Preface

Colorectal disorders are common diseases that are often chronic in nature. We are now working with an increasingly older population. This population trend increases the number of individuals with colorectal neoplasia, inflammatory bowel disease, diverticular disease, and constipation. We therefore thought that the beginning of the new millennium was an extremely relevant and timely period to prepare a new book about colorectal disorders.

The purpose of *Colonic Diseases* is to provide a bridge between basic and clinical research and the present clinical care of individuals with colonic disorders. *Colonic Diseases* examines the origins and treatment of common colorectal disorders, and it blends new outcomes and epidemiological research with molecular mechanisms of disease to improve our present and future understanding of colonic diseases and their management.

Colonic Diseases has been divided into three parts: Colorectal Physiology, Investigation of Disease Processes, and Colorectal Disease. Part I provides an extensive overview of normal colonic physiology. Part II utilizes the expertise of active investigators who are studying the pathophysiology of colonic disorders, and includes a survey of techniques that are used in clinical research of colonic diseases. Understanding the mechanisms of disease development may provide important clues for future therapy. In Part III potential symptoms, pathological and radiological findings, the differential diagnosis, presently recommended evaluation and therapy, and potential future alternative therapies for common colorectal diseases are reviewed.

Colonic Diseases is intended for gastroenterologists, gastrointestinal fellows, and scientists in gastrointestinal research who are interested in bridging basic and clinical research and diseases processes. This book will be a useful reference resource for primary care physicians who care for patients with chronic colonic disorders, and may also prove of interest to colorectal surgeons, although it is not designed to be a textbook for the performance of colorectal surgery.

I wish to dedicate this book to Dr. Joseph B. Kirsner, who inspired our great interest in colonic diseases at the University of Chicago, and to Dr. Joseph Szurszewski, who promoted a strong quantitative approach to basic colonic physiology at the Mayo Clinic in Rochester.

I would like to acknowledge the great patience of my wife, Nancy, and my daughter, Kristina, during the preparation of this book. I wish to thank Ms. Debbie Williams for her excellent secretarial and managerial assistance.

Timothy R. Koch, MD

2 Normal Motility and Smooth Muscle Function

Mary Francis Otterson

Contents

1. INTRODUCTION

The gastrointestinal tract normally functions to move ingested food, in an organized fashion, from the oropharynx, through the stomach, small intestine and colon and into the rectum, from which it can be expelled. The primary function of the colon is to absorb water and electrolytes from the chyme delivered and, thus, determine the frequency, consistency, and volume of stools eliminated. The colon (i) mixes luminal contents so that they are optimally exposed to the absorptive mucosal surface; (ii) slowly propels feces caudally to allow adequate time for the absorption of water, electrolytes, and metabolic products of bacterial degradation; (iii) allows storage of feces; and (iv) rapidly and efficiently propels feces during defecation. Transit time through the colon is significantly slower than through the proximal bowel and is achieved through contractions that are less coordinated. The discoordination is due to highly variable frequency and phase unlocking of electrical activity within the colon.

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2. INDIVIDUAL PHASIC CONTRACTIONS

The colon exhibits both short and long duration contractions (Fig. 1). This is in contrast to the stomach and small intestine, where only short duration contractions are observed. In both humans and dogs, short duration contractions last less than 15 s and occur at a frequency of 2–13/min. The frequency of the long duration is 0.5–2/min. The short and long duration contractions may occur independently of one another, or the short duration contractions may be superimposed upon the long duration contractions. The long duration contractions may occasionally propagate in either an orad or caudad direction, however, the short duration contractions rarely appear to propagate. The viscosity of fecal contents may necessitate the longer duration contractions for efficient propulsion of contents. Both types of colonic phasic contractions are under myogenic, neural, and chemical control *(1)*.

