal anal sphincter are apparently excitatory, but their role in controlling the function of those sphincters is poorly understood. Otherwise, the chief function of sympathetic innervation is to cause vasoconstriction by stimulating contraction of vascular smooth muscle in the gut and to inhibit contraction of intestinal smooth muscle. Inhibition of motility is effected by three minor and one major means.

Circulating epinephrine and norepinephrine from the adrenal medulla inhibit intestinal motility, but the rate of uptake of the hormones from interstitial fluid by sympathetic nerve endings is so rapid that only the great rise in concentration occurring during massive sympathetic discharge has any significant effect upon gastrointestinal motility. Vasoconstriction itself has little or no effect upon motility, but diffusion of norepinephrine from sympathetic endings on blood vessels to nearby intestinal smooth muscle may be inhibitory. Again, on account of rapid uptake of the mediator, this is probably unimportant. Those smooth muscle cells, other than the ones in the sphincters, which are directly innervated by sympathetic fibers, are inhibited by norepinephrine released from the nerve fibers.

Most sympathetic fibers end in a dense network surrounding ganglion cells of the intramural plexuses. Those ganglion cells are excited by acetylcholine and by 5-hydroxytryptamine (serotonin) released from presynaptic terminals on or near the ganglion cells. The effect of norepinephrine from the sympathetic endings is to block the release of acetylcholine or 5-hydroxytryptamine from the excitatory presynaptic terminals, not to block the action of the two excitatory transmitters upon the ganglion cells. (In turn, acetylcholine released from excitatory terminals blocks release of norepinephrine from inhibitory terminals.) The effect of sympathetic stimulation is seen when there is ongoing activity within the plexuses. If, for example, gastric motility is enhanced by stimulation of vagal excitatory nerves to the stomach, stimulation of the hypothalamic defense area or of the surrounding pressor area produces prompt and often complete inhibition of gastric motility. When these hypothalamic areas are stimulated in the absence of simultaneous vagal excitation of the intramural plexuses, stimulation rarely has any effect on gastric motility. Reflex or direct stimulation of adrenergic fibers to the gut does not inhibit the effects of acetylcholine or its congeners upon gastric or intestinal motility, for the reason that the cholinergic mediator acts directly upon intestinal smooth muscle.

Afferent Fibers

Nerves of the digestive tract contain many visceral afferent fibers, which can be divided into two classes:


LONGITUDINAL MUSCLE LAYER
CIRCULAR MUSCLE LAYER
MUSCULARIS MUCOSAE
MUCOSA
A
Sympathetic ganglia
Preganglionic
Postganglionic
Blood vessels
Diffusion of mediator
Secretory cells
EFFERENT SYMPATHETIC INNERVATION
B
Vagal nucleus
Medulla
Vagus nerves preganglionic
Myenteric plexus
Submucous plexus
Secretory cells
Endocrine cells
Pelvic and splanchnic nerves
Sacral cord
Secretory cells
PARASYMPATHETIC INNERVATION
Postganglionic cholinergic and adrenergic
C
Blood vessels
Endocrine cells
Secretory cells
Mechano-receptors
Mechano- and chemo-receptors
Chemo-receptors
Mechano-receptors
Secretory cells
PERIPHERAL REFLEX SYSTEM

