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Pain Bugs: Gut Microbiota and Pain Disorders

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Abstract
The microbiota-gut-brain axis is a complex and dynamic multi-directional 'communication superhighway' within the body including the central nervous system, the autonomic nervous system, the neuroendocrine and neuroimmune systems, the lymphatic system, the enteric nervous system and the gastrointestinal microbiota. The mechanisms of communication are slowly being unravelled and involve the main systems mentioned along with the by-products produced such as neuropeptides, neurotransmitter, hormones and immune modulators. Over the last decade increasing evidence points to an essential role of this axis in many fundamental neural processes and brain disorders. **However, the limited clinical and preclinical studies do not clearly delineate a role for gut microbiota in the pathophysiology of pain state. The most researched area is in irritable bowel syndrome and in visceral pain studies in animal models. However, one cannot overlook the involvement of the microbiota in symptoms that are comorbid with chronic pain especially affective disorders. In this review we synthesise the available information** highlighting the gut microbiota in visceral, inflammatory, and neuropathic pain states, including fibromyalgia, migraine, cancer and chemotherapy-associated pain. Given its part in many effector systems, there is a clear need for more focused investigations on the mechanism of action of the microbiota in human pain states, as current treatment strategies are often ineffective or provide limited relief.

The Gut Microbiota: Mechanisms of Action

The significance of the bi-directional communication between the gut and the brain in health and disease has long been appreciated. However, in the past two decades, the microbiota (the trillions of microorganisms including bacteria, bacteriophage, archaea, protozoa and fungi that live within and on our bodies) has emerged as one of the key regulators of gut-brain function throughout the lifespan. It has been determined that many factors can influence the establishment of the core microbiota that informs host development across the lifespan including infection, mode of birth delivery, use of antibiotic medications, the nature of nutritional provision, environmental stressors and host genetics [1]. This in turn has led to the appreciation of microbiota-gut-brain communication in a myriad of disorders including psychiatric, metabolic, neurodevelopmental, age-related and neurodegenerative disorders [1]. Studies, largely in animal models, have shown that the microbiota regulates fundamental neural processes, from neurogenesis and myelination, to activation of microglia and neuroinflammatory processes [2] all of which are implicated in pain processes. Despite this there has surprisingly been little focus on the role of the microbiota in the initiation, development, maintenance and progression of pain disorders. The microbiota and the brain communicate with each other via various routes including the immune and inflammatory system, endocrine mechanisms, tryptophan metabolism, enteric and vagus neural communication, as well as through microbial metabolites such as short chain fatty acids, branched chain amino acids, peptidoglycans as well as many other peptides and secondary messenger biomolecules. Indeed, many of these metabolites have been identified in pain processing.

Pain types

Pain is a multimodal experience combining a discriminative sensory component with a complex graded emotional response. This physiological survival facility is usually transient or rapid (acute pain) and is inherent to all sentient organisms to protect against potential or existing tissue damage. Both acute and chronic pain can be debilitating, and can influence one's state of mind and contribute to comorbid symptoms including stress, anxiety and depression, which in turn can amplify the psychological intensity of the pain [3]. In this review we focus more on chronic pain conditions. Crudely, pain types can be categorised as nociceptive pain, inflammatory pain or pathological pain. Nociceptive pain is our classical response to a painful stimulus such as a pin-prick, where pain receptors on our extremities sense the stimulus and transmit the signal to our brains. vasoactive amines and peptides, eicosanoids, proinflammatory cytokines, and acute-phase proteinsthe inflammatory process prevents further tissue damage and ultimately results in healing and restoration of tissue function, but prolonged inflammation due to infection or tissue damage can be detrimental and painful to the host. Pathological pain can be a disease state caused by damage to the nervous system or by its abnormal function (examples including neuropathic pain, fibromyalgia, migraine and headache) [4].

Within these categories, the pain can be further sub-characterised as somatic (musculoskeletal, skin and deep tissue) or visceral (relating to internal organs). The anatomical pathways and signalling mechanisms involved in somatic/musculoskeletal pain and responses to acute nociceptive insults and acute inflammatory pain are relatively well defined. However, the mechanisms underlying visceral pain, neuropathic pain and chronic pain, and their treatment are proving a difficult target for therapeutic intervention.

