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REVIEW ARTICLE

Lower gastrointestinal functions

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Abstract *The human colon serves to absorb water and electrolytes, store intraluminal contents until elimination is socially convenient, and salvage nutrients by bacterial metabolism of carbohydrates that have not been absorbed in the small intestine. The anorectum is responsible for fecal continence and defecation. This article is a broad perspective of the current status and a personal perspective of future challenges in understanding lower gastrointestinal functions in health and disease in humans.*

Keywords *anorectum, colon, functions, lower gastrointestinal, motility, pathophysiology, physiology, sensation.*

The human colon serves to absorb water and electrolytes, store intraluminal contents until elimination is socially convenient, and salvage nutrients by bacterial metabolism of carbohydrates that have not been absorbed in the small intestine. In a broad sense, we understand how the colon and anorectum execute their functions and the major sensorimotor dysfunctions which impair functioning. In recent years, there has been remarkable progress in understanding serotoninergic modulation of lower gastrointestinal (GI) functions, making a positive diagnosis and appreciating the prevalence of functional GI disorders, identifying morphological and other abnormalities in irritable bowel syndrome (IBS), and recognizing severe enteric neuropathology in some patients with colonic motor dysfunction. We recognize that pelvic floor dysfunctions cause constipation and are amenable to biofeedback therapy and that fecal incontinence is a multi-faceted disorder, attributable not only to anal sphincter weakness, but also to rectal sensorimotor dysfunctions. Having identified major disturbances, akin to low lying fruit, the challenges of elucidating the etiology of these disorders and identifying which disturbances are relevant, pose formidable challenges, particularly as not only symptom severity but also the nature of symptoms fluctuate over time. This chapter will highlight our understanding and the corresponding gaps in the important themes listed in the Table 1). Because there is remarkable variation in colonic structure among species, caution is necessary when making physiological extrapolations among species. While this article will primarily focus on colonic functions in intact humans, it will integrate concepts derived from *in vitro* studies, which often provide the driving force for expanding our horizons.

COLONIC PERISTALSIS

In comparison with circular smooth muscle, the contribution of longitudinal smooth muscle to colonic functions has been less well studied. During peristalsis in the guinea-pig colon, longitudinal and circular muscles contract and also relax synchronously in response to circumferential distention.[1] Between the cecum and rectosigmoid junction, the longitudinal layer is not a continuous coat but rather organized in three thick bands, the teniae, with a thin layer of longitudinal muscle in between these bands.[2] Consequently, the circular muscle bulges outward between the teniae, forming pouches which foster mixing.[3] Conversely, when circular muscle contracts, prominent folds, which project deeply into the lumen, are

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Table 1 Critical conceptual gaps in understanding lower gastrointestinal functions and dysfunctions

What is the relationship between colonic tone and transit in health and disease?
What is the relationship between colonic wall motion, pressure changes, and transit in health and disease?
What are the mechanisms of colonic reverse peristalsis?
What is the link between colonic secretory and sensorimotor functions in health and disease?
Do symptoms and objective findings facilitate a more refined characterization of phenotypes in lower gastrointestinal dysfunctions?
What evidence is there for sensorimotor dysfunctions and/or other putative pathophysiologic mechanisms among subjects with IBS in the community?
Can these phenotypes be defined by non-invasive biomarkers (e.g. colonic sensorimotor dysfunctions)?
What is the longitudinal stability of these phenotypes?
How reliable are *in vitro* and *in vivo* studies for predicting drug effects on symptoms in patients with functional GI disorders?

formed. It has been estimated that a shortening of the circular muscle by 17% reduces the luminal caliber by 59% in the presence of, but by only 31% in the absence of teniae. While circumferential stretch induces peristalsis (i.e. orad contraction and anad relaxation), longitudinal stretch inhibits peristalsis via nitric-oxide release in the guinea-pig distal colon.[4]

Author's perspectives

Intraluminal pressure changes primarily reflect circular smooth muscle function. To exploit the progress made by recent *in vitro* studies, techniques to assess longitudinal smooth muscle contraction in humans, similar to those used in the oesophagus, are needed. Reflex colonic relaxation induced by longitudinal stretch may explain how the left colon adapts to absorb an increased fluid load in humans.[5]