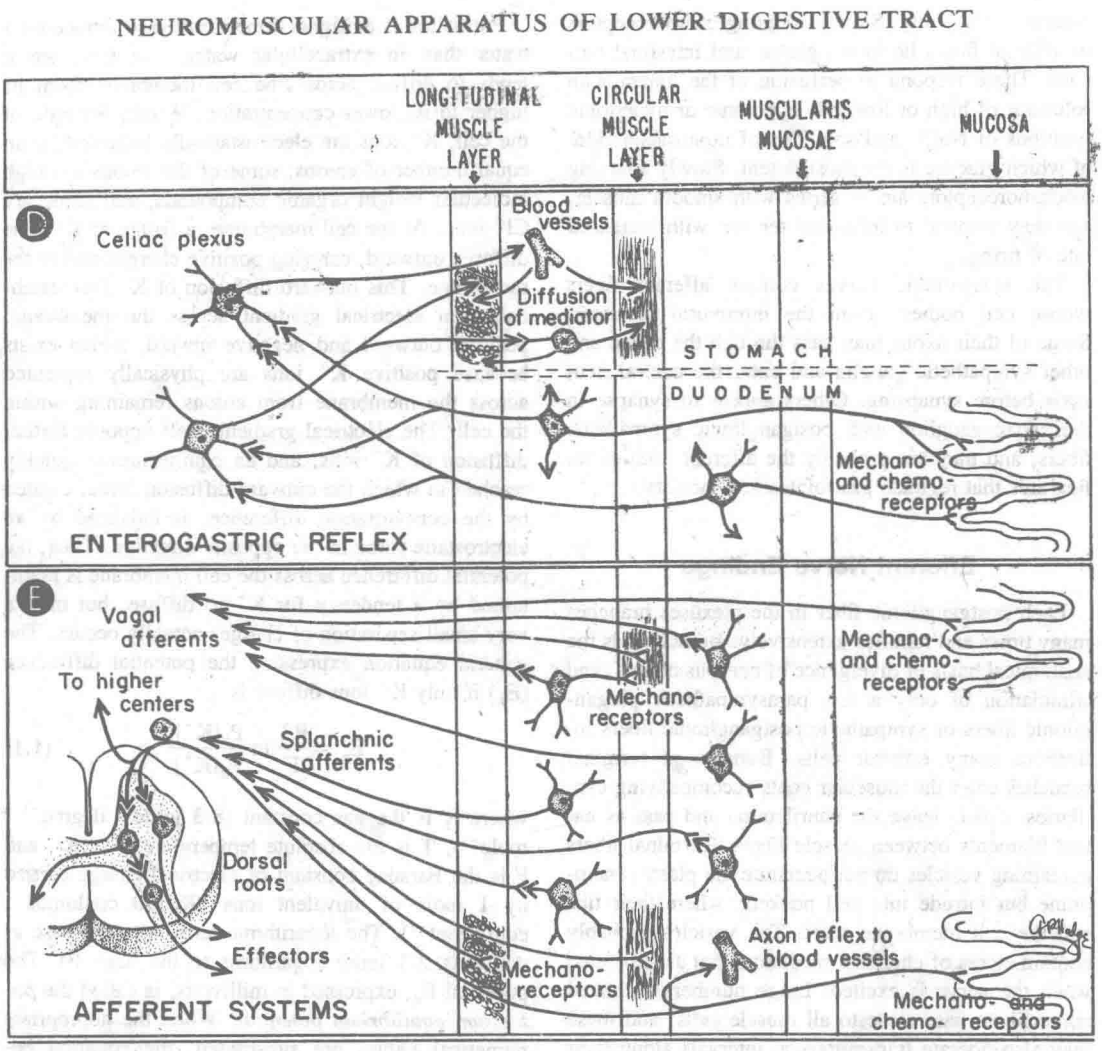


Fig 1–1.—Efferent and afferent innervation of the digestive tract. **A,** efferent sympathetic innervation. **B,** parasympathetic innervation. **C,** peripheral reflex system. **D,** enterogastric reflex. **E,** afferent systems. See Table 2–1 for detailed listing of the nerve tracts, their mediators, and their effects.

those having their cell bodies in centrally located ganglia and those having their cell bodies within the myenteric plexuses. Those of the first class have sensory endings in the mucosal epithelium, in the plexuses, and within the muscle layers. Their fibers pass centrally with the vagus and with the sympathetic rami to the dorsal roots. Cell bodies of afferent vagal fibers are in the nodose ganglion, and those of nerves traveling centrally with the sympathetics are in the dorsal root ganglia. Among the latter are the dorsal root dilators, whose action on intestinal blood vessels is the same as that of cutaneous dorsal root dilators on the vessels of the skin. Of the 30,000 fibers contained in the vagus nerves of the cat, at least 80% are afferent, and so are 50% of the 30,000 fibers in sympathetic nerves to the gut.