Pain Pathways

The perception of pain and discomfort involves complex mechanisms, including molecular and cellular transduction mechanisms and neuronal plasticity, that lead to peripheral activation of

sensory nerves and, at a central level, regulation of thalamic and corticolimbic signalling pathways (**see Figure 1**). Acutely, after an event such as injury, stress or infection the nociceptive information coding for heat (inflammation) or pain, is propagated from the site of origin to vagal afferents or through ascending spinal pathways to the brain. Nociceptors in the viscera, and in skin and tissue respond to mechanical stimulation such as distension or pressure, tissue damage and chemical stimulation because of inflammation, infection or ischaemia.
However, following prolonged or chronic activation, neurons involved in transmitting nociceptive information can also become sensitised or dysfunctional leading to the conductance of a painful signal to what should be an innocuous stimulus (neuropathic pain). Dysfunction of the pain pathways in the anatomical loci at the site of injury, or neural communication from site of injury along the spinal cord to the brain and supraspinal regions involved in descending pain facilitation and inhibition may lead to chronic, repeated and often unpredictable bouts of pain, and may be the root from which neuropathic pain stems. Thus, by targeting key bioactive chemicals or receptor systems on these sensory afferent neurons, or those at supraspinal sites, the sensation of all pain types (nociceptive, inflammatory and neuropathic) could be significantly ameliorated.

Potential Microbiota-Driven Mechanisms in Pain Regulation

Locally, the gut contains a number of different receptor types involved in the processing of pain response including the transient receptor potential channels, of the vanilloid subtype (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 [5]. Gastrointestinal microbiota can activate these receptors directly or indirectly through immune responses [6] at the mucosal surface during infection, inflammation and autoimmunity, or via formyl peptides and protease release, pH changes, polyunsatturated fatty acid (PUFA) release, short chain fatty acid (SCFA) production, neurotransmitter production and hormone secretion [7]. Bacteria have also been shown to induce calcium flux and action potentials in nociceptor neurons [8].

As well as influencing local immune responses at the gut epithelium, microbiota can synthesise and release neurotransmitters and SCFAs, regulate steroid and bile acid metabolism, as well as influence the release of neuropeptides and hormones from enteroendocrine cells of the intestines. Some of these could potentially play a role in pain types such as migraine by contributing to vasoconstriction. A recent comprehensive study [9] has also highlighted a critical role for gastrointestinal microbiota in central microglia maturation, morphology and immunological function - an event that may extrapolate to spinal microglia, but this is as yet untested. Given the integrative role of microglia in numerous central processes including neuroinflammation, it is plausible that this contribution from the microbiota could influence central pain processing. Gastrointestinal microbiota 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 [10] including monoamines. Microbial metabolites can also influence epigenetic mechanisms, by altering substrate concentrations or by direct inhitibiton of enzymatic machinery in epigenetic pathways [11]. Potentially, these circulating cytokines, chemokines, endocrine messengers and microbial by-products can infiltrate the blood and lymphatic systems, or influence neural messages carried by the vagal and spinal afferent neurons to impact on centrally, and spinally-mediated events, to differentially modulate response to nociceptive, inflammatory and neuropathic pain types.

Below, we synthesise the evidence for microbiota in pain responding, however the temporal profile of microbiota-mediated influence on pain response to acute and chronic pain remains, as yet, a critical and unaddressed question.

Evidence for a role of Gastrointestinal Microbiota in Pain Response

Clinical and preclinical studies investigating the role of microbiota in nociceptive (visceral and somatic), inflammatory and neuropathic pain are limited. Much of the clinical evidence for gastrointestinal microbiota in pain response has focussed on nociceptive disorders of the gut, while preclinical studies incorporate nociceptive, neuropathic and inflammatory pain responses throughout the body.

Visceral Pain

Germ-free mice (reared in an enclosed sterile germ-free environment devoid of any microorganisms) were shown to have increased sensitivity to pain in the colorectal distension model [12], an animal model of visceral pain. Further evidence for an active role of the gut microbiota in pain response is with the use of antibiotics to deplete bacterial load. In naïve animals, antibiotic-mediated depletion of gastrointestinal microbiota decreased visceral pain-related response in mice [13] and rats [14], and early-life exposure to antibiotics predisposed animals to visceral sensitivity in adulthood [15]. Recently, the transplantation of faecal matter containing the gut microbes (faecal matter transplant, or FMT) from irritable bowel syndrome (IBS) patients with characterised by hypersensitivity to colorectal distension was transplanted to germ-free rats, and the response to colorectal distension was enhanced in these animals [16], again suggesting a role for gut microbes in the manifestation and pathophysiology of the disease.

In humans, FMT and probiotic supplementation have been investigated in visceral pain disorders including functional gastrointestinal disorders (FGID's) such as functional dyspepsia, IBS and infant colic - and clinical and preclinical evidence for a role for the gut microbiota in visceral pain is synthesised in a recent review [17]. Currently, data on FMT on pain in FGIDs are too limited to draw conclusions [18]. In terms of visceral sensitivity to pain in IBS sufferers, very few randomised double-blind, placebo-controlled studies have reported a beneficial effect of probiotics, or probiotic mixes on symptomology including pain/discomfort, distension/bloating, urgency and digestive dysfunction. A role for probiotics in paediatric [19] functional gastrointestinal disorders is well reviewed in a recent article reporting modest or weak effects on pain intensity or frequency. Clinical studies manipulating the microbiota to alleviate symptoms in visceral and/or inflammatory pain associated with myocardial infarction (heart attack), dysmenorrhea, appendicitis, bladder pain are lacking, with only one study reporting a reduction in pelvic pain with comorbid IBS symptomology following antibiotic (rifaximin) treatment [20].