TECHNIQUES FOR ASSESSING COLONIC AND ANORECTAL SENSORIMOTOR FUNCTIONS IN HUMANS

Our cardinal concepts of normal colonic motor patterns are largely based on fluoroscopic studies conducted in animals and humans almost 100 years ago! [6] Later, manometry and colonic transit were developed to minimize radiation exposure. The barostat was used to assess gastric and subsequently colonic tone. Recording myoelectrical activity with serosal, mucosal or intraluminal electrodes is fraught with technical difficulties and has fallen out of favor. Only transit studies are routinely used to assess colonic motor functions in clinical practice. Some referral centers offer stationary or ambulatory manometry while the barostat is primarily a research tool.

In contrast to manometry, a barostat can also assess colonic tone, pressure–volume relationships and sensation.[7,8] Tone, which by convention is measured as the volume of a balloon inflated to a fixed (i.e. 'operating') pressure, provides a useful index of colonic motor functions. Firstly, measurements of colonic tone are less variable than pressure activity recorded by manometry, making it easier to detect pharmacologic or disease-related perturbations.[8] Secondly, a balloon apposed to the colonic mucosa is more accurate for identifying contractions which do not occlude the lumen, particularly when the colonic diameter is greater than 5.6 cm. While tone can be continuously recorded, phasic pressure activity is only present for approximately 50% of the recording duration. Thirdly, while manometry only identifies contractions, a barostat can also record colonic relaxation.[9] Fourthly, changes in colonic tone and phasic activity may be discordant. For example, CCK-8 and the selective serotonin reuptake inhibitor citalopram inhibited tone but increased phasic activity in the distal colon.[10,11] Megacolon may be associated with reduced tonic but preserved phasic responses to a meal.[12]

With imaging, initially by ultrasound and more recently with magnetic resonance imaging (MRI), the pelvic floor is more accessible.[13–15] Imaging has also enhanced our understanding of anorectal structure and functions (Fig. 1). With new dynamic MRI techniques, images of anorectal and pelvic floor motion can be acquired and reconstructed in real time, i.e. every 1.2–2 s. In contrast to barium cystoproctography, the pelvic organs can be visualized with minimal preparation because of the intrinsic T2-weighted signal differences among them. There is no radiation exposure. Cross-sectional imaging eliminates problems related to superimposition, magnification and measurement associated with traditional fluoroscopy. Because dynamic imaging uses time-efficient pulse sequences, high spatial resolution static (i.e. anatomic) information can be acquired during the same study. The clinical applications of imaging are discussed further below.

Author's perspectives

Despite their limitations, existing techniques for assessing colonic sensorimotor functions in humans do reasonably well at measuring function in a relatively inaccessible, inhospitable organ without exces-

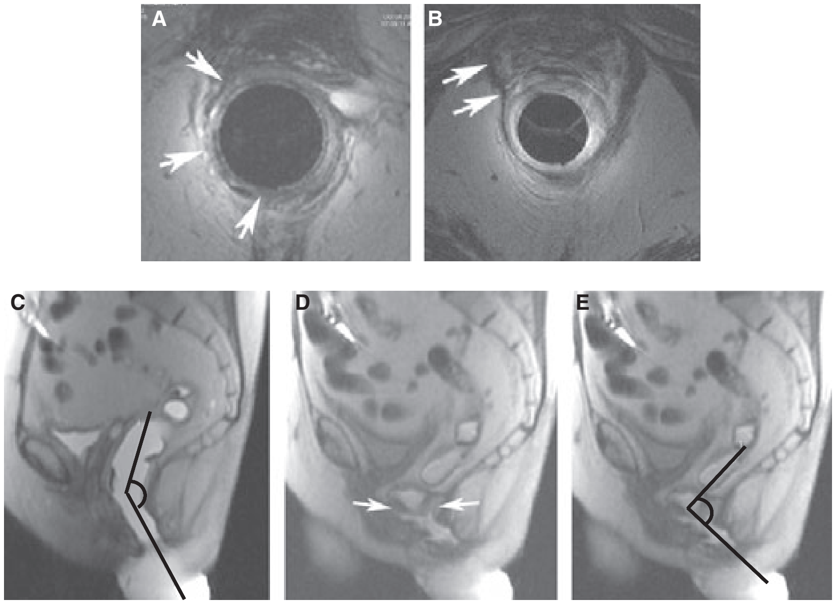

Figure 1 Static and dynamic pelvic floor imaging in defecatory disorders. In this, 69-year-old woman with symptoms of difficult defecation and fecal incontinence endoanal imaging revealed a right sided tear and atrophy of the internal and external sphincters respectively (A, arrows), and right puborectalis atrophy (B, arrows). Dynamic MR imaging shows a patulous anal canal at rest (C), rectal intussusception (D, arrows) and a reduction rather than widening of the anorectal angle during defecation (E).