Numerous vago-vagal reflexes, whose afferent and efferent fibers are both in vagal nerves, influence se-

cretion and motility. Slowly adapting chemoreceptors of afferent fibers lie in the gastric and intestinal mucosa. These respond to perfusion of the lumen with solutions of high or low pH, hypotonic or hypertonic solutions of NaCl, and solutions of monosaccharides of which glucose is the most potent. Slowly adapting mechanoreceptors are in series with smooth muscle, and they respond to increased tension with increased rate of firing.

The sympathetic nerves contain afferent fibers whose cell bodies lie in the intramural plexuses. Some of their axons may pass through the celiac and other sympathetic ganglia and enter the central neuraxis before synapsing. Others appear to synapse in the celiac ganglion with postganglionic sympathetic fibers, and they are probably the afferent limb of reflex arcs that regulate gastrointestinal motility.

Efferent Nerve Endings

Each postganglionic fiber in the plexuses branches many times and ramifies extensively. Branching is the anatomical basis of divergence of nervous effects, and stimulation of only a few parasympathetic preganglionic fibers or sympathetic postganglionic fibers influences many effector cells. Bundles of terminal branches enter the muscular coats accompanying capillaries. Fibers leave the neurilemma and pass as naked filaments between muscle fibers. Terminal fibers containing vesicles do not penetrate the plasma membrane but intrude into cell pockets, where their tips and the cell membrane meet. The vesicles probably contain stores of chemical mediators that are liberated when the nerve is excited. Large numbers of naked nerve fibers pass close to all muscle cells, and these may also liberate transmitters at intervals along their length. Nerve fibers approaching one cell are derived from many cell bodies, and influences having widespread origins converge on a single cell.

Membrane Potentials

Contraction of a smooth muscle cell follows electrical changes in its membrane. The electrical changes, in turn, depend upon electrolyte distribution between the cell and the extracellular fluid, upon the permeability of the cell membrane, and upon electrogenic pumps within the membrane.

Potassium is at higher concentration in intracellular water than in extracellular water, and therefore it tends to diffuse across the cell membrane from its higher to its lower concentration. Within the bulk of the cell, K^+ ions are electrostatically balanced by an equal number of anions; some of the anions are high molecular weight organic compounds, and some are Cl^- ions. At the cell membrane, a fringe of K^+ ions diffuses outward, carrying positive charges across the membrane. This outward diffusion of K^+ ions establishes an electrical gradient across the membrane, positive outward and negative inward, which exists because positive K^+ ions are physically separated across the membrane from anions remaining within the cell. The electrical gradient itself opposes further diffusion of K^+ ions, and an equilibrium is quickly reached in which the outward diffusion force, created by the concentration difference, is balanced by an electrostatic force in the opposite direction. Thus, the potential difference across the cell membrane is maintained by a tendency for K^+ to diffuse, but only a very small separation of charges actually occurs. The general equation expressing the potential difference (E_K) if only K^+ ions diffuse is

$$E_K = \frac{RT}{F} \ln \frac{P_K[K^+]_o}{P_K[K^+]_i} \qquad (1.1)$$

where R is the gas constant (8.3 joule · degree^{-1} · mole^{-1}), T is the absolute temperature (311 K), and F is the Faraday constant of electrical charge carried by 1 mole of univalent ions (96,500 coulombs · equivalent^{-1}). The logarithmic term is to the base *e*, which is 2.3 times logarithms to the base 10. The potential E_K, expressed in millivolts, is called the *potassium equilibrium potential*. When the appropriate numerical values are substituted, the equation becomes

$$E_K = 61 \log_{10} \frac{P_K[K^+]_o}{P_K[K^+]_i} \qquad (1.2)$$

The values in brackets are K^+_i and K^+_o, the concentrations (more accurately, the activities) of K^+ ions inside and outside the cell. Each concentration is multiplied by the constant P_K, which expresses the permeability of the membrane to K^+ ions. This is an essential factor, for if the membrane were not at all permeable to K^+ ions, no fringe of K^+ ions could diffuse through it, and there could be no potential dif-

ference across the membrane, despite the existence of a concentration difference. When the contribution of K^+ ions alone is being considered, values of P_K greater than zero cancel out. In cat circular intestinal muscle, the electrolyte concentration of extracellular fluid is equal to that of an ultrafiltrate of plasma, and the K^+_o concentration is 4 mEq/kg H_2O. Intracellular concentrations are difficult to measure, but a good estimate of K^+_i is 164 mEq/kg of cell water. When these values are substituted in equation (1.2), a potassium equilibrium potential of -101 mV is obtained. This is the maximum potential difference K^+ could contribute.