3. MYOGENIC CONTROL

The interior of the smooth muscle cell is maintained electronegative relative to the extracellular fluid. This negative potential is called the resting membrane potential. The resting membrane potential depolarizes periodically and this is termed electrical control activity (ECA) or slow waves (Fig. 2). When neural or chemical stimulation is present, the amplitude of depolarization may exceed an excitation threshold potential. This causes voltage-sensitive calcium channels to open and produces an inward calcium current. Alternately, internal calcium stores may be mobilized. A burst of rapid electrical oscillations called electrical response activity (ERA), spikebursts, or action potentials (2–5) results. ERA has a one-to-one relationship with individual phasic contractions (Fig. 2). Because ERA can only occur during the depolarization phase of ECA, the frequency of individual phasic contractions is determined by and limited to the frequency of ECA. Beyond this myogenic control, it must be understood that neural and chemical stimulation may not be present during every cycle of ECA and, thus, contractions do not occur at maximal frequency (Fig. 2).

The frequency of human colonic ECA ranges from 2–13 cycles/min. Within the ascending and sigmoid colon, 2–9 cycles/min is the dominant frequency. This narrows to a range of 9–13 cycles/min in the transverse and descending colon *(6)*.

Long duration contractions within the colon are controlled by intermittent bursts of membrane potential oscillations called contractile electrical complexes (CECs) *(7)*. The frequency of membrane potential oscillations within a CEC occur in the range of 25–40 cycles/min. These oscillations generally exceed the contractile excitation threshold and produce a long duration contraction of the colon that has duration equal to that of the CEC. The oscillations of ERA associated with a CEC have been called continuous ERA, because the activity persists throughout the duration of several ECA cycles. CECs and the long duration contractions they represent most frequently propagate in a caudal direction, but occasionally propagate in an orad direction.

4. NEURAL CONTROL

Control of colonic contractile activity rests within the enteric, autonomic, and central nervous system. Just as within the rest of the gastrointestinal tract, the enteric nervous system plays a prominent role in the moment-to-moment control of contractile activity. The autonomic nervous system, both sympathetic and parasympathetic, exerts significant influences and may play a role in pathologic states, such as irritable bowel syndrome. Finally, because of the ability of animals and humans to willfully control the timing of the voluntary release of feces, the central nervous system plays a critical role in colonic contractile function.

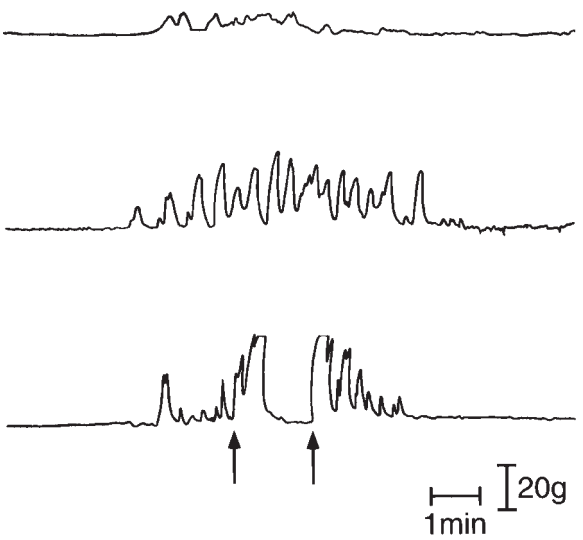

Fig. 1. The topmost tracing demonstrates long duration contractions in the proximal colon of the dog approx 5 cm distal to the ileocolonic junction. The second tracing is short duration colonic contractions at the same recording site. The final tracing shows two GMCs of the proximal colon. Note the suppression of contractile activity often the first GMC. Within the small intestine, GMCs have a specific electrical recording that is distinct from other contractions. This is not true in the colon.

