

Visceral pain: role of the microbiome-gut-brain axis

Kieran Rea, Siobhain M. O' Mahony, Timothy G. Dinan and John F. Cryan
(University College Cork, Ireland)

A growing body of preclinical and clinical evidence supports a relationship between the complexity and diversity of the microorganisms that inhabit our gut (human gastrointestinal microbiome) and health status. These microbes can influence centrally regulated emotional behaviour through mechanisms including microbially derived bioactive molecules, mucosal immune and enteroendocrine cell activation, as well as vagal nerve stimulation.

Changes to the microbial environment, as a consequence of illness, stress or injury can lead to a broad spectrum of local physiological and behavioural effects including a decrease in gut barrier integrity, altered gut motility, inflammatory mediator release, as well as nociceptive and distension receptor sensitization. Impacts at a central level include alterations in the hypothalamic-pituitary-adrenal axis, neuroinflammatory events and concomitant changes to neurotransmitter systems. Thus, both central and peripheral pathways associated with pain manifestation and perception are altered as a consequence of the microbiome-gut-brain axis imbalance.

The dogmatic approach of antibiotic treatment in the latter century, for the treatment of many diseases and conditions, has undergone a radical change. We are 90% microbe, and pragmatism suggests that we manipulate this ecosystem for the treatment of various ailments, stress dysfunction and affective disorders, including the alleviation of visceral pain.

Pain is an unpleasant experience combining a sensory component with a complex emotional response. This physiological survival mechanism is conserved throughout evolution to protect against potential or existing tissue damage. While the anatomical pathways and signalling mechanisms involved in pain signalling from skin and deep tissue are relatively well defined, the mechanisms underlying pain from internal organs (visceral pain) and its treatment are proving a difficult target for therapeutic intervention. Visceral pain is believed to affect up to 40% of the population at some stage in their lifetime and is commonly associated with an aching or throbbing sensation with varying degrees of discomfort, and is often difficult to localize to a precise anatomical region.

Although visceral pain disorders include myocardial infarction (heart attack), dysmenorrhoea, appendicitis, bladder pain and pelvic pain it is the functional gastrointestinal disorders (FGIDs) including irritable bowel syndrome (IBS) that represent the more common forms of visceral pain. IBS alone affects an estimated 10–15% of the population in developed countries with an estimated economic burden to healthcare systems in the billions.

The perception of visceral pain and discomfort from the gastrointestinal tract involves complex mechanisms. These include sensitization of sensory nerves in the periphery, and dysregulation of thalamic and corticolimbic signalling pathways within the

central nervous system (CNS). Of interest, there is substantial overlap in the brain areas underlying visceral pain and those that are involved in the processing of psychological stress, a key predisposing factor for visceral hypersensitivity.

Visceral pain pathways

After an event such as injury, stress or infection, the sensory information coding for visceral pain is sent from the site of origin to the spinal cord, and then through ascending spinal and vagus nerve pathways to the brain. Pain receptors in the viscera respond to mechanical stimulation such as distension or pressure, tissue damage and chemical stimulation as a consequence of inflammation, infection or ischaemia. These receptors are localized on bare nerve endings containing transient receptor potential (TRP) channels that detect tissue damage or injury. Agents that activate TRP channels include globulin, protein kinases, arachidonic acid, prostaglandins, histamine, nerve growth factor, substance P, calcitonin gene-related peptide, serotonin, acetylcholine, ATP and changes in pH.

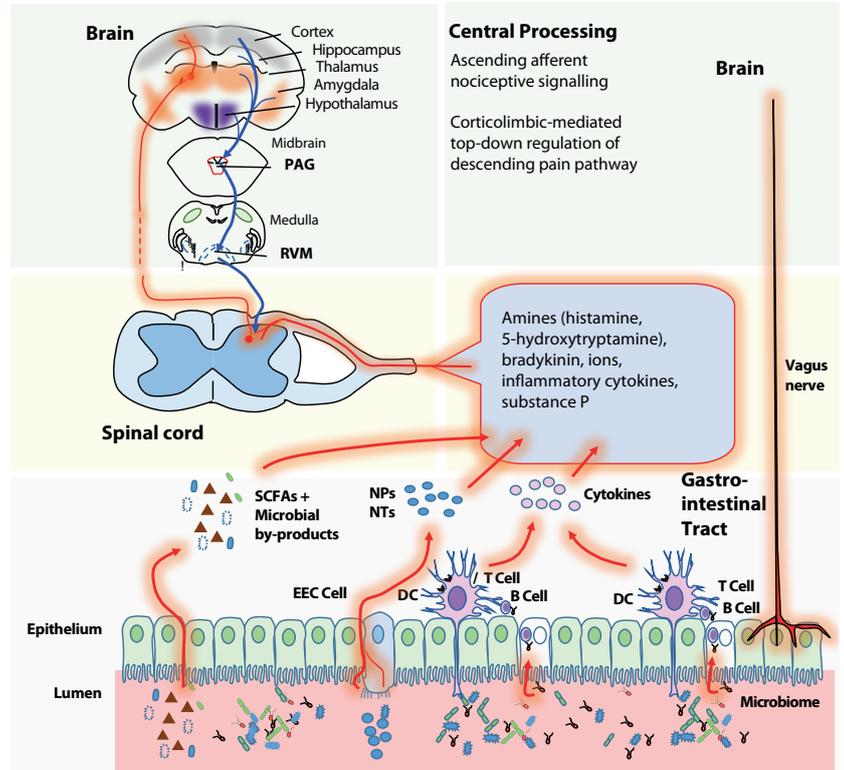
At the dorsal horn of the spinal cord, biochemically active agents including substance P, glutamate, aspartate, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), somatostatin, calcitonin gene-related peptide (CGRP) and galanin are released

