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Contribution of Gut Microbes to Gastrointestinal Motility Disorders

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The community of microorganisms living in our intestine is ~10 times greater in number than the total number of somatic and germ cells that compose our body. Our relationship with colonizing gut microbes begins at birth. The specific constitution of this microbial community or microbiome varies between individuals and between the various regions of the gastrointestinal tract. The relationship between individual microbial species and the host ranges from commensalisms to mutualism to parasitism. Evidence increasingly confirms that the biology of gut bacteria and the human host including the motility of our gastrointestinal tract are inseparable. What happens when the balanced relationship between the human host and gut microbiota is disturbed? Recent evidence suggests that a shift in the host-gut microbial relationship as exemplified by small intestinal bacterial overgrowth (SIBO) may contribute to the pathogenesis of IBS. The results of two prospective, randomized, double-blinded, placebo-controlled studies using nonabsorbable antibiotics suggest that an antibiotic sensitive mechanism located in the small intestine is responsible for bloating and other symptoms of IBS. A 75% global symptomatic improvement was reported by IBS patients when abnormal bacterial fermentation suggesting SIBO was eliminated. Small intestinal bacterial overgrowth would be the best explanation for such a mechanism. Methane, a gaseous byproduct of microbial fermentation slows transit and is associated with constipation. These findings argue for the role of gut microbes in gastrointestinal motility disorders and the need for new diagnostic and treatment approaches directed at small intestinal bacterial overgrowth.

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INTRODUCTION

The community of microorganisms living in our intestine approaches densities up to one trillion microbes per milliliter of luminal contents in the distal gut (1). The size of the gut microbial population is ~10 times greater than the total of number somatic and germ cells that compose our body (2). This ecosystem includes between 500 and 1000 different species of bacteria. The specific makeup depends on the region of the gut and also varies significantly between individuals (3,4). Thus the gut microbial community should be viewed as a symbiont to the human host, both integral and inseparable from human biologic function. While the metabolic, structural, and physiologic effects of the gut microbiota on the human host are not completely identified nor fully elucidated (5,6), the gut microbiota are implicated in host immune modulation, nutrient acquisition, energy regulation, drug metabolism, and a wide spectrum of other host functions (7,8). In this review, we will examine the influence of the gut microbiota on intestinal motility. We will then explore what happens to human health when the host-gut microbial balance is disturbed using irritable bowel syndrome as the example.

THE HOST-MICROBIAL RELATIONSHIP BEGINS AT BIRTH

The gastrointestinal tract of the newborn is sterile at the time of delivery. However, host factors begin to influence the establishment of the gut microbial ecosystem far in advance of the fetus entering the extra-uterine environment. Prenatal factors such as the use of antibiotics by the mother or the degree of stress experienced by the pregnant woman are strong determinants of how gut microflora will be established (9). Soon after birth, microbes begin to actively colonize every surface of the body, including the gastrointestinal tract. Host factors weigh heavily in determining the pattern of microbial colonization. For example, preterm infants are known to establish a different microbial flora compared to term infants (10–13).

Colonization of the gastrointestinal tract is swift. Vaginally delivered neonates pass bacteria in their stools as early as the first day after birth. *Escherichia coli* and Enterococcus species usually appear first, fol-

lowed by the obligate anaerobes, including the Bifidobacterium species (14,15). By the tenth day after birth, the typical healthy, term neonate has established a dense and complex intestinal microbiota (16). Host factors such as nutrition source (breast feeding versus formula), hygiene, exposure to pathogens, and use of antibiotics continue to influence the overall makeup of the microbiota, with the diversity of the microbial community stabilizing by the second year after birth (17–20). This community is largely compartmentalized to the distal gut, with the concentration of microbes reaching 10^{11} per mL in the cecum but only $10^{0\text{-}2}$ per mL in the jejunum (21,22). Fermentation represents one of the signature metabolic activities of gut bacteria, producing hydrogen, methane and hydrogen sulfide. Hydrogen production by bacterial fermentation is usually limited to the distal gut and depends on undigested starch reaching colonic bacteria (23,24). The clearance of hydrogen gas depends on methanogenic or sulfate-reducing bacteria which convert hydrogen to methane or hydrogen sulfide respectively (25). Because these three gases are unique to bacterial metabolism, they serve as signatures of an active gut microflora.

THE INTEGRATED EXISTENCE OF HOST AND GUT MICROBIOTA

Much of what we know regarding the impact of the intestinal microflora on host biology is derived from the comparison of germ-free and conventionally-raised animals. We have learned that resident microbes are critical to normal structural development of the host gastrointestinal tract. Gross examinations demonstrate that the cecums of germ-free rats are up to ten times the normal size (26). Postnatal development of normal intestinal vasculature also depends on gut microbes (27). Gut microbes also influence the physiology of the host including regulation of nutrition and energy storage (28–30).