sively perturbing its normal environment. Transit provides an extremely useful non-invasive snapshot of overall colonic function. Transit measurements by scintigraphy are fairly reproducible in healthy subjects and irritable bowel syndrome (IBS).[16] Perhaps, transit measurements by radio-opaque markers are not very reproducible in severe constipation.[17] Thus, the intra-individual reproducibility of measuring colonic transit and motor activity warrants further scrutiny.

Intraluminal pressure changes do not capture radial asymmetry of colonic contractions.[18] Moreover, the relationship between intraluminal pressure changes and colonic movements is not fully understood, as discussed below.[19] Simultaneous assessments of colonic wall motion, pressure changes and flow in real time, either by studies integrating existing techniques (e.g. combined scintigraphy and manometry) or by applying newer techniques (e.g. dynamic MRI, radiotelemetry capsules to measure transit and pressure activity) to assess colonic motor functions might be fruitful.

NORMAL COLONIC MOTOR ACTIVITY AND MOTOR DYSFUNCTIONS IN DISEASE

Colonic motor activity is irregular (i.e. not rhythmic) and includes tonic and phasic components. Motor activity is normally suppressed at night but increases after awakening, often inducing the urge to defecate. Predominant motor patterns differ in the right and left colons.[6] To-and-fro contractions between the ascending and proximal transverse colon facilitate mixing and imply not only anad but also orad (i.e. 'reverse') peristalsis. Propagation in the distal transverse and descending colon is accomplished by distally migrating tonic contractile rings. High-amplitude propagated contractions (HAPCs) occur on an average of six times (range 2–24) per day, often after awakening and meals, propagate contents over several segments, and may be associated with the urge to defecate. In health, propagating contractions moved contents over longer distances than non-propagating contractions.[19] However, only one-third of propagating contractions are accompanied by propulsion of colonic contents, perhaps because even non-propagating contractions may induce a pressure gradient.[19,20]

In addition to augmenting colonic motor (i.e. tone and phasic) activity, recent studies suggest that feeding also increases colonic sensation and affects recto-colonic reflexes.[21] This response, which is mediated by neurohumoral mechanisms, may explain the postprandial urge to defecate and abdominal discomfort in health and IBS.

Some patients with 'functional' bowel symptoms have motor disturbances. In general, diarrhea is associated with rapid transit and increased motility (i.e. more frequent HAPCs and an exaggerated colonic motor response to eating) while 'functional' constipation is associated with slow colonic transit and reduced motility. However, normal and slow transit constipation are not always associated with normal and reduced motility, respectively.[22,23] Thus, constipation has been associated with *increased* phasic motility in the sigmoid colon which may retard colonic transit.[24]

Conversely, diarrhea has been associated with *reduced* motility (i.e. fewer non-segmenting contractions).[25]

Author's perspectives

The mechanisms of colonic reverse propulsion, which has been attributed to the slow wave frequency gradient in the feline colon, warrant further study.[26] The mechanisms of diurnal fluctuation (i.e. increased motor activity upon awakening), which is impaired in slow transit constipation, have not been studied.[27] The role of clock genes, which have been described in the murine gastrointestinal (GI) tract, deserve to be explored.[28] Except for loss of colonic nerves and interstitial cells of Cajal (ICCs) in a subset of patients with slow transit constipation or megacolon, the etiology and pathophysiology (e.g. neuropathologic or humoral disturbances) of colonic motor dysfunctions remain a mystery.[29] A priority is to identify biomarkers for these disorders. Abnormal colonic motor patterns, and specifically inertia, as defined by impaired colonic motor responses to a meal and pharmacologic stimuli (e.g. neostigmine and bisacodyl), may provide a biomarker for the phenotype characterized by a loss of colonic nerves and ICCs. The natural history of colonic sensorimotor dysfunctions has not been evaluated. Forty-five years ago, Connell, speculated that increased motility in younger constipated patients evolved into reduced motility in older constipated patients.[24]