from the nerve terminals of the visceral primary afferents to send the nociceptive signal to second order neurons. Under normal physiological conditions, these neurons are under 'gated' control. However, once a certain threshold of stimulation is exceeded, these neurons are no longer suppressed and the nociceptive information coding for general location and intensity projects to supraspinal sites. The two major ascending pain pathways in mammals are the spinothalamic and the spinoparabrachial tracts, which encode the sensory-discriminatory and affective aspects of pain respectively. Once the nociceptive information has been processed in the CNS, the descending pathways (from brain to spinal cord) can exert an inhibitory or facilitatory effect on the sensation of pain. Sensitization of pain receptors, as a consequence of repeated or prolonged activation, can lead to chronic, and often unpredictable bouts of visceral pain. Thus, by targeting key bioactive chemicals or receptor systems on these sensory afferent neurons, the sensation of visceral pain could be significantly ameliorated. More recently, a new player has emerged in the regulation of visceral pain signals – the gut microbiome.

The microbiome

The human gut harbours a complex and dynamic microbial ecosystem. We each harbour a unique microbiome signature of bacteria, archaea, yeasts, single-celled eukaryotes, as well as helminth parasites and viruses, including bacteriophage. Under normal homeostatic conditions, this microbial population helps maintain intestinal peristalsis, mucosal integrity, pH balance, immune priming and protection against invading pathogens. Numbering approximately 100 trillion, these microorganisms have an estimated collective mass of 1–2 kg, approximately the same weight as the human brain. Genes within the human gut microbiome significantly outnumber host human genes and are capable of producing a plethora of centrally acting compounds, influencing virtually all aspects of human physiology and biology.

The microbiome-gut-brain axis is a complex bi-directional system including the CNS, the neuroendocrine and neuroimmune systems, the autonomic nervous system, the enteric nervous system (ENS), and, of course, the gut microbiome. Through endocrine, immune and neuropeptide/neurotransmitter systems, the microbiome can relay information about the health status of the gut. This in turn can profoundly impact upon neuronal signalling in the brain and, as a result, impact emotional systems and behavioural response; thus, visceral pain pathways are poised to be regulated by the microbiome.



Microbiome regulation of visceral pain

Microbiome and visceral pain

Sensitization of primary afferent nociceptors (pain receptors) may lead to visceral hypersensitivity in FGIDs. A number of different receptor types are involved in the process of peripheral sensitization including the TRPV family, proteinase activated receptors, cholecystokinin receptors, serotonin receptors, cannabinoid receptors, as well as an array of ion channels including ATP-gated ion channels, voltage-gated sodium and calcium channels, and acid-sensing ion channels. The gastrointestinal microbiome can activate these receptors directly or indirectly through immune responses at the mucosal surface during infection, inflammation and autoimmunity, formyl peptides and protease release, polyunsaturated fatty acid (PUFA) release, short chain fatty acid (SCFA) production, neurotransmitter production and hormone secretion. The gastrointestinal microbiome can also stimulate the release of the body's natural pain-suppressing biomolecules including opioids from innate neutrophils and monocytes, endocannabinoids from colonic tissue, as well as other pain modulators including monoamines. Microbial metabolites can also influence epigenetic mechanisms, by altering substrate concentrations or by direct inhibition of enzymatic machinery in epigenetic pathways. However, the extent

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to which these mechanisms either individually or collectively affect the aetiology of FGIDs remains unaddressed.

From a physiological perspective relevant to IBS visceral sensitivity, stress can influence gut motility, alter gastrointestinal secretions and exacerbate intestinal permeability – all of which can have a negative impact on gastrointestinal microbiome number and diversity. While most individuals are routinely exposed to intermittent stress, some are more susceptible and this can lead to stress-related disorders and related comorbidities. It may well be that this maladaptive stress response is mediated by a lack or overexpression of a specific gastrointestinal microbiome.