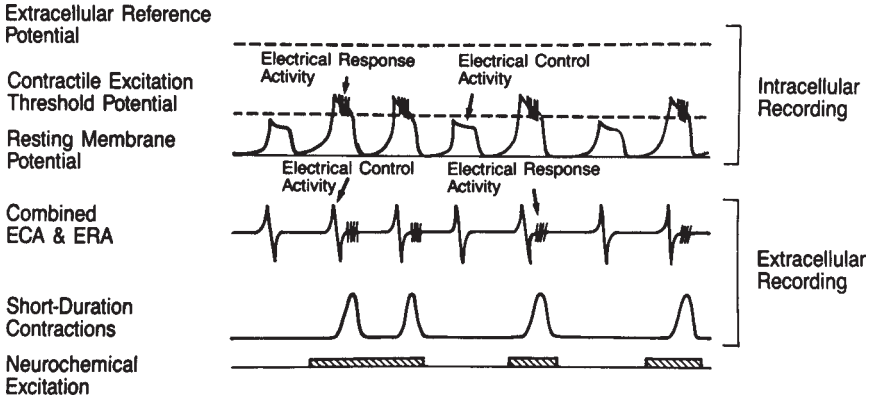

Fig. 2. The top tracings demonstrate the relationship between intracellularly recorded myoelectric activity, neurochemical excitation, and contractions. Resting membrane potential is negative with respect to the extracellular reference potential. In the absence of neurochemical excitation, the ECA depolarizations do not exceed the excitation threshold potential. Therefore, no ERA burst occurs nor contraction occurs. In contrast, during the second, third, fifth, and seventh ECA cycle, neurochemical excitation occurs, ECA depolarization exceeds the excitation threshold, an ERA burst occurs, and the muscle contracts. The lower electrical tracings demonstrate the relationship to extracellular myoelectric activity. Extracellular electrodes record from a large number of smooth muscle cells. The shape of the electrical recording depends upon whether the electrode is bipolar or monopolar and the distance between the poles of the recording device. (Reproduced from ref. *2* with permission)

5. ENTERIC NEURAL CONTROL

The enteric nervous system within the colon is organized in to two plexuses, the myenteric and the submucosal. The myenteric neurons are located between the circular and longitudinal muscle layers, and the submucosal plexus can be found within the muscularis propria. Nerve cell bodies within each plexus are organized and grouped into ganglia that range in size from several to 40 distinct soma. The neurons thought to be responsible for the control of colonic contractile activity consist of motor neurons, sensory neurons, and interganglionic and interplexus neurons.

Enteric motor neurons project axons to both the circular and longitudinal muscle layers. Each enteric neuron affects several smooth muscle cells. These neurons may be either excitatory or inhibitory. The excitatory neurotransmitter is acetylcholine and, in vivo, all spontaneous colonic contractile activity can be inhibited with atropine. There is some evidence that glutamate may also act as an excitatory neurotransmitter, much as what has been described within the central nervous system. The precise identification of the inhibitory neurotransmitter is more controversial. These nonadrenergic noncholinergic (NANC) neurons have several putative inhibitory neurotransmitters. These include nitric oxide, adenosine triphosphate (ATP) and vasoactive intestinal polypeptide (VIP) *(1,8–13)*. Both the excitatory and inhibitory motor neurons of the gut receive input from other enteric neurons as well as sympathetic and parasympathetic extrinsic neurons.

In addition to the cholinergic excitatory and NANC inhibitory neurons, a variety of peptidergic neurons have been mapped within the gut wall using immunohistochemistry. There is directionality to these neurons. For example, within the guinea pig small intestine, myenteric substance P and enkephalin-containing neurons project in an orad direction, and neuropeptide Y and gastrin-releasing peptide project in a caudad direction. The precise role of these peptidergic neurons in the control of human in vivo contractile activity has yet to be determined. It is possible that the role of these neurotransmitters may be elucidated with novel molecular techniques that allow the over expression or deletion of these peptides from the enteric nervous system.

Sensory neurons perceive mechanical and chemical stimulation from the luminal contents of the gut and project onto enteric as well as prevertebral and higher centers. This neural input provides the signal for both local enteric reflexes as well as higher reflexes. Substance P is one of the substances found within these sensory neurons. Sensory neurons synapse upon both the inhibitory and excitatory motor neurons and may act by stimulation or inhibition of spontaneous contractions.

Interganglionic neurons provide pathways to allow communication within the ganglia, while interplexus neurons project from one plexus to another. These neurons are critical for the coordination of colonic motor activity as well as epithelial transport.