The measured resting membrane potential of intestinal smooth muscle is always less than the potassium equilibrium potential, and consequently there must be additional determinants of the membrane potential.

Sodium and Chloride Potentials

The two other ions whose diffusion affects the resting membrane potential are sodium and chloride.

The concentration of Na^+ ions in extracellular fluid is about 153 mEq/kg H_2O. The best estimate of the concentration of Na^+ ions within intestinal smooth muscle cells is 19 mEq/kg H_2O, which is greater than the concentration in nerve or striated muscle. Because the diffusion gradient is inward, diffusion of Na^+ ions causes a potential difference across the cell membrane opposite to that of K^+ ions. The equation for the Na^+ equilibrium potential is

$$E_{Na} = 61 \log_{10} \frac{P_{Na}[Na^+]_o}{P_{Na}[Na^+]_i} \qquad (1.3)$$

Here, the factor P_{Na} is the permeability of the membrane to Na^+ ions. Using the values given for Na^+_o and Na^+_i, the maximum contribution of Na^+ to the membrane potential is calculated to be 55 mV.

Chloride concentration outside the cell is 132 mEq/kg H_2O, and its concentration inside intestinal smooth muscle cells is estimated to be 55 mEq/kg H_2O. The diffusion gradient, like that of sodium, is inward; but, because Cl^- ions carry a negative charge, the diffusion potential is, like that of K^+ ions, positive outward. The equation for the Cl^- equilibrium potential is

$$E_{Cl} = 61 \log_{10} \frac{P_{Cl}[Cl^-]_i}{P_{Cl}[Cl^-]_o} \qquad (1.4)$$

Here P_{Cl} is the permeability to Cl^- ions, and the difference in charge is allowed for by placing the inside concentration in the numerator. The calculated contribution of Cl^- ions to the membrane potential is -23 mV.

Because the actual resting membrane potential is more negative than the chloride equilibrium potential, chloride cannot be passively distributed between extracellular and intracellular fluids. It is probable that chloride ions are actively accumulated within the cells.

Resting Membrane Potential

The general expression for the membrane potential produced by the tendency of the three ions to diffuse is

$$E = 61 \log_{10} \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o} \qquad (1.5)$$

This equation is clearly not simply the sum of the three equations for the individual ions; it is, rather, the equation relating the three ions to the membrane potential derived on the assumption that the electrical field within the membrane is constant with respect to the distance through the membrane. It is called the *constant field equation*. The assumption is equivalent to saying that the charge density within the membrane has negligible effects on movement of ions through it. If the equation is rewritten

$$E_m = 61 \log_{10} \frac{[K^+]_o + \frac{P_{Na}}{P_K}[Na^+]_o + \frac{P_{Cl}}{P_K}[Cl^-]_i}{[K^+]_i + \frac{P_{Na}}{P_K}[Na^+]_i + \frac{P_{Cl}}{P_K}[Cl^-]_o} \qquad (1.6)$$

the role of the permeability constants is obvious: the actual membrane potential depends on the ratios of the permeability of sodium and chloride to that of potassium.

The potassium permeability constant for guinea pig taenia coli has been calculated to be 11×10^{-8} cm · sec^{-1}; $P_{Na} = 1.8 \times 10^{-8}$ and $P_{Cl} = 6.7 \times 10^{-8}$ in the same units. The ratio P_{Na}/P_K is 0.16, and the ratio P_{Cl}/P_K is 0.61. Substitution of these values in equation (1.6) gives a calculated membrane potential of -37 mV. The calculated value is lower than that deter-