COLONIC BIOMECHANICAL PROPERTIES

Consistent with its primary role as a reservoir which mixes and stores contents, the right colon is more compliant than the left. Colonic pressure–volume (p–v) relationships, which are measured by distending a highly compliant balloon with a barostat, are reproducible within subjects and are responsive to pharmacologic modulation and disease, discussed further below.[30] Static biomechanical mechanical properties, reflecting muscle tone and passive components, are measured after the phasic contractile response to distention subsides.[30] Dynamic properties also include this phasic response, which may be exaggerated when the rectum is distended rapidly.[31,32] Perhaps, this explains why rapid rectal distention is more likely than slow distention to be perceived in healthy subjects and to evoke visceral hypersensitivity in IBS.[31,33,34] The rate of distention is also physiologically relevant because the rectum may be distended more rapidly in patients with diarrhea-predominant IBS and accelerated colonic transit,[35,36] thereby overwhelming rectal accommodation and fecal continence.

Author's perspectives

A barostat does not directly measure luminal radius and wall thickness, which are required to compute wall tension and stress, respectively.[37] The influence of extra-rectal structures on rectal pressure–volume relationships is unknown. While imaging during balloon distention or impedance planimetry can overcome these limitations, their impact on understanding biomechanical properties is unknown.[38,39]

Sinusoidal oscillation can assess the colonic response to repetitive stimulation. This technique has been extensively used to understand normal airway function and mechanisms of broncho-constriction in asthma.[40] During sinusoidal oscillation, the colonic pressure waveform can be decomposed into components which are in phase with balloon volume (i.e. elastance) and flow (i.e. resistance). This technique demonstrates that the colonic contractile response to distention is influenced by the distention rate.[41] Further studies are necessary to ascertain if colonic 'interrogation' by sinusoidal oscillation can uncover neuromuscular irritability in IBS.

COLO-COLONIC REFLEXES

Colo-colonic reflexes mediated via local nervous pathways through the prevertebral ganglia and independent of central nervous system activity have been well characterized in animal preparations.[42] Rectal distention by a balloon to sub-noxious levels induces colonic relaxation in humans.[43] During postprandial but not fasting conditions, colonic relaxation during rectal distention is less pronounced in IBS.[21] Sympathetic stimulation and opiates also relax the colon and may explain the pathophysiology of acute colonic pseudo-obstruction.

Author's perspectives

Perhaps, colonic relaxation induced by rectal distention explains delayed left colonic transit in defecatory disorders. A preliminary study suggests that postprandial colonic contractile responses improved after biofeedback therapy in patients with obstructed defecation,[44] but results were not significant. This question needs to be assessed in further studies in which colo-colonic reflexes are also compared before and after pelvic floor biofeedback therapy.

COLONIC INNERVATION

Intrinsic nerves regulate colonic motility. The extrinsic input, which includes sympathetic and parasympathetic components, modulates the enteric nervous system. Studies with the α_2-adrenergic agonist and antagonist clonidine and yohimbine, respectively, confirm that the sympathetic nervous system tonically inhibits colonic motor function in humans.[45]

Author's perspectives

Reduced sympathetic inhibition probably explains accelerated colonic transit and diarrhea in dysautonomia.[46] In IBS, the prevalence of cardiovascular autonomic dysfunctions as documented by rigorous tests is relatively low.[47] However, the possibility of selective GI sympathetic dysfunction, which can be assessed by measuring superior mesenteric artery flow, should be considered.[48]

Parasympathetic denervation is recognized to occur in conditions (e.g. spinal cord injury) or after surgical procedures that interrupt the sacral parasympathetic supply (e.g. low anterior resection). The extent to which hysterectomy, which is a very common operation that entails dissection of the rectovaginal septum, is associated with denervation is unclear.[49]

RELATIONSHIP BETWEEN INTRALUMINAL CONTENTS AND COLONIC FUNCTIONS

The colon is uniquely responsive to its intraluminal milieu. In the proximal colon, bacteria ferment organic carbohydrates to short-chain fatty acids (SCFA), which are rapidly absorbed from the colon, augment sodium, chloride and water absorption, and constitute the preferred metabolic fuel for colonocytes. *In vitro* studies suggest that physiological concentrations of SCFA (<100 mmol L^{-1}) are often excitatory, perhaps by releasing 5-HT. Higher concentrations generally inhibit motility.[50] Colonic perfusion with SCFA induced HAPCs and/or accelerated colonic transit in healthy subjects.[51] Oleic acid, which is a long-chain fatty acid, also accelerated colonic transit at high concentrations, perhaps comparable with those attained in malabsorption.

