MICROBIOME

Bacterial broadband

The involvement of intestinal bacteria in gut–brain communication could help to explain the mysteries of irritable bowel syndrome, but the search continues for definitive evidence.

BY MICHAEL EISENSTEIN

Most people prefer to imagine a healthy distance between their brain and colon, but in fact the two are intimately linked. Neuronal lines of communication help the brain to control the digestive process, and messages relayed back by the gut can influence both perception and behaviour.

Evidence for another important player in this dialogue is coming to light. The human digestive tract is host to a massive and diverse community of bacteria that aid digestion and strengthen immunity — and over the past decade, scientists have observed that the gut microbiota also interact with the central nervous system (CNS). As a result, mental health and even neurological development might both shape and be shaped by the composition and behaviour of these bacteria.

Symptoms as diverse as gastrointestinal distress, physical pain and depression may all converge on the health of our bacterial communities. This could be especially relevant in irritable bowel syndrome (IBS), in which physical effects such as constipation and diarrhoea often co-exist with psychiatric problems such as anxiety and post-traumatic stress. Animal

experiments offer some evidence of bacterial involvement in the condition, whereas studies in people with IBS show that a dose of healthy probiotic bacteria could mitigate both digestive discomfort and psychiatric symptoms.

These and other findings suggest that the microbiota act as crucial ‘first responders’, relaying health-related signals between the digestive tract and the brain. Perturbations in this gut–brain–microbiome axis may play a central part in IBS, but much of the evidence for this is patchy or circumstantial. Many questions remain about the extent to which this axis influences IBS pathology, about whether defects in microbiota are a cause or a consequence of the condition, and about how to turn this knowledge into treatments.

MIND–BODY CONNECTION

The existence of a brain–gut axis is not a particularly avant-garde idea. The roots of the concept go back to the late nineteenth century, when the physicians William James and Carl Lange first proposed that emotional response might be directly modulated by signals transmitted from the viscera to the brain (see page S102).

The intestinal wall maintains bidirectional

communication with the CNS through the vagus nerve, which runs from the brainstem to the gut and manages numerous unconscious tasks throughout the body, such as maintaining heart rate. The vagus nerve also relays essential stress-response signals. Its interaction with the gut regulates almost every aspect of the passage of digested material through the intestines — explaining why CNS disorders are so often accompanied by digestive problems.

“If you have alterations in the brain, you will almost certainly have altered output to the gut because the two organs are that closely connected,” says Emeran Mayer, a gastroenterologist at the David Geffen School of Medicine, University of California, Los Angeles. Conversely, feedback signals from the gut to the brain can go well beyond obvious hungry-versus-full messages; abnormalities in the digestive system can directly shape both cognitive and emotional state.

Research over the past few decades has clarified the role of this gut–brain axis in IBS. For example, brain-imaging studies by Mayer and colleagues have identified both structural and functional alterations in the CNS associated with IBS, including notable changes in specific brain regions that respond to pain and

SARAH J. COLEMAN

discomfort¹. Mayer's group has also identified top-down effects of psychosocial trauma and post-traumatic stress — especially from early in life. “In patients with IBS,” says Mayer, “up to 60% indicate that stress is the factor that triggered either the first onset or the exacerbation of symptoms.”

Furthermore, many people with IBS have associated psychiatric issues, and some find that mental-health-oriented treatments can improve their gastrointestinal symptoms. “Cognitive behavioural therapy, hypnotherapy and psychodynamic therapy are all quite effective,” says Magnus Simrén, a clinical gastroenterologist at the University of Gothenburg in Sweden. And although trials of such interventions for IBS have proved challenging to perform and interpret, he notes that “they have still been quite impressive when it comes to their effectiveness in treating IBS”.

Numerous lines of evidence also link IBS to perturbations of the gut microbiome. Many IBS cases arise after a gastrointestinal infection, which can markedly change the composition of the gut microbiota both directly, by killing off certain beneficial species, and indirectly, by damaging the intestinal environment that supports them (see page S114). Drugs can also influence the health of the microbiome. John Cryan and his colleagues at University College Cork in Ireland have shown that rats treated early in life with a cocktail of antibiotics that kills off certain types of gut microbe can experience long-lasting gut hypersensitivity² — a common symptom of IBS.

However, the IBS microbiome data are still swimming into focus. Each gram of human colon tissue can contain up to one trillion bacteria, representing at least ten major categories (or phyla) that comprise many poorly characterized subtypes. This means that most microbiotal data represent high-level surveys rather than detailed censuses.