6. AUTONOMIC NEURAL CONTROL

Sympathetic neural control of the colon occurs through the lumbar, splanchnic, and hypogastric nerves. The parasympathetic neural control occurs through the vagal and pelvic (sacral) nerves. A surprising large proportion of these extrinsic nerves, particularly the vagus, consist of sensory afferent fibers *(14,15)*. Each projection of these autonomic nerves may affect a number of enteric ganglia *(16)*. The autonomic nerves can be thought of as providing the conduit for central nervous system input to the reflexes that occur throughout and between the different regions of the colon. The autonomic nervous system also provides a pathway for the reflexive interactions between the colon and other organs.

7. CENTRAL NEURAL CONTROL

Under normal circumstances, the central nervous system does not regulate the moment-to-moment control of the colon. We do not voluntarily control the passage of feces through our colon. However, the CNS is capable of modulating colonic contractile activity during situations such as voluntary defecation and during involuntary situations, such as extreme stress *(17–22)*. Signals to and from the central nervous system take place through the autonomic nervous system and, eventually, the enteric nervous system.

8. CHEMICAL CONTROL

Chemical control of the contractile activity of the colon refers to regulation via chemicals or hormones released from endocrine or paracrine cells or glands. These chemicals may affect colonic motility through actions upon the smooth muscle, enteric neurons, sympathetic or parasympathetic neurons, or the central nervous system. One example of how endocrine substances may influence colonic motility is hypothyroidism. When a patient is hypothyroid, the colonic transit time may be profoundly slowed. In contrast, hyperthyroidism accelerates transit time.

Chemical control of the colon may be physiologic, pathologic, or pharmacological. Physiologic control of motility is exerted by endogenous substances released in normal amounts that control the normal contractile patterns of the colon during the fasted and fed state. Pathologic control refers to the control exerted by the abnormal release of substances during a disease process. Examples include substances released by carcinoid tumors, the response to injury or surgery (ileus), or the ill-defined effects of stress upon colonic motility. When substances, such as therapeutic drugs are administered, they may exert pharmacological control of colonic motility. These substances may be synthesized within living systems. Erythromycin and opioids are two substances that exert a pharmocologic effect upon the colon's contractile activity.

9. MOLECULAR BASIS OF ELECTRICAL AND CONTRACTILE RHYTHMICITY

Enzymatically dispersed smooth muscle cells have been used extensively to identify specific ionic components within colonic tissue. Some functional effects of specific ionic channels can be inferred from the vast work accomplished in this area.

There is wide diversity in the molecular configuation of voltage-dependant K^+ channels. The responses of smooth muscle cells to slow wave depolarization depend, in large part, on the extent to which these various types of K^+ channels are expressed *(23)*. Inhibitory regulation of smooth muscle may act through activation of these channels.

While both the α- and β- subunits of Ca^{2+}-activated K^+ channels have been cloned from colonic smooth muscle, their role is less clear. These Ca^{2+}-activated K^+ channels are also referred to as BK channels. The negative membrane potential of gastrointestinal smooth muscle makes activation of this channel less than optimal. It has been postulated that BK channels may serve as a brake on excitatory activity *(24)*.

There are also inward rectifier and ATP-sensitive K^+ channels that may act to repolarize smooth muscle, thus preserving phasic electrical and mechanical activity.

The predominant Ca^{2+} channel in smooth muscle is an L-type channel. Blockade of Ca^{2+} channels reduces the duration and amplitude of electrical slow waves. It should be noted that L-type channel blockade does not eliminate ECA or the slow wave.

The final type of channel discussed in this chapter is the Cl^- channel. These have not been studied as extensively, but are thought to be an important component of the acetyl choline response in tissue. Because of the importance of cholinergic excitatory input to colonic motility, these channels may prove to be quite influential *(24)*.