SCFA have been reported to have several therapeutic effects *in vitro* studies. They regulate proliferation, differentiation, gene expression, immune function and colonic wound healing. Fecal SCFA concentrations are reduced and may contribute to impaired sodium absorption in acute diarrhea.[52] SCFA potentially reduce inflammation in ulcerative colitis and diversion colitis. Butyrate has also been hypothesized to reduce the risk of colon cancer.

Dihydroxy bile acids (i.e. deoxycholic and chenodeoxycholic acids) stimulate colonic secretion, increase colonic motility, and enhance colonic sensation at relatively low concentrations.[51] Moreover, rectal infusion of chenodeoxycholic acid at physiologic concentrations stimulated proximal colonic propagated contractions and increased rectal sensitivity.[53] Idiopathic bile acid malabsorption, which can be diagnosed by low retention of selenium-75-homocholic acid-taurine ([^{75}Se]HCAT) after oral administration, may explain diarrhea in some patients with 'irritable bowel syndrome'.[54]

Author's perspectives

Assessing colonic secretion in humans is arduous, which may partly explain the lack of recent studies in this area. Conceivably, the effects of short- and long-chain fatty acids may explain why some patients with IBS, particularly those with mild fat malabsorption (i.e. 7–14 gm day^{-1}), have accelerated colonic transit. We do not know if the colonic microbial pattern influences its contents and thereby sensorimotor functions. Conversely, the inhibitory effects of higher concentrations of SCFA may explain the inconsistent effects of dietary fiber and lactulose on colonic transit; indeed fecal SCFA concentrations are inversely correlated with distal colonic transit during lactulose administration in humans.[55] Idiopathic bile acid malabsorption is a well-defined but probably under-recognized entity because ([^{75}Se]HCAT) is not available for human use in the US. Alternative techniques to identify bile acid malabsorption are necessary. Human intervention studies are necessary to evaluate the exciting, multifaceted benefits of SCFA.

PHARMACOLOGY

Over the past 10 years, there has been limited progress in understanding the pharmacologic mechanisms regulating colonic or anorectal sensorimotor functions or in translating potential therapeutic targets identified *in vitro* studies for treating patients. Colonic motor activity in humans is regulated by muscarinic, α2-adrenergic, serotoninergic 5-HT3 and nitrergic mechanisms.[8] With the withdrawal of 5-HT$_4$ agonists from the market, the therapeutic armamentarium for lower GI disorders is limited to non-selective muscarinic antagonists (e.g. hyoscyamine), clonidine and 5-HT$_3$ antagonists for diarrhea, osmotic agents and lubiprostone for constipation, neostigmine, which is a cholinesterase inhibitor, for acute colonic pseudoobstruction and centrally acting agents (e.g. SSRIs) to modulate visceral hypersensitivity. Recent studies suggest that alvimopan, a μ-opioid receptor antagonist, also accelerates colonic transit in healthy subjects,[56] dexloxiglumide, a CCK-1 receptor antagonist, delays proximal colonic transit in IBS patients,[57] and linaclotide, which is a guanylate cyclase C agonist, accelerates colonic transit by stimulating secretion. Contrary to *in vitro* studies, progesterone stimulates colonic motility (i.e. accelerated colonic transit) in healthy subjects.[58] There is no evidence that synergistic therapy is superior to single agents for constipation.

Author's perspectives

A major challenge is to develop *in vitro* and *in vivo* animal models which predict efficacy in humans and to devise appropriate endpoints for preclinical trials in humans. Some agents (e.g. the NK_3 antagonist talnetant, serotoninergic 5-HT_4 receptor antagonist piboserod) which appeared promising in animal models were not effective in humans. These differences may result from differences in species and/or to redundant mechanisms in whole humans. Assessments of colonic transit, motor activity and sensation in healthy subjects may predict efficacy or lack thereof in IBS (e.g. octreotide, piboserod and fezotodine). The linaclotide and lubiprostone data underscore the need for exploring the link between secretion and motility.