Interestingly, adverse early-life events are linked with a maladaptive stress response and might increase the vulnerability of individuals to visceral sensitivity and other stress-related disorders later in life. While it is difficult to conclusively attribute early-life stress and associated changes in the gastrointestinal microbiome with the presentation of visceral sensitivity in later life in humans, the use of animals to establish this link has been very informative.

Evidence for gastrointestinal microbiome involvement in visceral pain response

Animals raised in a sterile environment (germ-free mice) have an exaggerated stress response and reduced perception of pain following different inflammatory stimuli. Antibiotic-mediated depletion of the gastrointestinal microbiome decreased visceral pain-related response in experimentally naïve mice and rats, and early-life exposure to antibiotics predisposed animals to visceral hypersensitivity in adulthood. Recently, faecal matter from viscerally hypersensitive IBS patients was transplanted to germ-free rats, and the response to distension of the colon was enhanced in these animals. Accumulating empirical evidence supports a role for probiotics, which positively

influence the gastrointestinal microbiome, in the treatment of visceral sensitivity – provided vagus nerve integrity is maintained.

In contrast to the provocative preclinical evidence for a role of the gut microbiome in visceral pain, clinical studies remain inconclusive with a large ‘non-responder’ population in many probiotic trials. Anecdotal evidence suggests that antibiotics, in particular rifaximin, may be useful in treating bacterial infections that may be contributing to the discomfort and pain associated with FGIDs and inflammation, however further research is required to confirm these assertions. It is clear that longitudinal, placebo-controlled, double-blind studies with whole-system analysis and complimentary brain imaging are necessary to integrate central, peripheral and behavioural alterations before, during and after the treatment of visceral pain. The mounting evidence for the microbiome in affective processing cannot be overlooked. Alterations of the gastrointestinal microbiome have been directly linked to immunity, inflammatory, motility and neurological changes that are hallmark characteristic of FGIDs. And while there is still much to learn about the relative contribution of the microbiome to various aspects of visceral pain, the re-emergence of the gastrointestinal microbiome as a therapeutic target offers an exciting new advent of pain research. ■





Kieran Rea is Laboratory Manager in the Microbiota-Gut-Brain Axis Group in the APC Microbiome Institute, University College Cork, Ireland. Kieran has a BSc (Hons) in Biochemistry and MSc in Neuropharmacology from the National University of Ireland, Galway. He worked with Lundbeck A/S, Copenhagen, Denmark and completed his PhD in Neuropharmacology at Rijksuniversiteit Groningen, The Netherlands. He worked as a Postdoctoral Researcher at the Department of Pharmacology and Therapeutics in NUI Galway before he was appointed to his current position. Kieran's research interests include the neurobiological mechanisms by which stress impacts on pain, inflammation, mood disorders and cognition. Email: kieran.rea@ucc.ie



Siobhain O' Mahony is a lecturer in the Department of Anatomy and Neuroscience at UCC, and a Principal Investigator with the APC Microbiome Institute. She holds a BSc (Hons) in Neuroscience from UCC, and a Master's in Neuropharmacology

from NUI, Galway. She worked in the Department of Psychiatry and Neuropsychology in the University of Maastricht, The Netherlands and obtained her PhD from the department of Psychiatry, UCC. She completed a postdoctoral position with GlaxoSmithKline and continued her research in the APC Microbiome Institute. Her research interests include mechanisms whereby early-life stress can impact on behaviour and physiology in later life. Email: somahony@ucc.ie



Timothy G. Dinan is Professor of Psychiatry and a Principal Investigator in the APC Microbiome Institute at University College Cork, Ireland. He was previously Chair of Clinical Neurosciences and Professor of Psychological Medicine at St Bartholomew's

Hospital, London, UK. He has worked in research laboratories on both sides of the Atlantic and has a PhD in Pharmacology from the University of London, UK. He has published over 400 papers and numerous books on pharmacology and neurobiology. He is on the Editorial Boards of several journals. Email: t.dinan@ucc.ie



John F. Cryan is Professor and Chair at the Department of Anatomy & Neuroscience, and a Principal Investigator in the APC Microbiome Institute, UCC, Ireland. His research interests include understanding the interaction between the brain, gut and

microbiome and how it applies to stress, psychiatric and immune-related disorders across the lifespan. He has over 350 peer-reviewed articles and his awards include UCC Researcher of the Year 2012, the University of Utrecht Award for Excellence in Pharmaceutical Research 2013 and being named on the Thomson Reuters Highly Cited Researcher list in 2014. He is President-elect of the European Behavioural Pharmacology Society. Email: j.cryan@ucc.ie

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