10. INTERSTITIAL CELLS OF CAJAL

By light microscopy, the best marker for interstitial cells of cajal (ICC) appeared to be immunoreactivity for c-kit. Ultrastructurally, ICCs are characterized by the presence of many mitochondria, bundles of intermediate filaments, and gap junctions, which linked ICC with each other. However, ICC are morphologically heterogeneous and have unique features, depending on their tissue and organ location, as well as species. ICC in the deep muscular plexus of the small intestine and in the submuscular plexus of the colon are the most like smooth muscle cells and have a distinct basal lamina and numerous caveolae. In contrast, ICC of Auerbach's plexus at all levels of the gastrointestinal tract are the least like smooth muscle cells. They most closely resemble unremarkable fibroblasts. ICCs within the circular muscle layer appear intermediate in form *(25)*. Isolation of the ICCs for use in in vitro experiments has been extremely difficult. Many experts in this field believe that contamination with fibroblasts led to early confusion regarding the role and characteristics of the ICC.

Increasing evidence has suggested that the ICCs act as pacemaker cells and possess unique ionic conductances, which may trigger slow wave or ECA within the smooth muscle cells of the bowel *(24)*. Clearly, the conductance of both smooth muscle cells and ICCs affect one another and the total electrical activity displayed. The electrical responses generated from this complex array of electrically active and coupled cells cannot be modeled and predicted from studies either on isolated myocytes or ICCs. In addition, previous studies on the electrical behavior of smooth muscle cells have grouped all myocytes together. Evidence now suggests that the activities of the circular and longitudinal muscle cells can vary widely and that the electrical activity of myocytes within a given muscle layer can be widely different *(25–27)*. This suggests a level of fine control that develops sequentially region by region within an organ such as the colon *(28)*.

11. ORGANIZED GROUPS OF CONTRACTIONS

In most species, including humans, individual contractions of the colon are organized into groups separated from one another by quiescent states. In many species, colonic contractile states propagate primarily in a caudal direction. Occasionally, they may propagate in an orad direction. This facilitates the mixing and absorptive function of the colon. Within the colon, when colonic contractile states propagate more than half of the length of the colon in either direction, they have been defined as colonic migrating motor complexes (MMC) (Fig. 3) *(29–31)*. This definition is arbitrary but helps to classify and interpret in vivo manometric, electrical and contractile tracings. In contrast to the MMC, which is seen in the small intestine, colonic MMCs are not disrupted by a meal, although the frequency of the MMCs and their characteristics may be altered, depending upon the size and content of the meal *(30,31)*.

Rectal motor complexes are intermittent periods of contractile activity that occur in the fasted state and after feeding and have not been associated with proximal intestinal motility or the rapid eye movement (REM) stage of sleep *(32)*.

12. SPECIAL SITUATION CONTRACTIONS

Giant migrating contractions (GMCs) of the colon have been recorded from humans as well as animal models of contractile activity. GMCs of the proximal colon are associated with mass

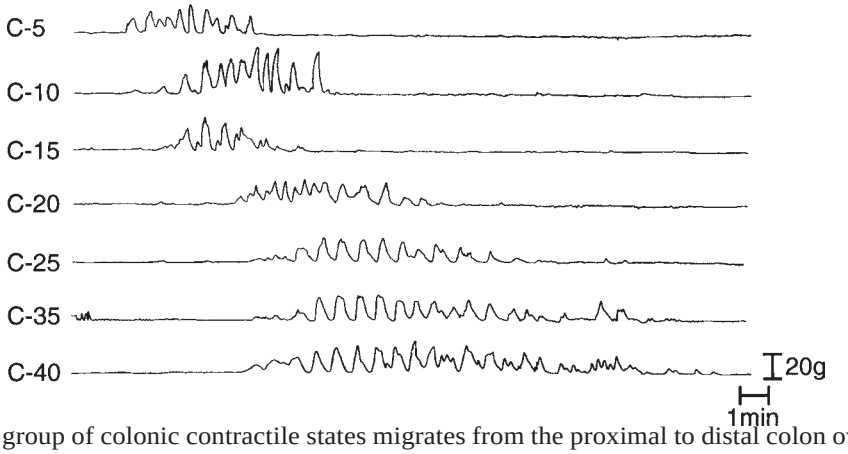

Fig. 3. This group of colonic contractile states migrates from the proximal to distal colon over greater than half of the length of the colon and can be described as a colonic MMC. The letter C to the left of the tracings represents colon. The numbers following C are the distance from the ileocolonic junction in centimeters. These recordings were performed in a canine model.