The intricate nature of the host-gut microbial relationship is also reflected in the concept of "global systems biology," which investigates the interactions of mammalian transcriptomes, proteomes and metabolomes, and the gut microbiota on host metabolic regulation. Efforts in developing personalized health care, in which therapy and drug dosing are adjusted for indi-

vidual variances in metabolism, have revealed the gut microbiota's influence on drug activity and toxicity. For example, studies have identified ethnic differences in the conversion of the highly toxic cardiac drug digoxin to its reduced metabolites (31). The inactivation of digoxin is directly linked to the metabolic activity of anaerobic gut flora, suggesting that variability in responses to drugs and toxins between individuals may be linked to differences in gut microbial complement (32). The integrated biology of host and gut bacteria makes it increasingly clear that our genetic spectrum needs to be viewed as an amalgam of genes derived from the human genome as well as the genomes of our affiliated microbial partners (28).

GUT MICROBES INFLUENCE INTESTINAL MOTILITY

Germ free animals have delayed gastric emptying and slowed intestinal transit compared to conventionally raised counterparts (33). The effect of the gut microbiota on intestinal motility occurs through several recognized mechanisms. Intestinal microflora releases substances that stimulate the enteric nervous system and primary afferent neurons. This process not only occurs in the setting of infection and inflammation but also in the healthy gut (34).

The end products of bacterial metabolism affect gut motor function via neuromodulation as well as direct effects on intestinal smooth muscle contractility (35–38). The cyclic recurrence and distal propagation of interdigestive migrating motor complexes (MMCs) are linked to intestinal bacterial flora. Introduction of gut microbes to germ-free rats stimulated interdigestive intestinal motility and accelerated intestinal transit (39,40).

The gut microbiota participates in the regulation of gastrointestinal endocrine cells and influences the release of biologically active peptides (41). Gut bacteria are known to produce neuroendocrine hormones such as GABA, contributing to hepatic encephalopathy in humans (42). It has been proposed that gut microbial hormones may have other functions such as the modulation of host immunity (43). The presence of intestinal flora is in fact essential to the normal development of the gut immune system (44). As further evidence of a bidirectional relationship, the release of gastrointestinal immune mediators modulates intestinal motility (45).

IMPACT OF GUT MOTILITY ON MICROFLORA

The gastrointestinal microbiota is a dynamic system constantly undergoing cell death and proliferation. This affords an opportunity for multiple factors to influence the shape and composition of the microbiota. Gastric secretion, host diet, biliary and pancreatic secretion, mucous secretion, and local immune function are some of the factors that control the proliferation of gut bacteria. Gastrointestinal motility turns out to be one of the most influential determinants of gut microfloral growth. While the presence of gut microbes is essential for the appropriate generation of MMCs, the MMC is also a propulsive force that acts as an intestinal housekeeper. Any disruption of the MMCs results in expansion of distal gut flora into the small intestine or small intestinal bacterial overgrowth (46,47). Inter-subject variability in intestinal transit time as well as in the composition of intestinal flora has been reported. It is unclear whether alterations in transit are a cause or consequence of alterations in gut flora (48,49).

IRRITABLE BOWEL SYNDROME IS AN ALTERATION IN THE HOST-GUT MICROBIAL RELATIONSHIP

What happens when the balanced integration of human host and gut microbiota is disturbed? One disorder that may be explained by a shift in the host-gut bacterial relationship is irritable bowel syndrome. IBS is a common disorder that affects greater than 15% of the general population (50). Studies have demonstrated that IBS is associated with altered gut motility (51), peripheral (52) and central (53) sensory dysfunction, and an exaggerated response to stress (54). However, multiple proposed pathophysiologic mechanisms have failed to provide a framework for understanding all of the findings associated with IBS. As a result, IBS is a frustrating condition to both patients and clinicians. In the absence of a framework of understanding, we have relied upon symptom-based clinical criteria for diagnosis and drugs that target symptoms rather than the cause as treatment. Symptom-targeting treatments, however, are unable to offer lasting efficacy. When

medications are discontinued, symptoms reappear, reminding the patient that nothing has been done to address the underlying cause of the disease process.

TREATING THE CAUSE RATHER THAN THE SYMPTOMS

The results of two randomized control trials are now available to support the role of gut microbes in IBS. In a prospective, randomized, double-blinded, placebo-controlled study, the effect on IBS of a nonabsorbable antibiotic that is active against gut bacteria was compared to that of placebo. The outcome of the study was based on the absolute percent improvement in bowel symptoms seven days after treatment. A lactulose breath test was performed to detect hydrogen and methane as evidence of bacterial fermentation. The results of the breath test were blindly read to determine if arbitrary criteria for normal gas profile were met by each patient: "no rise of breath hydrogen or methane concentration before 90 minutes of lactulose intake with a definitive rise never more than 20 parts per million during 180 minute measurement" (55). Before treatment, 84% of IBS patients in the study failed to meet these criteria, whereas only 20% of control subjects failed to meet the criteria. After treatment, those IBS patients who were randomized to receive antibiotics demonstrated a greater absolute improvement in symptoms.