Inflammatory Pain

One of the first examples linking microbiota to pain demonstrated a lower pain response in germ-free mice to externally applied inflammatory mediators to the paw [21], yet further studies investigating inflammatory pain response in germ-free or antibiotic-treted animals are lacking. In the clinic, FMT is medically accepted as a highly successful procedure for the eradication of *C. difficile* infection and associated symptoms including abdominal pain [22]. A recent review [23] and metadata analysis [24] captures the efficacy of microbial based treatments including probiotic treatments, and FMT in the treatment of inflammatory bowel disease and associated inflammatory pain response. In summary, the efficacy of FMT in the treatment of IBD was mixed [25] with studies reporting 20-33% clinical remission in pain in ulcerative colitis, reduction in pain index in 50-75% Crohn's disease individuals, and mixed

effects 0-80% in pouchitis. An interesting study investigating the anti-inflammatory effect of **bacterial exopolysaccharide** (high molecular weight polymers that certain bacteria can secrete into their local environment to benefit their growth and proliferation), determined that it was effective in reducing carrageenan-induced inflammatory pain and mechanical hyperalgesia in rats [26].

Somatic and Neuropathic Pain

Studies investigating the involvement of gastrointestinal microbiota on somatic pain (musculoskeletal, cutaneous (skin) or tissue pain) are also limited. Given the rise in antibiotic resistant pathogens in recent years, it is surprising that there is relatively little work on skin microbiota and pain response. A recent review focussing on work by Chiu and Woolf highlights that skin bacteria are able to interact directly with neurons to cause pain, irrespective of their effect on the host inflammatory response [27]. Arthritic pain although clearly linked with inflammation is focused on the joints. Despite evidence for a role for microbiota, in particular *Prevotella copri* in untreated new-onset rheumatoid arthritis patients [28-30] and evidence from animal studies [31] suggesting activation of autoreactive t-cells in the intestine, human studies are only now being undertaken to investigate the effects of FMT in arthritis [32], and the limited randomised control trials and relatively low numbers in probiotic studies have not yielded any clear consensus as to the efficacy of probiotics in arthritis [33,34].

In a recent preclinical study it was determined that gastrointestinal microbiota contribute to chemotherapy-induced neuropathic pain [35] via TLR4 expressed on hematopoietic cells, including macrophages. Germ-free and antibiotic-treated animals had lower pain responses than their naïve controls. A clinical study with probiotic treatment reported efficacy in pain management in post-chemotherapy abdominal pain in colorectal cancer patients [36], an event that is caused by chemotherapy-induced gastrointestinal toxicity of the gut microbiome-host immune system [37].

There are no conclusive studies providing a role for the gastrointestinal microbiota in migraine. However, evidence suggests that migraine is associated with gastrointestinal disorders [38], and a compositional analysis from oral microbiota in the American gut project [39] report that microbes that reduce nitrate, nitrite and nitric oxide (all linked with migraine) are higher in migraine sufferers. Clinical studies have reported a moderate reduction in number, duration and or intensity of migraine events with probiotic administration [40,41] and much further work in this research field is warranted given the ability of microbes to release bioactive molecules involved in vasoconstriction and vasodilation. To date, studies investigating the effect of microbiota manipulation in the treatment of fibromyalgia, a chronic widespread muscle and joint pain disorder, are limited to one study reporting no alleviation of pain following probiotic administration [42].

In a preclinical neuropathic pain model, where the sciatic nerve is ligated to become sensitised to previously innocuous pressure, the transfer of microbiota from pain-sensitive animals to antibiotic-treated mice conferred a painful phenotype [43], again reinforcing an involvement of microbes in pain response. Select probiotics did not alleviate painful stimuli in a neuropathic and inflammatory pain model [44]. Only one case report observed a beneficial effect of microbiota manipulation in neuropathic pain management, with an improvement in diabetic neuropathy being observed following FMT [45].

Conclusions and Future Directions

With the recent advances in sequencing technologies and the accelerating bioinformatics pipelines we are increasingly becoming more aware of the role and functions of the trillions of microbes in our gut and how they can contribute to overall health. However, the constitution

of each individual's gut commensals is unique, and their relationship with their host physiology and genetics will likely in the future lead to personalised medicines for the treatment of many disorders including pain.