Microbiologist Willem de Vos of Wageningen University in the Netherlands was among the first to profile microbiome changes in large numbers of people with IBS³. His team's surveys revealed some notable trends, including a reduction in the numbers of ‘good’ species, such as those that belong to *Bifidobacterium*, that typically form the bedrock of a healthy microbiota, and an increase in *Ruminococcus* species that are associated with infection. “We’ve seen some patterns, and there’s reason to believe that there are robust signatures of IBS,” he says. But the results so far are conflicting. Some researchers have observed reduced microbial diversity in IBS, whereas others — including Mayer's group — have seen the opposite.

Healthy microbiota are thought to collaborate with host epithelial cells to maintain the intestinal wall. Destabilization of this relationship could compromise the gut and impair digestion or excretion — defining symptoms of IBS. De Vos, together with Robin Spiller at the

University of Nottingham, UK, showed that alterations to the microbiota in people who developed IBS after an infection were accompanied by striking changes in intestinal gene expression⁴. Importantly, these correlated with alterations in specific subpopulations of gut bacteria. Moreover, these changes seem to be self-perpetuating in people with IBS.

“Some people with *Campylobacter* infections get diarrhoea for a while and then go back to normal,” de Vos says. “But others don’t go back and have recurrent problems.” In other words, he says, their microbiome falls into what is known as an “alternative stable state” that locks them into IBS.

A BACTERIAL BRIDGE

Only in the past few years have researchers come to suspect that all three elements — gut, microbiota and brain — intersect in IBS. Early evidence for a brain–microbiome connection came in 2011 from scientists at the Karolinska Institute in Stockholm. They demonstrated that ‘germ-free’ rodents that have been reared under sterile conditions and lack a microbiota have a reduced anxiety response in various laboratory tests relative to those with intact bacterial communities⁵. Other studies with germ-free animals have shown that disruptions in the microbiota can increase sensitivity to pain and bring on cognitive symptoms that resemble depression and anxiety.

New evidence sheds light on the mechanism of the gut microbiota's impact on nervous-system function. Researchers in Japan have found that germ-free mice produce lower than normal levels of dopamine and adrenaline⁶, two important molecules in the CNS response

“The animal data are almost hard to believe because they’re so dramatic.”

to stress. The microbiota also influence production of serotonin — an intriguing finding given that this neurotransmitter plays a central part in gut motor function and digestion, as well as in various cognitive and mood disorders.

Roughly 95% of the body's serotonin is produced in the digestive tract, and a team led by Elaine Hsiao, now at the David Geffen School of Medicine, has demonstrated in mice that a particular subset of gut bacteria directly stimulates intestinal serotonin synthesis and release⁷. “This is one of the most interesting papers in this field from the last ten years,” says Mayer. “Those serotonin-producing cells in the gut can be viewed as the main hub for communication between the gut and brain, because they’re exposed to what we eat and to signals produced by the gut microbes, and innervated by connections to the vagus nerve.”

Several mouse studies suggest that the vagus nerve serves as some sort of ‘hotline’ by which gut microbes communicate directly with the CNS (see ‘A complicated conversation’). Cryan and his colleagues have found that the effects on

the CNS of a probiotic bacterial strain seem to depend on signals relayed by the vagus nerve⁸. “That immediately tells us that vagal pathways may be relevant to IBS, and the microbiome could be shepherding that,” Cryan says. A team led by Premysl Bercik, a gastroenterologist at McMaster University in Hamilton, Ontario, has likewise provided evidence that probiotics can treat anxiety-like symptoms in a mouse model of colitis — but only if this nerve remains intact and functional⁹.

The brain can also affect the microbiota and potentially contribute to the onset or exacerbation of IBS. Cryan, Bercik and others have used mouse models to show that early-life stress can change the composition of gut microbial communities, although they are yet to work out how. “Many patients who are under stress will experience diarrhoea or a change in their bowel habits as a consequence, and this could potentially affect their microbiotal composition,” says Bercik.

Although IBS is not recognized as an inflammatory disorder per se, there is evidence that inflammatory processes might be hyper-responsive in people with IBS, which offers another route by which the CNS might modulate the microbiome. “Depression is well known to be a pro-inflammatory state,” says Eamonn Quigley, a clinical gastroenterologist at Houston Methodist Hospital in Texas. “We know the brain can influence the immune system in general, which can definitely affect the microbiome.” But he stops short of labelling this as a causal mechanism by which the CNS influences IBS symptoms.

A UNIFYING THEORY

Collectively, these data suggest that IBS could arise from disturbances of one or more physiological processes, which reinforce each other to exacerbate the disease state. “None of the previous theories were able to explain IBS fully,” says Bercik. “The microbiota could be one of the unifying links.” The CNS response to early-life trauma could, for instance, trigger changes in the microbiota, which might then impede intestinal function and alter signalling to the brain, further amplifying the stress response. Or perhaps a gastrointestinal infection or inflammatory response to a food allergy could trigger a similar feedback cycle. “It’s kind of ridiculous to pin it down to just one of these factors because they all fit into this big jigsaw puzzle,” says Mayer.