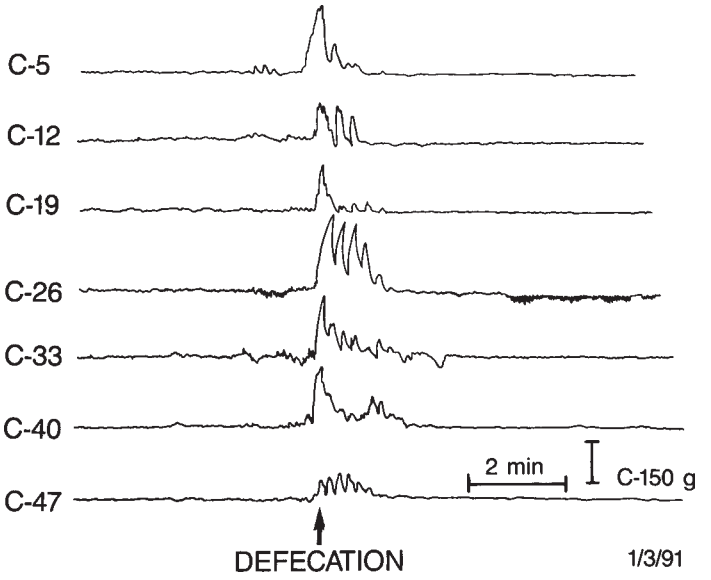

Fig. 4. GMCs of the colon are powerful high amplitude long duration contractions that are associated with mass movements in the proximal colon and defecation when they occur within the distal colon. When increased in frequency, GMCs can be associated with uncontrollable diarrhea. See Fig. 3 for details.

movements of feces (Figs. 1 and 4). When these specialized contractions occur within the distal colon, they are associated with defecation (Fig. 4). With increased frequency of GMCs, semi-liquid stool may be delivered into the distal colon and result in diarrhea that may be difficult to control. There is no discrete electrical activity that has been identified that represents the GMC. Rather, these impressive contractile events appear as a burst of ERA, indistinguishable from another phasic contraction within the colon.

During individual phasic contractions of the small intestine, longitudinal muscle lengthens while circular muscle contracts. In contrast, when longitudinal muscle contracts, circular muscle lengthens. It is impossible to determine, using strain gauge technology, whether the increase in length of the muscles is passive or active. In comparison, during special situation contractions, such as GMCs, there is a period of overlap when both the circular and longitudinal muscle layers contract. Presumably, there is a similar effect in the colon, although this has not been proven. Thus, during a GMCs, when both the circular and longitudinal muscles contract, there is foreshortening and contraction of the bowel to effectively propel intestinal contents forward.

The enteric neural control of GMCs is unclear. They are increased in frequency during inflammatory states, including enteric infections. Abdominal exposure to ionizing radiation also increases the frequency of GMCs *(33)*.

13. COORDINATION OF COLONIC MOTOR ACTIVITY WITH THE DISTAL SMALL INTESTINE

Colonic MMCs are not coordinated within the small intestine *(31)*. However, colonic GMCs, particularly within the proximal colon, are frequently directly related to those that occur within the ileum *(33)*. In normal animals, approx 50% of these contractions propagate from the small intestine into the proximal colon. In pathologic states, such as following irradiation when the frequency of GMCs is dramatically increased, the proportion of GMCs coordinated across the ileocolonic junction is also increased. These contractions effectively move enteric contents from the small bowel, across the ileum, and into the colon. This contributes to diarrhea due to insufficient time allowed for the reabsorption of bile salts.

14. SUMMARY

Normal colonic contractile activity occurs primarily through local regional control with higher central nervous system influences. These motor functions of the colon allow the animal optimal absorption of water and electrolytes and controlled expulsion of waste. As we understand more of the normal physiology of the colon, we have begun to appreciate normal variants and also the hallmarks of disease or disrupted function. The vocabulary of contractile events produced by the colon remains relatively limited, and pathologic contractile disturbances can be catagorized into excess or insufficient frequency of normal contractile events. Thus, a keen understanding of normal physiology and the control mechanisms remains important to the understanding of disease processes that affect motility.

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