Currently, the limited clinical and preclinical studies do not delineate a clear role for gut microbiota in pain. The best evidence is clearly in visceral pain states both in animal models and in irritable bowel syndrome However, one cannot overlook the involvement of the microbiota in symptoms that are comorbid with chronic pain especially affective disorders. It is also becoming clear that many medications used to manage pain can have direct or indirect effects on the microbiota composition [46,47].

There is a clear need for large longitudinal cohort studies analysing the microbiome in almost all pain states. This needs to be coulped with longitudinal, placebo-controlled, double-blind studies with whole-system analysis and [48] complimentary brain imaging and biomarker development to integrate central, peripheral and behavioural alterations before, during and after treatment of pain.

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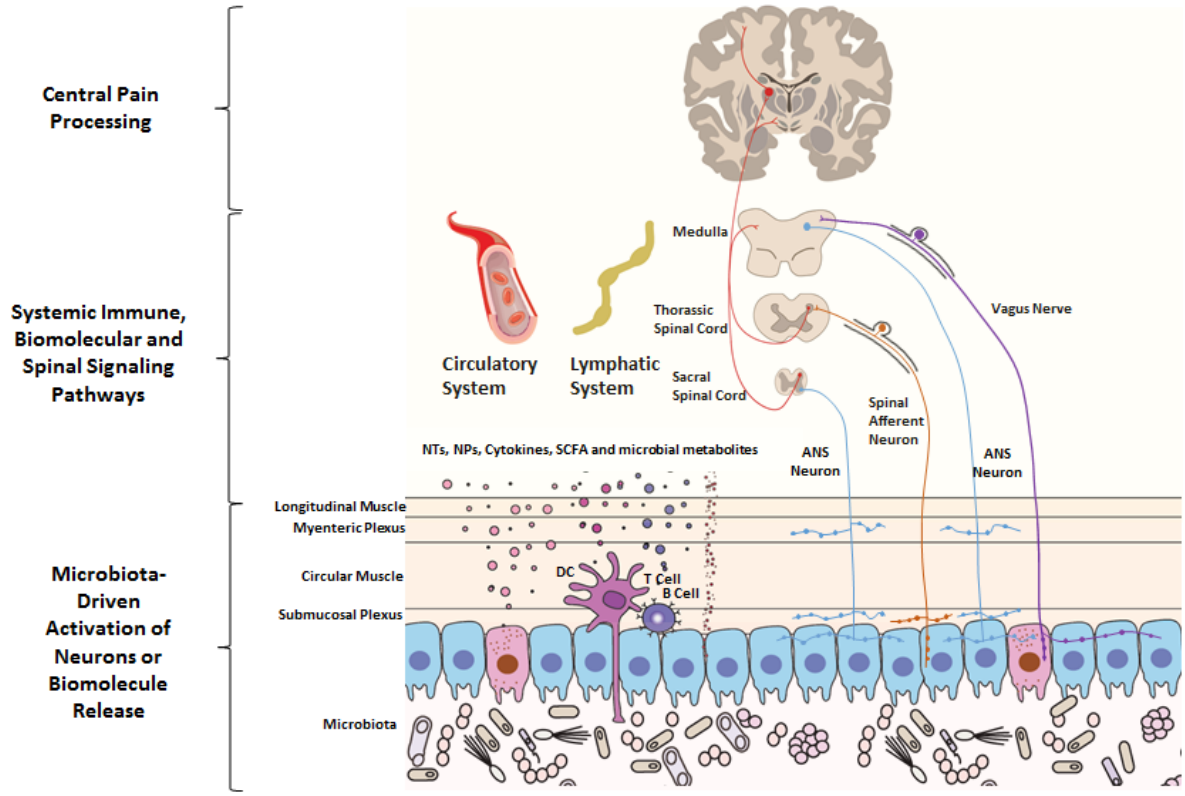


Figure: 1 *Schematic outlining the potential role of gut microbiota in nociceptive, inflammatory and neuropathic pain. The microbiota may communicate nociceptive information to the brain via various routes including the immune and inflammatory systems, endocrine mechanisms, enteric and vagus neural communication, as well as through microbial metabolites such as short chain fatty acids, branched chain amino acids, neurotransmitter, peptidoglycans and other peptides and secondary messenger biomolecules. Nociceptive signals are propagated via spinal afferent nerves through the spinal cord to the brain, while inflammatory or neuropathic nociceptive signals may be communicated via vagal signals, or through biomolecules in the lymphatic or circulatory system that can cross the blood brain barrier to mediate central pain processing.*

ANS: Autonomic nervous system; DC: Dendritic cell; NT: Neurotransmitter; NP: Neuropeptide; SCFA: Short-chain fatty acids