FUNCTIONAL DISORDERS (IRRITABLE BOWEL SYNDROME)

Although experts agree that IBS is a common disorder primarily characterized by disturbed bowel habits which cannot be explained by overt findings, there is ongoing debate regarding the identity of the disorder, its pathophysiology and its management. Several factors or disturbances [i.e. colonic motor dysfunctions, increased visceral sensitivity, psychosocial stressors, mild colonic inflammation possibly related to acute gastroenteritis, bacterial overgrowth and luminal irritants (e.g. due to bile acids)] have each been identified in subsets of patients with IBS. With the exception of postinflammatory IBS, most studies have been predominantly conducted in referred patients at secondary or tertiary centers and are prone to various biases. Therefore, the contribution of these mechanisms to IBS in the community is unclear.

VISCERAL HYPERSENSITIVITY AND HYPERALGESIA

There is compelling evidence that approximately 40–60% of patients with IBS have visceral hypersensitivity manifest as lower sensory thresholds, altered viscerosomatic referral and by higher unpleasantness ratings during rectal distention.[59] Rectal hypersensitivity has been linked with pain and bloating but not with altered bowel habits, which are a sine qua non for the diagnosis of IBS.[60] Associations between symptom severity and rectal sensation are variable. At best, age, gender and rectal sensation together explained 48% of the variance in symptom severity in IBS.[60] There is a modest correlation between improvement in symptoms and rectal sensitivity with therapy.

Conceptually, visceral hypersensitivity can be attributed to peripheral, spinal and/or central mechanisms. Visceral hypersensitivity has driven interest in cerebral imaging by MRI and PET during rectal distention. In general, patterns of cerebral activation during rectal distention in health are comparable across studies. However, differences in cerebral activation between health and IBS are inconsistent and challenging to interpret.[61] For example, reduced activation of primary and secondary somatosensory cortices in IBS is puzzling because somatic hyposensitivity is not a consistent feature of IBS.

Author's perspectives

Perhaps differences in study populations, study design and imaging techniques explain the inconsistent differences between health and IBS and the variable associations between visceral hypersensitivity and symptom pattern, symptom severity and psychological symptoms (e.g. anxiety). Thus far, functional brain imaging has not substantially enhanced our understanding of normal and abnormal visceral perception, perhaps because these 'first generation' cerebral imaging studies were primarily descriptive and had several limitations. Moreover, the experimental and statistical approaches did not provide a real-time perspective of cerebral activation during distention. These limitations are extensively detailed elsewhere [61,62] Some of the confounding factors [e.g. gender and comorbid conditions (e.g. fibromylagia)] that influence the response to colorectal distention are now recognized. Because strong distentions may activate cognitive processes which affect cerebral activation, the Milwaukee group used non-noxious stimuli and demonstrated that cerebral activation during rectal distention even with subliminal stimuli is more intense in IBS.[63] These studies have set the stage for carefully designed, adequately powered, hypotheses-driven, studies to elucidate the specific central mechanisms contributing to visceral hypersensitivity in IBS.[64]

Although rectal hypersensitivity in IBS is generally considered to be a primary phenomenon, there is accumulating evidence that perception is partly related not to distention *per se*, but to the contractile response to distention or a tendency to report pain.[31,65] Moreover, motor disturbances (i.e. reduced compliance or an exaggerated contractile response to distention) may contribute to rectal hypersensitivity in IBS and in atypical chest pain.[31,66]

NEWER CONCEPTS IN IBS

Clinical and epidemiologic observations suggest that some people have persistent symptoms after an episode of acute and particularly after severe gastroenteritis, i.e. postinfectious IBS.[67] Similar to IBS in general, psychological factors, local factors (lymphocytes, mast cells and enterochromaffin cells) and visceral hypersensitivity have been implicated to cause postinfectious IBS, which probably accounts for one in seven patients with IBS.