The degree of symptom improvement depended on whether or not antibiotic treatment resulted in a conversion of the breath test gas profile to meet the preset criteria. If antibiotic treatment resulted in successful conversion of breath test profile, a $75 \pm 6.4\%$ improvement was reported by patients. Even if antibiotic treatment did not convert the breath test profile to meet preset criteria, treated patients experienced a $36.7 \pm 6.1\%$ improvement. This compares to an $11.9 \pm 3.7\%$ improvement in patients treated with placebo. The results of this study suggest that IBS symptoms are due to an antibiotic-sensitive mechanism that can be localized to the intestine.

If IBS symptoms were to be caused by an antibiotic-sensitive mechanism, could the improvement of symptoms persist even after treatment is withdrawn? In a second prospective, randomized, double-blinded, placebo-controlled study, the effect on IBS symptoms of a non-absorbable antibiotic that spares colonic flora

was compared. Patients randomized to the nonabsorbable small bowel active antibiotic reported significant improvement of symptoms over placebo for 10 weeks even after treatment was stopped (56). Such sustained improvement contrasts with the pattern seen with symptom-directed treatment, where the beneficial effect is lost upon withdrawal of therapy. Such sustained improvement after a course of this antibiotic point to an antibiotic-sensitive mechanism located in the small intestine as the underlying cause of IBS. Small intestinal bacterial overgrowth is the best available explanation for such a mechanism (57). These randomized control studies provided level 1 experimental evidence for a gut microbial origin of IBS.

ROLE OF IMPAIRED INTERDIGESTIVE MOTILITY IN SIBO

Abnormal expansion of distal gut microbial community into the small bowel potentially occurs in any condition that disrupts gastrointestinal motility. Bowel obstruction, pseudo-obstruction, autonomic neuropathy, radiation enteropathy, and scleroderma are some of the conditions that allow for the overgrowth of intestinal bacteria (58–61). The proliferation of bacteria in each of these conditions has been explained by a disruption of gut motility. Compared to healthy controls, the frequency of MMC phase III activity is significantly reduced in IBS patients (62). The bidirectional nature of the gut motility-microbial relationship results in a cyclic perpetuation of pathology. Altered motility allows unchecked overgrowth of bacteria, while the metabolic activity of the over-proliferated microbiota produces substances known to alter motility. Effective therapy must target the eradication of abnormal gut flora as well as the correction of the underlying perturbance in motility in order to delay time to relapse of SIBO. For example, improvement of MMC cycling in scleroderma results in a reduction of SIBO (63).

HOW CAN A SHIFT IN HOST-GUT MICROBIAL BALANCE EXPLAIN BOTH CONSTIPATION AND DIARRHEA IN IBS

Intestinal exposure to bacteria can incite a host immune response and activate the enteric nervous sys-

tem. This well-coordinated defense mechanism is designed to increase intestinal transit and clear the intestine of offending luminal contents. The patient experiences an overactive bowel with cramping abdominal pain and diarrhea (64). In studies of IBS patients, qualitative changes in gas production could be specifically correlated with differences in symptom presentation. Methane production was consistently associated with the constipation-predominant sub-group of IBS patients (65). The presence of methane slows intestinal transit by converting the pattern of motility from peristaltic to nonperistaltic (66) and reduces postprandial plasma levels of serotonin (67), a mediator of the peristaltic reflex (68). A role for gut bacteria as a factor in constipation is further suggested by the observation that patients with chronic idiopathic constipation have improved stool frequency and consistency after a course of antibiotics (69).

APPROACH TO DIAGNOSIS OF INTESTINAL BACTERIAL OVERGROWTH

There is no accurate way to sample and identify small intestinal bacterial overgrowth using the approach of aspiration and culture from the duodenum. Not only are we technically limited in our ability to access the small bowel beyond the Ligament of Treitz but more than 80% of gut microbial strains cannot be cultured by any means (70). With these severe limitations, in place of aspiration and culture, a lactulose breath test may be used to detect abnormal patterns of bacterial fermentation as a signature of small intestinal bacterial overgrowth, which is specifically aided by the fact that hydrogen and methane are exclusively of microbial origin.

SO WHERE ARE WE NOW

Evidence is now available to support the role of gut microbes in gastrointestinal motility disorders with accumulating data pointing to the utility of a new approach to IBS based on targeting small intestinal bacterial overgrowth. The identification of gut microbes as contributors to motility disorders holds promise for improved diagnostic and treatment approaches for some of the most challenging problems in gastroenterology. ■

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