This grand unifying theory of IBS is appealing, but is yet to garner strong experimental support. For one thing, links between the gut–brain–microbiome axis and IBS are built mainly on a foundation of animal studies, which may poorly reflect the physiological disruptions of patients. The germ-free rodents that have produced such striking data, for example, have an extreme phenotype that is never seen in humans. “We need to understand how this works with the milder

A COMPLICATED CONVERSATION

The interplay between the digestive tract and the central nervous system is well-established. Signals produced by the gut microbiota are thought to influence this gut-brain axis. If they do, disruptions to this community of bacteria could have a role in exacerbating symptoms of irritable bowel syndrome.

perturbations of the microbiota that we see in humans,” says Simrén.

Many studies of stress and its effects on IBS have relied on models in which a rodent pup is separated from its mother for hours at a time in the first few weeks after birth. The resultant stress effects can last the animal’s lifetime, with symptoms that resemble human IBS. “They’re hypersensitive, they have hyperactive motility of the colon, stomach emptying slows and they’re more anxious,” says Mayer. But this maternal-separation model has not proved entirely persuasive. “It’s fantastic that they look like they have IBS, but it’s not the same thing,” de Vos says. Indeed, given the apparent heterogeneity of IBS, many scientists agree that it seems far-fetched to imagine that any one animal model will ever tell the full story.

As a clinician, Mayer recognizes the seriousness of this gulf. “The animal data are almost hard to believe because they’re so dramatic,” he says, noting that, so far, no results have been faithfully replicated in a well-designed human study. One of the biggest problems is the paucity of human-microbiome data. Many studies of IBS have relied on faecal samples from small numbers of patients, who may have been inappropriately grouped together despite displaying different symptom patterns. “We need to have hundreds of patients in our studies to really see where there are differences between groups,” says Simrén. Early studies also failed to account for gender differences or the confounding effects

of dietary habits, which can make a huge difference to microbial composition.

Another important consideration is how the microbiome changes over time. An initial bacterial community is established at birth, but develops as a person matures. Given the apparent link between early-life events and subsequent development of IBS, researchers need to understand the potential effects of disruptions to the microbiota in childhood. “If we look at the microbiome of human IBS patients and notice only modest changes, that’s not telling you what happened early on,” says Cryan. “You could have changes from early life that potentially affected brain-gut signalling permanently.”

There is also the possibility that the crucial element is how the microbiome functions, rather than what it comprises. This could help to explain why bacterial surveys of IBS have yielded such ambiguous results. “The same bacteria can exert different functions based on the environment and the food that we are supplying them with,” says Bercik. The upshot is that it may be more informative to focus on the microbiome’s biochemical output than on its composition.

Despite the uncertainties in the evidence, there are intriguing findings from patients that lend weight to the hypothesis that the microbiome’s influence on gut-brain communication is relevant to IBS. A small study by Quigley and his colleagues¹⁰ showed

that people with IBS who have psychiatric symptoms can be distinguished from those without, purely by differences in their microbiota. Mayer’s team is also continuing to pursue its brain-imaging work — preliminary results show that certain microbial profiles seem to correlate with changes in brain regions involved in pain perception and processing.

CAUSE AND EFFECT

What is still missing is solid evidence of gut microbiota causality in IBS pathology. “We don’t know yet what is the chicken and what is the egg,” says Mayer. Tinkering with patient microbiomes could help scientists to address this question. Mayer and his University of California, Los Angeles, colleague Kirsten Tillisch have found that healthy women who consumed a dairy drink containing probiotic bacteria had altered activity in brain areas associated with perception of emotions and of pain and discomfort¹¹. This is important evidence of microbiota-to-brain feedback, but the effect is yet to be investigated in patients.

In 2015, Bercik and his colleagues reported preliminary data that showed that giving probiotics to patients significantly alleviated their depression — and provided a measure of IBS relief. And numerous studies indicate that such treatments can lessen gastrointestinal symptoms more generally. “There’s no question that probiotics have an effect,” says Quigley. “What’s more difficult to sort out is why they have an effect and which ones have what effect.” De Vos, together with gastroenterologist Robert Brummer of Sweden’s Örebro University, is exploring the causality issue from the other end, with a clinical trial to assess the effects of transplanting faecal bacteria from healthy donors into people with IBS.

Even the microbiome champions acknowledge that a better microbial mix will not be the answer for every patient. But the consensus is that a clearer picture of the ‘good guys’ and ‘bad guys’ of the gut could one day allow doctors to quickly dispatch appropriate reinforcements to the bacterial battlements, and break patients out of the self-destructive IBS cycle. ■

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