Excess serotonin contributes to diarrhea in carcinoid syndrome. Perhaps encouraged by the therapeutic potential of serotoninergic modulation, several groups have studied and identified serotoninergic disturbances [e.g, reduced serotonin reuptake transporter (SERT) expression and increased p11 expression in colonic mucosal biopsies] in IBS.[68,69] There is conflicting evidence for reduced SERT expression in IBS.

The role of small intestinal bacterial overgrowth, which is debated below, rests primarily on a higher prevalence of bacterial overgrowth, diagnosed by abnormal hydrogen breath tests, in IBS than in controls.[70–72] Moreover, antibiotic therapy improves symptoms in some patients with IBS.

Author's perspectives

Postinfectious IBS The relative importance of psychological factors and persistent inflammation need clarification. If psychological factors are pre-eminent, the role of inflammation is unclear.[67] Differences in lymphocyte counts between postinfectious IBS and health are small. The evidence implicating mast cells and proteases is stronger.[73] The lack of a therapeutic response to prednisone in postinfectious IBS is puzzling.

Serotoninergic disturbances The evidence for colonic mucosal serotoninergic disturbances in IBS is conflicting and needs confirmation. Moreover, it is difficult to explain why diarrhea and constipation are both associated with reduced SERT expression.

Small intestinal bacterial overgrowth In contrast to breath tests, small intestinal cultures revealed a similar prevalence of bacterial overgrowth, defined by established criteria (i.e. $\geq 10^5$ colonic bacteria/mL) in IBS and controls.[74] However, mildly increased bacterial counts ($\geq 5 \times 10^3$ mL^{-1}) were more common in patients (43%) with IBS than in controls (12%). The relationship between these 'minor' disturbances and intestinal motility, and the role of altered colonic flora in IBS deserve to be explored further. Indeed, recent studies suggest that methane may affect intestinal motility and that methane production in breath tests is associated with constipation.[75] Moreover, hydrogen sulfide, which is a product of bacterial fermentation, is a prosecretory modulator in the guinea-pig and human colon.[76] The detailed characterization of the human intestinal genome provides a unique opportunity to investigate the relationship between intestinal flora and functional GI disorders.

DIVERTICULOSIS

Colonic diverticula are caused by mucosal outpouching through the circular muscle between tenia coli. Bleeding and perforation are significant and not uncommon complications. The pathophysiology of diverticulosis is undefined. Conceivably, increased elastin deposition and impaired relaxation of longitudinal muscle may narrow the colonic lumen, generate higher intraluminal pressures and formation of diverticula.[77] A recent study identified increased motor activity and perception of colonic distention in symptomatic diverticulosis.[78]

Author's perspectives

There are three important questions. Firstly, the sequence of events leading to diverticulosis needs to be evaluated by longitudinal studies in humans. Secondly, it is unclear whether sensorimotor dysfunctions occur only in symptomatic or also in asymptomatic diverticulosis. Thirdly, there is little direct evidence to support a link between a low fiber diet and diverticulosis.[26]

MECHANISMS OF NORMAL AND DISORDERED DEFECATION AND FECAL CONTINENCE

The mechanisms of defecation and fecal continence, which are both complex somatovisceral processes, are broadly understood.[79] However, there are several missing pieces in this puzzle. In brief, defecation is often preceded by HAPCs, which tend to occur upon awakening and after meals. Thereafter, rectal distention by stool evokes the desire to defecate and reflex relaxation of the internal anal sphincter and prompts voluntary actions (i.e. diaphragmatic contraction to raise intra-abdominal pressure coordinated with relaxation of the puborectalis and external anal sphincter) necessary for defecation. If defecation is inconvenient, rectal contractions and the sensation of urgency generally subside as the rectum accommodates to continued distention. This, together with voluntary contraction of the external anal sphincter and levator ani, permits defecation to be postponed when necessary.

A substantial proportion of patients with chronic constipation have pelvic floor dysfunction, which is diagnosed by a consideration of symptoms and anorectal tests.[80] Rigorous trials indicate that pelvic floor retraining by biofeedback therapy is the cornerstone for managing functional defecatory disorders. These concepts are not widely recognized in clinical practice and biofeedback therapy is available at select centers only. It is increasingly recognized that defecatory disorders may be caused not only by impaired relaxation and/or paradoxical contraction of the anal sphincter and/or pelvic floor muscles, but also by impaired rectal propulsion. However, the relationship of these phenotypes to the clinical presentation and the response to pelvic floor retraining, have not been studied.

While most attention has focused on anal sphincter weakness, disturbances of rectal compliance and perception, of stool consistency, mental faculties and mobility often contribute to fecal incontinence (FI). Pelvic floor imaging with MRI and ultrasound discloses a spectrum of anal sphincter and pelvic floor injury in FI.[13] Dynamic MRI can non-invasively assess anorectal and pelvic floor functions and can identify puborectalis dysfunction in FI. In addition to a weak pelvic barrier, there is increasing evidence for rectal sensorimotor dysfunctions in FI. Moreover, reduced rectal capacity is associated with rectal hypersensitivity and with the symptom of urgency in FI.[13,81] In women without an underlying neurologic disorder, obstetric trauma, disordered bowels and perhaps a pudendal neuropathy are the commonest factors implicated to cause FI. However, most women develop FI several decades after vaginal delivery.

Author's perspectives

Normal mechanisms It is essential that appropriate animal models be used. For example, sympathetic input contributes to baseline tone and the contractile response in the internal anal sphincter in humans and monkeys but not in rabbits and mice.[82] The human external sphincter is primarily composed of type 1 (i.e. fatigue-resistant) fibers in humans and type 2 fibers in cats and rabbits.

We do not understand the relative contributions of rectal contraction and abdominal wall motion to propulsive forces during defecation, of internal and external sphincter functions to anal resting tone, and of myogenic tone and sympathetic innervation to internal sphincter function in humans. New techniques will be required to address these questions.

Defecatory disorders The risk factors (e.g. obstetric anal sphincter injury) for functional defecatory disorders have not been addressed. Techniques to evaluate and understand the contribution of rectal contraction to normal and disordered defecation are essential. It is unclear if reduced rectal sensation, which affects a subset of patients with defecatory disorders, is primary or secondary. Longitudinal studies are necessary to characterize the natural history of defecatory disorders. The mechanisms of delayed left colonic transit, which is frequently associated with defecatory disorders, need to be elucidated.

Fecal incontinence There has been substantial progress in understanding the pathophysiologic mechanisms of FI and their relationships with symptoms in FI. The next, and perhaps more challenging steps, are to define the contributions of disordered bowel habits, obstetric anal sphincter injury and other putative risk factors to FI in women by case–control studies. The available evidence suggests that disordered bowel habits are more important risk factors for FI than obstetric anal sphincter injury among women in the community.[83]

The contribution of sympathetic nerve dysfunction to internal sphincter weakness is unknown. Not infrequently, there is a discrepancy, perhaps partly explained by neurogenic injury, between the severity of external sphincter weakness and anal sphincter injury. However, needle electromyography, which is the only technique that can reliably assess external sphincter neurogenic injury, is not widely available. An extensive literature documenting pudendal neuropathy by prolonged pudendal nerve latencies in FI is of questionable utility given the substantial limitations of this technique.[84] It is unclear if reduced rectal capacity is attributable to reversible (e.g. increased tone) or pharmacologically irreversible mechanisms (e.g. fibrosis).

CONCLUDING REMARKS

This review encapsulates the considerable progress toward understanding the complexity of normal and disordered colonic and anorectal functions in health and disease. There is increasing evidence that these conditions (e.g. IBS and pelvic floor dysfunctions) include several phenotypes, which may be defined not only by symptoms, but also by biomarkers, be they physiologic, histologic, genetic, serologic or immunologic. These phenotypes may also guide selection of therapy. However, in order to accomplish this paradigm shift, true biomarkers need to be separated from epiphenomena and the stability of these biomarkers needs to be documented in longitudinal studies conducted in representative patient populations. Otherwise, it is likely that these abnormalities, like others in previous years, will fall out of favor.

Thus, human colonic motility remains, as Truelove suggested 40 years ago, in a 'state of flux'.[85] Now, we face different challenges, which will require increasing the number of clinician–investigators engaged in the field and more effective collaboration between basic science and clinical investigation; the left hand must know what the right hand is doing. As most centers are strong in basic or clinical research but not both, augmenting funding mechanisms that require collaborations between basic and clinical scientists will perhaps provide the strongest impetus for integration.

CONFLICTS OF INTEREST

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